Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
Health Technology Assessment
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Results section 8.1

Comparison progesterone vs placebo
Comparison other interventions vs progesterone

From the HTA-report:
Progesterone, cerclage, pessary, or acetylsalicylic acid for prevention of preterm birth in singleton and multifetal pregnancies

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Abbreviations/Acronyms

17-OHPC 17-alpha-hydroxyprogesterone caproate
ART assisted reproductive technology
ASA acetylsalicylic acid
ASQ ages and stages questionnaire
BPD bronchopulmonary dysplasia
CDI child developmental inventory
CI confidence interval
CL cervical length
cm centimetre
d days
g gram
GDM gestational diabetes mellitus
HDP hypertensive disorders in pregnancy
HTA health technology assessment
ICP intrahepatic cholestasis in pregnancy
ICTRP International Clinical Trials Registry Platform
im intramuscular injection
IVF in vitro fertilization
IVH intraventricular haemorrhage
IQR interquartile range
LY life year
MD mean difference
mg milligram
mm millimetre
NEC necrotizing enterocolitis
NICU neonatal intensive care unit
PPROM preterm prelabour rupture of membranes
PROSPERO the international prospective register of systematic reviews
PTB preterm birth
RCT randomised controlled trial
RD risk difference
RDS respiratory distress syndrome
ROP retinopathy of prematurity
RR relative risk/risk ratio
SBU assessment of social service
SD standard deviation
SEK Swedish krona
SOF summary of findings
sPTB spontaneous preterm birth
SR systematic review
TVS transvaginal sonography
UK United Kingdom
US United States
VGR Region Västra Götaland
WHO World Health Organization

Comparison progesterone vs placebo in singleton pregnancies

Included studies

Thirty RCTs reporting on singleton pregnancies were included, and two long-term follow-up reports of RCTs (Cuijpers et al., 2020; Northen et al., 2007), in total 32 publications (Appendix 2). Seventeen trials were classified as having low risk of bias, and 13 as having high risk of bias (Table 1). Three trials were not placebo-controlled, and as high risk of bias trials, not included in analyses on which conclusions were based. Five trials included both singleton and twin pregnancies, two of these presented results separately for singletons and twins while three trials did not (percent twins 1.5% [Crowther et al., 2017], 2.7% [Johnson et al., 1975] and 9.6% [Fonseca et al., 2007]). In total, 9363/9558 women/newborns were included in these trials.

One secondary publication (Gyamfi et al., 2009) reported on GDM in subgroups from two original trials. In addition, two systematic reviews contributed to the meta-analyses with individual participant data (EPPPIC, 2021; Romero et al., 2018), one systematic review (Simons et al., 2020) and one HTA-report (Norman et al., 2018) contributed with long-term follow-up data.

Setting

Seven of the RCTs were carried out in the USA, two in Europe, 12 in the Middle East, the rest were performed in Pakistan, India, Brazil, Japan, Zambia, or were multinational studies.

Population

All trials included asymptomatic women with increased risk for preterm birth, mainly history of preterm birth (any or spontaneous preterm birth before 37 or 34 gestational weeks), short cervix (defined as a sonographic cervical length ≤30 mm, 25 to <30 mm, ≤25 mm, 10 to ≤20 mm, ≤15 mm), or both. Two trials included women with pregnancies after assisted reproductive technology (ART) as risk factors. One trial included women with HIV as risk factor.

Intervention

The interventions included different routes of administration: vaginal progesterone (capsule, gel, or pessary) (13 trials), im injection of progesterone (17-OHPC) (14 trials) or oral progesterone (three trials). Doses of vaginal progesterone varied between 90 and 400 mg per day. Doses of oral progesterone varied between 400 and 600 mg per day. Doses of 17-OHPC were similar across trials (250 mg 17-OHPC im per week), except in one small trial (Hauth et al., 1983, which used 1000 mg/week). All but three trials used placebo as control (two used standard care and one used im injection of vitamin B as control).

The included trials differed in inclusion criteria regarding gestational age at onset of intervention (onset of intervention was in early vs late second trimester) and treatment duration (treatment was stopped between 34 and 37 gestational weeks).

Trials with low risk of bias reported an adequate compliance or adherence to treatment (≥80% of prescribed medication) for >90% of patients participating in nine trials (Blackwell et al., 2020; Crowther et al., 2017; Fonseca et al., 2007; Glover et al., 2011; Grobman et al., 2012; Hassan et al., 2011; Meis et al., 2003; O'Brien et al., 2007; Price et al., 2021). Norman et al., 2016, reported adequate compliance for 66% of women in the progesterone group and 71% in the placebo group and Van Os et al., 2015 for 43% and 50%, respectively. Six trials with low risk of bias did not report compliance (Ashoush et al., 2017; Cetingoz et al., 2011; DaFonseca et al., 2003; Hayashi et al., 202; Majhi et al., 2009; Rai et al., 2009).

Table 1. Risk of bias assessment (Low/High) of included original RCTs.

Singleton pregnancies	Risk of bias	**Multifetal pregnancies**	Risk of bias	**Mixed singleton and multifetal**	Risk of bias
Articles reporting progesterone vs placebo					
Aflatoonian, 2013	High	Awwad, 2015	Low	Aboulghar, 2012	High
Ali, 2020	High	Briery, 2009	High	Cetingoz, 2011	Low
Ashoush, 2017	Low	Brizot, 2015	Low	Crowther, 2017	Low
Azargoon, 2016	High	Caritis, 2009	Low	Fonseca, 2007	Low
Blackwell, 2020	Low	Combs, 2010	Low	Johnson, 1975	High
Da Fonseca, 2003	Low	Combs, 2011	Low		
Glover, 2011	Low	Lim, 2011	Low		
Grobman, 2012	Low	Norman, 2009	Low		
Hassan, 2011	Low	Rehal, 2021	Low		
Hauth, 1983	High	Rode, 2011	Low		
Hayashi, 2021	Low	Rouse, 2007	Low		
Ibrahim, 2010	High	Serra, 2013	Low		
Jabeen, 2012	High	Wood, 2012	Low		
Jafarpour, 2020	High				
Majhi, 2009	Low				
Meis, 2003	Low				
Norman, 2016	Low				
O'Brien, 2007	Low				
Price, 2021	Low				
Rai, 2009	Low				
Saghafi, 2011	High				
Shadab, 2018	High				
Shahgheibi, 2016	High				
Van Os, 2015	Low				
Yemini, 1985	High				
Articles reporting other interventions vs progesterone					
Cruz-Melguizo, 2018	Low	Dang, 2019	Low		
Keeler, 2009a	Low				

Directness, study limitations, and precision

Some of the included trials had some problems with directness, which was affected by ethnicity (i.e. many studies included a high proportion of Black women) and there was a high rate of preterm birth in the control group in some studies.

Risk of bias in the individual trials are presented graphically in colour within the forest plots (legend in Table 2), and as an overall assessment of study limitations in the outcome tables in Appendix 4.1. The majority of trials had no serious study limitations. Conclusions are solely based on trials with low risk of bias.

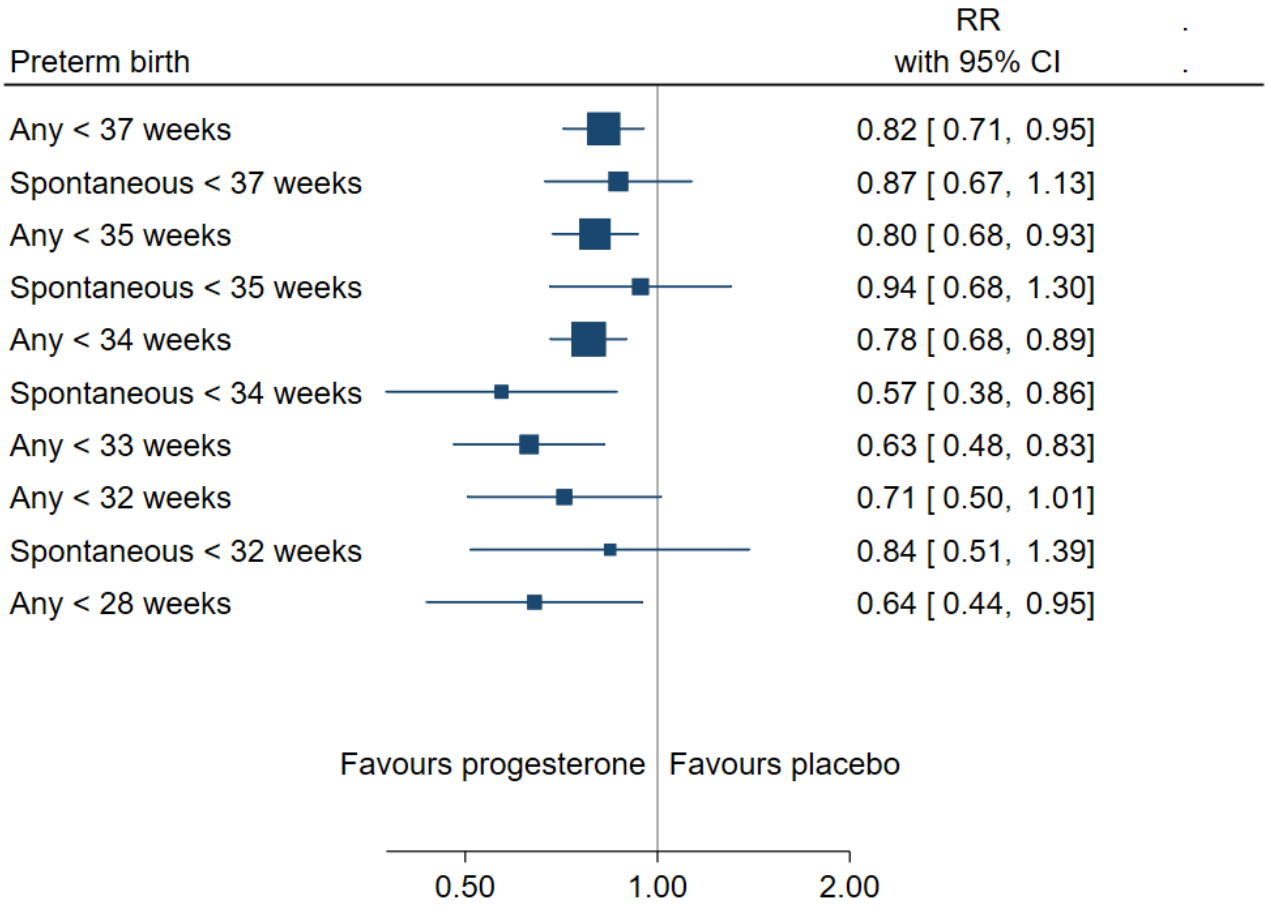
The trials were generally underpowered for outcomes as neonatal mortality, neonatal and maternal morbidity. Furthermore, three trials were stopped early (Meis et al., 2003; Grobman et al., 2012; Van Os et al., 2015).

Results per outcome

Preterm birth in singletons across gestational weeks

The pooled estimates from meta-analyses of trials reporting any or spontaneous preterm birth (<37, <35, <34, <33, <32, and <28 gestational weeks), from low risk of bias trials are summarised in Figure 1.

Figure 1. Summary graph of pooled estimates from meta-analyses comparing progesterone and placebo in women with a singleton pregnancy and any type of risk factor for preterm birth, from trials with low risk of bias regarding the outcomes any and spontaneous preterm birth before different gestational weeks.



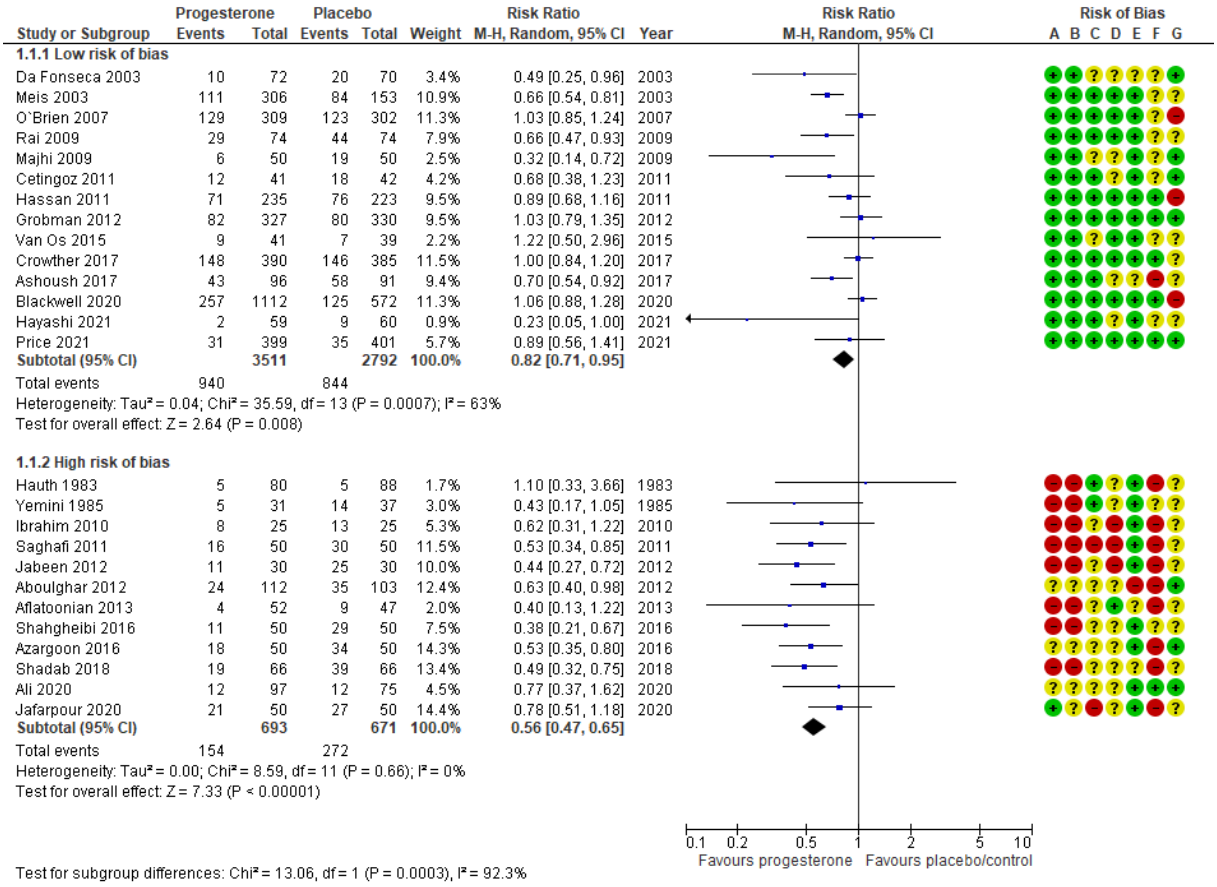
The pooled estimates (RR) ranged from 0.57 to 0.94 across the span of gestational weeks, comparing progesterone with placebo including all routes of administration and different risk factors, indicating a favourable effect of progesterone. The pooled estimates were in general numerically lower at shorter gestational lengths, although with lower precision.

Table 2. Risk of bias legend to the colour plot within the following forests plots

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Conflict of interest bias

Any preterm birth <37 weeks (Appendix 4.1.1.a and Figure 2)
A meta-analysis of 14 trials with low risk of bias, including 6303 women, showed a reduction in the rate of any preterm birth, RR 0.82 (95% CI 0.71 to 0.95). The crude event rate across trials was 30.2% without progesterone. The pooled weighted RD was -6.6 percentage points (95% CI -10.8 to -2.3).

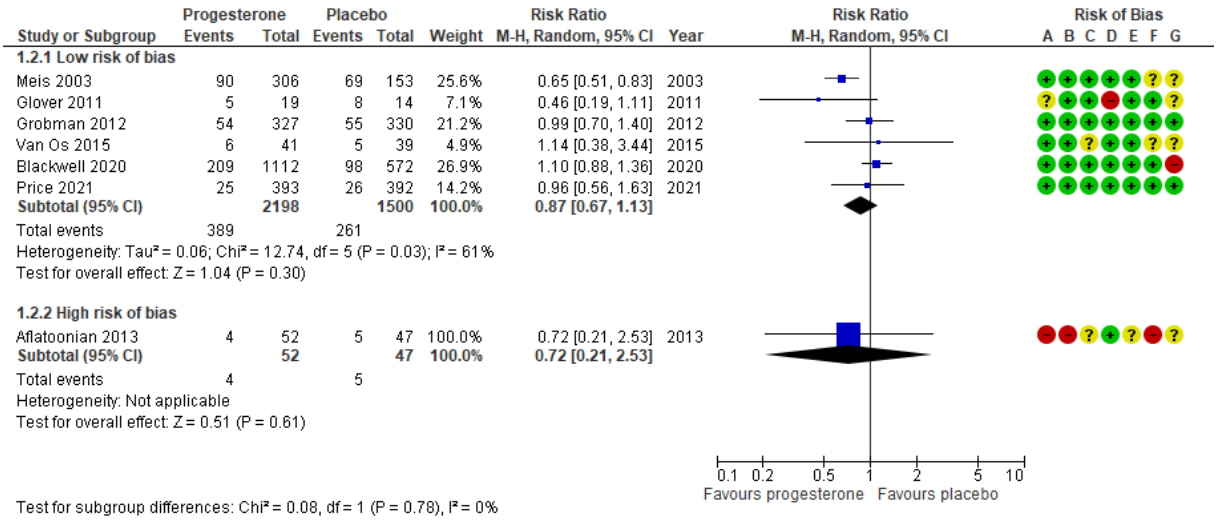
Figure 2. Outcome: Any preterm birth <37 weeks.



Conclusion: Progesterone compared with placebo reduces the risk of any preterm birth before 37 gestational weeks in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕⊕⊕).

Spontaneous preterm birth <37 weeks (Appendix 4.1.1.b and Figure 3)
A meta-analysis of six trials with low risk of bias, including 3698 women, showed no difference in the rate of spontaneous preterm birth, RR 0.87 (95% CI 0.67 to 1.13). The crude event rate across trials was 17.4% without progesterone. The pooled weighted RD was -2.4 percentage points (95% CI -7.3 to 2.4).

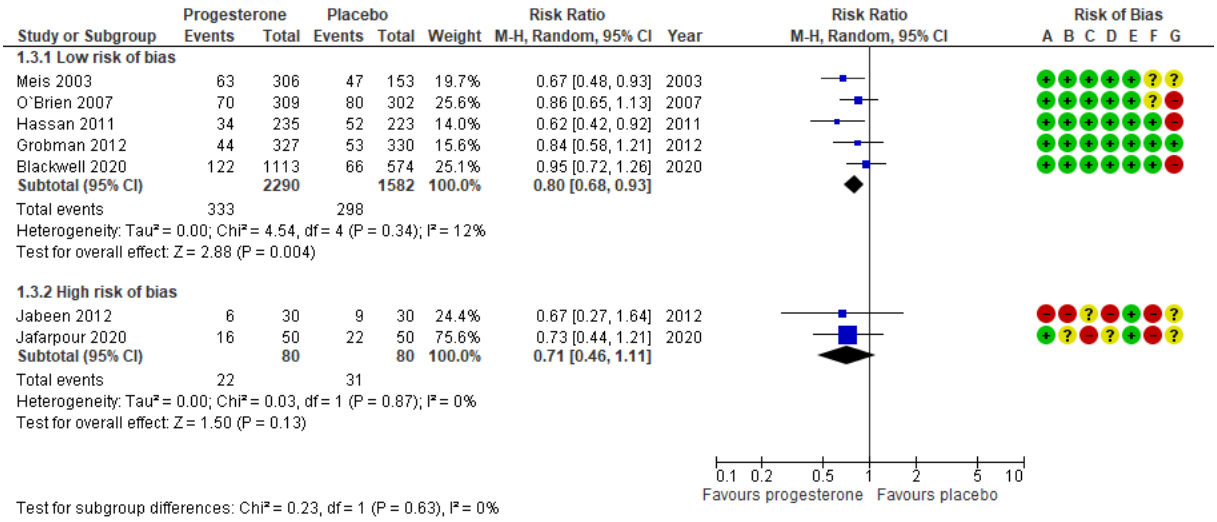
Figure 3. Outcome: Spontaneous preterm birth <37 weeks.



<u>Conclusion:</u> Progesterone compared with placebo probably result in no difference in the risk of spontaneous preterm birth before 37 gestational weeks in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Any preterm birth <35 weeks (Appendix 4.1.2.a and Figure 4**)**
A meta-analysis of five trials with low risk of bias, including 3872 women, showed a significant reduction in the rate of any preterm birth, RR 0.80 (95% CI 0.68 to 0.93). The crude event rate across trials was 18.8% without progesterone. The pooled weighted RD was -4.1 percentage points (95% CI -7.8 to -0.5).

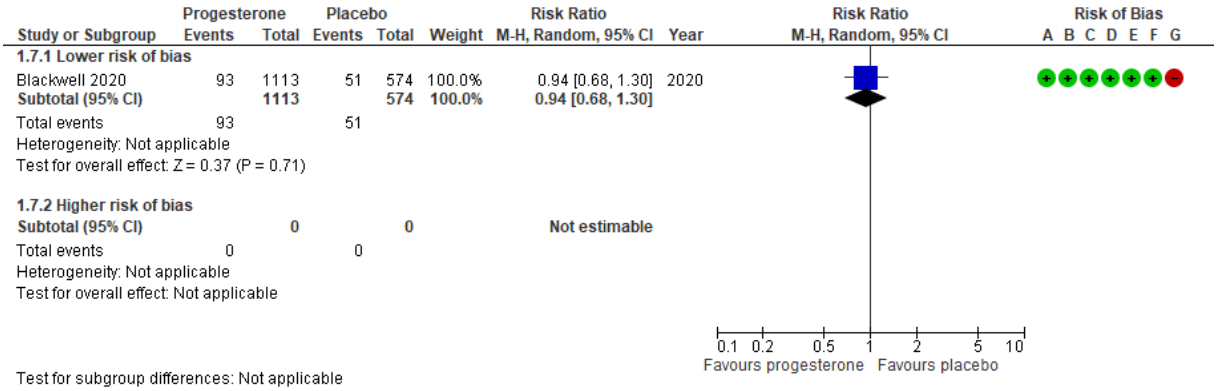
Figure 4. Outcome: Any preterm birth <35 weeks.



Conclusion: Progesterone compared with placebo probably reduces the risk of any preterm birth before 35 gestational weeks in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <35 weeks (Appendix 4.1.2.b and Figure 5**)**
One trial with low risk of bias, including 1687 women with a previous spontaneous preterm birth, compared 17-OHPC with placebo, showed no difference in the rate of spontaneous preterm birth, RR 0.94 (95% CI 0.68 to 1.30). The crude event rate across trials was 8.9% without progesterone. The RD was -0.5 percentage points (95% CI -3.4 to 2.3).

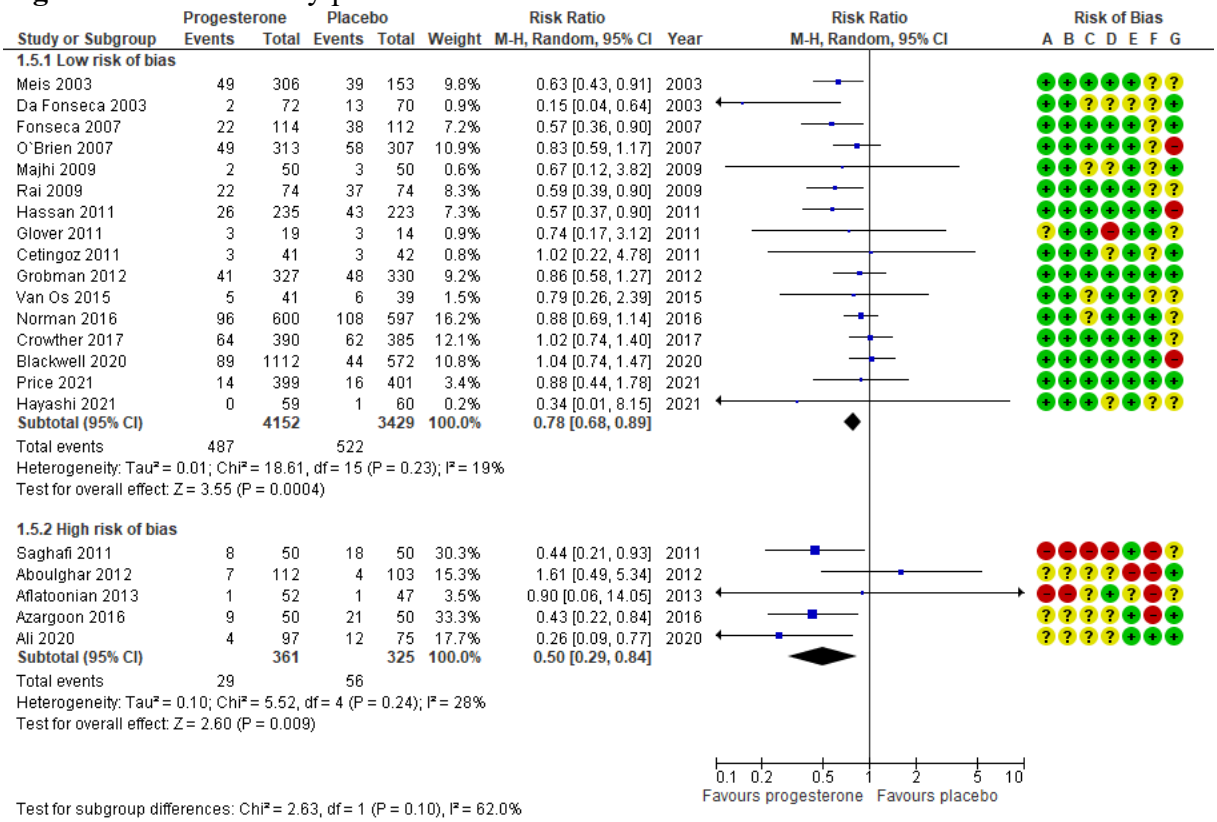
Figure 5. Outcome: Spontaneous preterm birth <35 weeks.



Conclusion: 17-OHPC compared with placebo probably results in no difference in the risk of spontaneous preterm birth before 35 gestational weeks in women with a singleton pregnancy and previous spontaneous preterm birth (GRADE ⊕⊕⊕◯).

Any preterm birth <34 weeks (Appendix 4.1.3.a and Figure 6)
A meta-analysis of 16 trials with low risk of bias, including 7581 women, showed a reduction in the rate of any preterm birth, RR 0.78 (95% CI 0.68 to 0.89). The crude event rate across trials was 15.2% without progesterone. The pooled weighted RD was -3.5 percentage points (95% CI -5.8 to -1.2).

Figure 6. Outcome: Any preterm birth <34 weeks.

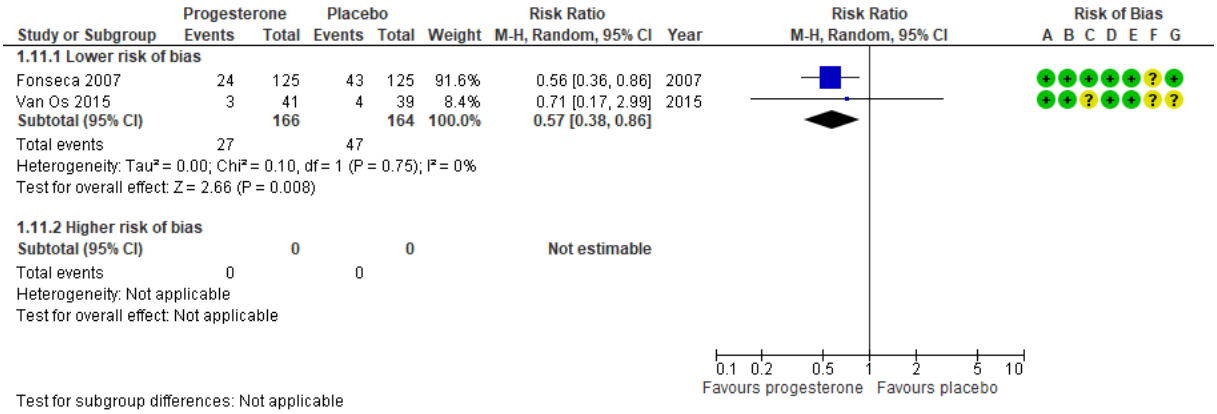


Results from Meis 2003, Fonseca 2007, O'Brien 2007, Hassan 2011, Glover 2011, Crowther 2017, Blackwell 2020 were retrieved from the IPD meta-analysis by Stewart et al. (EPPPIC, 2021).

Conclusion: Progesterone compared with placebo reduces the risk of any preterm birth before 34 gestational weeks in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕⊕⊕).

Spontaneous preterm birth <34 weeks (Appendix 4.1.3.b and Figure 7)
A meta-analysis of two trials with low risk of bias, including 330 women (Fonseca et al., 2007 with 9.6% twins included) showed a significant reduction in the rate of spontaneous preterm birth; RR 0.57 (95% CI 0.38 to 0.86). A sensitivity analysis excluding Fonseca et al., 2007 due to inclusion of 9.6% twins, removed 92% of the sample size and resulted in a very imprecise estimate (RR 0.71 (95% CI 0.17 to 2.99). The crude event rate across trials was 28.6% without progesterone. The pooled weighted RD was -9.4 percentage points (95% CI -22.3 to 3.4).

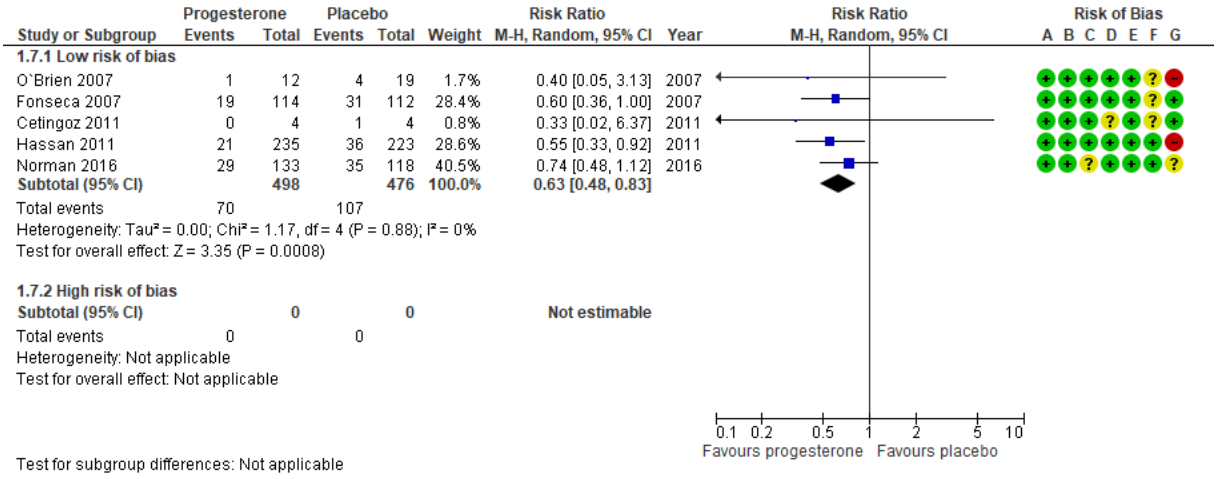
Figure 7. Outcome: Spontaneous preterm birth <34 weeks.



Conclusion**:** Vaginal progesterone, compared with placebo may reduce the risk of spontaneous preterm birth before 34 gestational weeks in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Any preterm birth <33 weeks (Appendix 4.1.4.a and Figure 8)
A meta-analysis of five trials with low risk of bias, including 974 women showed a significant reduction in the rate of preterm birth, RR 0.63 (95% CI 0.48 to 0.83). The crude event rate across trials was 22.5% without progesterone. The pooled weighted RD was -8.4 percentage points (95% CI -13.0 to -3.8).

Figure 8. Outcome: Any preterm birth <33 weeks. All patients had a short cervical length according to inclusion criteria (Hassan and Fonseca) or constitute subgroups of the other trials.



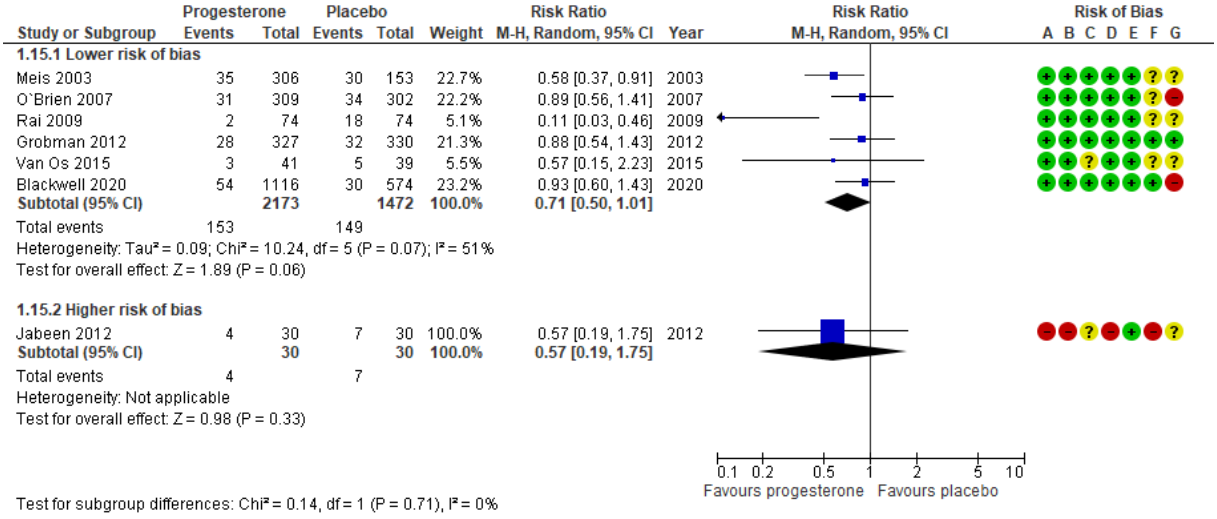
Results for singletons from O'Brien 2007, Fonseca 2007, Cetingoz 2011, and Norman 2016 were retrieved from the IPD meta-analysis by Romero et al., 2018.
Cut-off for cervical length was ≤25 mm in all trials but two, Fonseca 2007 used ≤15 mm and Hassan 2011 included 10-20 mm.

Conclusion: Vaginal progesterone, not considering dosage, compared with placebo probably reduces the risk of any preterm birth before 33 gestational weeks in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <33 weeks
No trial reported on spontaneous preterm birth <33 weeks.

Any preterm birth <32 weeks (Appendix 4.1.5.a and Figure 9)
A meta-analysis of six trials with low risk of bias, including 3645 women showed no difference in the rate of any preterm birth, RR 0.71 (95% CI 0.50 to 1.01). The crude event rate across trials was 10.1% without progesterone. The pooled weighted RD was -4.6 percentage points (95% CI -9.2 to -0.1).

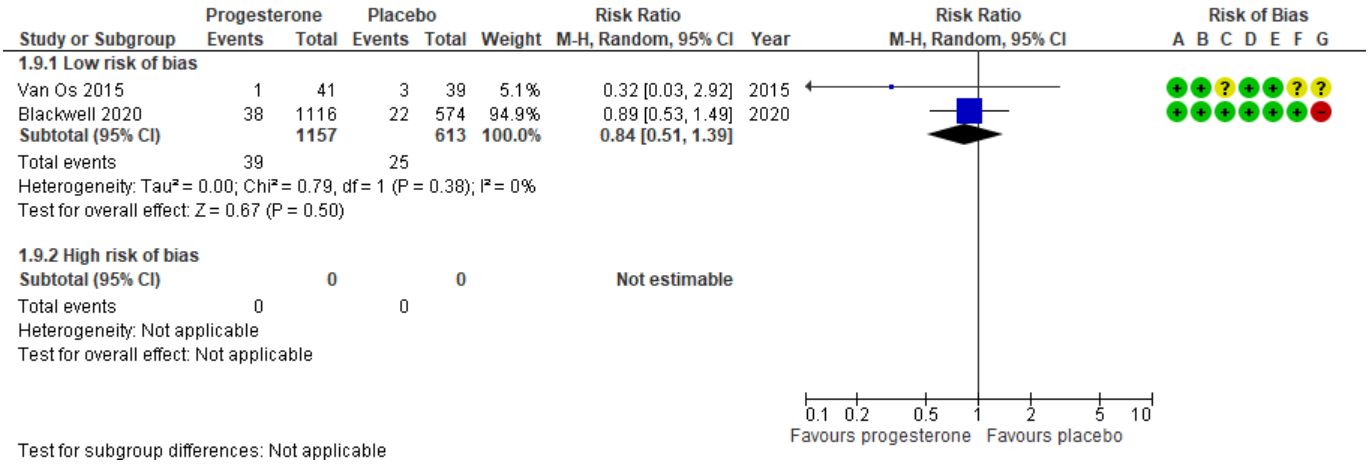
Figure 9. Outcome: Any preterm birth <32 weeks.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of any preterm birth before 32 gestational weeks, although the CI may imply a reduced risk, in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕◯◯).

Spontaneous birth <32 weeks (Appendix 4.1.5.b and Figure 10)
A meta-analysis of two trials with low risk of bias, including 1770 women showed no difference in the rate of spontaneous preterm birth, RR 0.84 (95% CI 0.51 to 1.39). The crude event rate across trials was 4.1% without progesterone. The pooled weighted RD was -0.6 percentage points (95% CI -2.5 to 1.2).

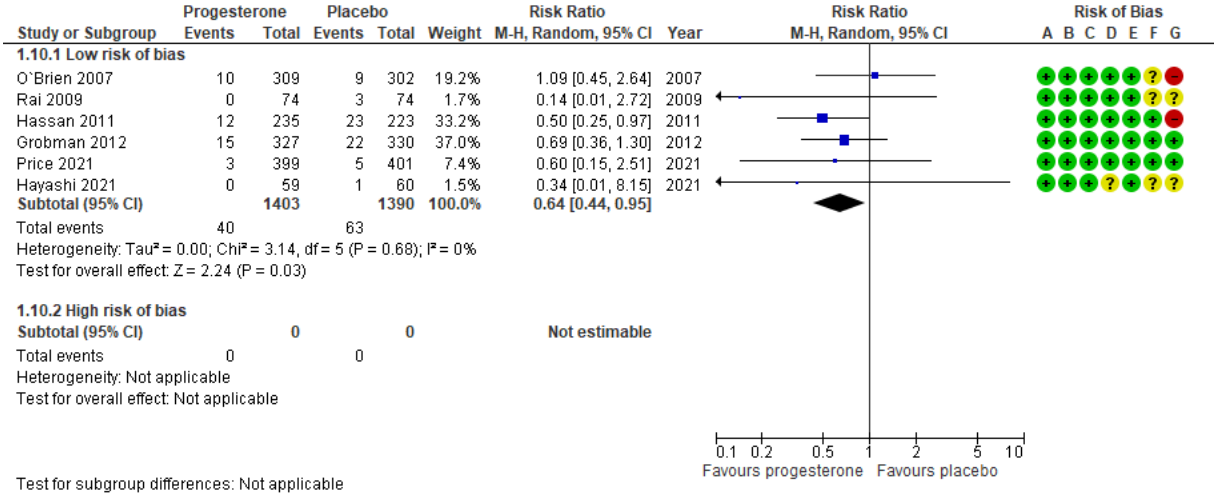
Figure 10. Outcome: Spontaneous preterm birth <32 weeks.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of spontaneous preterm birth before 32 gestational weeks in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕◯◯).

Any preterm birth <28 weeks (Appendix 4.1.6.a and Figure 11)
A meta-analysis of six trials with low risk of bias, including 2793 women showed a reduction in the rate of any preterm birth, RR 0.64 (95% CI 0.44 to 0.95). The crude event rate across trials was 4.5% without progesterone. The pooled weighted RD was -1.4 percentage points (95% CI -3.1 to 0.2).

Figure 11. Outcome: Any preterm birth <28 weeks.



Conclusion: Progesterone compared with placebo probably reduces the risk of any preterm birth before 28 gestational weeks in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous birth <28 weeks
No trial reported on spontaneous preterm birth <28 weeks.

Subgroup analyses (Figures 63-70, pages 49-53)
Exploratory subgroup analyses among trials with low risk of bias were performed for administration route (vaginal progesterone, im 17-OHPC or oral progesterone) and pre-specified subgroup analyses for specific risk factors (history of spontaneous preterm birth or short cervical length). No trials reporting results in subgroups of patients with cervical surgical treatment for cervical intraepithelial neoplasia were identified. Also, within each stratum of administration route, subgroup analyses based on history of spontaneous preterm birth and short cervical length were conducted. Meta-analyses were performed for any preterm birth before 37 and 34 weeks and are presented in Subgroup analyses.
Table 3 shows the summary estimates from the meta-analyses.

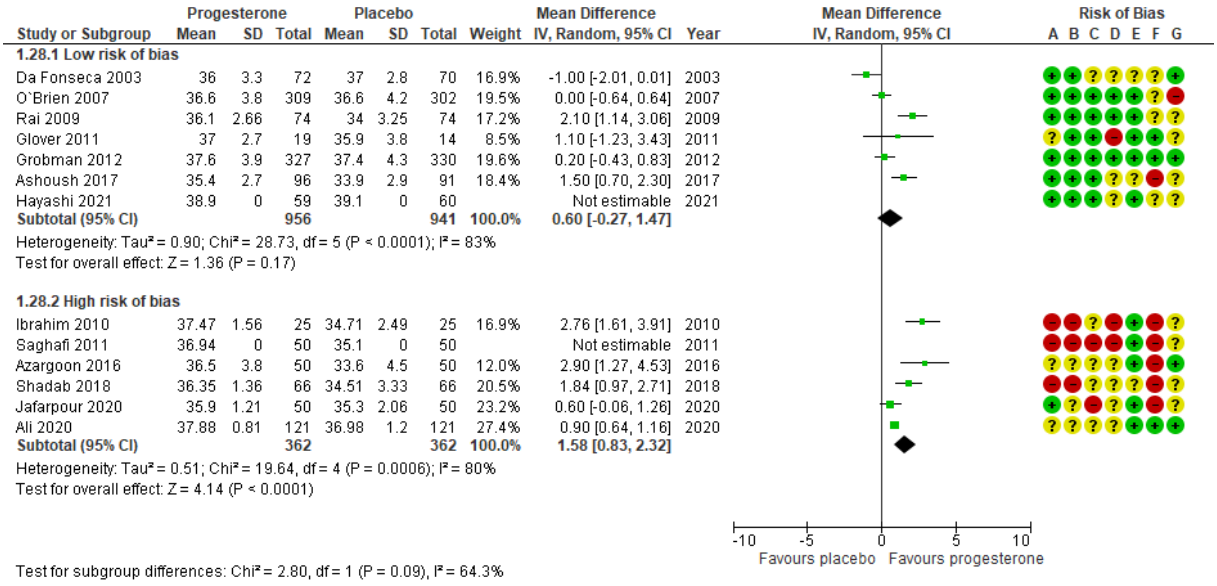
The exploratory subgroup analyses of different administration routes did not reveal any obviously and consistently more efficacious route (Figures 63-64). Although oral progesterone was associated with a statistically significant effect, the results were hampered by small sample sizes.
Among specific risk factors, history of spontaneous preterm birth was consistently of statistical significance in terms of demonstrating benefit from progesterone treatment (Figures 65-66). Subgroup analyses of administration route among women with the risk factors previous history of preterm birth or short cervical length are presented in Figures 67-70. Vaginal progesterone was associated with a statistically significant effect in reducing any preterm birth <34 weeks in women with a short cervix.

Table 3. Summary estimates from subgroup meta-analyses exploring the effect of progesterone vs placebo according to administration route and specific risk factors in women with a singleton pregnancy.

Outcomes **Administration route** **Risk factor**	**Number of RCTs (women)**	**Relative effect** **RR (95% CI)** In bold if difference is statistically significant RR <1 indicates favourable outcome of progesterone	**Absolute effect (%)**
Administration route			
Any PTB <37 weeks			
17-OHPC im	4 (3600)	0.89 (0.69 to 1.16)	22.4 vs 22.3
Vaginal progesterone	8 (2416)	0.85 (0.71 to 1.02)	33.6 vs 37.1
Oral progesterone	2 (335)	**0.69 (0.55 to 0.85)**	42.4 vs 61.8
Any PTB <34 weeks			
17-OHPC im	4 (3600)	0.84 (0.66 to 1.06)	9.0 vs 10.1
Vaginal progesterone	10 (3800)	**0.77 (0.62 to 0.94)**	14.0 vs 17.8
Oral progesterone	2 (181)	**0.60 (0.40 to 0.90)**	26.9 vs 45.5
Risk factor			
Any PTB <37 weeks			
History of spontaneous preterm birth	9 (4189)	**0.78 (0.65 to 0.94)**	30.4 vs 36.6
Short cervix	4 (1314)	0.93 (0.71 to 1.22)	24.8 vs 26.4
Any PTB <34 weeks			
History of spontaneous preterm birth	9 (4044)	**0.78 (0.62 to 0.98)**	11.9 vs 15.7
Short cervix	5 (1540)	**0.68 (0.53 to 0.86)**	12.1 vs 17.8
Administration route: 17-OHPC im **Risk factor: history of preterm birth**			
Any PTB <37 weeks	2 (2143)	0.84 (0.52 to 1.34)	26.0 vs 28.8
Any PTB <34 weeks	2 (2143)	0.81 (0.49 to 1.34)	9.7 vs 11.4
Administration route: 17-OHPC im **Risk factor: short cervix**			
Any PTB <37 weeks	1 (657)	1.03 (0.79 to 1.35)	25.1 vs 24.2
Any PTB <34 weeks	1 (657)	0.86 (0.58 to 1.27)	12.5 vs 14.5
Administration route: vaginal **Risk factor: history of preterm birth**			
Any PTB <37 weeks	5 (1711)	0.79 (0.59 to 1.05)	35.4 vs 38.4
Any PTB <34 weeks	5 (1720)	0.81 (0.55 to 1.20)	13.9 vs 16.3
Administration route: vaginal **Risk factor: short cervix**			
Any PTB <37 weeks	3 (657)	0.81 (0.44 to 1.49)	24.5 vs 28.6
Any PTB <34 weeks	4 (883)	**0.59 (0.43 to 0.80)**	11.8 vs 20.3

Gestational age in singletons (Appendix 4.1.7 and Figure 12)
A meta-analysis of six trials with low risk of bias, including 1778 women showed no mean difference in gestational age, 0.60 (-0.27 to 1.47) weeks, corresponding to approximately four days longer (two days less to ten days longer) gestational length in the progesterone group.

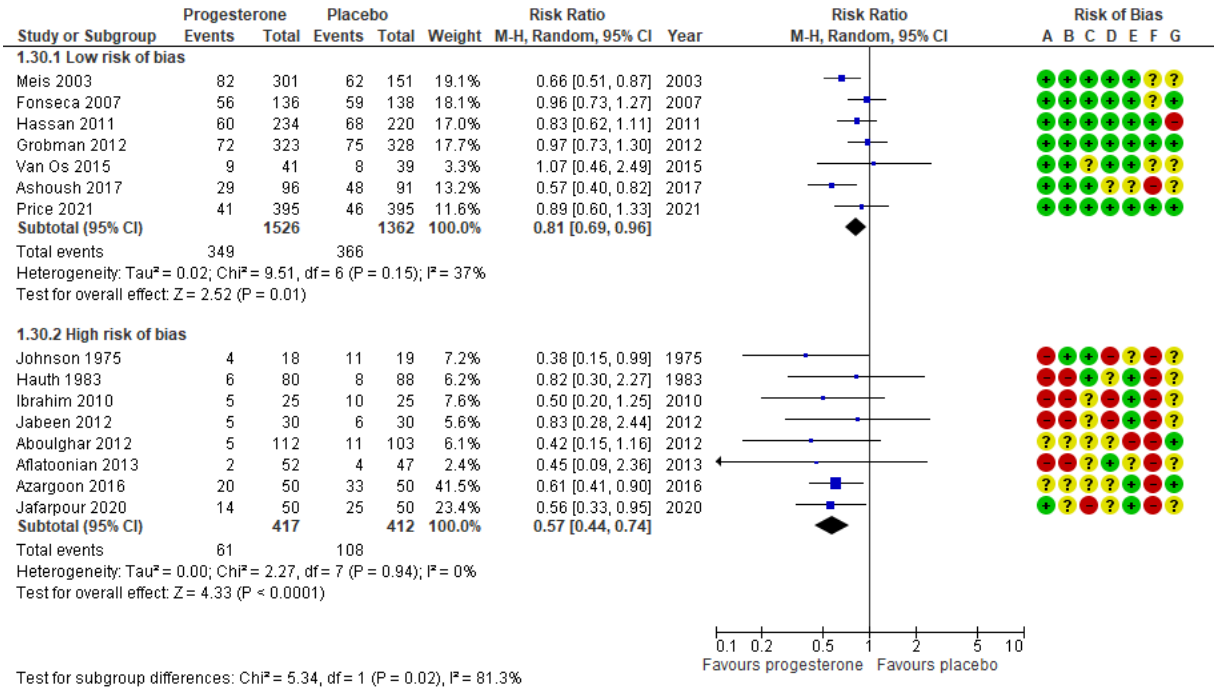
Figure 12. Outcome: Gestational age at delivery (weeks).



Conclusion: Progesterone compared with placebo may result in no difference in gestational age in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕◯◯).

Low birth weight in singletons (Appendix 4.1.8 and Figure 13)
A meta-analysis of seven trials with low risk of bias, including 2888 neonates showed a reduction in the rate of low birth weight, RR 0.81 (95% CI 0.69 to 0.96). A sensitivity analysis excluding Fonseca et al., 2007 (due to inclusion of 9.6% twins) did not alter the result (RR 0.78 (95% CI 0.66 to 0.94). The crude event rate across trials was 26.9% without progesterone. The pooled weighted RD was -6.2 percentage points (95% CI -12.2 to -0.1).

Figure 13. Outcome: Low birth weight (<2500 g).

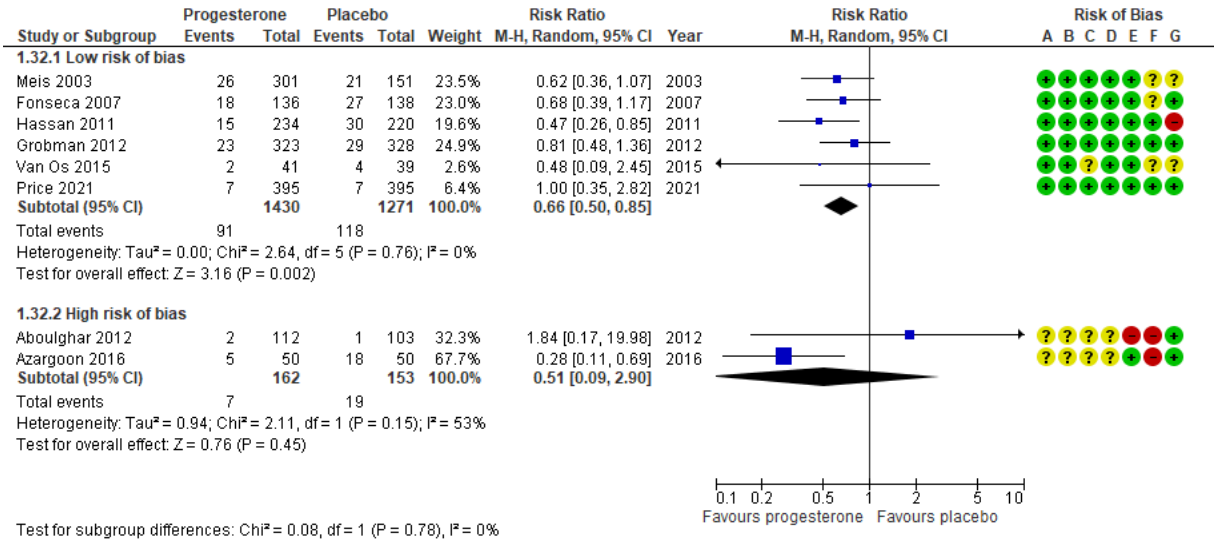


Johnson 1975 included 2.7% twins.

Conclusion: Progesterone compared with placebo probably reduces the risk of low birthweight in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Very low birth weight in singletons (Appendix 4.1.9 and Figure 14)
A meta-analysis of six trials with low risk of bias, including 2701 neonates showed a reduction in the risk of very low birth weight, RR 0.66 (95% CI 0.50 to 0.85). A sensitivity analysis excluding Fonseca et al., 2007 (due to inclusion of 9.6% twins) did not alter the result (RR 0.65 (95% CI 0.48 to 0.87). The crude event rate across trials was 9.3% without progesterone. The pooled weighted RD was -3.6 percentage points (95% CI -7.3 to 0.2).

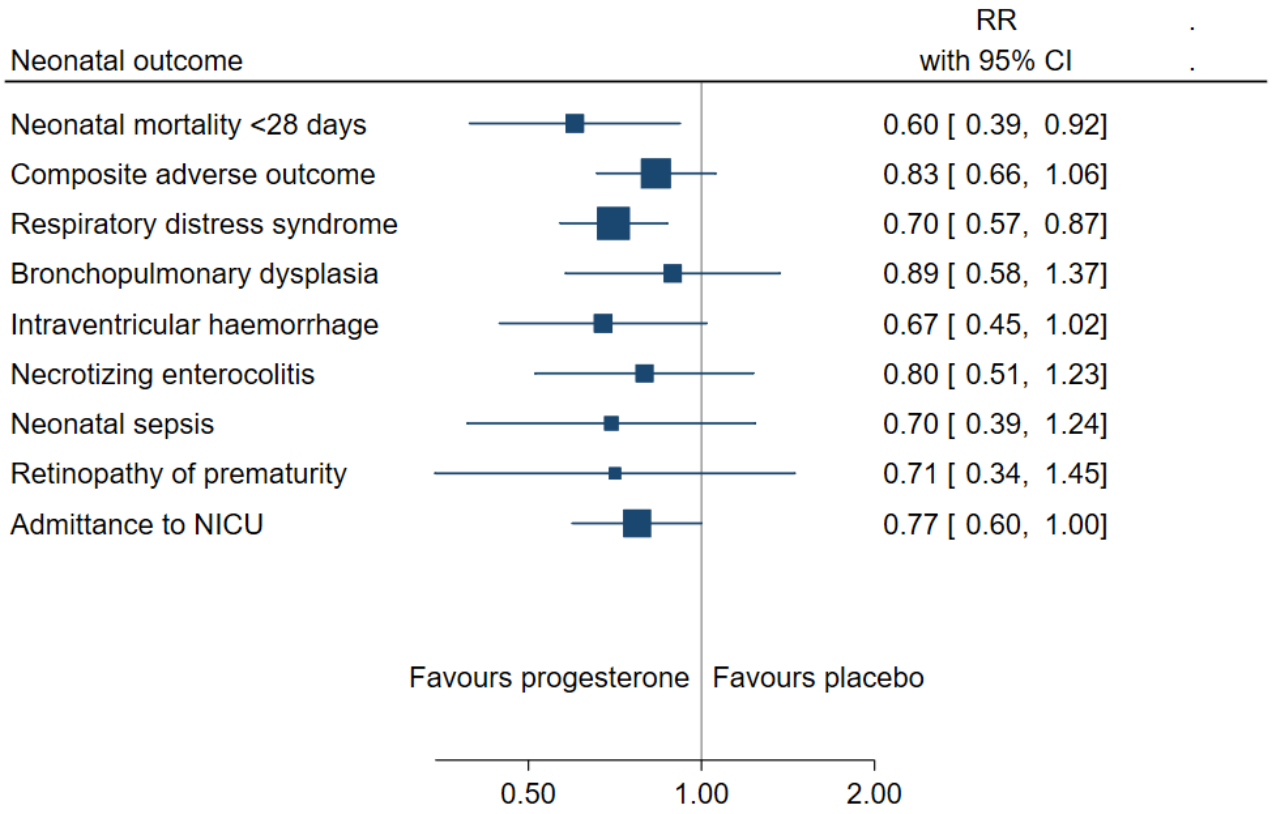
Figure 14. Outcome: Very low birth weight (<1500 g).



Conclusion: Progesterone compared with placebo reduces the risk of very low birth weight in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕⊕⊕).

Mortality and morbidity in neonates from singleton pregnancies
Pooled estimates from meta-analyses of low risk of bias trials reporting mortality and morbidity in singletons are summarised in Figure 15.

Figure 15. Summary graph of pooled estimates from meta-analyses comparing progesterone and placebo in women with a singleton pregnancy and any type of risk factor for preterm birth, from trials with low risk of bias regarding neonatal outcomes.



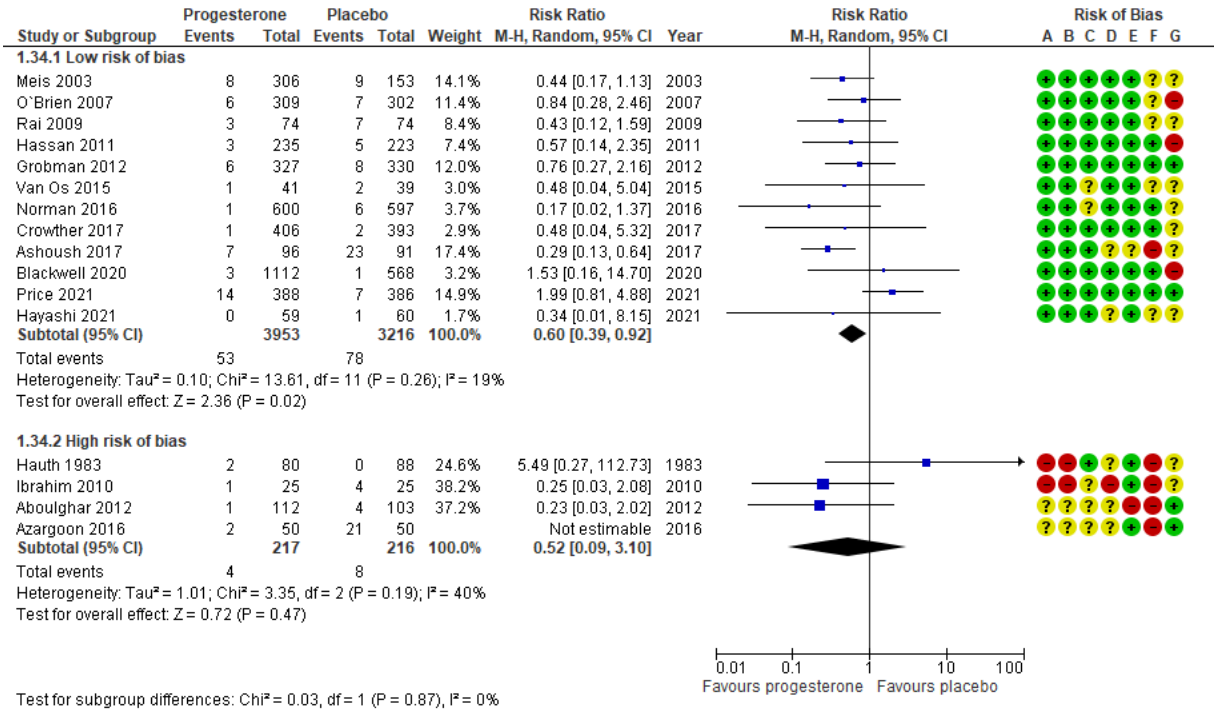
The pooled estimates (RR) ranged from 0.60 to 0.89 for neonatal mortality and serious morbidity, comparing progesterone with placebo including all routes of administration and different risk factors. The pooled estimate was lowest for neonatal mortality. Serious imprecision affected certainty of evidence for all outcomes except for respiratory distress syndrome.

Perinatal mortality (Appendix 4.1.10)
Twelve trials reported perinatal mortality in singleton pregnancies. No meta-analysis was performed due to different or lack of definitions in the trials.

Neonatal mortality <7 days
No trial reported mortality <7 days.

Neonatal mortality <28 days (Appendix 4.1.11 and Figure 16)
A meta-analysis of 12 trials with low risk of bias, including 7169 neonates, showed a reduction in the rate of neonatal mortality <28 days, RR 0.60 (95% CI 0.39 to 0.92). The crude event rate across trials was 2.4% without progesterone. The pooled weighted RD was -0.7 percentage points (95% CI -1.7 to 0.4).

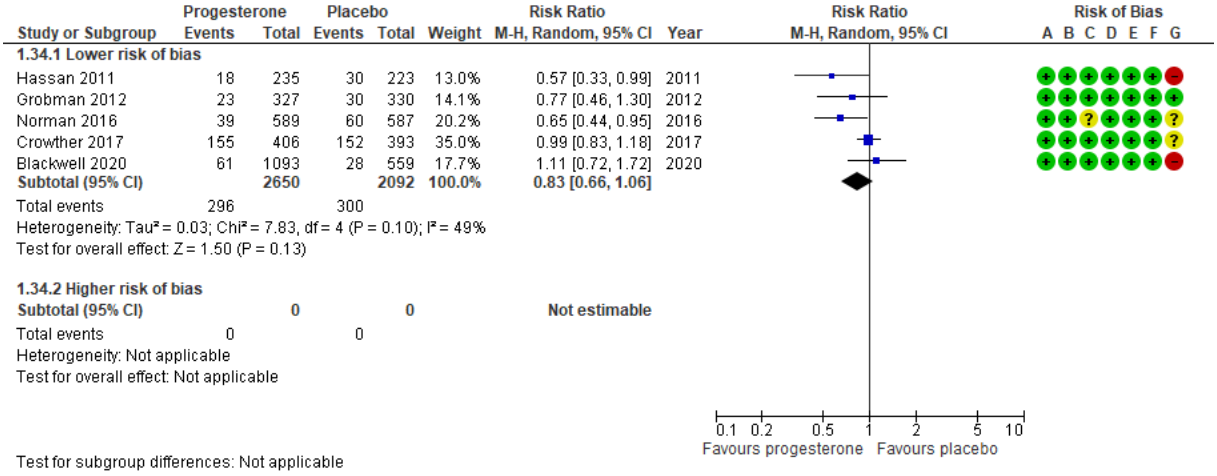
Figure 16. Outcome: Neonatal mortality <28 days.



Conclusion: Progesterone compared with placebo may reduce the risk of neonatal mortality <28 days in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Composite adverse neonatal outcome (Appendix 4.1.12 and Figure 17)
A meta-analysis of five trials with low risk of bias, including 4742 neonates showed no difference in the rate of composite adverse neonatal outcome, RR 0.83 (95% CI 0.66 to 1.06). The crude event rate across trials was 14.3% without progesterone. The pooled weighted RD was -1.9 percentage points (95% CI -4.3 to 0.5).
Four trials included in the composite adverse outcome any of intrauterine fetal death, neonatal death, intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, respiratory distress syndrome, or confirmed sepsis. Grobman et al., 2012 and Crowther et al., 2017 also included retinopathy of prematurity and Crowther et al., 2017 also included low Apgar score <4 at 5 min and small for gestational age (<3rd centile). Norman et al., 2016 defined the composite outcome as any of neonatal mortality, brain injury on ultrasound, or bronchopulmonary dysplasia.

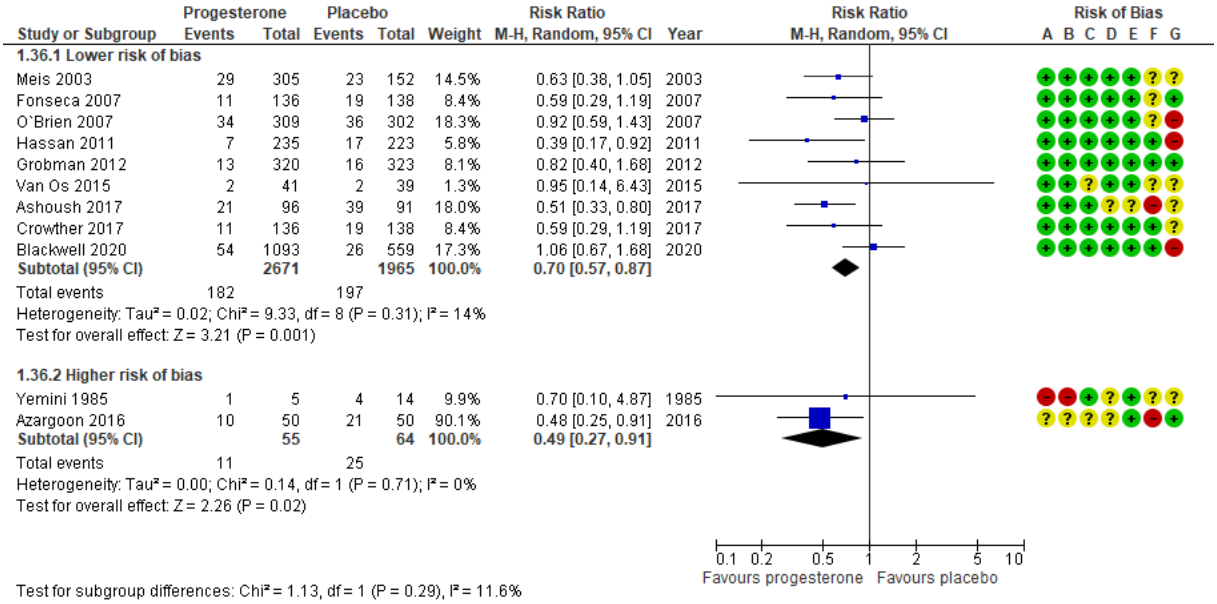
Figure 17. Outcome: Composite adverse neonatal outcome.



Conclusion: Progesterone compared with placebo, may result in no difference in the risk of a composite outcome of neonatal morbidity in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Respiratory distress syndrome (RDS) (Appendix 4.1.13 and Figure 18)
A meta-analysis of nine studies with low risk of bias, including 4636 neonates showed a significant reduction in the rate of RDS, RR 0.70 (95% CI 0.57 to 0.87). The crude event rate across trials was 10.0% without progesterone. The pooled weighted RD was -3.2 percentage points (95% CI -5.9 to -0.5).

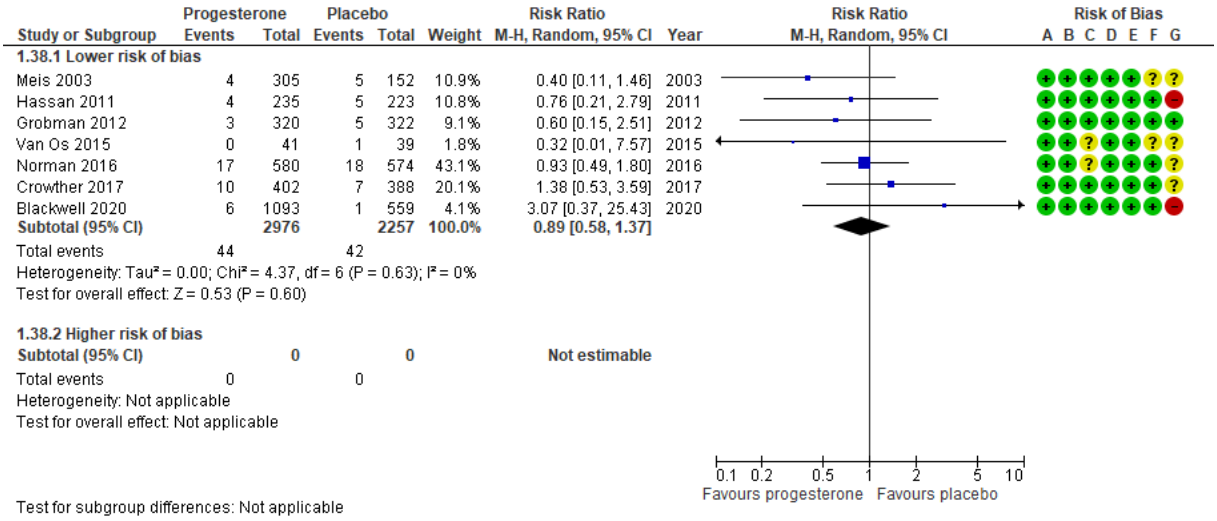
Figure 18. Outcome: Respiratory distress syndrome.



Conclusion: Progesterone compared with placebo probably reduces the risk of RDS in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Bronchopulmonary dysplasia (BPD) (Appendix 4.1.14 and Figure 19)
A meta-analysis of seven trials with low risk of bias, including 5233 neonates showed no difference in the rate of BPD, RR 0.89 (95% CI 0.58 to 1.37). The crude event rate across trials was 1.9% without progesterone. The pooled weighted RD was 0.1 percentage points (95% CI -0.4 to 0.7).

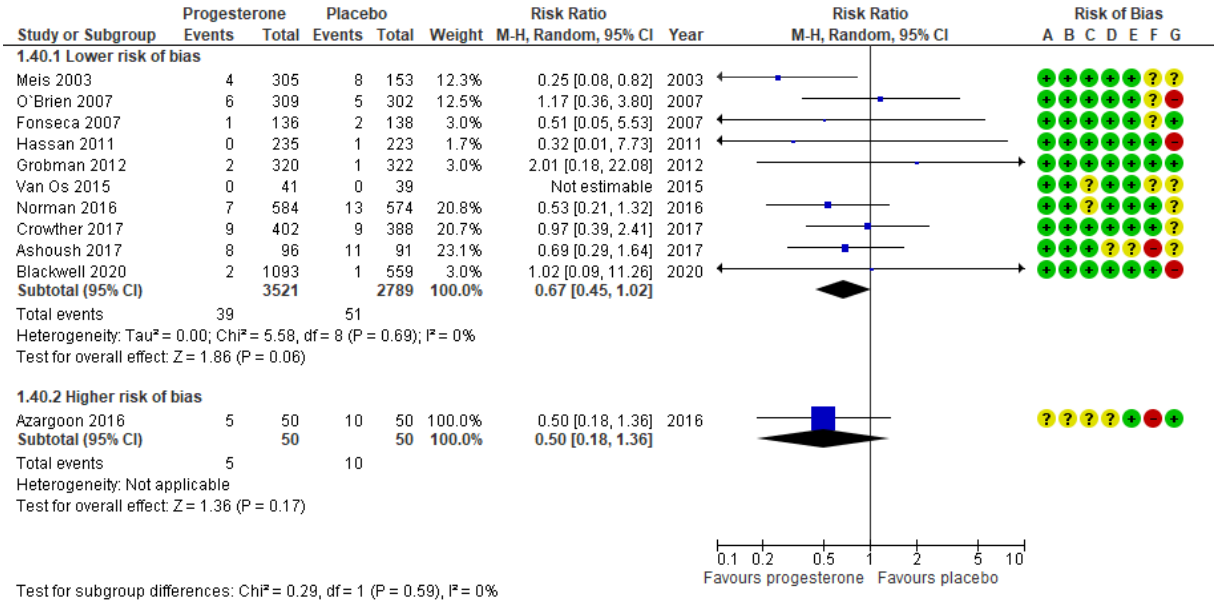
Figure 19. Outcome: Bronchopulmonary dysplasia.



Conclusion: Progesterone compared with placebo may result in no difference in BPD in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Intraventricular haemorrhage (IVH) (Appendix 4.1.15 and Figure 20)
A meta-analysis of 10 trials with low risk of bias, including 6310 neonates showed no difference in the rate of IVH, RR 0.67 (95% CI 0.45 to 1.02). A sensitivity analysis excluding Fonseca et al., 2007 (due to inclusion of 9.6% twins), yielded a RR of 0.69 (95% CI 0.45 to 1.04). The crude event rate across trials was 1.8% without progesterone. The pooled weighted RD was -0.3 percentage points (95% CI -1.0 to 0.4).

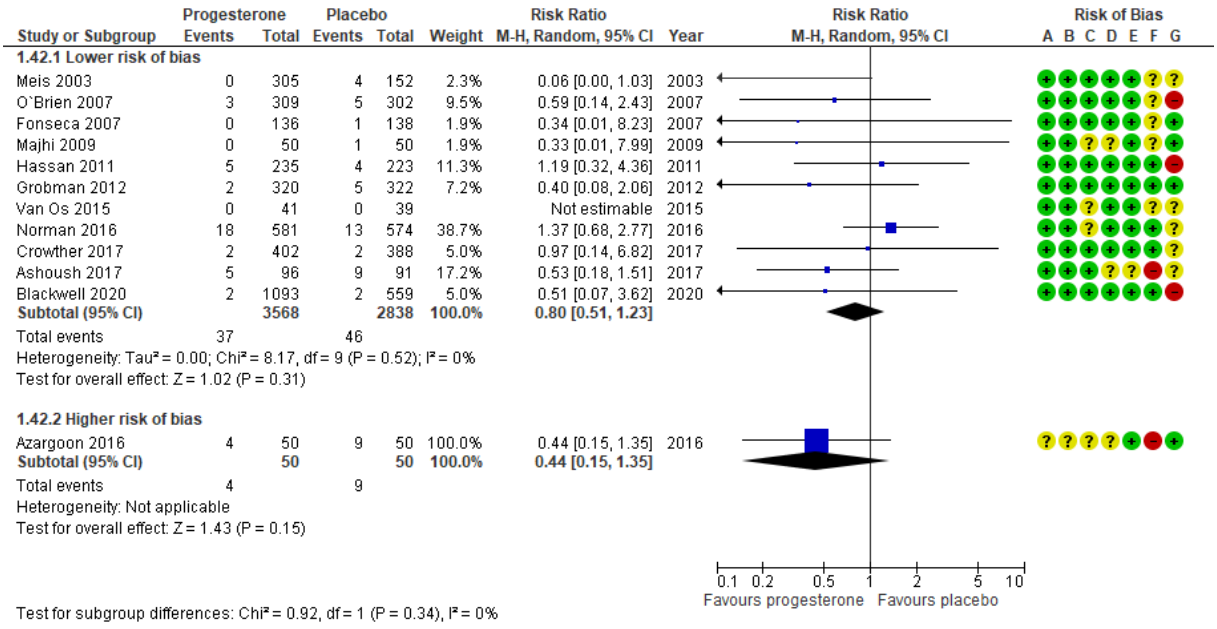
Figure 20. Outcome: Intraventricular haemorrhage.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of IVH in singletons, although the CI may imply a reduced risk, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth
(GRADE ⊕⊕◯◯).

Necrotizing enterocolitis (NEC) (Appendix 4.1.16 and Figure 21)
A meta-analysis of 11 trials with low risk of bias, including 6406 neonates showed no difference in the rate of NEC, RR 0.80 (95% CI 0.51 to 1.23). A sensitivity analysis excluding Fonseca et al., 2007 (due to inclusion of 9.6% twins), yielded a RR of 0.81 (0.52 to 1.26). The crude event rate across trials was 1.6% without progesterone. The pooled weighted RD was -0.3 percentage points (95% CI -0.7 to 0.2).

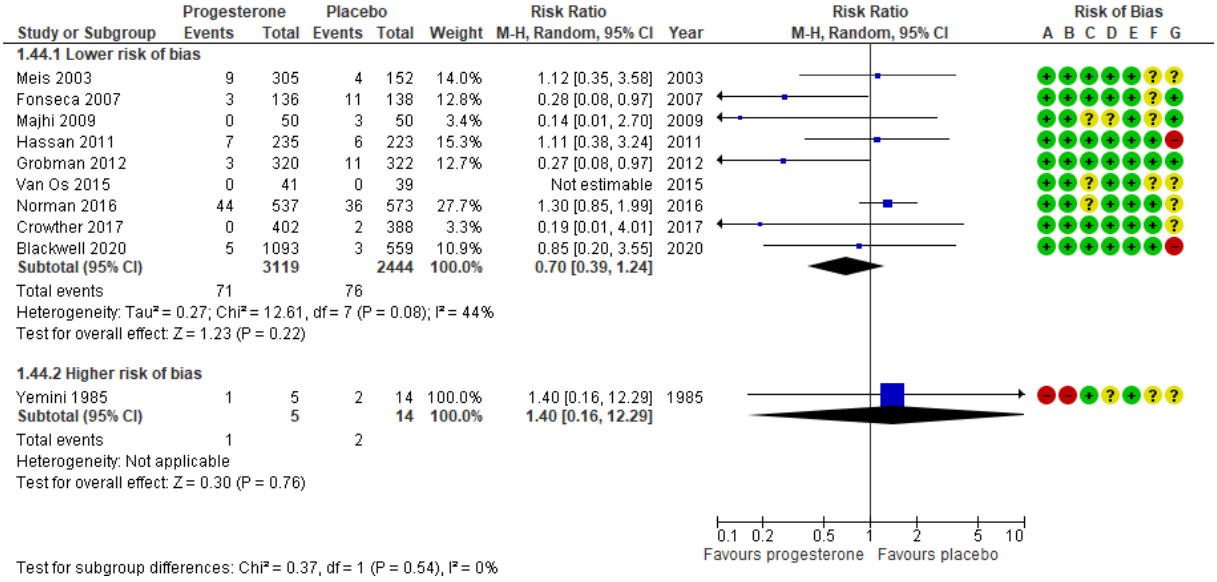
Figure 21. Outcome: Necrotizing enterocolitis.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of NEC in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Neonatal sepsis (Appendix 4.1.17 and Figure 22)
A meta-analysis of nine trials with low risk of bias, including 5563 neonates showed no difference in the rate of neonatal sepsis, RR 0.70 (95% CI 0.39 to 1.24). A sensitivity analysis excluding Fonseca et al., 2007 (due to inclusion of 9.6% twins), yielded a RR of 0.85 (95% CI 0.50 to 1.45). The crude event rate across trials was 3.1% without progesterone. The pooled weighted RD was -0.5 percentage points (95% CI -1.4 to 0.4).

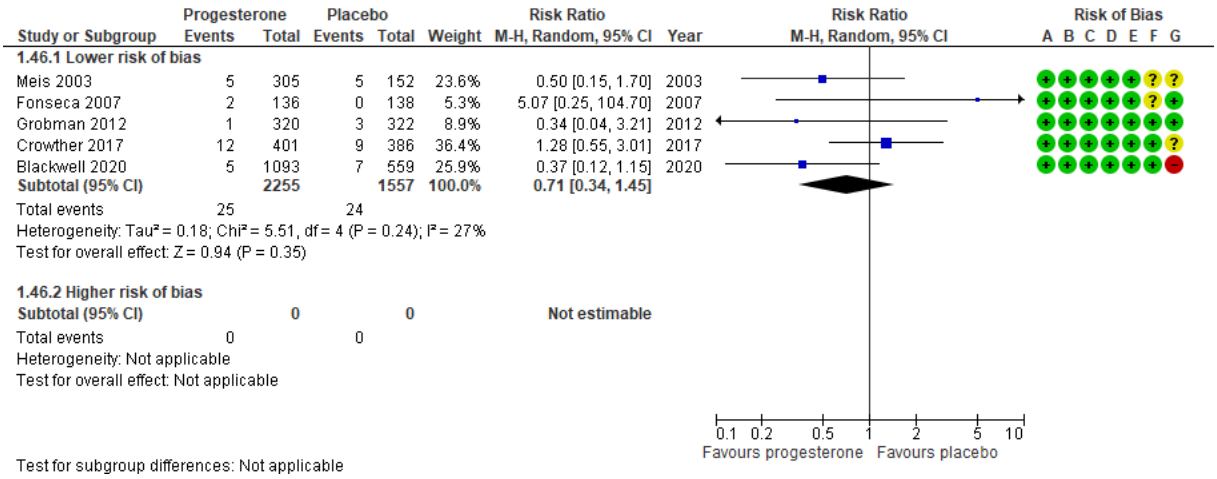
Figure 22. Outcome: Neonatal sepsis.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of neonatal sepsis or other infection in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Retinopathy of prematurity (ROP) (Appendix 4.1.18 and Figure 23)
A meta-analysis of five trials with low risk of bias, including 3812 neonates showed no difference in the rate of ROP, RR 0.71 (95% CI 0.34 to 1.45). A sensitivity analysis excluding Fonseca et al., 2007 (due to inclusion of 9.6% twins), yielded a RR of 0.65 (95% CI 0.33 to 1.29). The crude event rate across trials was 1.5% without progesterone. The pooled weighted RD was -0.4 percentage points (95% CI -1.2 to 0.3).

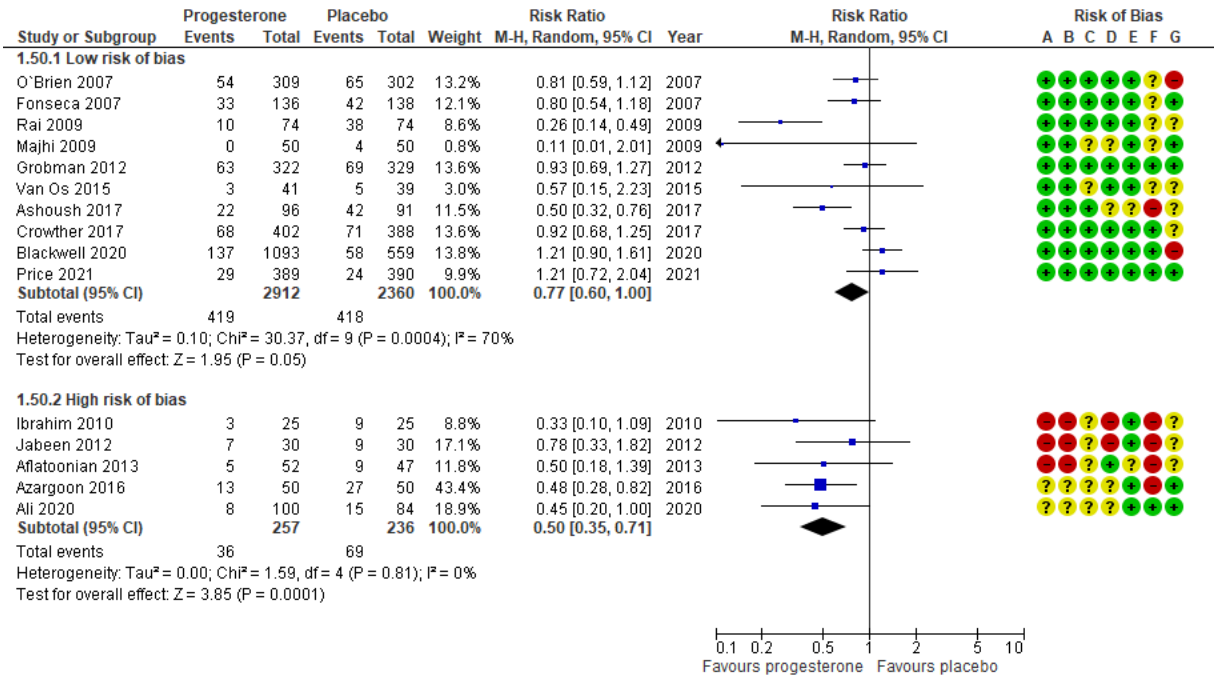
Figure 23. Outcome: Retinopathy of prematurity.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of ROP in singletons, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth (GRADE ⊕⊕◯◯).

Admittance to neonatal intensive care unit (Appendix 4.1.19 and Figure 24)
A meta-analysis of ten studies with low risk of bias, including 5272 neonates showed no difference in the rate of NICU admission, RR 0.77 (95% CI 0.60 to 1.00). A sensitivity analysis excluding Fonseca et al., 2007 (due to inclusion of 9.6% twins), yielded a RR of 0.76 (0.57 to 1.02). The crude event rate across trials was 17.7% without progesterone. The pooled weighted RD was -6.1 percentage points (95% CI -11.0 to -1.3).

Figure 24. Outcome: Admittance to neonatal intensive care unit (NICU).



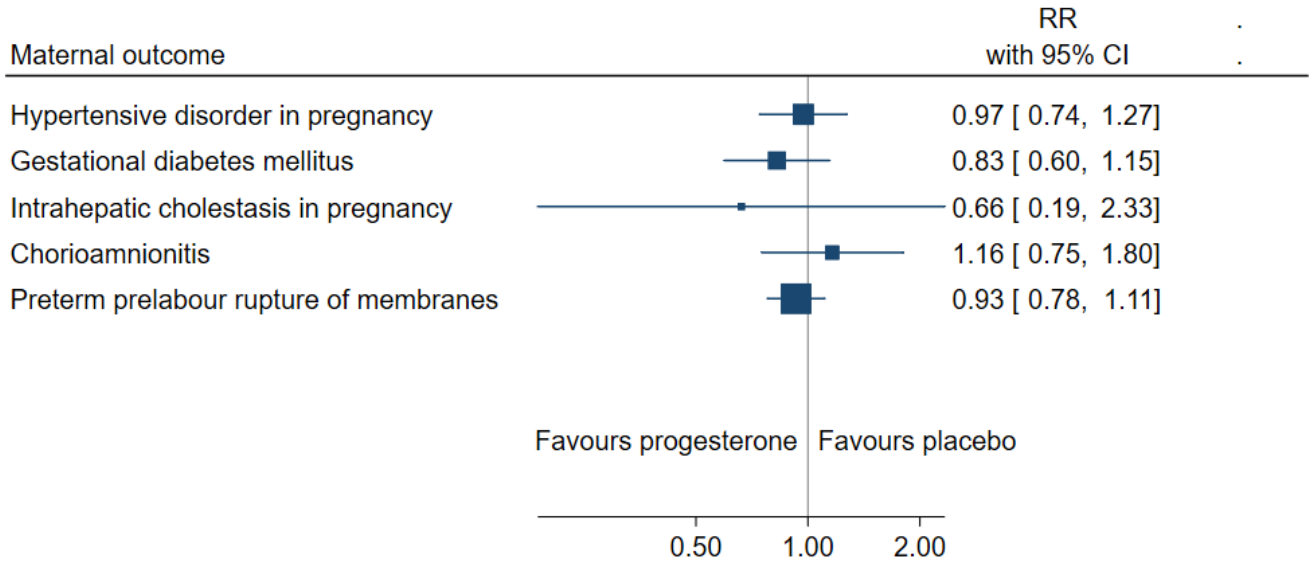
Conclusion: Progesterone compared with placebo may result in no difference in admittance to NICU of singletons, although the CI may imply a reduction, neither considering administration route and dosage, nor type of maternal risk factor for preterm birth
(GRADE ⊕⊕◯◯).

Long-term child outcomes in singletons (Appendix 4.1.20)
Three trials (1715 children) examined long-term child outcome in singletons (Cuijpers et al., 2020 [follow up of Van Os et al., 2015, Triple P]), Norman et al., 2016 [OPPTIMUM], Northen et al., 2007 [follow up of Meis et al., 2003]). All three trials were included in a systematic review by Simons et al., 2020. Follow-up rate was between 71 and 80%. A meta-analysis of two reports (Cuijpers et al., 2020, n=57 children [unpublished data), Norman et al., 2018 [OPPTIMUM], n=833 children) showed no difference in neurodevelopment assessed by the Bayley-III Cognitive Composite score at two years between children exposed to progesterone versus placebo (Standardised Mean Difference -0.04, 95% CI -0.26 to 0.19) (Simons et al., 2020). Northen et al., 2007 used the Ages and Stages Questionnaire (ASQ) at 4 to 5 years of age and found no difference between the groups. General health, anthropometry and behaviour were similar between the groups.

Conclusion: Progesterone compared with placebo may result in no difference in cognitive development, general health or behaviour in singletons, neither considering administration route, nor type of maternal risk factor for preterm birth.

Mortality and morbidity in women with singleton pregnancies
Pooled estimates from meta-analyses of low risk of bias trials reporting maternal morbidity are summarised in Figure 25.

Figure 25. Summary graph of pooled estimates from meta-analyses comparing progesterone and placebo in women with a singleton pregnancy and any type of risk factor for preterm birth, from trials with low risk of bias regarding maternal outcomes.

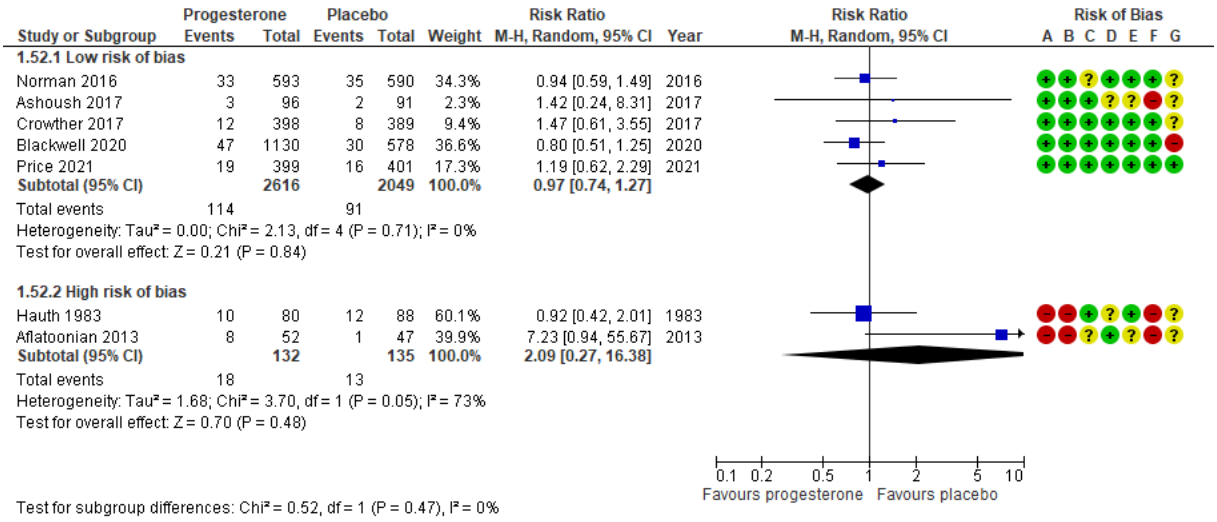


The pooled estimates (RR) were <1 (0.66 to 0.94) for maternal morbidity except for chorioamnionitis (RR 1.14) comparing progesterone with placebo including all routes of administration and different risk factors. Serious imprecision affected certainty of evidence for all outcomes except for preterm prelabour rupture of membranes.

Maternal mortality (Appendix 4.1.21)
One trial from Zambia on an HIV-population reported one maternal death in the placebo group (1/401).

Hypertensive disorders in pregnancy (HDP) (Appendix 4.1.22 and Figure 26)
A meta-analysis of five trials with low risk of bias, including 4665 women showed no difference in the rate of HDP, RR 0.97 (95% CI 0.74 to 1.27). The crude event rate across trials was 4.0% without progesterone. The pooled weighted RD was 0.1 percentage points (95% CI -1.1 to 1.2).

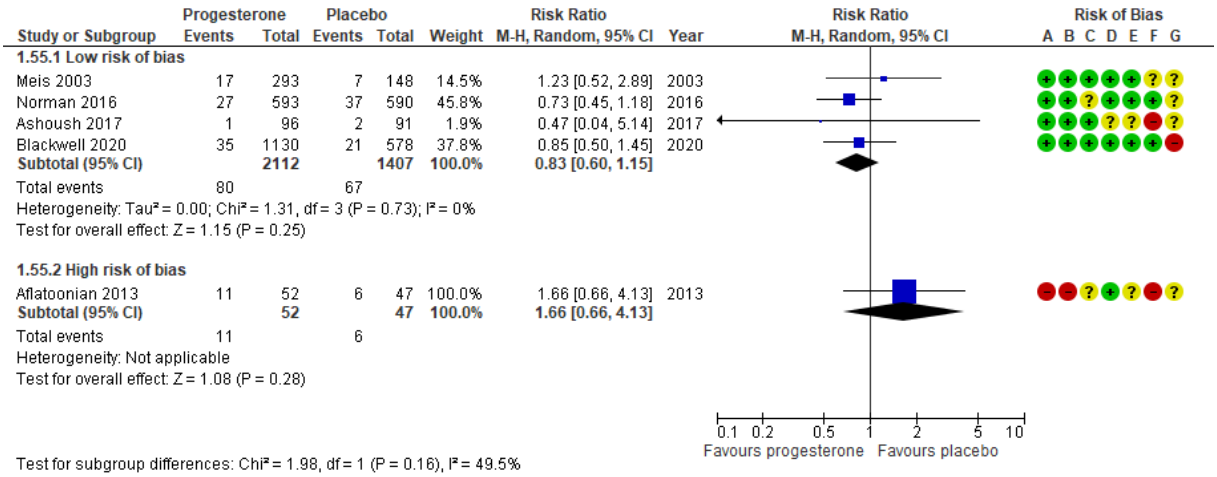
Figure 26. Outcome: Hypertensive disorder in pregnancy.



Conclusion: Progesterone compared with placebo probably results in no difference in the risk HDP in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕⊕◯).

Gestational diabetes mellitus (GDM) (Appendix 4.1.23 and Figure 27)
A meta-analysis of four trials with low risk of bias, including 3519 women showed no difference in the rate of GDM, RR 0.83 (95% CI 0.60 to 1.15). The crude event rate across trials was 4.8% without progesterone. The pooled weighted RD was -0.8 percentage points (95% CI -2.1 to 0.5).

Figure 27. Outcome: Gestational diabetes mellitus.

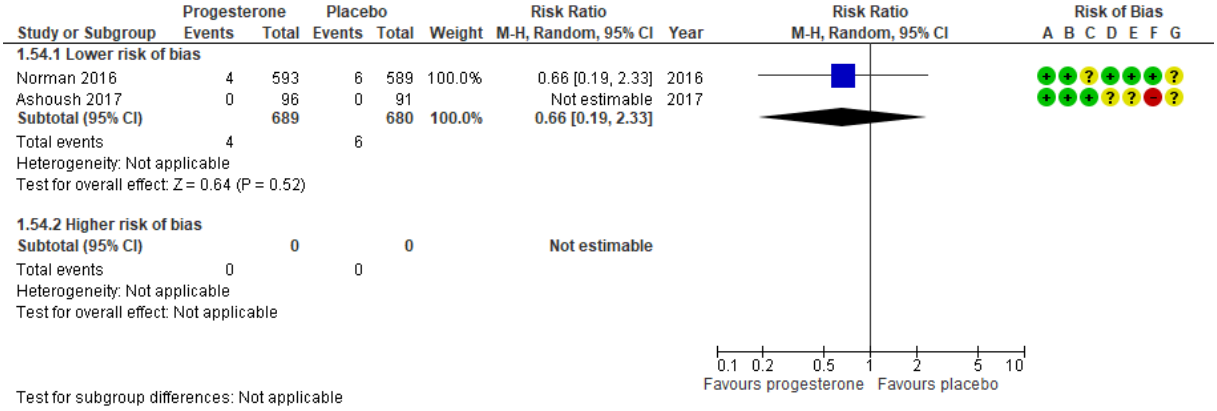


Data from Meis 2003 was retrieved from a secondary publication, Gyamfi 2009, reporting specifically on GDM.

Conclusion: Progesterone compared with placebo may result in no difference in the risk of GDM in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕◯◯).

Intrahepatic cholestasis in pregnancy (ICP) (Appendix 4.1.24 and Figure 28)
A meta-analysis of two trials with low risk of bias (one without events), including 1369 women showed no difference in the rate of ICP, RR 0.66 (95% CI 0.19 to 2.33). The crude event rate across trials was 0.9% without progesterone. The RD was -0.3 percentage points (95% CI -1.2 to 0.7).

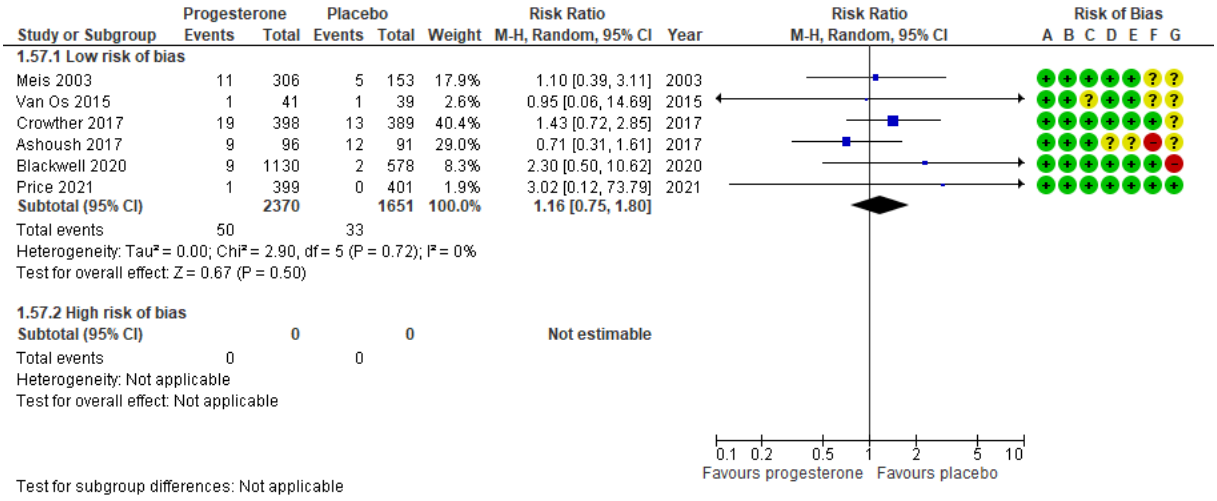
Figure 28. Outcome: Intrahepatic cholestasis.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of ICP in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕◯◯).

Infections (chorioamnionitis) (Appendix 4.1.25 and Figure 29)
A meta-analysis of six trials with low risk of bias, including 4021 women showed no difference in the rate of chorioamnionitis, RR 1.16 (95% CI 0.75 to 1.80). The crude event rate across trials was 2.0% without progesterone. The pooled weighted RD was 0.4 percentage points (95% CI -0.1 to 0.8).

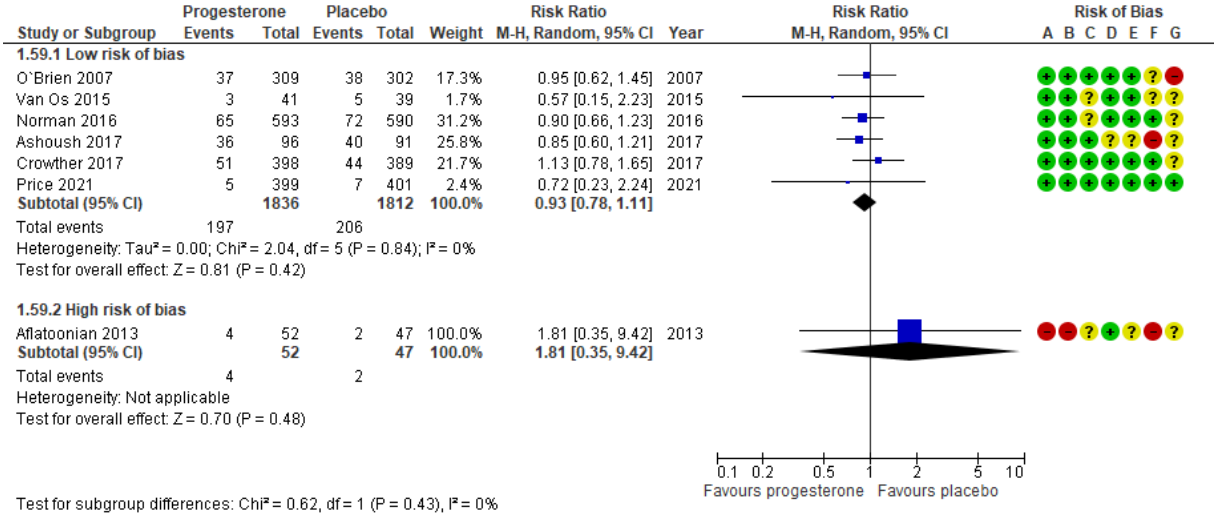
Figure 29. Outcome: Chorioamnionitis.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of chorioamnionitis in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕◯◯).

Preterm prelabour rupture of the membranes (PPROM) (Appendix 4.1.26 and Figure 30)
A meta-analysis of six trials with low risk of bias, including 3648 women showed no difference in the rate of PPROM, RR 0.93 (95% CI 0.78 to 1.11). The crude event rate across trials was 11.4% without progesterone. The pooled weighted RD was -0.5 percentage points (95% CI -1.9 to 0.8).

Figure 30. Outcome: Preterm prelabour rupture of membranes (PPROM).



Conclusion: Progesterone compared with placebo results in no difference in the risk of PPROM in women with a singleton pregnancy, neither considering administration route and dosage, nor type of risk factor for preterm birth (GRADE ⊕⊕⊕⊕).

Comparison progesterone vs placebo in multifetal pregnancies

Included studies

Eighteen RCTs, three subgroup analyses of RCTs (Gyamfi et al., 2009, Klein et al., 2011, Megli et al., 2020), and two long-term follow-up reports of RCTs (McNamara et al., 2015, Vedel et al., 2016) were included, in total 23 publications (Appendix 2). Fifteen RCTs were classified as having low risk of bias, and three as having high risk of bias (Table 1). Three trials (Aboulghar et al., 2012; Cetingoz et al., 2011; Johnson et al., 1975) included both singleton and twin pregnancies and presented results separately for singletons and twins. Nine RCTs included only twin pregnancies (Awwad et al., 2014; Briery et al., 2009; Brizot et al., 2015; Coombs et al., 2011, Norman et al., 2009; Rehal et al., 2021; Rode et al., 2011; Rouse et al., 2007; Serra et al., 2013), as did the two follow-up reports (McNamara et al., 2015; Vedel et al., 2016). Two trials included only triplet pregnancies (Caritis et al., 2009; Combs et al., 2010). One trial (Wood et al., 2012) included twin and triplet pregnancies, and one trial included twin, triplet and quadruplet pregnancies (Lim et al., 2011).
In addition, three systematic reviews (Romero et al., 2017 with an update Romero et al., 2022, EPPPIC, 2021) contributed with individual participant data for some outcomes, including data for twins from two trials with mixed singletons and twins (Fonseca et al., 2007, low risk of bias, Crowther et al., 2017, low risk of bias). In total, 5370/10,827 women/newborns were included in the meta-analyses.

Setting

Six trials were single centre studies carried out in Egypt, Lebanon, USA, Brazil and Turkey, eight were national multicentre studies carried out in the USA (four trials), the Netherlands, United Kingdom, Spain, and Canada, and four were multinational studies (Crowther et al., 2017; Fonseca et al., 2007; Rode et al., 2011; Rehal et al., 2021) carried out in United Kingdom, Chile, Brazil, Greece, Spain, Bulgaria, Italy, Belgium, France, Austria, Denmark. Australia, New Zeeland and Canada.

Population
Three trials (Aboulghar et al., 2012; Combs et al., 2011; Serra et al., 2013) included only dichorionic twin pregnancies. One of the triplet trials included only trichorionic triplet pregnancies (Combs et al., 2010) and the other included both dichorionic and trichorionic triplet pregnancies (Caritis et al., 2009). Six twin studies (Awwad et al., 2014; Brizot et al., 2015; Norman et al., 2009; Rehal et al., 2021; Rode et al., 2011; Rouse et al., 2007) included both monochorionic and dichorionic twin pregnancies (15-23% monochorionic pregnancies).
Three trials excluded all women with prior preterm birth or spontaneous preterm birth (Combs et al., 2010; Combs et al., 2011; Lim et al. 2011). One trial with both singleton and twin pregnancies (Fonseca et al., 2007) exclusively included those with a short cervical length (defined as a cervical length ≤15 mm). Three trials (Lim et al., 2011, Brizot et al., 2015, Klein et al., 2011) presented results for subgroups of women with a short cervix (<25 mm, ≤25 mm, and ≤30 mm, respectively). Two trials presented results for subgroups of women with a previous preterm birth (Klein et al., 2011, Megli et al., 2020). One trial included only ART pregnancies (Aboulghar et al., 2012), two trials excluded ART pregnancies (Briery et al., 2009; Brizot et al., 2015), and in ten trials ART pregnancies comprised between 25% and 95% of the study population. Five trials had no information on use of ART.

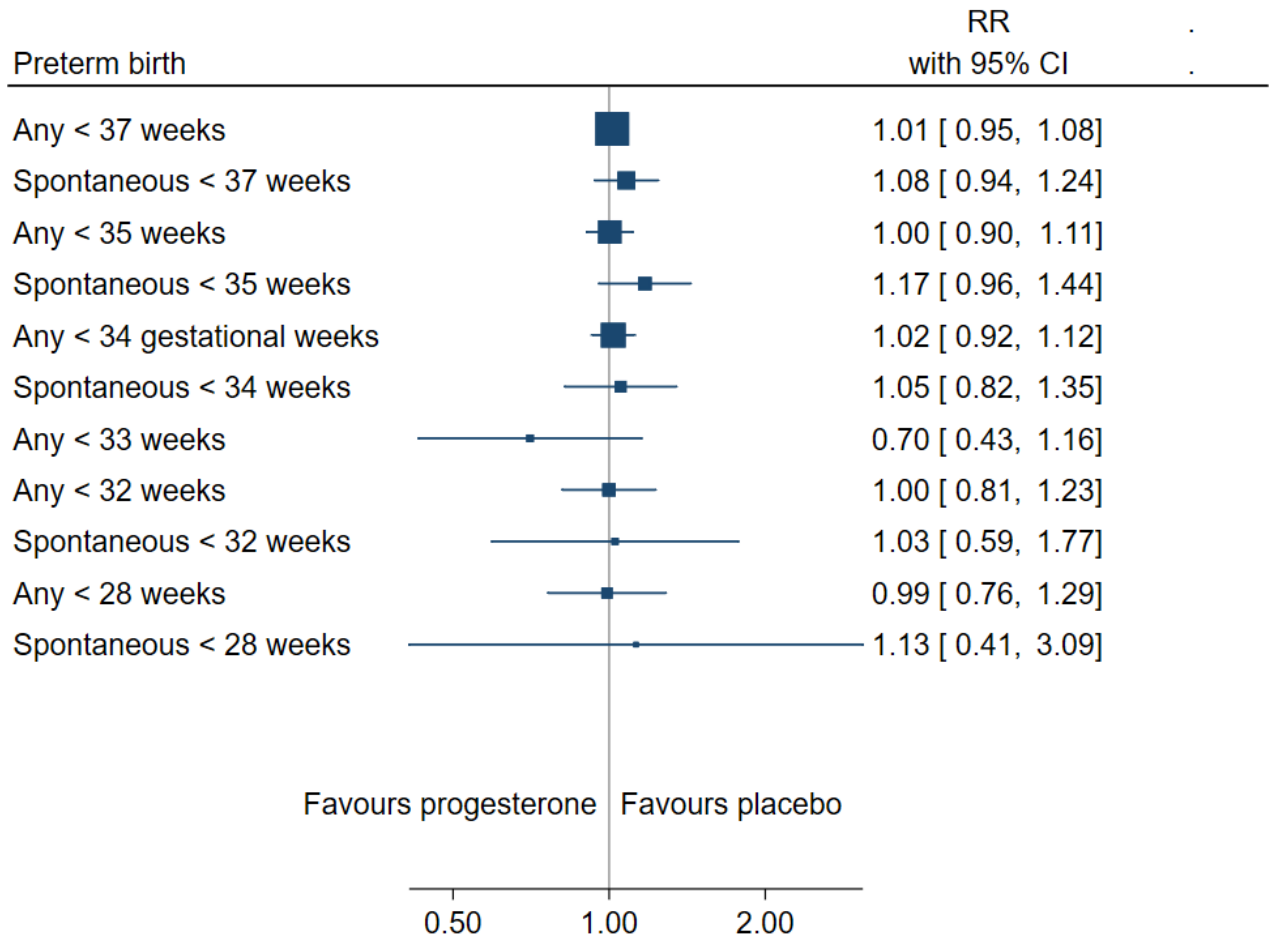
Intervention
The interventions included different routes of administration: vaginal progesterone (capsule, gel, or pessary) (nine trials) and im injection of 17-OHPC (seven trials). Doses of vaginal progesterone varied between 90 and 600 mg per day. Doses of 17-OHPC were similar across trials (250 mg 17-OHPC im per week). All trials used placebo as control and were double-blinded. The intervention started in the first trimester between 11 and 14 weeks in one trial (Rehal et al., 2021) and in the second trimester between 16 and 24 weeks in the other trials. Treatment was stopped between 34 and 36 weeks of pregnancy.
Trials with low risk of bias reported an adequate compliance or adherence to treatment (≥80% of the prescribed medication) for >90% of patients participating in ten trials. Three trials with low risk of bias reported compliance between 77% and 85% (Rehal et al., 2021; Rode et al., 2011; Serra et al., 2013). Norman et al., 2009 (low risk of bias) reported adequate compliance for 54% of women in the progesterone group and 60% in the placebo group. Compliance was not reported in one trial (Cetingoz et al., 2011, low risk of bias).

Directness, study limitations, and precision
Some of the trials had problems with directness, which was affected by ethnicity and the use of ART (i.e. many studies included a high proportion of Black women and/or a high proportion of ART pregnancies). Three of the 18 trials were conducted in European countries with an ethnicity similar to the Swedish population (Lim et al., 2011; Rode et al., 2011; Serra et al., 2013).
Risk of bias in the individual trials are presented graphically in colour within the forest plots (legends in Table 2) and as an overall judgement of study limitations in the outcome tables in Appendix 4.1. Most trials had no serious study limitations. Conclusions are solely based on trials with low risk of bias. The trials were generally underpowered for outcomes as neonatal mortality, neonatal and maternal morbidity.

Results per outcome

Preterm birth in multifetal pregnancies across gestational weeks
Pooled estimates from meta-analyses of low risk of bias trials reporting any or spontaneous preterm birth (<37, <35, <34, <33, <32, and <28 gestational weeks) are summarised in Figure 31.

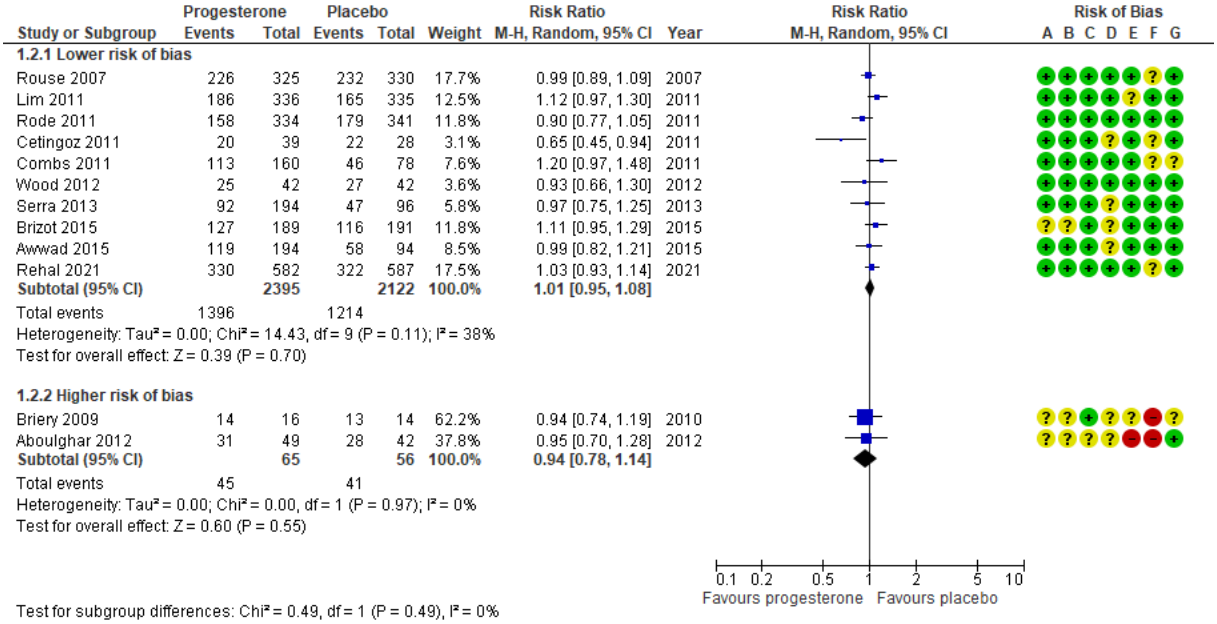
Figure 31. Summary graph of pooled estimates from meta-analyses comparing progesterone and placebo in women with a multifetal pregnancy with or without additional risk factor(s) from trials with low risk of bias regarding the outcomes any or spontaneous preterm birth before different gestational weeks.



The pooled estimates (RR) ranged from 0.80 to 1.17, comparing progesterone with placebo including all routes of administration and different risk factors, with no significant difference in the rate of any preterm or spontaneous preterm birth across the span of gestational weeks.

Any preterm birth <37 weeks (Appendix 4.1.1.a and Figure 32)
A meta-analysis of ten trials with low risk of bias, including 4517 women, showed no difference in the rate of any preterm birth, RR 1.01 (95% CI 0.95 to 1.08). The crude event rate across trials was 57.2% without progesterone. The pooled weighted RD was -0.7 percentage points (95% CI -3.4 to 4.8).

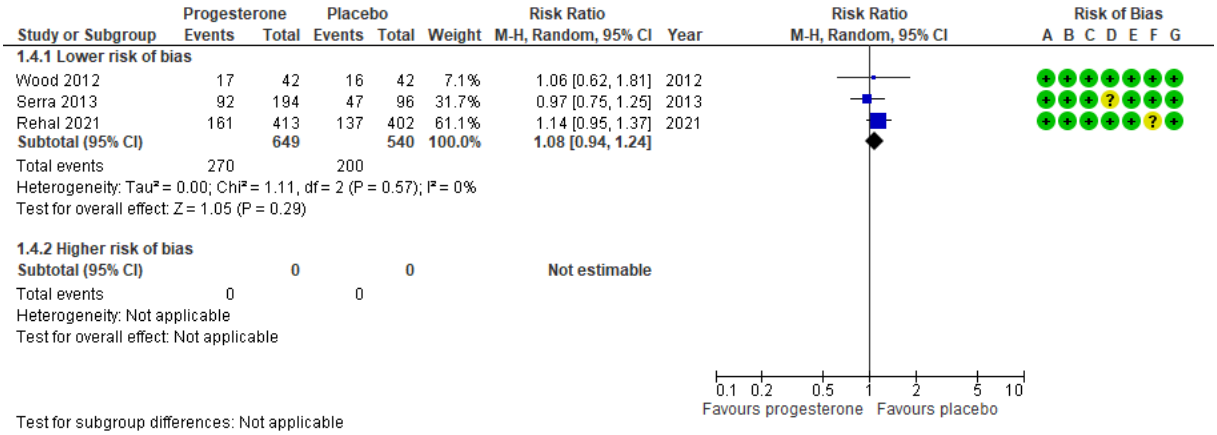
Figure 32. Outcome: Any preterm birth <37 weeks.



Conclusion: Progesterone compared with placebo probably results in little or no difference in the risk of any preterm birth before 37 gestational weeks in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <37 weeks (Appendix 4.1.1.b and Figure 33)
A meta-analysis of three trials with low risk of bias, including 1189 women, showed no difference in the rate of spontaneous preterm birth, RR 1.08 (95% CI 0.94 to 1.24). The crude event rate across trials was 37.0% without progesterone. The pooled weighted RD was 3.4 percentage points (95% CI -2.2 to 9.0).

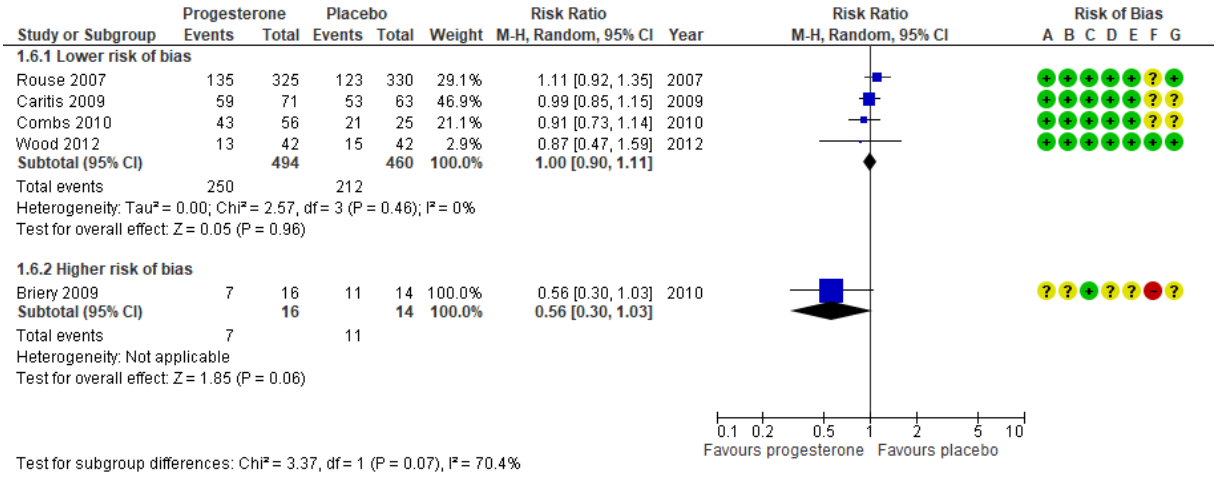
Figure 33. Outcome: Spontaneous preterm birth <37 weeks.



Conclusion: Vaginal progesterone compared with placebo probably results in no difference in the risk of spontaneous preterm birth before 37 gestational weeks in women with a multifetal pregnancy, neither considering dosage, nor additional risk factor(s) for preterm birth
(GRADE ⊕⊕⊕◯).

Any preterm birth <35 weeks (Appendix 4.1.2.a and Figure 34**)**
A meta-analysis of four trials with low risk of bias, including 954 women, showed no difference in the rate of any preterm birth, RR 1.00 (95% CI 0.90 to 1.11). The crude event rate across trials was 46.0% without progesterone. The pooled weighted RD was 1.2 percentage points (95% CI -4.6 to 7.0).

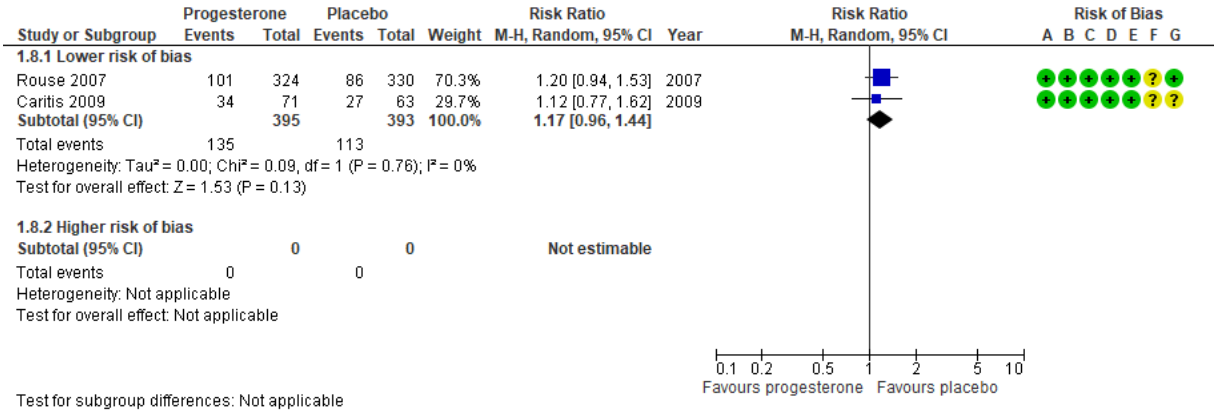
Figure 34. Outcome: Any preterm birth <35 weeks.



Conclusion: Progesterone compared with placebo results in little or no difference in the risk of any preterm birth before 35 gestational weeks in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Spontaneous preterm birth <35 weeks (Appendix 4.1.2.b and Figure 35**)**
A meta-analysis of two trials with low risk of bias, including 788 women, compared 17-OHPC with placebo, showed no difference in the rate of spontaneous preterm birth, RR 1.17 (95% CI 0.96 to 1.44). The crude event rate across trials was 28.8% without progesterone. The pooled weighted RD was 5.1 percentage points (95% CI -1.3 to 11.5).

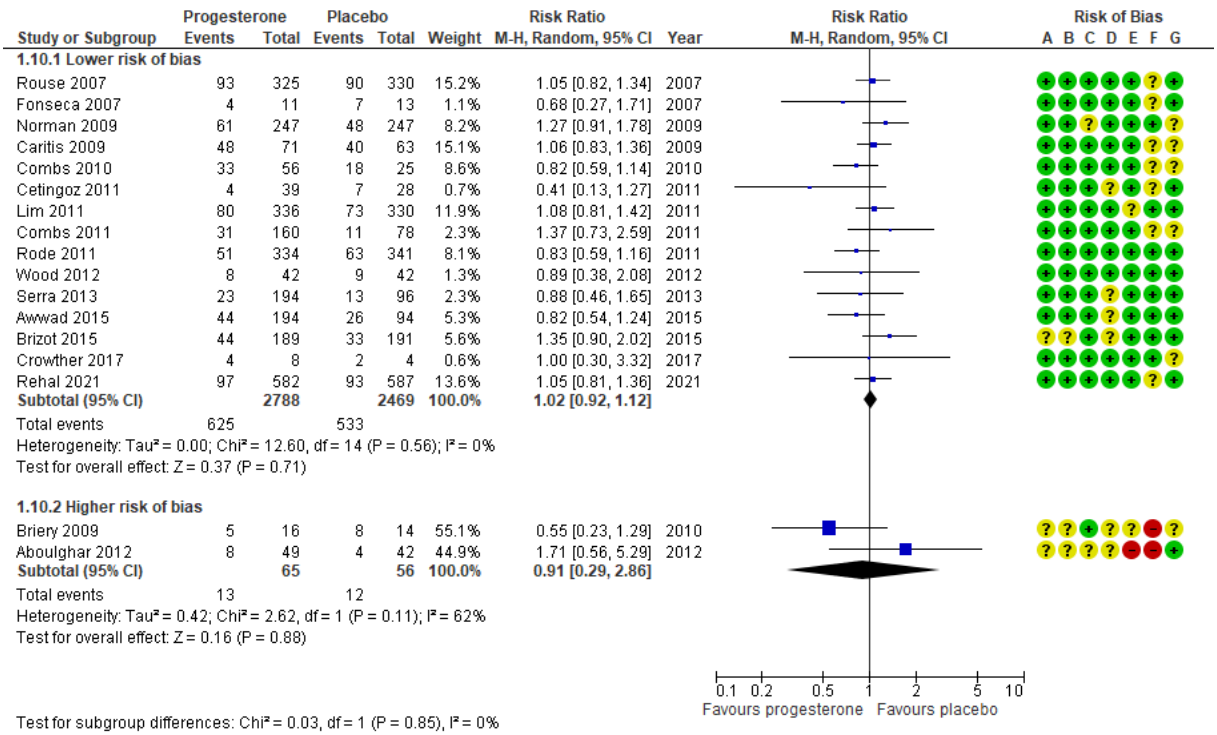
Figure 35. Outcome: Spontaneous preterm birth <35 weeks.



Conclusion: 17-OHPC, compared with placebo probably results in no difference in the risk of spontaneous preterm birth before 35 gestational weeks in women with a multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Any preterm birth <34 weeks (Appendix 4.1.3.a and Figure 36)
A meta-analysis of 15 trials with low risk of bias, including 5257 women, showed no difference in the rate of any preterm birth, RR 1.02 (95% CI 0.92 to 1.12). The crude event rate across trials was 21.6% without progesterone. The pooled weighted RD was 0.6 percentage points (95% CI -1.6 to 2.7).

Figure 36. Outcome: Any preterm birth <34 weeks.

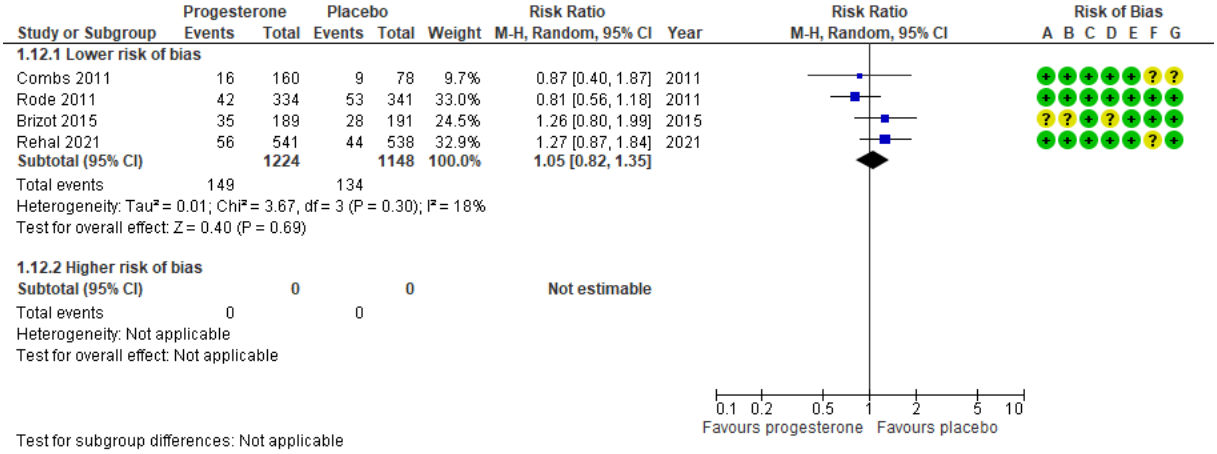


Results from Rouse 2007, Fonseca 2007, Caritis 2009, Lim 2011, Wood 2012, Awwad 2015, Crowther 2017 were retrieved from the IPD meta-analysis by Stewart et al. (EPPPIC, 2021).

Conclusion: Progesterone compared with placebo results in no difference in the risk of any preterm birth before 34 gestational weeks in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Spontaneous preterm birth <34 weeks (Appendix 4.1.3.b and Figure 37)
A meta-analysis of four trials with low risk of bias, including 2372 women showed no difference in the rate of spontaneous preterm birth, RR 1.05 (95% CI 0.82 to 1.35). The crude event rate across trials was 11.7% without progesterone. The pooled weighted RD was 0.7 percentage points (95% CI -1.6 to 3.6).

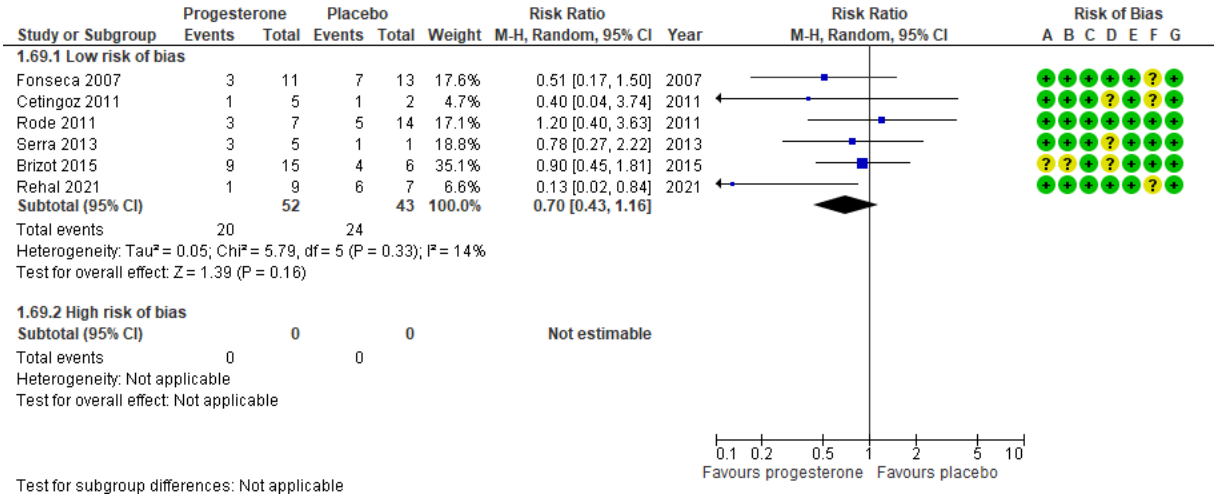
Figure 37. Outcome: Spontaneous preterm birth <34 weeks.



Conclusion: Progesterone compared with placebo results in no difference in the risk of spontaneous preterm birth before 34 gestational weeks in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Any preterm birth <33 weeks (Appendix 4.1.4.a and Figure 38)
A meta-analysis of six trials with low risk of bias, including 95 women with short cervical length and a twin pregnancy showed no difference in the rate of preterm birth, RR 0.70 (95% CI 0.43 to 1.16). The crude event rate across trials was 55.8% without progesterone. The pooled weighted RD was 29.4 percentage points (95% CI -58.9 to 0.1).

Figure 38. Outcome: Any preterm birth <33 weeks. All patients had a twin pregnancy and short cervical length according to inclusion criteria (Fonseca) or constitute subgroups of the other trials.



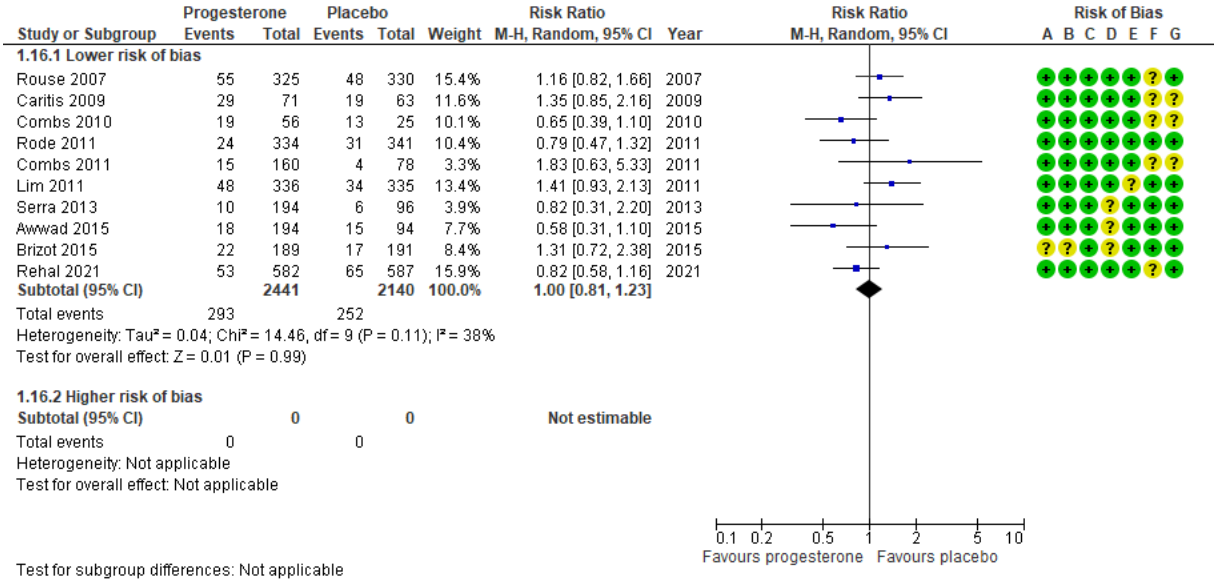
Results were retrieved from the IPD meta-analyses by Romero et al., 2017 and Romero et al., 2022.
Dosage/administration: 200 mg vaginal progesterone/d in all but one trial, Cetingoz 2011 used 100 mg.
Cut-off cervical length: ≤25 mm in all but one trial, Fonseca 2007 used ≤15 mm.

Conclusion: Vaginal progesterone, not considering dosage, compared with placebo may result in no difference in any preterm birth before 33 gestational weeks in women with a twin pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <33 weeks
No trial reported spontaneous preterm birth <33 weeks.

Any preterm birth <32 weeks (Appendix 4.1.5.a and Figure 39)
A meta-analysis of ten trials with low risk of bias, including 4581 women showed no difference in the rate of any preterm birth, RR 1.00 (95% CI 0.81 to 1.23). The crude event rate across trials was 11.8% without progesterone. The pooled weighted RD was 0.3 percentage points (95% CI -2.1 to 2.8).

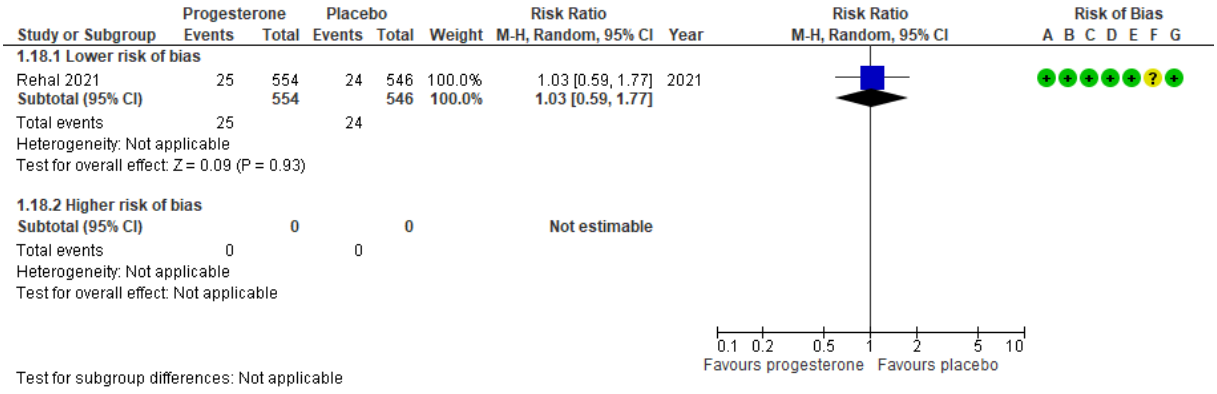
Figure 39. Outcome: Any preterm birth <32 weeks.



Conclusion: Progesterone compared with placebo results in no difference in the risk of any preterm birth before 32 gestational weeks in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Spontaneous birth <32 weeks (Appendix 4.1.5.b and Figure 40)
One trial with low risk of bias, including 1100 women with a twin pregnancy showed no difference in the rate of spontaneous preterm birth, RR 1.03 (95% CI 0.59 to 1.77). The crude event rate across trials was 4.4% without progesterone. The pooled weighted RD was 0.1 percentage points (95% CI -2.3 to 2.6).

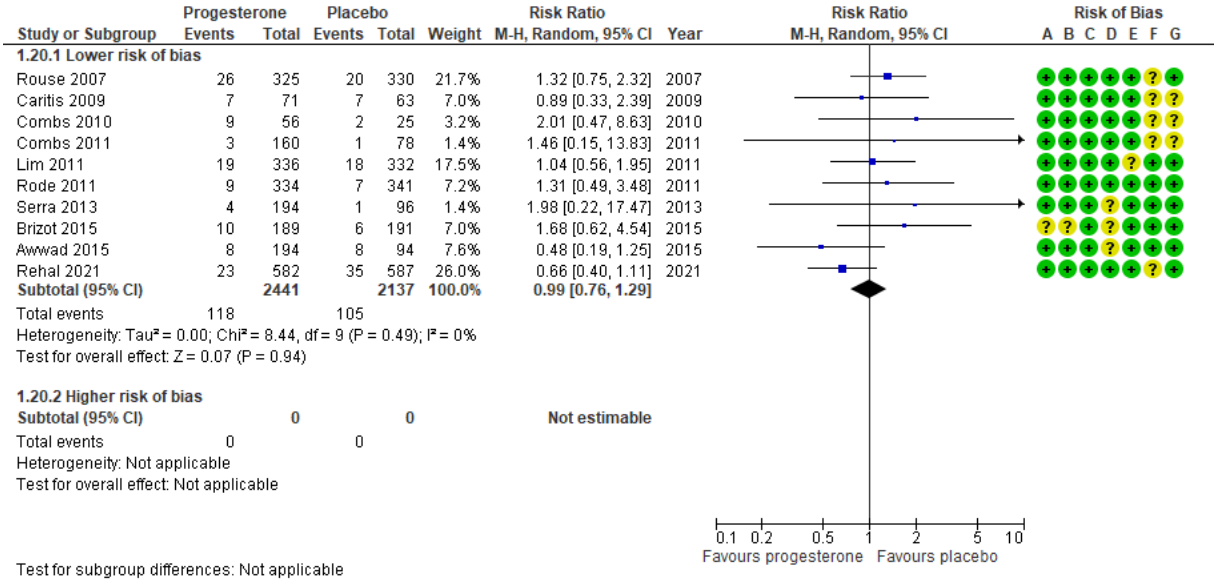
Figure 40. Outcome: Spontaneous preterm birth <32 weeks.



Conclusion: Vaginal progesterone compared with placebo may result in no difference in the risk of spontaneous preterm birth before 32 gestational weeks in women with a twin pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Any preterm birth <28 weeks (Appendix 4.1.6.a and Figure 41)
A meta-analysis of ten trials with low risk of bias, including 4578 women showed no difference in the rate of any preterm birth, RR 0.99 (95% CI 0.76 to 1.29). The crude event rate across trials was 4.9% without progesterone. The pooled weighted RD was 0.2 percentage points (95% CI -0.9 to 1.3).

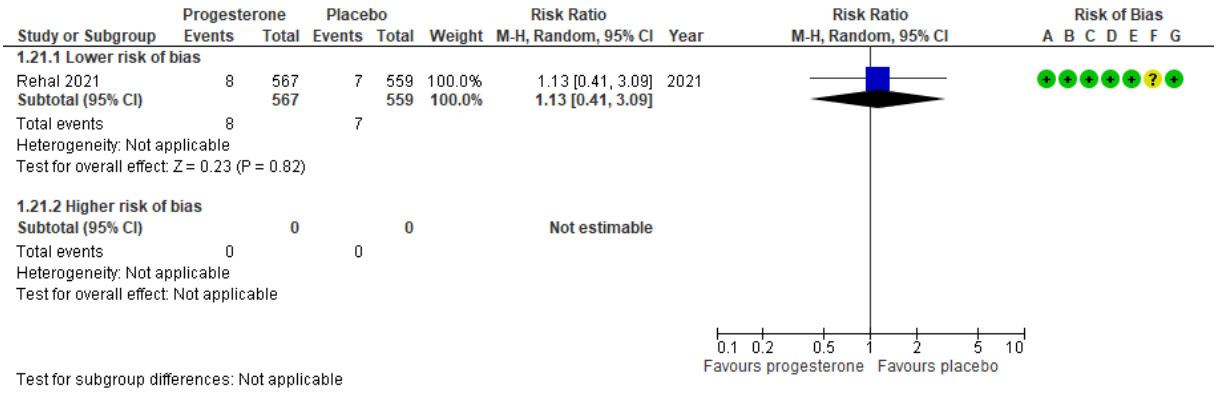
Figure 41. Outcome: Any preterm birth <28 weeks.



Conclusion: Progesterone compared with placebo results in no difference in the risk of any preterm birth before 28 gestational weeks in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Spontaneous birth <28 weeks (Appendix 4.1.6.b and Figure 42)
One trial with low risk of bias, including 1126 women with a twin pregnancy showed no difference in the rate of spontaneous preterm birth, RR 1.13 (95% CI 0.41 to 3.09). The crude event rate across trials was 1.2% without progesterone. The pooled weighted RD was 0.2 percentage points (95% CI -1.2 to 1.5).

Figure 42. Outcome: Spontaneous preterm birth <28 weeks.



Conclusion: Vaginal progesterone compared with placebo may result in no difference in the risk of spontaneous preterm birth before 28 gestational weeks in women with a twin pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Subgroup analyses (Figures 71-75, pages 53-55)
Exploratory subgroup analyses among trials with low risk of bias were performed for administration route (vaginal progesterone or i.m.17-OHPC), and for specific risk factors (history of preterm birth or short cervical length). Meta-analyses were performed for any preterm birth before 37 and 34 weeks and forest plots are presented in Subgroup analyses. Table 4 shows the summary estimates from the meta-analyses.

Table 4. Summary estimates from subgroup meta-analyses exploring the effect of progesterone vs placebo in women with a multifetal pregnancy, according to administration route and specific risk factors for preterm birth.

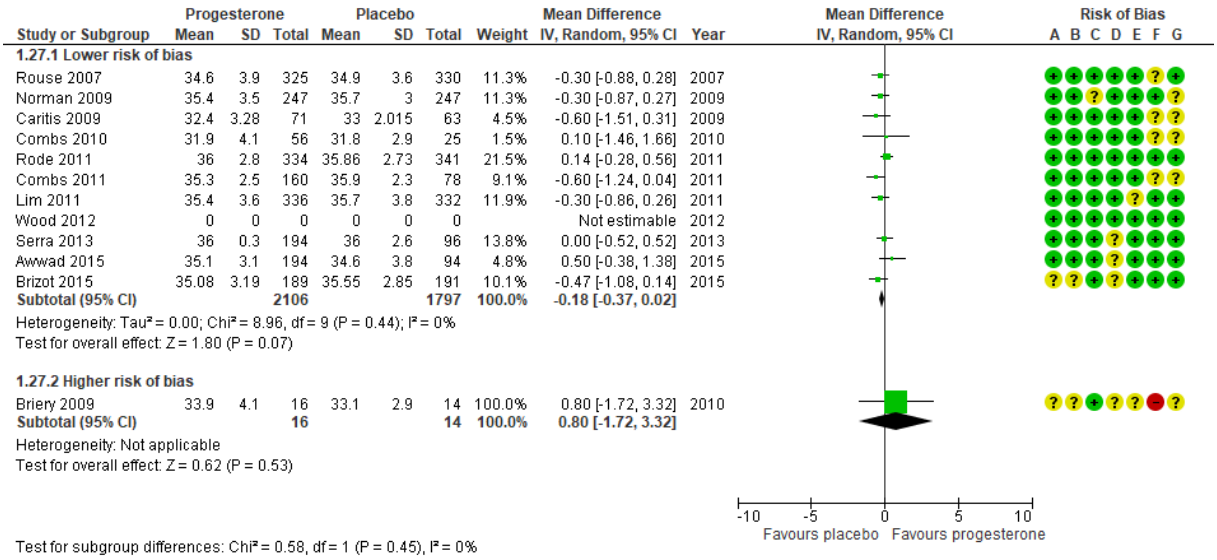
Outcomes **Administration route** **Risk factor**	**Number of RCTs (women)**	**Relative effect** **RR (95% CI)** In bold if difference is statistically significant RR <1 indicates favourable outcome of progesterone	**Absolute effect (%)**
Administration route			
Any PTB <37 weeks			
17-OHPC im	4 (1852)	1.05 (0.96 to 1.15)	63.4 vs 59.9
Vaginal progesterone	6 (2665)	0.97 (0.87 to 1.08)	54.5 vs 55.5
Any PTB <34 weeks			
17-OHPC im	6 (2062)	1.01 (0.89 to 1.14)	28.8 vs 28.0
Vaginal progesterone	9 (3195)	1.03 (0.88 to 1.20)	18.0 vs 17.8
Risk factor			
Any PTB <37 weeks			
History of spontaneous preterm birth	NR		
Short cervix	2 (48)	0.92 (0.71 to 1.20)	83.9 vs 94.1
Any PTB <34 weeks			
History of spontaneous preterm birth	2 (94)	0.73 (0.36 to 1.50)	29.5 vs 40.0
Short cervix	3 (106)	0.87 (0.62 to 1.22)	50.0 vs 51.8

The exploratory subgroup analyses of different administration routes did not reveal any obviously more efficacious route. Exploratory subgroup analyses according to the specific risk factors (history of preterm birth or short cervical length) did not demonstrate any benefit from progesterone treatment for any of the groups.

Gestational age and birth weight

Outcome gestational age in multifetal pregnancies (Appendix 4.1.7 and Figure 43)
A meta-analysis of ten trials with low risk of bias, including 3903 women showed no mean difference in gestational age, -0.18 (-0.37 to 0.02) weeks, corresponding to approximately one day less (three to zero days less) gestational length in the progesterone group.

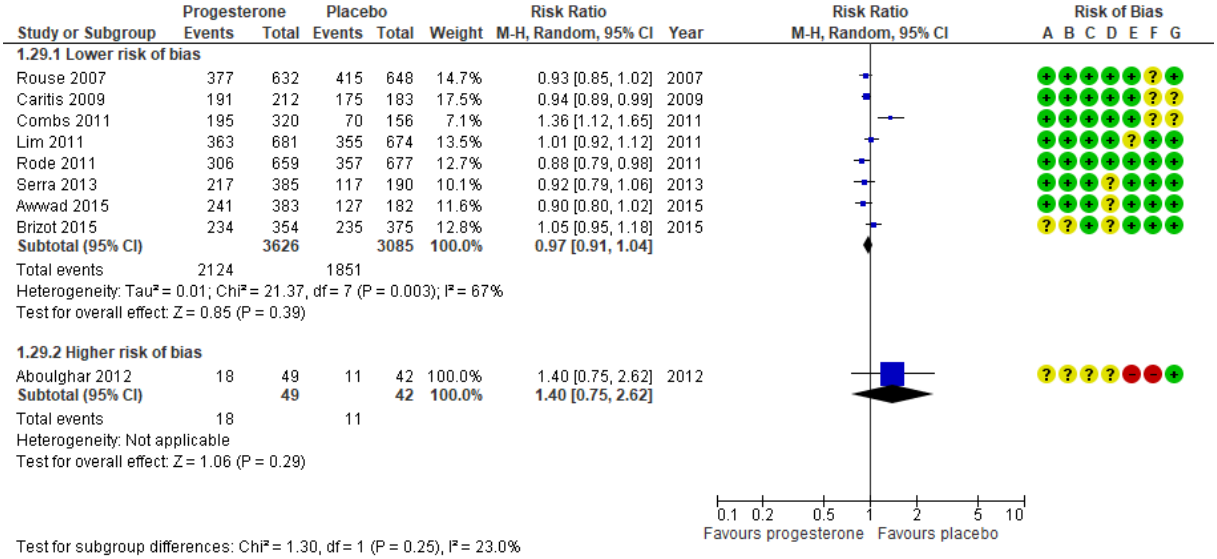
Figure 43. Outcome: Gestational age at delivery (weeks).



Conclusion: Progesterone compared with placebo results in little or no difference in gestational age, in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Outcome low birth weight (<2500 g) in multifetal pregnancies (Appendix 4.1.8, Figure 44)
A meta-analysis of eight trials with low risk of bias, including 6711 neonates showed no difference in the rate of low birth weight, RR 0.97 (95% CI 0.91 to 1.04). The crude event rate across trials was 60.0% without progesterone. The pooled weighted RD was -1.6 percentage points (95% CI -5.8 to 2.7).

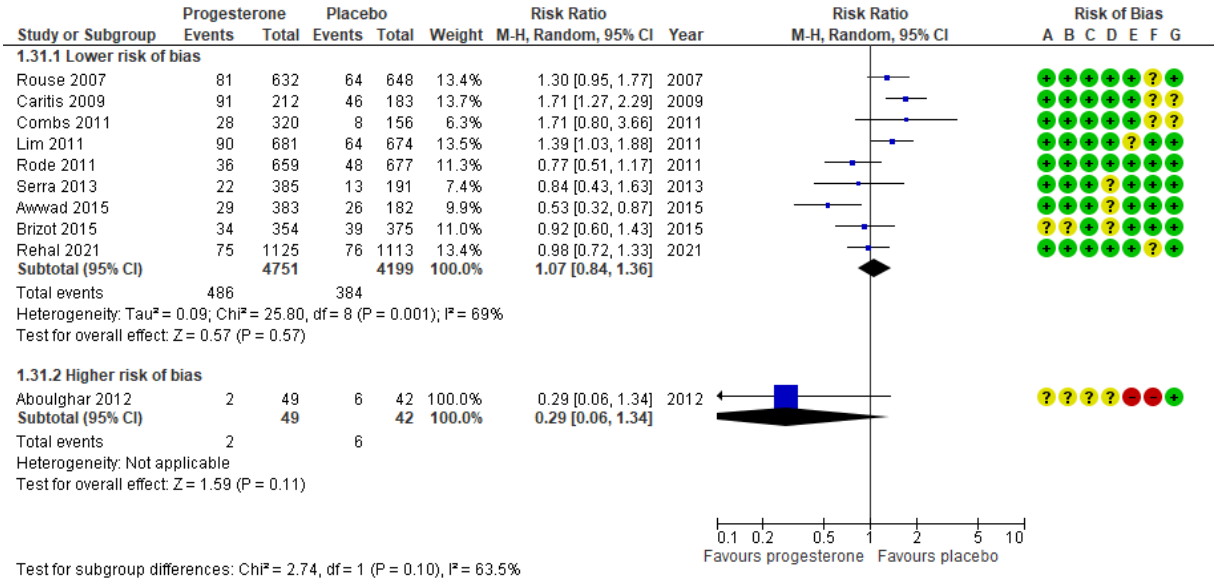
Figure 44. Outcome: Low birth weight (<2500 g).



Conclusion: Progesterone compared with placebo results in little or no difference in the risk of low birth weight in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Very low birth weight (<1500 g) in multifetal pregnancies (Appendix 4.1.9 and Figure 45)
A meta-analysis of five trials with low risk of bias, including 8950 neonates showed no difference in the rate of very low birth weight, RR 1.07 (95% CI 0.84 to 1.36). The crude event rate across trials was 9.1% without progesterone. The pooled weighted RD was 1.1 percentage points (95% CI -1.4 to 3.6).

Figure 45. Outcome: Very low birth weight (<1500 g).

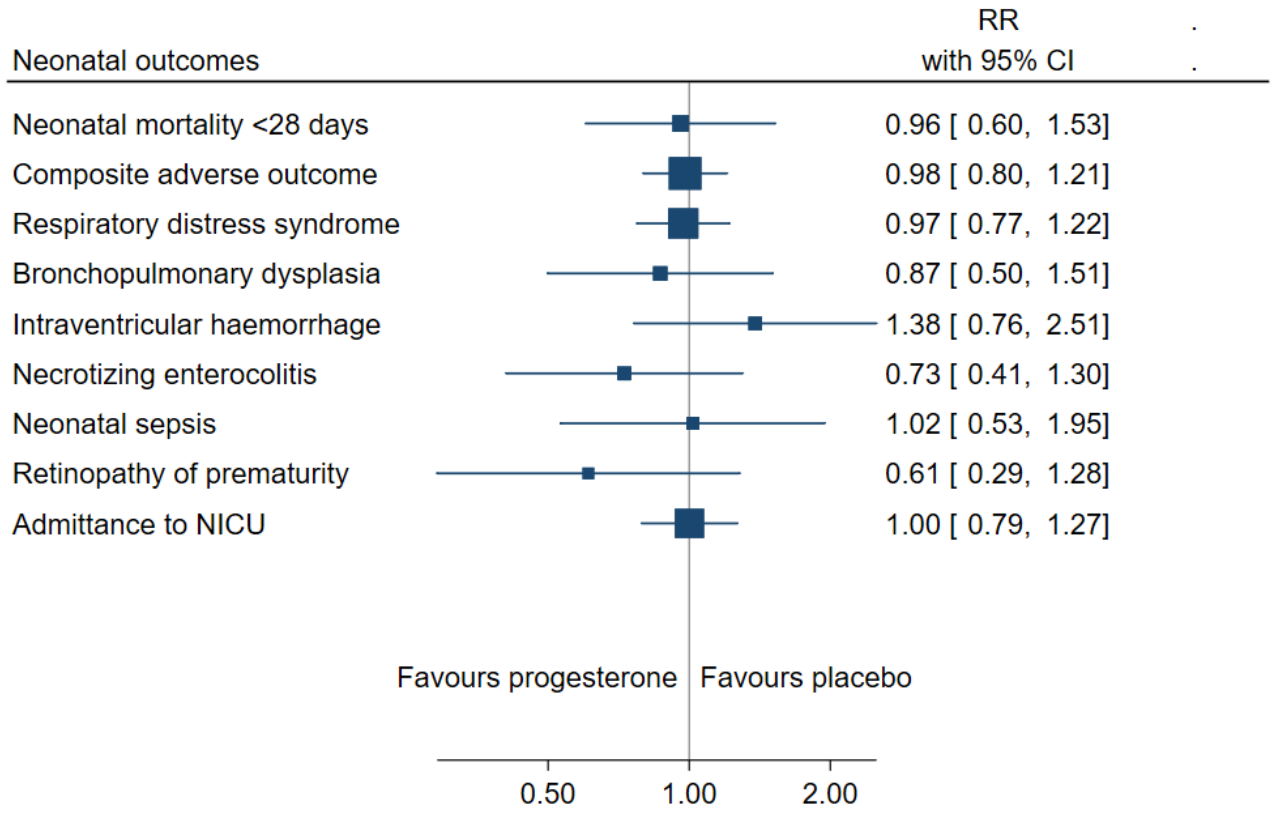


Conclusion: Progesterone compared with placebo probably results in no difference in the risk of very low birth weight in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE⊕⊕⊕◯).

Mortality and morbidity in neonates from multifetal pregnancies

Pooled estimates from meta-analyses of low risk of bias trials reporting mortality and morbidity in multifetal pregnancies are summarised in Figure 46.

Figure 46. Summary graph of pooled estimates from meta-analyses comparing progesterone and placebo in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth, from trials with regarding neonatal outcomes.



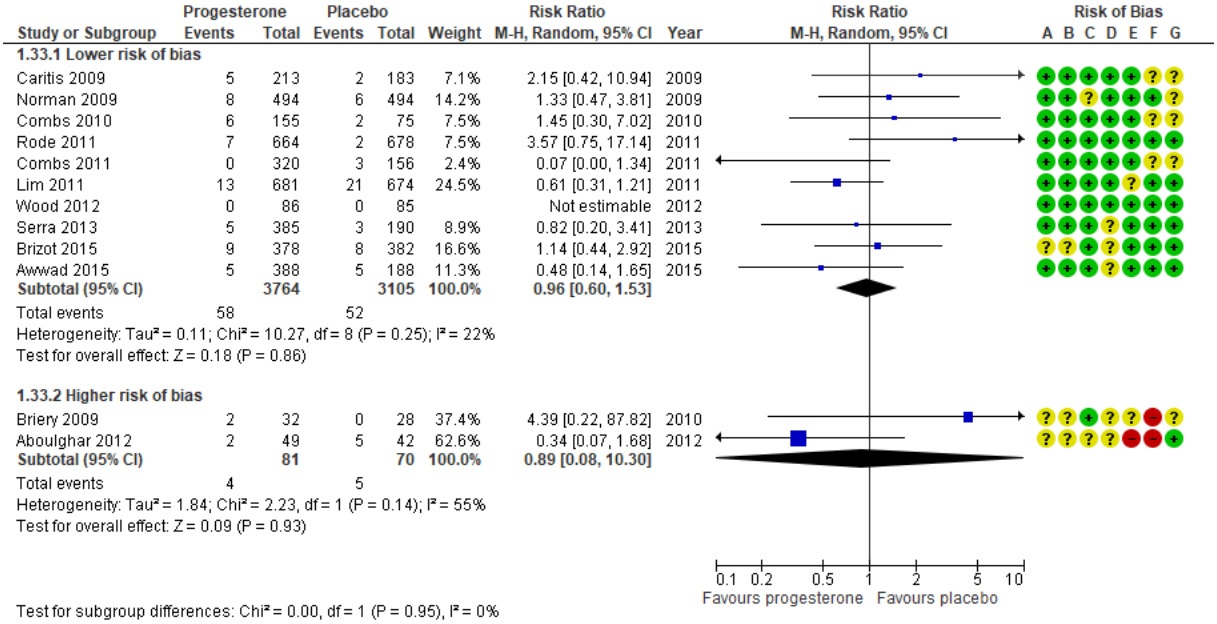
The pooled estimates (RR) ranged from 0.61 to 1.38 for neonatal mortality and serious morbidity, comparing progesterone with placebo including all routes of administration and different risk factors, with no significant difference for any neonatal outcome. Serious imprecision affected certainty of evidence for many of the outcomes.

Perinatal mortality (Appendix 4.1.10)
Twelve trials reported perinatal mortality in multifetal pregnancies. No meta-analysis on perinatal mortality was performed due to different or lack of definitions in the trials.

Neonatal mortality <7 days
No trial reported neonatal mortality <7 days.

Neonatal mortality <28 days (Appendix 4.1.11 and Figure 47)
A meta-analysis of ten studies with low risk of bias, including 6869 neonates, showed no difference in the rate of neonatal mortality <28 days, RR 0.96 (95% CI 0.60 to 1.53). The crude event rate across trials was 1.7% without progesterone. The pooled weighted RD was 0.0 percentage points (95% CI -0.6 to 0.7).

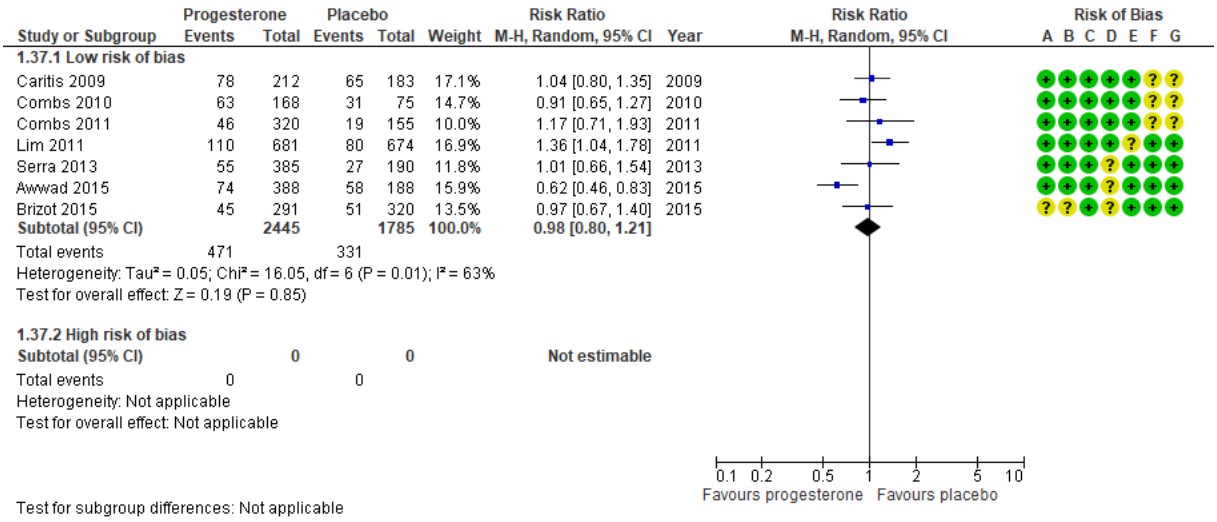
Figure 47. Outcome: Neonatal mortality <28 days.



Conclusion: Progesterone compared with placebo probably results in no difference in the risk of neonatal mortality <28 days in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE⊕⊕⊕◯).

Composite adverse neonatal outcome (Appendix 4.1.12 and Figure 48)
A meta-analysis of seven trials with low risk of bias, including 4230 neonates showed no difference in the rate of composite adverse neonatal outcome, RR 0.98 (95% CI 0.80 to 1.21). The crude event rate across trials was 18.2% without progesterone. The pooled weighted RD was -0.5 percentage points (95% CI -4.5 to 3.5).
All studies included intraventricular haemorrhage, necrotizing enterocolitis, respiratory distress syndrome, pneumonia, or confirmed sepsis in the composite adverse outcome. Awwad et al. (2015), Serra et al. (2013), Caritis et al. (2009), and Combs et al. (2010, 2011) included periventricular leukomalacia. Awwad et al. (2015) and Serra et al. (2013) included patent ductus arteriosus. Awwad et al. (2015) and Serra et al. (2013) did not include mortality in the composite adverse neonatal outcome, while the other trials did.

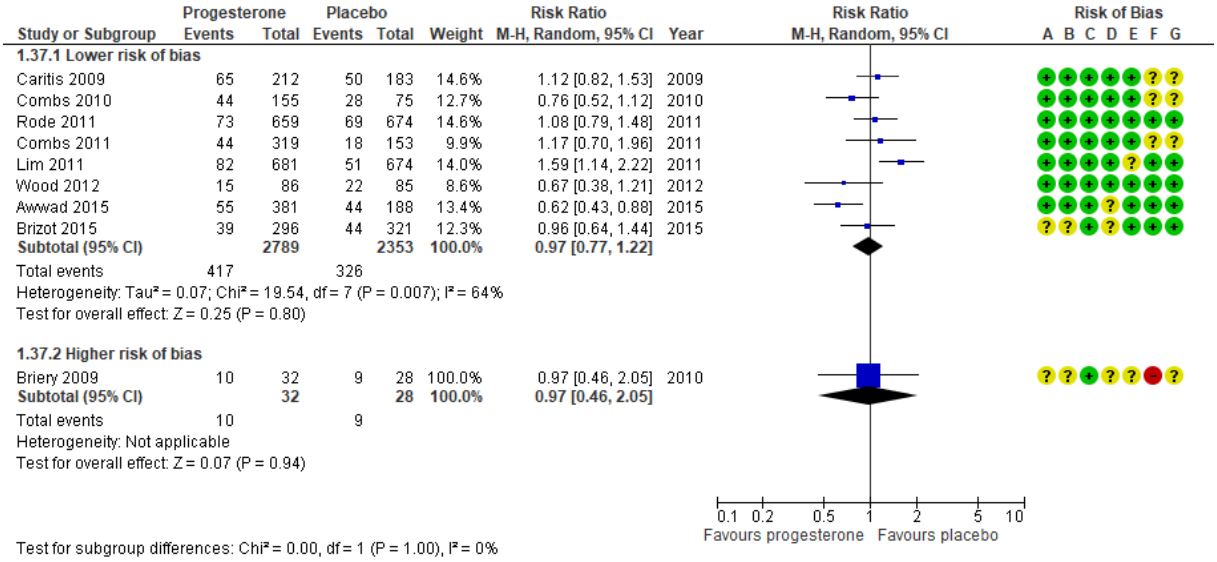
Figure 48. Outcome: Composite adverse neonatal outcome.



Conclusion: Progesterone compared with placebo may result in no difference in a composite adverse neonatal outcome in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Respiratory distress syndrome (RDS) (Appendix 4.1.13 and Figure 49)
A meta-analysis of eight trials with low risk of bias, including 5142 neonates showed no difference in the rate of RDS, RR 0.97 (95% CI 0.77 to 1.22). The crude event rate across trials was 13.8 without progesterone. The pooled weighted RD was -0.5 percentage points (95% CI -4.0 to 2.9).

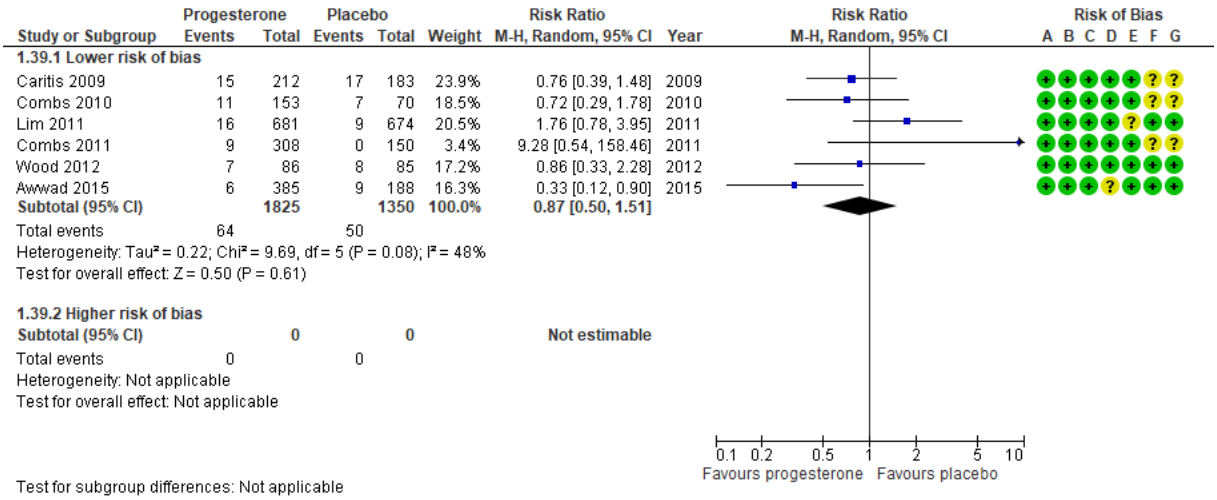
Figure 49. Outcome: Respiratory distress syndrome.



Conclusion: Progesterone compared with placebo probably results in no difference in the risk of RDS in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Bronchopulmonary dysplasia (BPD) (Appendix 4.1.14 and Figure 50)
A meta-analysis of six trials with low risk of bias, including 3175 neonates showed no difference in the rate of BPD, RR 0.87 (95% CI 0.50 to 1.51). The crude event rate across trials was 3.7% without progesterone. The pooled weighted RD was -0.2 percentage points (95% CI -2.7 to 2.3).

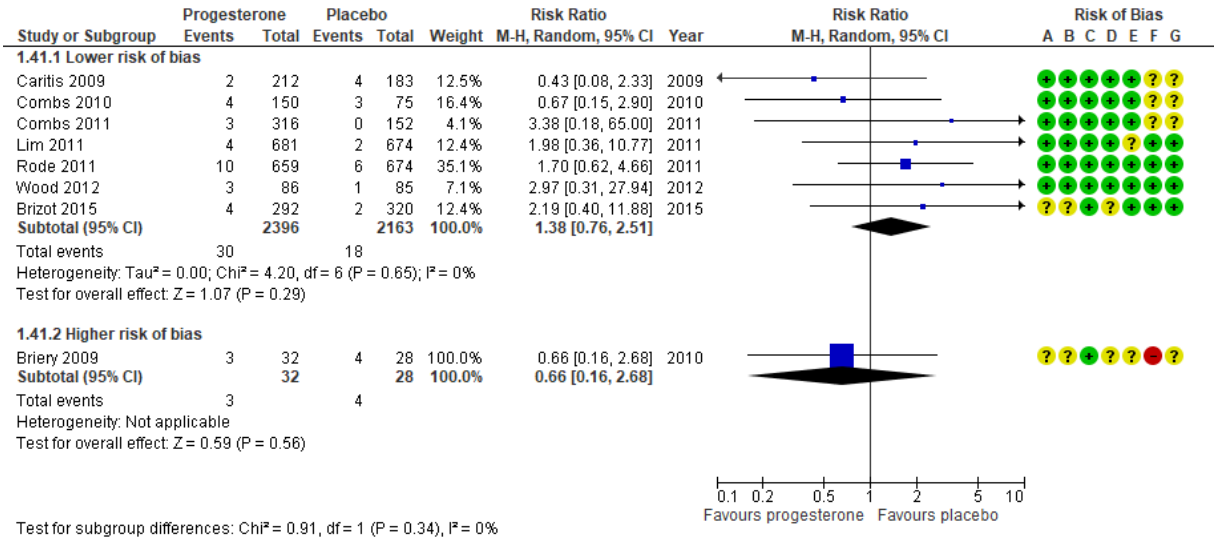
Figure 50. Outcome: Bronchopulmonary dysplasia.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of BPD in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Intraventricular haemorrhage (IVH) (Appendix 4.1.15 and Figure 51)
A meta-analysis of seven studies with low risk of bias, including 4559 neonates showed no difference in the rate of IVH, RR 1.38 (0.76 to 2.51). The crude event rate across trials was 0.8% without progesterone. The pooled weighted RD was 0.4 percentage points (95% CI -0.1 to 0.9).

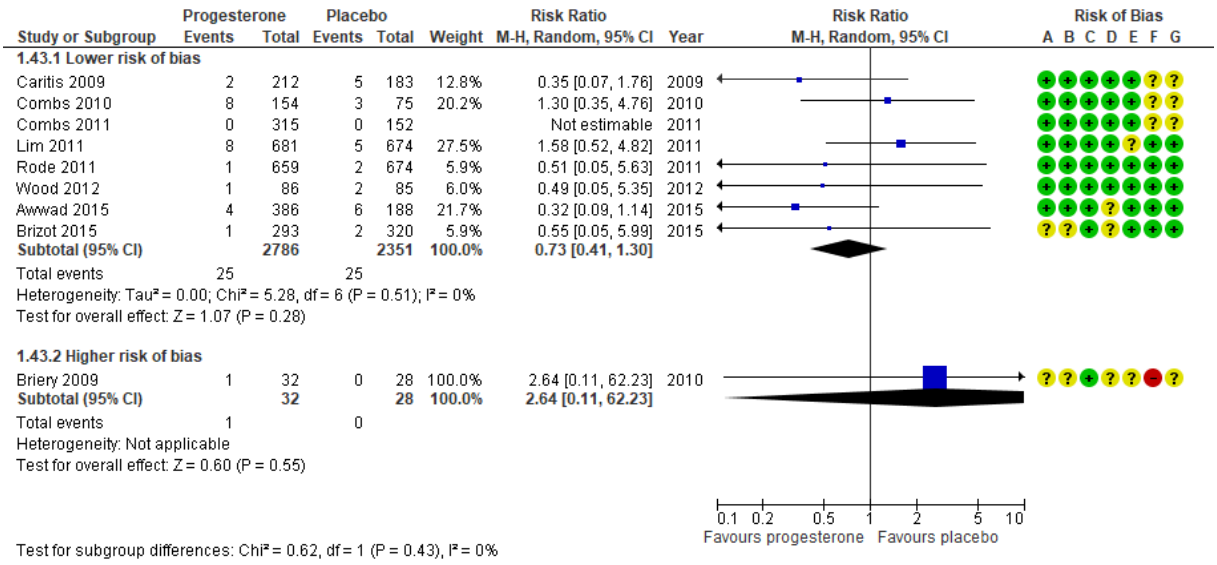
Figure 51. Outcome: Intraventricular haemorrhage.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of IVH in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Necrotizing enterocolitis (NEC) (Appendix 4.1.16 and Figure 52)
A meta-analysis of eight trials with low risk of bias, including 5137 neonates showed no difference in the rate of NEC, RR 0.73 (95% CI 0.41 to 1.30). The crude event rate across trials was 1.1% without progesterone. The pooled weighted RD was -0.1 percentage points (95% CI -0.5 to 0.2).

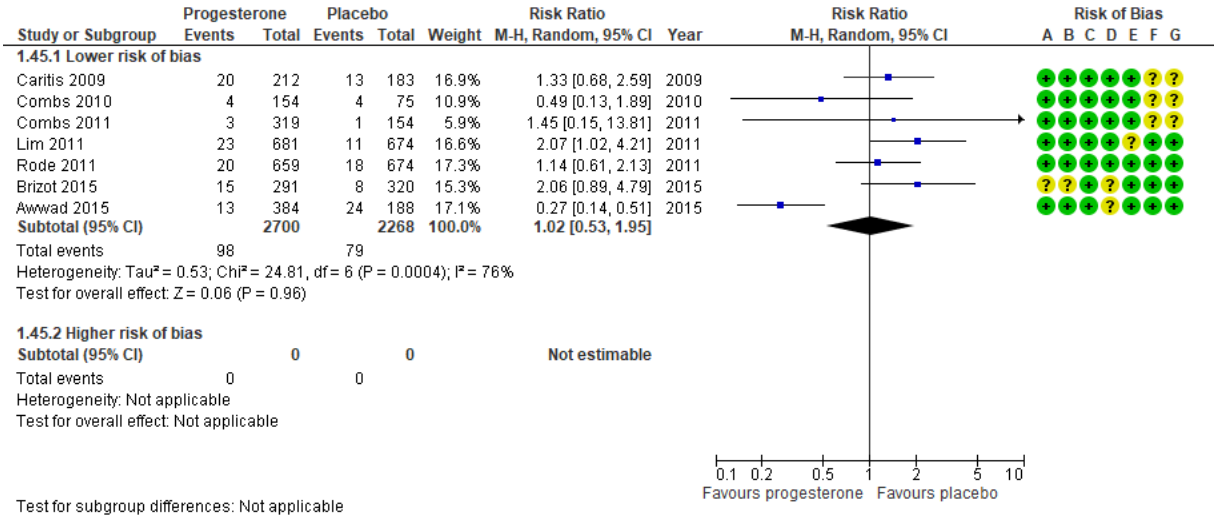
Figure 52. Outcome: Necrotizing enterocolitis.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of NEC in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Neonatal sepsis (Appendix 4.1.17 and Figure 53)
A meta-analysis of seven trials with low risk of bias, including 4968 neonates showed no difference in the rate of neonatal sepsis, RR 1.02 (95% CI 0.53 to 1.95). The crude event rate across trials was 3.5% without progesterone. The pooled weighted RD was 0.0 percentage points (95% CI -2.0 to 2.0).

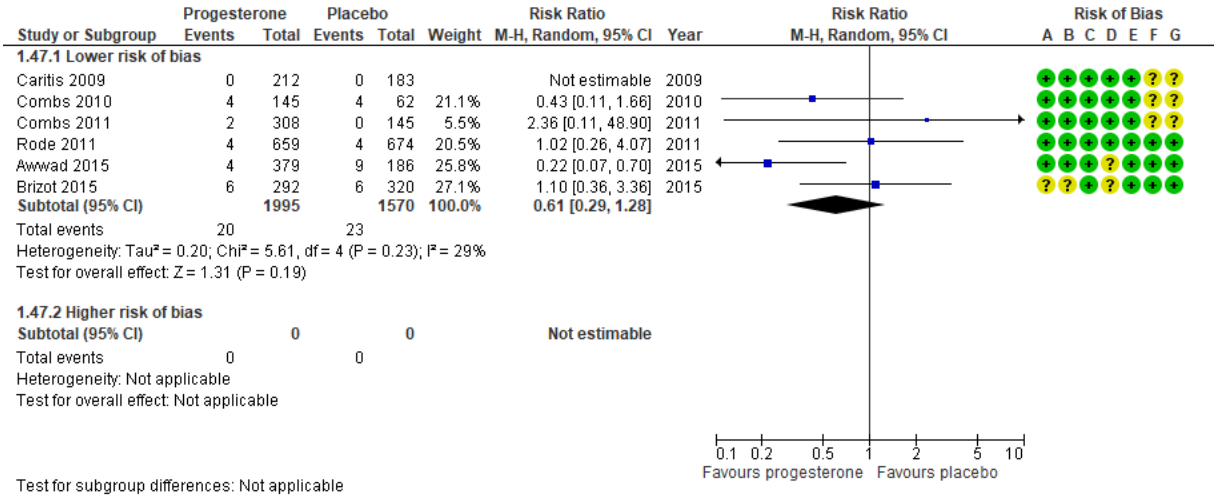
Figure 53. Outcome: Neonatal sepsis.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of neonatal sepsis or other infection in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Retinopathy of prematurity (ROP) (Appendix 4.1.18 and Figure 54)
A meta-analysis of six trials with low risk of bias, including 3565 neonates showed no difference in the rate of ROP, RR 0.61 (95% CI 0.29 to 1.28). The crude event rate across trials was 1.5% without progesterone. The pooled weighted RD was -0.2 percentage points (95% CI -1.3 to 0.8).

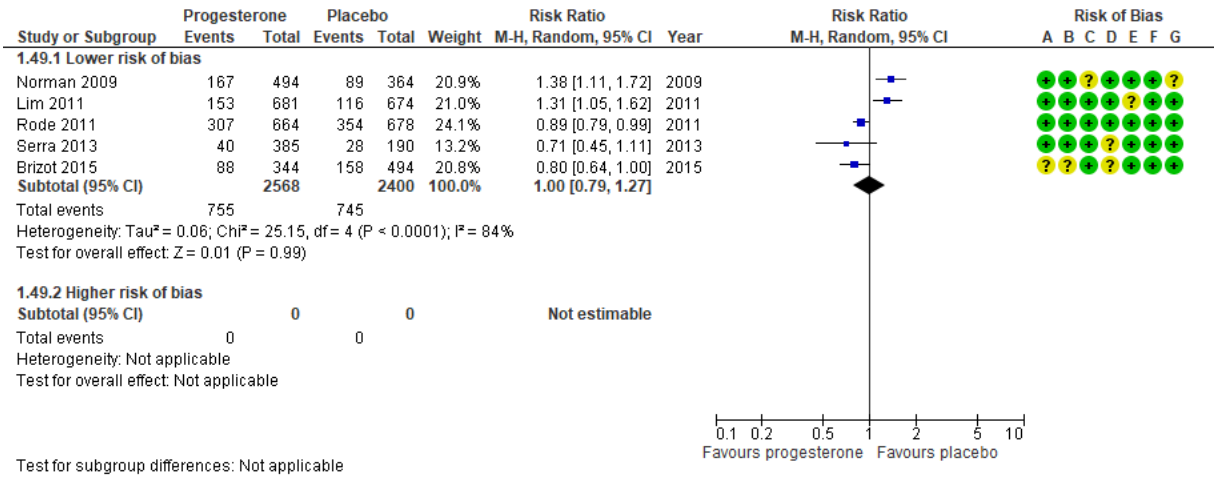
Figure 54. Outcome: Retinopathy of prematurity.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of ROP in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Admittance to neonatal intensive care unit (NICU) (Appendix 4.1.19 and Figure 55)
A meta-analysis of five trials with low risk of bias, including 4968 neonates showed no difference in the rate of NICU admission, RR 1.00 (95% CI 0.79 to 1.27). The crude event rate across trials was 31.0% without progesterone. The pooled weighted RD was -0.4 percentage points (95% CI -6.6 to 5.9).

Figure 55. Outcome: Admittance to neonatal intensive care unit (NICU).



Conclusion: Progesterone compared with placebo probably result in no difference in admittance to NICU in neonates from a multifetal pregnancy, neither considering administration route and dosage, nor additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

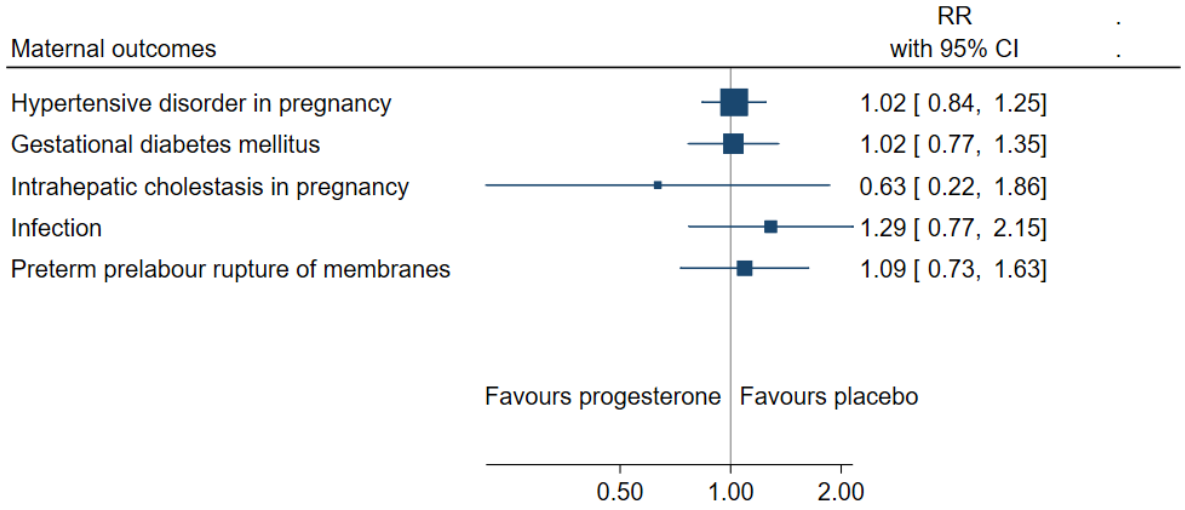
Long-term child outcomes in multifetal pregnancies (Appendix 4.1.20)
Three trials (3030 children) examined long-term child outcomes in twins (Rode et al., 2011, PREDICT-study, follow up at 6- and 18-months of age, Vedel et al., 2016, follow up to eight years of age [follow up of Rode et al., 2011, PREDICT-study], McNamara et al., 2015, follow up at three to six years of age [follow up of Norman et al., 2009, STOPPIT-study]). Rode et al. (2011) and Vedel et al. (2016) measured the neurodevelopment at different ages with Ages and Stages Questionnaire (ASQ) and McNamara et al. (2015) used Child Developmental Inventory (CDI) score. Follow-up rate was between 44% and 80%. Cognitive development, general health, anthropometry and behaviour were similar between the groups. No meta-analysis was performed because of the heterogeneity of the studies.

Conclusion: Vaginal progesterone compared with placebo may result in no difference in cognitive development, general health, or behaviour in twins, neither considering dosage, nor additional maternal risk factor(s) for preterm birth.

Maternal mortality and morbidity in women with a multifetal pregnancy

Pooled estimates from meta-analyses of low risk of bias trials reporting maternal morbidity are summarised in Figure 56.

Figure 56. Summary graph of pooled estimates from meta-analyses comparing progesterone and placebo in women with a multifetal pregnancy with or without additional risk factors from trials with low risk of bias regarding maternal outcomes.

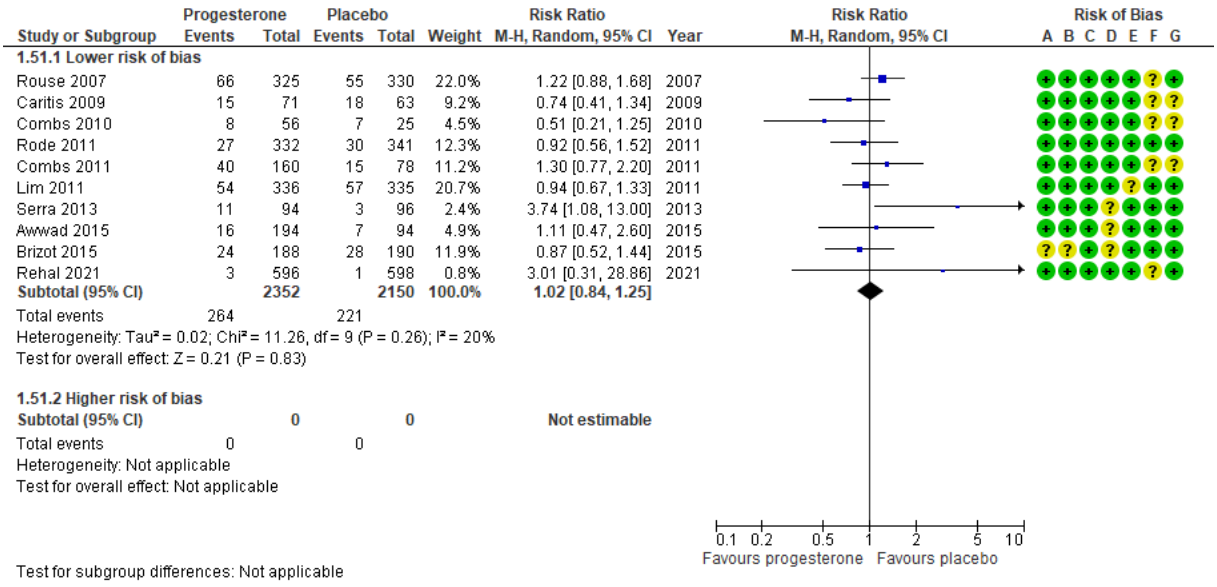


The pooled estimates (RR) were >1 (1.02 to 1.29) for maternal morbidity outcomes except for intrahepatic cholestasis (RR 0.63) comparing progesterone with placebo including all routes of administration and different risk factors with no significant difference for any outcome. Serious imprecision affected certainty of evidence for all outcomes except for hypertensive disorders in pregnancy.

Maternal mortality
No trial reported maternal mortality.

Hypertensive disorders in pregnancy (HDP) (Appendix 4.1.22 and Figure 57)
A meta-analysis of ten trials with low risk of bias, including 4502 women showed no difference in the rate of HDP, RR 1.02 (95% CI 0.84 to 1.25). The crude event rate across trials was 10.3% without progesterone. The pooled weighted RD was 0.6 percentage points (95% CI -1.1 to 2.3).

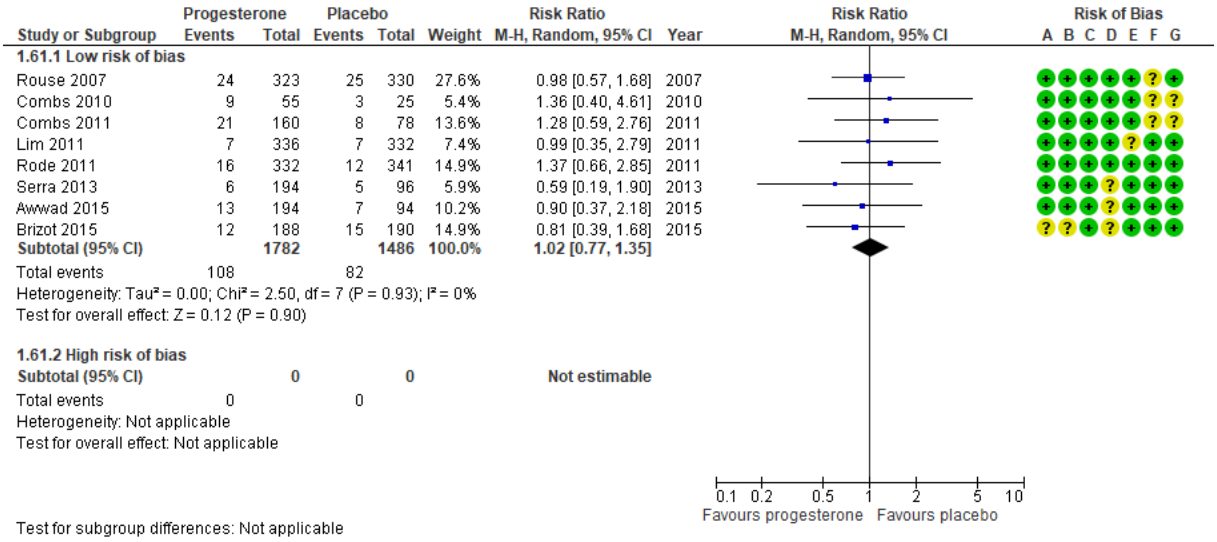
Figure 57. Outcome: Hypertensive disorder in pregnancy.



Conclusion: Progesterone compared with placebo results in no difference in HDP in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕⊕).

Gestational diabetes mellitus (GDM) (Appendix 4.1.23 and Figure 58)
A meta-analysis of eight trials with low risk of bias, including 3268 women showed no difference in the rate of GDM, RR 1.02 (95% CI 0.77 to 1.35). The crude event rate across trials was 5.5% without progesterone. The pooled weighted RD was 0.1 percentage points (95% CI -1.4 to 1.5).

Figure 58. Outcome: Gestational diabetes mellitus.

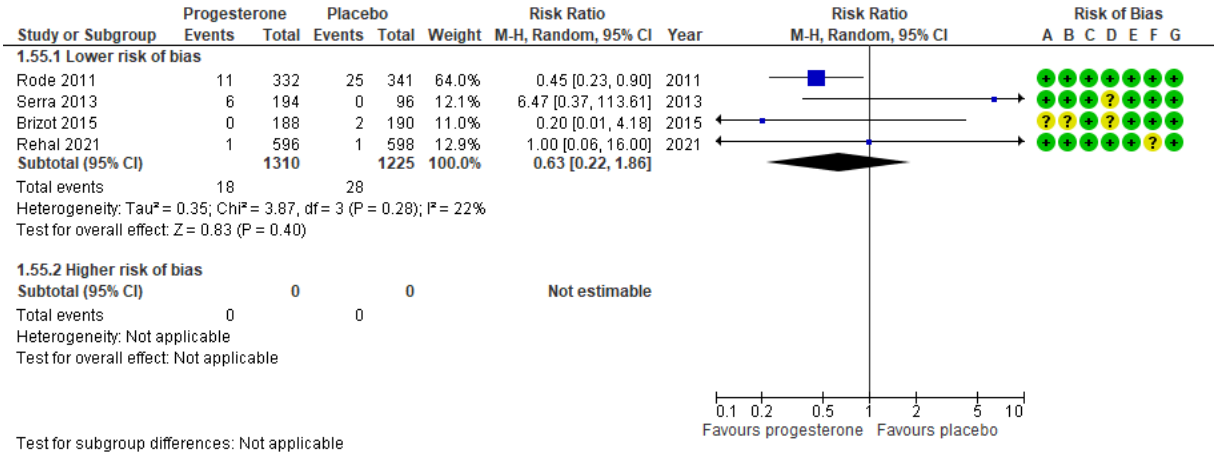


Data from Rouse 2007 was retrieved from a secondary publication, Gyamfi 2009, reporting specifically on GDM.

Conclusion: Progesterone compared with placebo probably result in no difference in the risk of GDM in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Intrahepatic cholestasis in pregnancy (ICP) (Appendix 4.1.24 and Figure 59)
A meta-analysis of four trials with low risk of bias, including 2535 women showed no difference in the rate of ICP, RR 0.63 (95% CI 0.22 to 1.86). The crude event rate across trials was 2.3% without progesterone. The pooled weighted RD was -0.4 percentage points (95% CI -3.1 to 2.3).

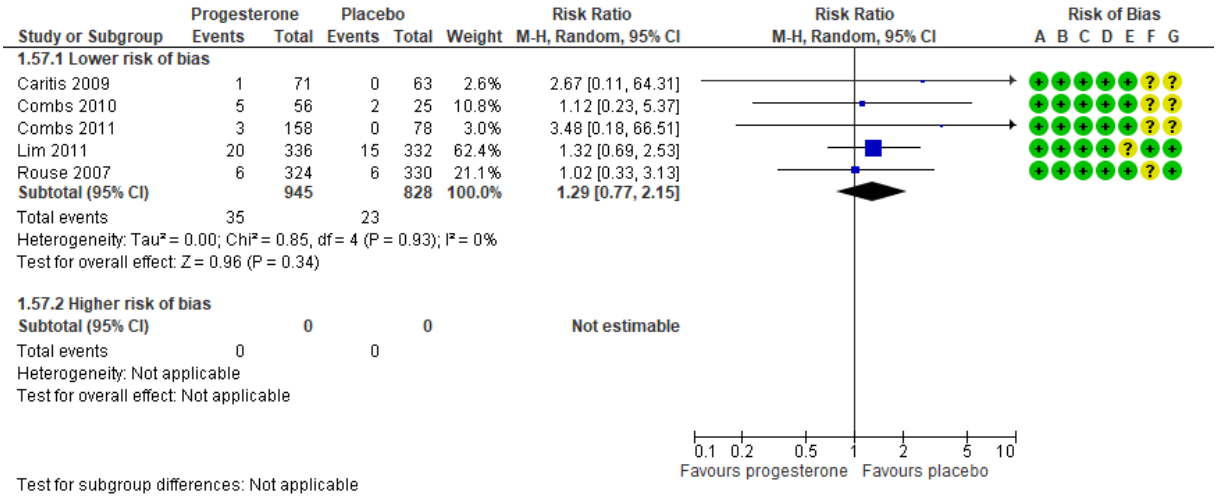
Figure 59. Outcome: Cholestasis.



Conclusion: Progesterone compared with placebo may result in no difference in the risk of ICP in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Infections (chorioamnionitis) (Appendix 4.1.25 and Figure 60)
A meta-analysis of five trials with low risk of bias, including 1773 women showed no difference in the rate of chorioamnionitis, RR 1.29 (95% CI 0.77 to 2.15). The crude event rate across trials was 2.8% without progesterone. The pooled weighted RD was 0.9 percentage points (95% CI -0.5 to 2.3).

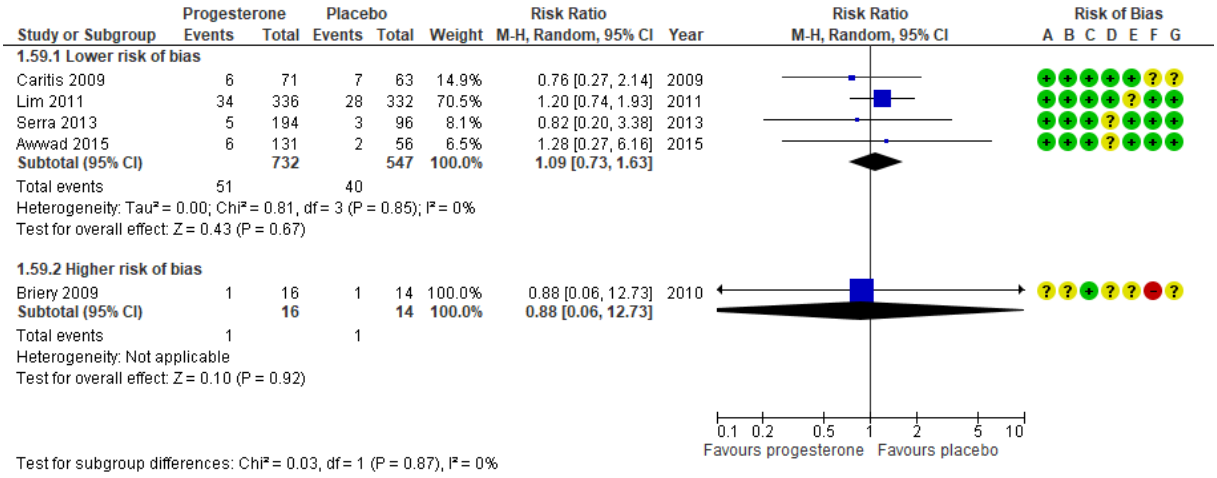
Figure 60. Outcome: Infection.



Conclusion: 17-OHPC compared with placebo may result in no difference in the risk of any infection in women with a multifetal pregnancy, neither considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Preterm prelabour rupture of the membranes (PPROM) (Appendix 4.1.26 and Figure 61)
A meta-analysis of four trials with low risk of bias, including 1279 women showed no difference in the rate of PPROM, RR 1.09 (95% CI 0.73 to 1.63). The crude event rate across trials was 7.3% without progesterone. The pooled weighted RD was 0.4 percentage points (95% CI -2.2 to 3.0).

Figure 61. Outcome: Preterm prelabour rupture of membranes (PPROM).



Conclusion: Progesterone compared with placebo probably results in no difference in the risk of PPROM in women with a multifetal pregnancy, neither considering administration route and dosage, nor additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Progesterone and adverse effects
No trials or cohort studies reporting on cancer in the woman were identified from the separate search addressing the intervention progesterone and the outcome cancer in the woman.

Interventions in comparison with progesterone

Three trials with low risk of bias were identified, two included singleton pregnancies and one twin pregnancies (Table 1). One trial, including 79 women with a singleton pregnancy, different risk factors for preterm birth and a short cervical length (25 mm or less), compared McDonald cerclage versus im 17-OHPC (250 mg weekly) (Keeler et al., 2009a). One trial, including 243 women with a singleton pregnancy and a short cervical length (25 mm or less), compared pessary versus vaginal progesterone (200 mg daily) (Cruz-Melguizo et al., 2018). The third trial, including 300 women with a twin pregnancy and short cervical length (less than 38 mm, 10th percentile), compared pessary versus vaginal progesterone (400 mg daily) (Dang et al., 2019). The trials were performed in the United States of America, Spain, and Vietnam, respectively. The results are presented in Appendix 4.1.1-4.1.26, after the progesterone vs. placebo trials.

Comparison cerclage vs 17-OHPC in singleton pregnancies

Women with different risk factors for preterm birth and a cervical length ≤25 mm had similar risk of spontaneous preterm birth <35 weeks (primary outcome) when treated with cerclage or 17-OHPC, RR 1.14 (95% CI 0.67 to 1.93), (Keeler et al., 2009a). The certainty of evidence was downgraded three levels due to non-blinding, discrepancies in ethnicity and very serious imprecision. No differences in preterm birth rates or neonatal mortality or morbidity were found. A post-hoc analysis showed that women in the cerclage group with cervical length ≤15 mm had lower risk of spontaneous preterm birth <37 and <35 weeks compared with the progesterone arm.

Conclusion: It is uncertain whether cerclage compared with 17-OHPC, results in any difference in spontaneous preterm birth before 35 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕◯◯◯).

Comparison pessary vs vaginal progesterone in singleton pregnancies

The Cruz-Melguizo et al. trial (2018) did not show non-inferiority (exceeded margin of 4%) for pessary versus vaginal progesterone for the primary outcome spontaneous preterm birth <34 weeks. The event rate was 14.0% in both groups and the RD was -0.11 percentage points (95% CI -8.85% to 8.62%). The certainty of evidence was downgraded two levels due to non-blinding and serious imprecision. No significant differences were found for secondary neonatal or maternal outcomes.

Conclusion: Pessary compared with vaginal progesterone, may results in no difference in spontaneous preterm birth before 34 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Comparison pessary vs vaginal progesterone in twin pregnancies

The trial including twins showed no difference in the primary outcome preterm birth <34 weeks comparing pessary with vaginal progesterone, RR 0.73 (95% CI 0.46 to 1.18) (Dang et al., 2019). The certainty of evidence was downgraded two levels due to non-blinding, subpopulation of mainly IVF pregnancies and very serious imprecision. The pessary group had lower rate of the composite adverse neonatal outcome (RR 0.70; 95% CI 0.43 to 0.93). There were also lower rates of low birth weight, RDS, neonatal sepsis, and admittance to NICU comparing pessary with vaginal progesterone. In a planned prespecified subgroup analysis of women with a cervical length ≤28 mm (10^{th} percentile) the composite adverse neonatal outcome was lower (RR 0.47; 95% CI 0.24 to 0.90) in the pessary group.

Conclusion: Pessary compared with vaginal progesterone, may results in no difference in spontaneous preterm birth before 34 gestational weeks, in women with a twin pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Subgroup analyses progesterone vs placebo

Subgroup analyses in singleton pregnancies

Exploratory subgroup analyses based on trials with low risk of bias

Figure 63. Outcome: Any preterm birth <37 weeks according to administration route.

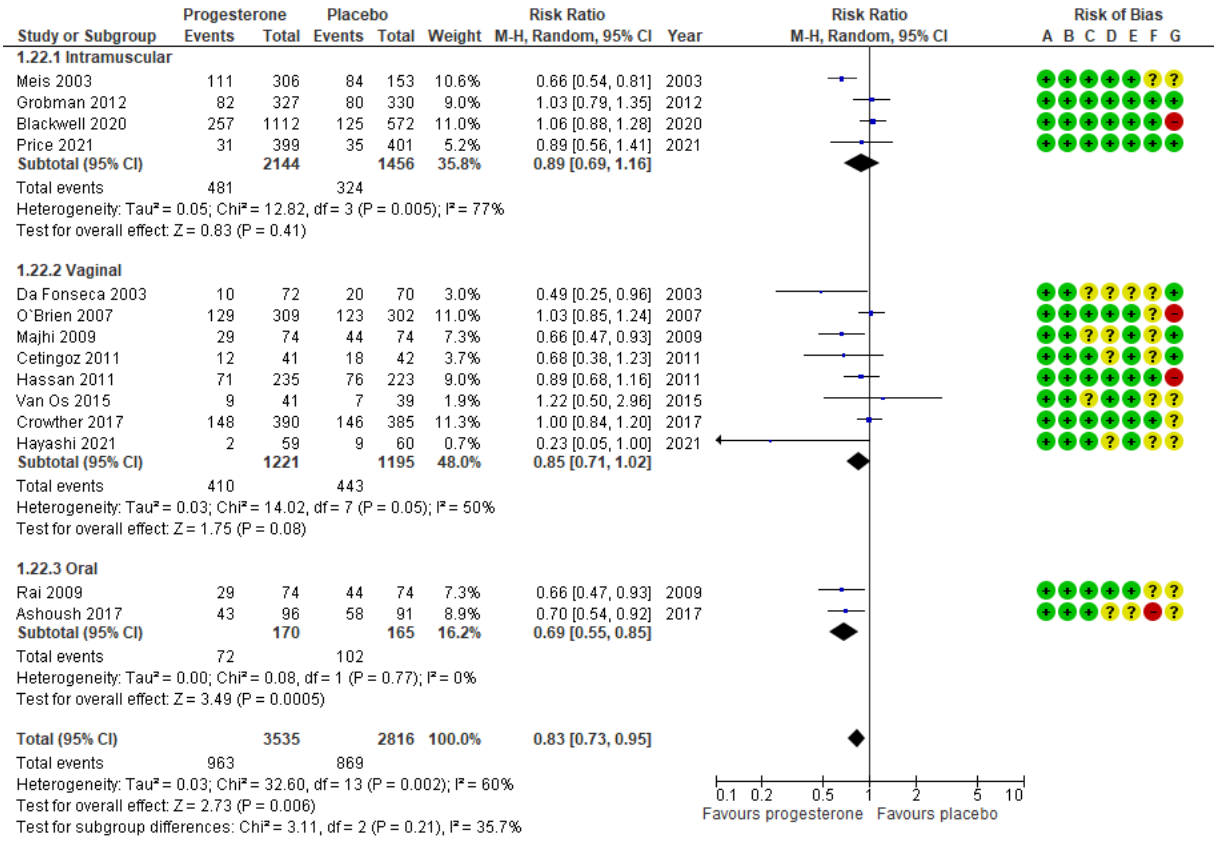
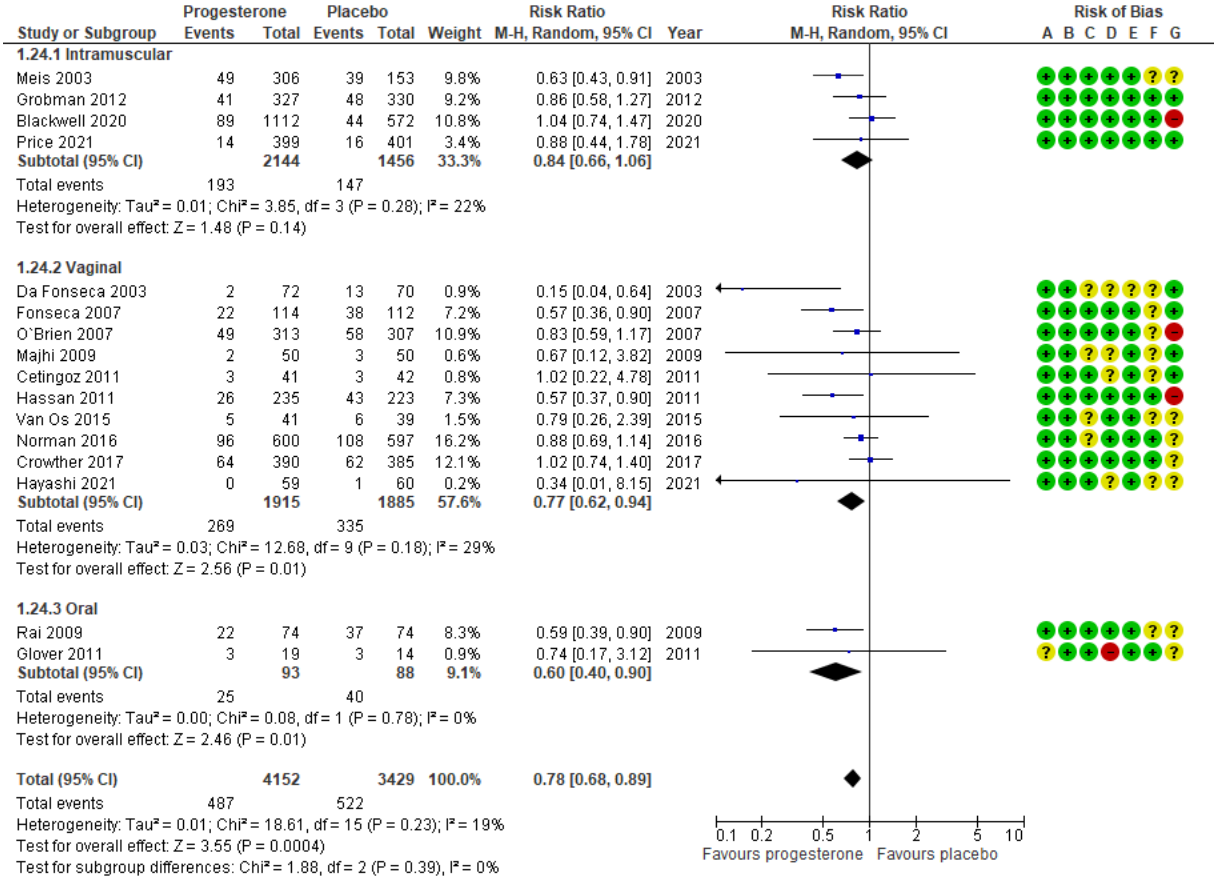


Figure 64. Outcome: Any preterm birth <34 weeks according to administration route.



Prespecified subgroup analyses based on trials with low risk of bias

Figure 65. Outcome: Any preterm birth <37 weeks according to risk factor.

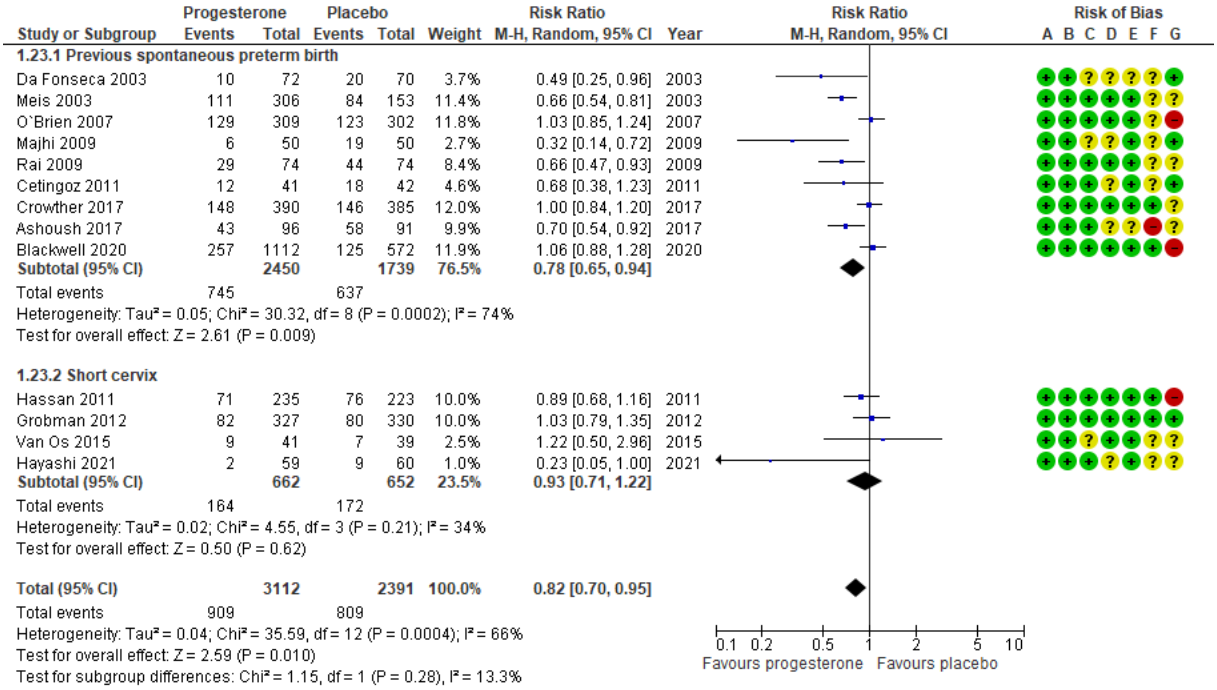
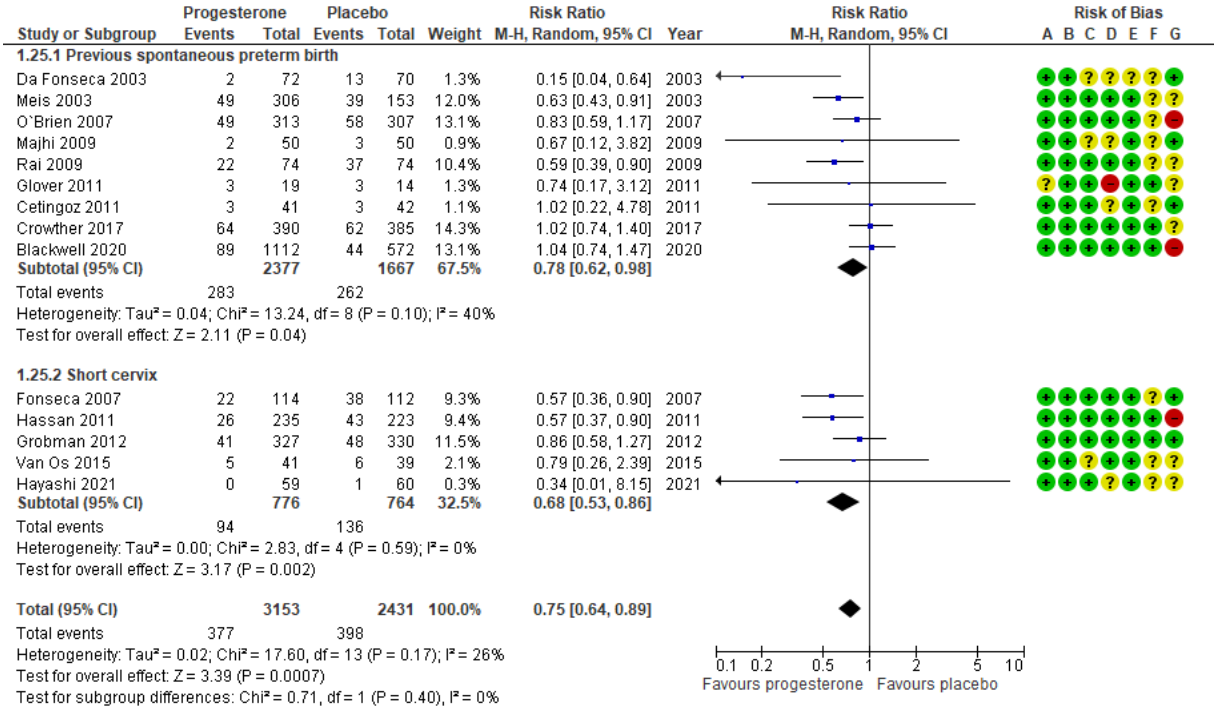


Figure 66. Outcome: Any preterm birth <34 weeks according to risk factor.



Cut-off cervical length: Fonseca 2007 ≤15 mm, Hassan 2011 10-20 mm, Grobman 2012 <30 mm, Van Os 2015 ≤30, and Hayashi 2021 included 25-<30 mm.

Figure 67. Outcome: Any preterm birth <37 weeks among women with a previous spontaneous preterm birth, according to administration route.

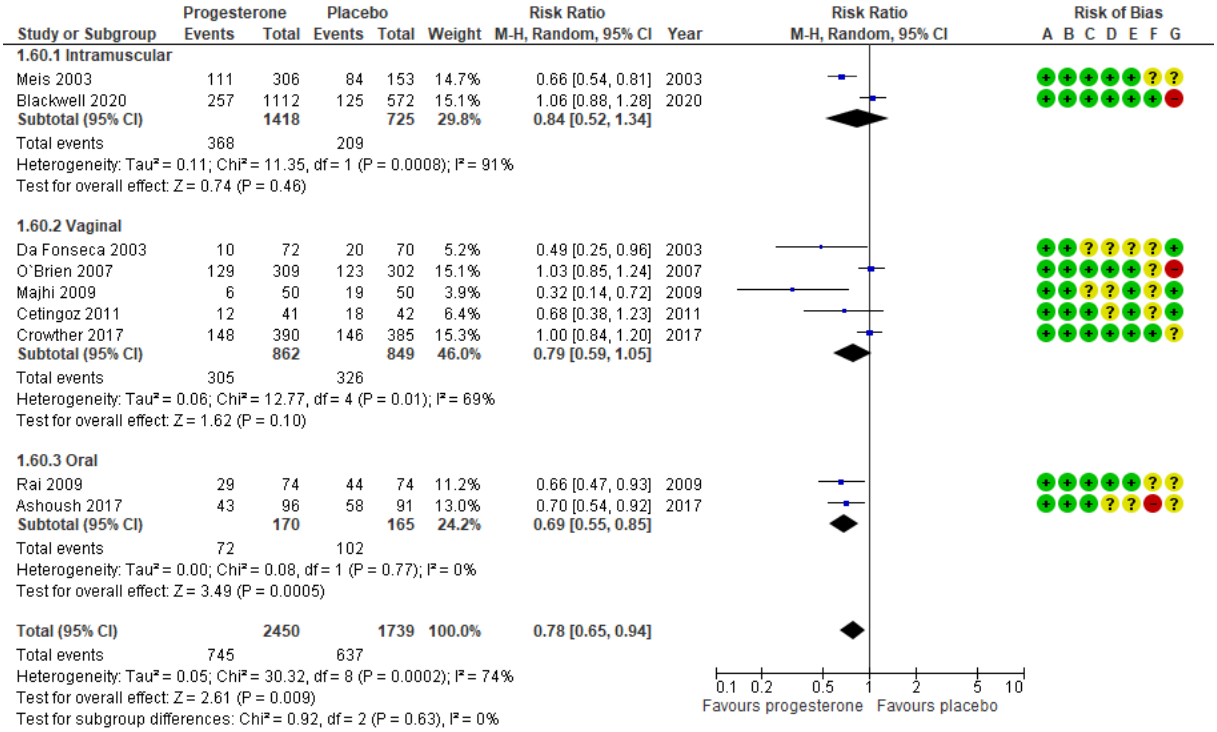


Figure 68. Outcome: Any preterm birth <34 weeks among women with a previous spontaneous preterm birth, according to administration route.

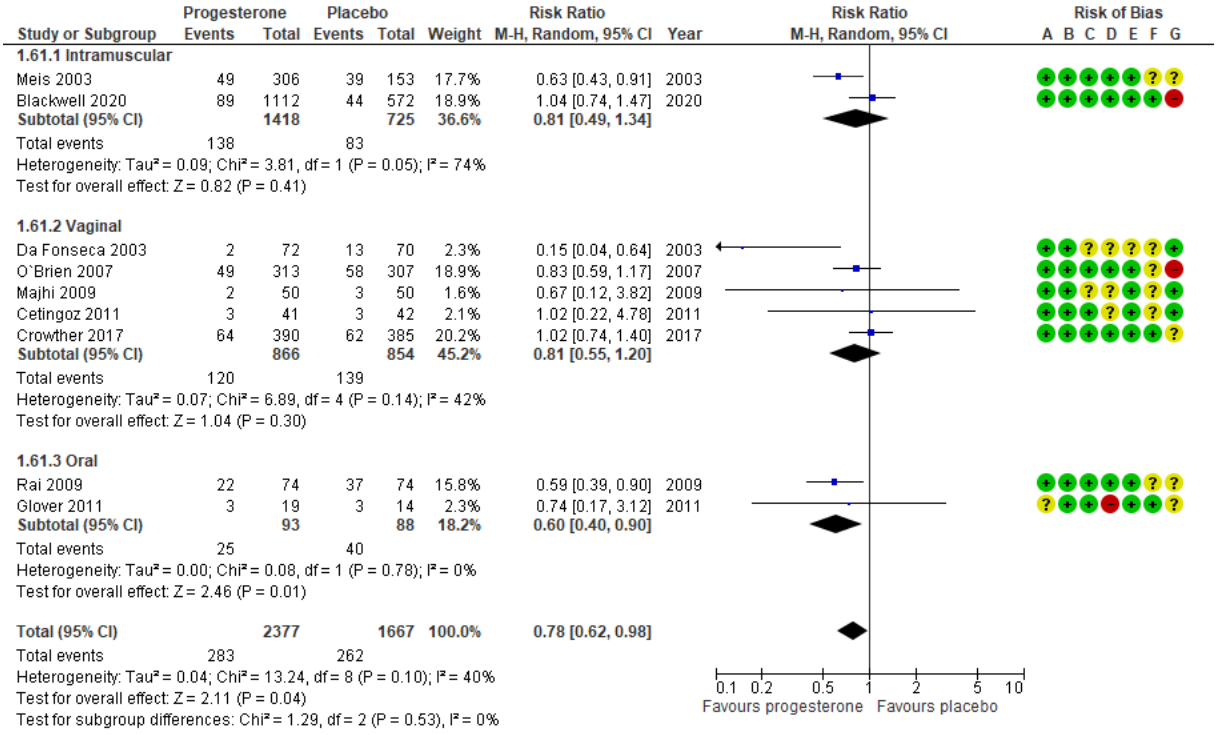
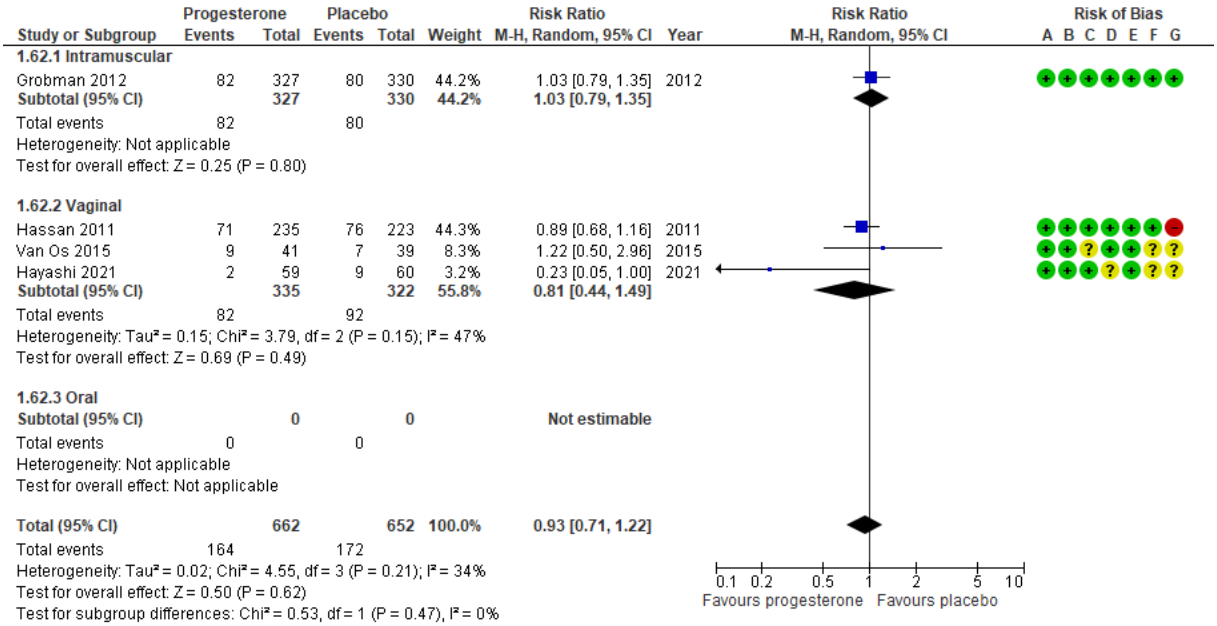
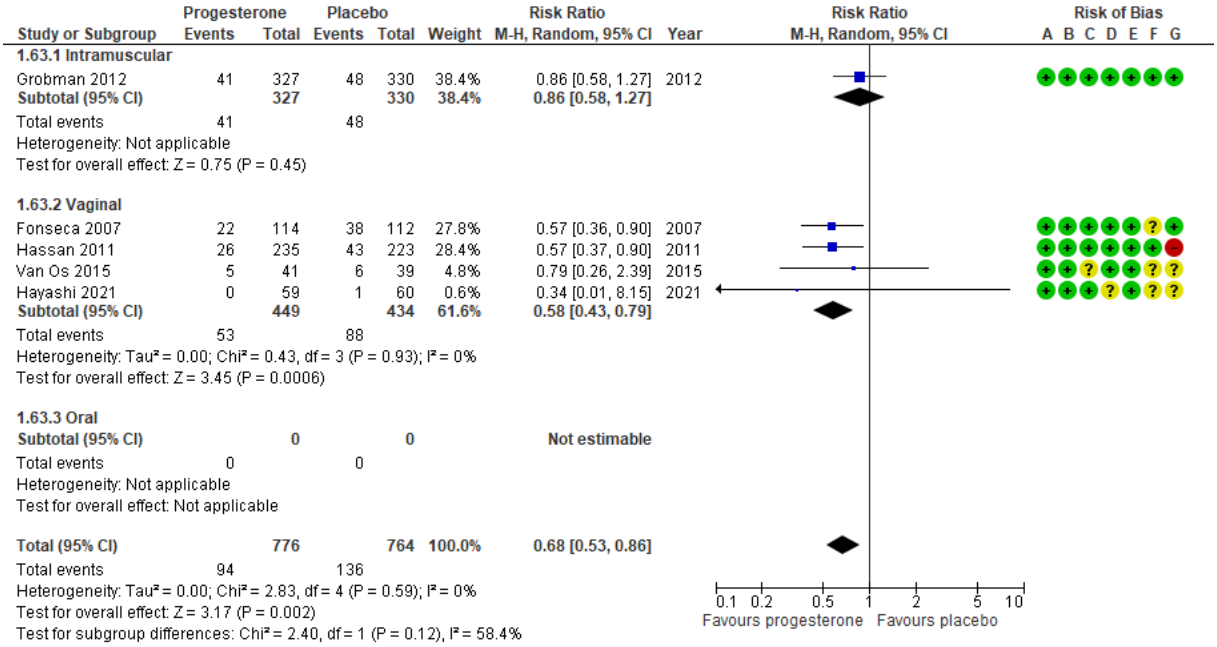


Figure 69. Outcome: Any preterm birth <37 weeks among women with short cervical length, according to administration route.



Cut-off cervical length: Grobman 2012 <30 mm, Hassan 2011 included 10-20 mm, Van Os 2015 ≤30 mm and Hayashi 2021 included 25-<30 mm.

Figure 70. Outcome: Any preterm birth <34weeks among women with short cervical length, according to administration route.



Cut-off for cervical length: Grobman 2012 <30 mm, Fonseca 2007 ≤15 mm, Hassan 2011 included 10-20 mm, Van Os 2015 ≤30 mm, and Hayashi 2021 included 25-<30 mm.

Subgroup analyses in multifetal pregnancies

Exploratory subgroup analyses based on trials with low risk of bias

Figure 71. Outcome: Any preterm birth <37 weeks according to administration route.

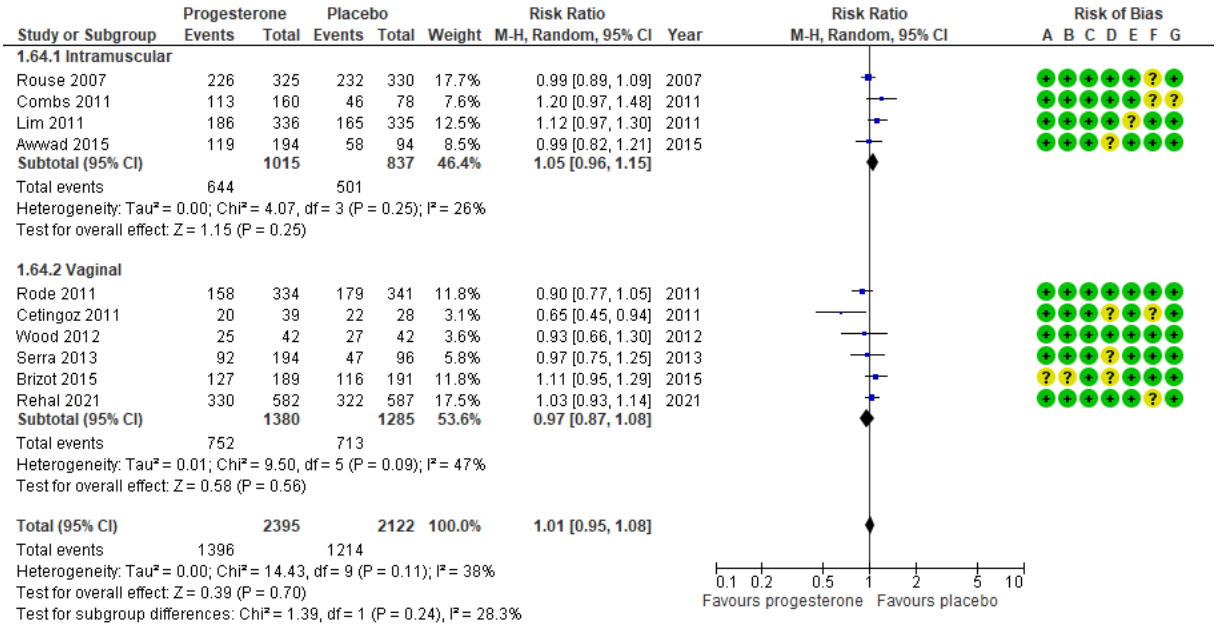
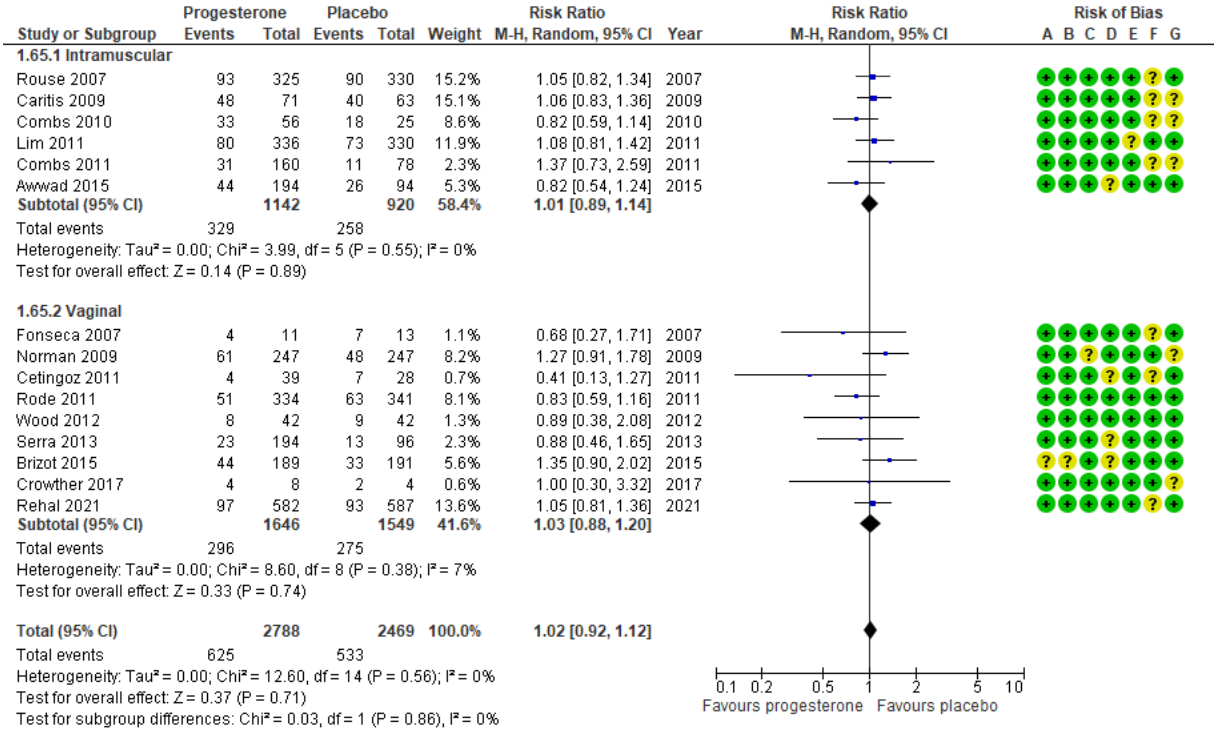
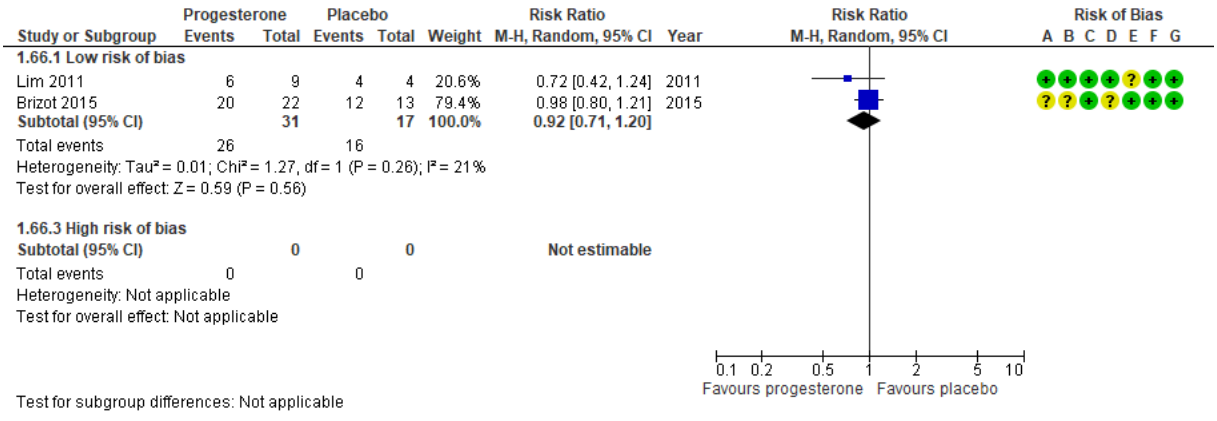


Figure 72. Outcome: Any preterm birth <34 weeks according to administration route.



Results from Rouse 2007, Fonseca 2007, Caritis 2009, Lim 2011, Wood 2012, Awwad 2015, Crowther 2017 were retrieved from the IPD meta-analysis by Stewart et al., 2021 (EPPPIC).

Figure 73. Outcome: Any preterm birth <37 weeks in women with short cervical length.

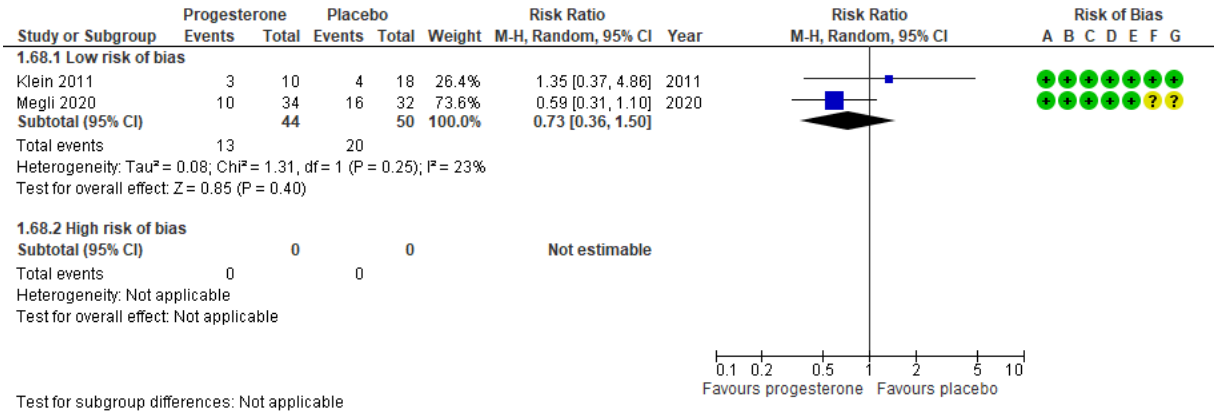


Dosage/administration. Cut-off cervical length: Lim 2011: 250 mg i.m. 17-OHCP/w. <25 mm
Brizot 2015: 200 mg vaginal progesterone/d. ≤25 mm

Figure 74. Outcome: Any preterm birth <34 weeks in women with short cervical length and vaginal progesterone administration.

Dosage/administration. 200 mg vaginal progesterone/d in all 3 trials.
Cut-off cervical length: Fonseca 2007: ≤15 mm, Brizot 2015: ≤25 mm, Klein 2011: ≤30 mm

Figure 75. Outcome: Any preterm birth <34 weeks in women with previous preterm birth.



Dosage/administration: Klein 2011: 200 mg vaginal progesterone/d
Megli 2020: 250 mg i.m. 17-OHPC/w

Project: Prevention of preterm birth
Appendix 4.1.1.a. Intervention progesterone
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 4/52 (7.7%)? RR 2.48 (95% CI: 0.81-9.94) p=0.203	Placebo 9/47 (19.1%)? Table 1 8/47? (17.0%)? Table 2	PO not stated Incorrect numbers in the article?	?	-	-
Ali, 2020 Egypt	Singletons	Indication for cerclage: previous second trimester loss, sPTD (<34 w) or short cervix (<25 mm)	I: 121 C:121	400 mg progesterone vag (pessary)/d 12/97 (12.4%) p=0.005	Placebo 12/75 (16.0%)	Not PO Progesterone was used as an adjuvant after cerclage NB PTB 28-34 weeks, with spontaneous abortion< 28 weeks = primary outcome was excluded	?	?	?
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 43/96 (44.8%) RR 0.7 (95% CI 0.54-0.92) p=0.01	Placebo 58/91 (63.7%)	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg progesterone supp vag/d 18/50 (36%) RR 0.53 (95% CI 0.35-0.80) (from MA)	Placebo 34/50 (68 %) RR 1.89 (95% CI 1.25-2.86) p=0.001	PO Results also for previous PTB and previous PTB and short TVS CL In article RR for controls vs intervention, RR for intervention vs controls from MA	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 257/1112 (23.1%) RR 1.06 (95% CI 0.88–1.28) No p value	Placebo 125/572 (21.9%)	Not PO	+	?	?
Da Fonseca, 2003 Brazil	Singletons	Previous sPTB, prophylactic cerclage, uterine malformations	I: 81 C:76	100 mg vaginal progesterone/d 10/72 (13.9%) p=0.03	Placebo 20/70 (28.6%)	PO not defined	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.1.a. Intervention progesterone
Outcome variable: Any preterm birth before 37 gestational weeks

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Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 82/327 (25.1%) RR 1.03 (95% CI 0.79-1.35) No p value	Placebo (castor oil) 80/330 (24.2%)	PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 71/235 (30.2%) RR 0.89 (95% CI 0.68-1.16) p=0.376	Placebo 76/223 (34.1%)	Not PO	?	?	+
Hauth, 1983 USA	Singletons	Women from an active –duty military population	I: 80 C: 88	17-OHPC 1000mg im/w 5/80 (6.3%) NS No p value, OR or RR	Placebo (castor oil) 5/88 (5.7%)	PO not defined	-	-	-
Hayashi, 2021 Japan TROPICAL	Singletons	Short TVS CL 25-<30 mm Previous PTB I: 11.9% C: 16.7%	I: 59 C: 60	200 mg vaginal progesterone/d 2/59 (3.4%) p=0.029 No RR	Placebo 9/60 (15%)	Not PO	?	?	-
Ibrahim, 2010 Egypt	Singletons	Previous PTB	I: 25 C: 25	17-OHPC 250 mg/w 8/25 (32%) RR 0.079 (95% CI 0.021-0.302)	Placebo (saline) 13/25 (52%)	PO not defined	-	-	-
Jabeen, 2012 Pakistan	Singletons	Previous sPTB	I: 30 C: 30	17-OHPC 250 mg/w 11/30 (36.7%) p< 0.001	Placebo (inert oil) 25/30 (83.3%)	PO	?	-	-
Jafarpour, 2020 Iran	Singletons	Previous PTB	I: 50 C: 50	17-OHPC 250 mg/w 21/50 (42%) RR 1.2 (95% CI 0.85-1.88) p=0.23	Routine prenatal care 27/50 (54%)	PO? (not defined)	?	-	-
Majhi, 2009 India	Singletons	Previous sPTB	I: 50 C: 50	100 mg vaginal progesterone/d 6/50 (12%) RR 0.315 (95% CI 0.137-0.724) p= 0.0027	No placebo 19/50 (38%)	PO?	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.1.a. Intervention progesterone
Outcome variable: Any preterm birth before 37 gestational weeks

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- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 111/306 (36.3%) RR 0.66 (95% CI 0.54-0.81) No p value	Placebo (castor oil) 84/153 (54.9%)	PO	?	?	?
O'Brien, 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 129/309 (41.7%) OR 1.08 (95% CI 0.76-1.52) No p value	Placebo 123/302 (40.7%)	Not PO	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 31/399 (8%) RR 0.9 (95% CI 0.6-1.4) No p value	Placebo 35/401 (9%)	Not PO	?	+	?
Rai, 2009 India	Singletons	Previous sPTB	I: 75 C:75	200 micronized oral progesterone/d 29/74 (39.2%) No RR or OR p=0.002	Placebo 44/74 (59.5%)	Not PO	-	?	?
Saghafi, 2011 Iran	Singletons	Previous PTB	I: 50 C: 50	17-OHPC 250 mg im/w 16/50 (32%) p<0.05	No placebo 30/50 (60%)	PO not defined Not stated but assumed to be only singletons	-	-	-
Shadab, 2018 Pakistan	Singletons	Previous sPTB	I: 66 C: 66	17-OHPC 250 mg im/w 19/66 (28.8%) No OR or RR p=0.00045	Vitamin B im as placebo 39/66 (59.1%)	PO not defined	-	-	-
Shahgheibi, 2016 Iran	Singletons	Previous sPTB, uterine mal-formations	I: 50 C: 50	17-OHPC 250 mg im/w 11/50 (22%) OR 0.69 (95% CI 0.58-0.83) No p value	Placebo 29/50 (58%)	PO not defined	-	-	-
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 9/41 (22%) RR1.25 (95% CI 0.52-3.03) No p value	Placebo 7/39 (18%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.1.a. Intervention progesterone
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Yemini, 1985 Israel	Singletons	Previous ≥2 PTB or ≥2 spontaneous miscarriages	I: 39 C: 40	17-OHPC 250 mg im/w 5/31(16.1%) p<0.05 RR not presented	Placebo 14/37 (37.8%)	Not PO All had cerclage Miscarriage occurred in 8 and 3 women	-	-	-
Awwad, 2015 Lebanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w 119/194 (61.3%) RR 1.0 (95% CI 0.6-1.6) p=0.95	Placebo (castor oil) 58/94 (61.7%)	PO	+	+	?
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16 C: 14	17-OHPC 250 mg im/w 14/16 (87.5%) p=0.565	Placebo 13/14 (92.9%)	Not PO Numbers for PTB <37 w calculated from Table 2	?	?	-
Brizot, 2015 Brazil	Twins DA	MC I: 25% C: 19% Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d 127/189 (67.2%) OR 1.32 (95% CI 0.85-2.06) No p value Subgroup analysis TVS CL ≤25 mm n=22 20/22 (90.9%)	Placebo 116/191 (60.7%) Subgroup analysis TVS CL ≤25 mm n=13 12/13 (92.3%)	Not PO Subgroup analysis TVS CL ≤25 mm	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 113/160 (71%) RR 1.2 (95% CI 1.0-1.5) p=0.08	Placebo (1 mL castor oil) 46/78 (59%)	Not PO	+	?	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 330/582 (56.7%)* OR 1.13 (95% CI 0.88-1.46)* 315/567 (55.6%)** OR 1.16 (95% CI 0.90-1.51)** No p values	Placebo 322/587 (54.9%)* 296/561 (52.8%)**	*any birth after randomisation to 37 w **any birth 24-37 w	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.1.a. Intervention progesterone
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334 C: 343	200 mg vaginal progesterone/d (pessary) 158/334 (47.3%) OR 0.8 (95% CI 0.6-1.1) No p values	Placebo 179/341 (52.5%)	Not PO	+	+	+
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w 226/325 (69.5%)* RR 1.0 (95% CI 0.9-1.1)*	Placebo 232/330 (70.3%)*	Not PO *PTB or fetal death <37 weeks (fetal death includes miscarriage, termination of pregnancy, and stillbirth)	+	?	+
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C:96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d 48/97 (49.5%) I2: 400 mg vaginal progesterone (pessary)/d 44/97 (45.4%) I1 + I2: 92/194 (47.4%) I1, I2, C= NS I1+I2 vs C= NS I1 vs I2=NS	Placebo 47/96 (49.0%)	PO?	?	?	-
Lim, 2011 The Netherlands AMPHIA	Multiple pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 C: 335	17-OHPC 250 mg im/w 186/336 (55%) RR 1.11 (95% CI 0.97-1.28) No p value Subgroup analyses TVS CL <35mm 22/37 (59%) RR 0.85 (95% CI 0.58-1.26) No p value TVS CL <25mm 6/9 (67%) No statistics	Placebo 165/335 (50%) Subgroup analyses TVS CL <35mm n=24 17/24 (71%) TVS CL <25mm 4/4 (100%)	Not PO Post hoc subgroup analysis TVS CL <35mm Prespecified subgroup analysis <25 mm	+	+	?
Wood, 2012 Canada	Twins and triplets	ART: I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42 C: 42	90 mg progesterone vaginal gel 8%/d 25/42 (60%) RR 0.93 (95% CI 0.66-1.30) p=0.823	Placebo 27/42 (64%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.1.1.a. Intervention progesterone
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Aboulghar 2012 Egypt	Mixed Singletons 215/306 (70.3%) DC twins 91/306 (29.7%)	ART pregnancies	Randomised I:161 C:152 Analysed I:161 (112 singletons, 49 sets of twins) C:145 (103 singletons, 42 sets of twins)	400 mg vaginal natural progesterone/d Singleton and twins 55/161 (34.2%) OR 0.672 (95% CI 0.42-1.0) Singletons 24/112 (21.4%) OR 0.53 (95% CI 0.28-0.973) p= 0.039 Twins 31/49 (63.3%) OR 0.86 (95% CI 0.36–2)	Placebo Singleton and twins 63/145 (43.3%) Singletons 35/103 (34.0%) Twins 28/42 (66.7%)	PO: any PTB (<37 w and <34 w for singletons and twins combined)	?	?	-
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0)	Twin pregnancy, previous sPTD, uterine mal-formation	I: 84 C: 76	100 mg vaginal progesterone/d Singletons and twins 32/80 (40%) Singletons 12/41 (29.3%) RR 0.68 (95% CI 0.38-1.23) (from MA) Twins 20/39 (51.3%) RR 0.65 (95% CI 0.45-0.94) (from MA)	Placebo Singletons and twins 40/70 (57.2%) OR 2 (95% CI 1.04–3.83) p=0.036 Singletons: 18/42 (42.9%) Twins 22/28 (78.6%) OR 3.48 (95% CI 1.16–10.46)	PO? Numbers for singletons calculated from table 3 (no statistics) OR in article for controls vs intervention. RR for intervention vs controls from MA in App. 5.1.1 and 5.1.2	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.1.a. Intervention progesterone
Outcome variable: Any preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d 148/406 (36.5%) Adj. RR 0.97 (95% CI 0.81–1.17) p=0.765 Adjusted for GA at randomisation, GA of previous PTB, and reason for previous PTB If no twin hade the outcome: 148/390 (37.9%)	Placebo 146/393 (37.2%) If no twin hade the outcome: 146/385 (37.9%)	Not PO NB neonatal outcome	+	+	?
Progesterone in comparison with other interventions									
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 mm in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 22/42 (52.4%) RR 1.14 (95% CI 0.77-1.68) No p value Post hoc analysis TVS CL ≤15 mm 10/22 (45.5%) RR 0.52 (95% CI 0.32-0.86) No p-value	17-OHPC 250 mg weekly 22/37 (59.4%) Post hoc analysis TVS CL ≤15 mm 13/15 (86.7%)	Not PO No indicated PTB i.e. any PTB= sPTB	+	?	-
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 73/148 (49%) RR 0.81 (95% CI 0.66-0.99) p=0.05 Subgroup analysis TVS CL ≤28 mm n=47 23/47 (49%) RR 0.66 (95% CI 0.46-0.94) p=0.02	Vaginal progesterone 400 mg/d 91/149 (61%) Subgroup analysis TVS CL ≤28 mm n=35 26/35 (74%)	Not PO	?	?	?

17-OHPC; 17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, HIV; human immunodeficiency virus I; intervention, im; intramuscular, IUFD; intrauterine fetal death, MA; meta-analysis, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NS; not significant, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.1.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 4/52 (7.7%) No p value	Placebo 5/47 (10.6%)	Not PO	?	-	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578	17-OHPC 250 mg im/w 209/1112 (18.8%) RR 1.10 (95% CI 0.88-1.36) No p value	Placebo 98/572 (17.1%)	Not PO	+	?	?
Glover, 2011 USA	Singletons	Previous singleton sPTB (<37 w)	I: 20 C:16	400 mg oral micronized progesterone/d 5/19 (26.3%) RR 0.55 (95% CI 0.26-1.16) p=0.15	Placebo 8/14 (57.1%)	PO	+	?	-
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 54/327 (16.5%) RR 0.99 (95% CI 0.70-1.40) No p value	Placebo (castor oil) 55/330 (16.7%)	Not PO	?	+	+
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 90/306 (29.4%) RR 0.65 (95% CI 0.51-0.83) No p value	Placebo (castor oil) 69/153 (45.1%)	Not PO	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 25/393 (6%) RR 1.0 (95% CI 0.6-1.6) No p value	Placebo 26/392 (7%)	Not PO	?	+	?
Van Os, 2015 The Netherlands	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 6/41 (15%) RR 1.17 (95% CI 0.39-3.52) No p value	Placebo 5/39 (13%)	Not PO	+	?	-
Rehal, 2021 UK (+5 other European countries)	Twins	MC: I: 23% C: 23% ART: I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 161/413 (39.0%) OR 1.36 (95% CI 1.00-1.83) No p value	Placebo 137/402 (34.1%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.1.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone/d 48/97 (49.5%) I2: 400 mg vaginal progesterone/d 44/97 (45.4%) I1 + I2: 92/194 (47.4%) I1 vs I2 vs C= NS I1+I2 vs C= NS I1 vs I2=NS No other statistics presented	Placebo 47/96 (49.0%)	Not PO Numbers calculated for sPTB, from numbers for indicated PTB in table 2	?	?	-
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets I: 2 (5%) C: 1 (2%)	I: 42 C: 42	90 mg progesterone vaginal gel 8%/d 17/42 (40%) RR 1.04 (95% CI 0.61-1.76) p=0.893	Placebo 16/42 (38%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.1.1.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 37 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Progesterone in comparison with other intervention									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 27/125 (22%) RD (rate in progesterone group minus the rate in pessary group) 0.41% (-9.90 to 10.73) p=0.94	200 mg vaginal progesterone/d 25 /118 (21%)	Not PO	+	?	?
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (history of sPTB, second trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 22/42 (52.4%) RR 1.14 (95% CI 0.77-1.68) No p value Post hoc analysis TVS CL ≤15 mm 10/22 (45.5%) RR 0.52 (95% CI 0.32-0.86) No p value	17-OHPC 250 mg/w 22/37 (59.4%) Post hoc analysis TVS CL ≤15 mm 13/15 (86.7%)	Not PO There was no indicated PTB i.e. any PTB= sPTB	+	?	-

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CI; confidence interval, CL cervical length, d; day, DCDA; dichorionic diamniotic, HIV; human immunodeficiency virus, I; intervention, im; intramuscular, MAR; medically assisted reproduction, PO; primary outcome, PTB; preterm birth, RD; risk difference, RR; risk ratio, sPTB; spontaneous preterm birth, TVS; transvaginal scan. w; week

Project: Prevention of preterm birth
Appendix 4.1.2.a. Intervention progesterone
Outcome variable: Any preterm birth before 35 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 122/1113 (11.0%) RR 0.95 (95% CI 0.71-1.26) No p value	Placebo 66/574 (11.5%)	PO	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 44/327 (13.5%) RR 0.84 (95% CI 0.58-1.21) No p value	Placebo (castor oil) 53/330 (16.1%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 34/235 (14.5%) RR 0.62 (95% CI 0.42-0.92) p=0.016	Placebo 52/223 (23.3%)	Not PO	?	?	+
Jabeen, 2012 Pakistan	Singletons	Previous sPTB	I: 30 C: 30	17-OHPC 250 mg im/w 6/30 (20%) No statistics	Placebo (inert oil) 9/30 (30%)	Not PO	?	-	-
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 63/306 (20.6%) RR 0.67 (95% CI 0.48-0.93) No p value	Placebo (castor oil) 47/153 (30.7%)	Not PO	?	?	?
O'Brien 2007 USA +4 other countries	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 70/309 (22.7%) OR 0.9 (95% CI 0.61-1.34) No p value	Placebo 80/302 (26.5%)	Not PO	?	?	?
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16 C: 14	17-OHPC 250 mg im/w 7 /16 (44%) p=0.117 No RR or OR	Placebo 11/14 (79%)	PO	?	?	-
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w 135/325 (41.5%)* RR 1.1 (95% CI 0.9–1.3)	Placebo 123/330 (37.3%)*	PO *PTB or fetal death <35 w (fetal death includes miscarriage, termination of pregnancy, and stillbirth)	+	?	+

Project: Prevention of preterm birth
Appendix 4.1.2.a. Intervention progesterone
Outcome variable: Any preterm birth before 35 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Wood, 2012 Canada	Twins and triplets	ART: I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42 C: 42	90 mg progesterone vaginal gel 8%/d 13/42 (31%) RR 0.87 (95% CI 0.47-1.59) p=0.817	Placebo 15/42 (36%)	Not PO	+	?	+
Caritis, 2009 USA SSTARS	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w 59/71 (83.1%) RR 1.0 (95% CI 0.9–1.1) No p value	Placebo 53/63 (84.1%)	PO	?	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR: I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w 43/56 (76%) RR 0.9 (95% CI 0.7–1.1) p=0.56	Placebo 21/25 (84%)	Not PO Errata, corrected 21, in article it was 13	+	?	?
Progesterone in comparison with other interventions									
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 16/42 (38.1%) RR 1.14 (95% CI 0.67-1.93) No p value Post hoc analysis TVS CL ≤15 mm 7/22 (31.8%) RR 0.48 (95% CI 0.24-0.97) No p value	17-OHPC 250 mg weekly 16/37 (43.2%) Post hoc analysis TVS CL ≤15 mm 10/15 (66.7%)	Not PO There was no indicated PTB i.e. any PTB = sPTB	+	?	-

17-OHPC; 17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, BMI; body mass index, C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, DCDA; dichorionic diamniotic, DC; dichorionic, GA; gestational age, I; intervention, im; intramuscular, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.2.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 35 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 93/1113 (8.4%) RR 0.93 (95% CI 0.67-1.30) No p value	Placebo 51/574 (8.9%)	Not PO	+	?	?
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w 101/324 (31.2)* RR 1.2 (95% CI 0.9-1.5) No p value	Placebo 86/330 (26.1)*	Not PO *sPTB or fetal death <35 w (fetal death includes miscarriage, termination of pregnancy, and stillbirth)	+	?	+
Caritis, 2009 USA STTARS	Triplets	Around 70% ART, 30% DC or unknown chorionicity	I: 71 C: 63	17-OHPC 250 mg im/w 34/71 (48%) RR 1.1 (95% CI 0.8-1.6) No p value	Placebo 27 /63 (43%)	Not PO	?	?	?
Progesterone in comparison with other interventions									
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 16/42 (38.1%) RR 1.14 (95% CI 0.67-1.93) No p value Post hoc analysis TVS CL ≤15 mm 7/22 (31.8%) RR 0.48 (95% CI 0.24-0.97) No p value	17-OHPC 250 mg im/w 16/37 (43.2%) Post hoc analysis TVS CL ≤15 mm 10/15 (66.7%)	PO There was no indicated PTB i.e. any PTB = sPTB	+	?	-

17-OHPC; 17-α-hydroxyprogesterone caproate, ART, assisted reproductive technology, C; control, CI, confidence interval, CL; cervical length, DC; dichorionic, I; intervention, im; intramuscular, MC; monochorionic, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB; spontaneous preterm birth, TVS transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Randomised controlled trials									
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 1/52 (1.9%)? No statistics for <34 w	Placebo 1/47 (2.1%)?	Incorrect numbers in the article?	?	-	-
Ali, 2020 Egypt	Singletons	Indication for cerclage: previous second trimester loss, sPTD (<34 w) or short cervix (<25 mm)	I: 121 C:121	400 mg progesterone vag (pessary)/d 4/97 (4.2%) p=0.005	Placebo 12/75 (16%)	Progesterone was used as an adjuvant after cerclage NB: PTB 28-34 weeks, i.e. excludes those who stopped treatment before 28 w, those who were lost to follow-up, and those who had an abortion before 28 w	?	?	?
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg progesterone supp vag/d 9/50 (18%) RR 0.43 (95% CI 0.22-0.84) p=0.04	Placebo 21/50 (42%) RR 2.33 (95% CI 1.19–4.58) p=0.009	Results also for previous PTB and, previous PTB and short TVS CL RR calculated for I vs C	-	?	-
Da Fonseca, 2003 Brazil	Singletons	Previous sPTB, prophylactic cerclage, uterine malformations	I: 81 C:76	100 mg vaginal progesterone/d 2/72 (2.8%) p=0.002	Placebo 13/70 (18.6%)	Not PO	?	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 41/327 (12.5%) RR 0.86 (95% CI 0.58-1.27) p=0.45 TVS CL <15 mm RR 0.86 (95% CI 0.44-1.67) TVS CL ≥15 mm RR 0.91 (95% CI 0.58-1.42) Interaction p value 0.82	Placebo (castor oil) 48/330 (14.5%)	Not PO RR and p-values for all TVS CLs calculated	?	+	+
Hayashi, 2021 Japan TROPICAL	Singletons	Short TVS CL 25-<30 mm Previous PTB I: 11.9% C: 16.7%	I: 59 C: 60	200 mg vaginal progesterone/d 0/59 (0%) p=1.0 No RR	Placebo 1/60 (1.7%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Majhi, 2009 India	Singletons	Previous sPTB	I: 50 C: 50	100 mg vaginal progesterone/d 2/50 (4%) RR 0.666 (95% CI 0.116–3.82) p= 0.64	No placebo 3/50 (6%)	PO≤34 w (PO also <37 w)	?	?	?
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg progesterone/day 96/600 (16%) aOR 0.86 (95% CI 0.61-1.22) p=0.67 CI for OR and p value adjusted for multiple primary outcomes	Placebo 108/597 (18%)	PO = <34 w or IUFD	+	+	+
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 14/399 (4%) RR 0.9 (95% CI 0.4-1.8) No p value	Placebo 16/401 (4%)	Not PO	?	+	?
Rai, 2009 India	Singletons	Previous sPTB	I: 75 C:75	200 micronized oral progesterone/d 22/74 (29.7%) No RR, OR or p value	Placebo 37/74 (50%)		-	?	?
Saghafi, 2011 Iran	Singletons	Previous PTB	I: 50 C: 50	17-OHPC 250 mg im/w 8/50 (16%) No RR, OR or p value	No placebo 18/50 (36%)	Not stated but assumed to be only singletons	-	-	-
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg vaginal micronized progesterone/d 5/41 (12%) RR 0.81 (95% CI 0.27–2.44) No p value	Placebo 6/39 (15%)	Not PO	+	?	-
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16 C: 14	17-OHPC 250 mg im/w 5/16 (31.3%) p=0.217 No RR or OR	Placebo 8/14 (57.1%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d 44/189 (23.3%) OR 1.45 (95% CI 0.85-2.49) No p value Subgroup analysis TVS CL ≤25mm n=22 16/22 (71.7%) OR 0.80(95% CI 0.1-4.89) No p value	Placebo 33/191 (17.3%) Subgroup analysis TVS CL ≤25mm n=13 10/13 (76.9 %)	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 31/160 (19%) RR 1.4 (95% CI 0.7–2.6) p=0.32	Placebo (1 mL castor oil) 11/78 (14%)	Not PO	+	?	?
Klein, 2011 Subgroup analysis of Rode (PREDICT) 2011 Austria & Denmark	Twins	Short cervix TVS CL ≤30 mm ≤10th percentile) or Previous PTB <34 w or late miscarriage >12 w	TVS CL ≤30 mm: I:17 C:30 Previous PTB <34 w or late miscarriage: I:10 C:18	200 mg vaginal progesterone/d TVS CL ≤30 mm 5/17 (29.4%) OR 0.63 (95% CI 0.18-2.23) p=0.47 Previous PTB 3/10 (30.0%) OR 1.50 (95% CI 0.26-8.64) p=0.65	Placebo TVS CL ≤30 mm 12/30 (40%) Previous PTB 4/18 (22.2%)	PO Subgroup analysis Assessment of directness and study limitations refer to the original study and not to the subgroups	+	+	-

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Megli, 2020 USA IPD of Rouse, 2007 (MFMU study) and Combs, 2011(Obstetrix Trial) trials	Twins DA	Previous PTB	I:34 I:32	17-OHPC 250 mg im/w 10/34 (29.4 %) p=0.09	16/32 (50%)	Not PO IPD with data from Rouse 2007 and Combs 2011 History of PTB not defined Assessment of directness, study limitations, and precision refer to the original studies and not to the subgroups	+	?	-
Norman, 2009 UK (9 hospitals) STOPPIT	Twins	MC twins I: 46/247 C: 45/247 No MA twins	I: 247 C: 247	90 mg vaginal progesterone /day (Crinone) 61/247 (24.7%) OR 1.36 (95% CI 0.89-2.09) p=0.16	Placebo 48/247 (19.4%)	PO = <34 w or IUFD (one or both twins) NB: Numbers slightly different in EPPPIC (only PTB and not IUFD?) I: 59/245 C: 45/245 RR: 1.28 (95% CI 0.91-1.80)	+	+	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 97/582 (16.7%)* OR 1.10 (95% CI 0.80-1.51) No p value 82/567 (14.5%)** OR 1.28 (95% CI 0.90-1.82) No p value	Placebo 93/587 (15.8%)* 67/561 (11.9%)**	Not PO *any birth after randomisation to 34 w **any birth 24-34 w	+	+	?
Rode, 2011 PREDICT Austria & Denmark	Twins	DA twins MC I:12.9% C: 16.6% MAR I:46.7% C:47.5%	I: 334 C: 343	200 mg progesterone pessary (Utrogestan)/d 51/334 (15.3%) OR 0.8 (95% CI 0.5-1.2) No p value	Placebo pessary 63/341 (18.5%)	PO	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C:96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d 13/97 (13.4%) I2: 400 mg vaginal progesterone (pessary)/d 10/97 (10.3%) I1 + I2: 23/194 (11.9%) I1, I2, C= NS I1+I2 vs C= NS I1 vs I2=NS	Placebo 13/96 (13.5%)	Not PO	?	?	-
Aboulghar 2012 Egypt	Mixed Singletons 215/306 (70.3%) DC twins 91/306 (29.7%)	ART pregnancies	Randomised I:161 C:152 Analysed I:161 (112 singletons, 49 sets of twins) C:145 (103 singletons, 42 sets of twins)	400 mg vaginal natural progesterone/d Singletons and twins 11/161 (8.2%) OR 0.686 (95% CI 0.3-1.56) Singletons 7/112 (3.3%) OR 0.68 (95% CI 0.15-3.11) No p value Twins 8/49 (16.3%) OR 0.62 (95% CI 0.2–1.76) No p value	Placebo Singletons and twins 14/145 (9.7%) Singletons 4/103 (3.9%) Twins 4 /42 (23.8%)	PO: any PTB (<37 w and <34 w for singletons and twins combined)	?	?	-
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0)	Twin pregnancy, previous sPTD, uterine mal-formation	I: 84 C: 76	100 mg vaginal progesterone/d Singletons and twins 7/80 (8.8%) Singletons 3/41 (7.3%) RR 1.02 (0.22-4.79) p=0.98 Twins 4/39 (10.3%)	Placebo Singletons and twins 17//70 (24.3%) OR 3.35 (95% CI 1.3–8.63) p=0.010 Singletons: 3/42 (7.1%) Twins 7/28 (25%) OR 2.9 (95% CI (0.76–11.2) P=0.200	Numbers for singletons calculated from table 3 (no statistics). RR calculated Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Fonseca, 2007 Brazil (multicenter inter-national, UK [5 centers], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 C: 125	200 mg vaginal progesterone /day (Utrogestan) 26/125 (20.8%) aRR 0.60 (0.35-0.94) p=0.02 RR adjusted for maternal age, BMI, smoking status, race, history of preterm birth, and cervical length at the time of randomisation.	Placebo 45/125 (36%)	Not PO See Stewart, 2021 (EPPPIC) for data on singletons and twins	?	?	+
Systematic reviews with individual patient meta-analysis (Only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles and not to the subgroups presented below									
EPPPIC, 2021	**Singletons**								
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 89/1112 (8.0%) RR 1.04 (95% CI 0.74-1.47)	Placebo 44/572 (7.7%)	Not PO	+	?	?
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5%) Twins n=12 (1.5%)	Previous sPTD <37 w	Singletons I: 390 C: 385	100 mg vaginal progesterone pessary/d Singletons 64/390 (16.4%) RR 1.02 (95% CI 0.74-1.40)	Placebo Singletons 62/385 (16.1%)	Not PO	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	Singletons I: 114 C: 112	200 mg vaginal progesterone /day (Utrogestan) Singletons 22/114 (19.3%) RR 0.57 (95% CI 0.36-0.90)	Placebo Singletons 38/112 (33.9%)	Not PO	?	?	+
Glover, 2011 USA	Singletons	Previous singleton sPTB (<37 w)	I: 20 C:16	400 mg oral micronized progesterone/d 3/19 (15.8%) RR 0. 74 (95% CI 0.17-3.12)	Placebo 3/14 (21.4%)	Not PO	+	?	-
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 26/235 (11.1%) RR. 0.57 (95% CI 0.37-0.90)	Placebo 43/223 (19.3%)	Not PO	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 49/306 (16.0%) RR 0.63 (95% CI 0.43-0.91)	Placebo (castor oil) 39/153 (25.5%)	Not PO	?	?	?
O'Brien, 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8% /d 49/313 (15.7%) RR 0.83 (95% CI 0.59-1.17)	Placebo 58/307 (18.9%)	Not PO	?	?	?
	Multifetal pregnancies								
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w 44/194 (22.7%) RR 0.82 (95% CI 0.54–1.24)	Placebo (castor oil) 26/94 (27.7%)	Not PO	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	Twins I: 11 C: 13	200 mg vaginal progesterone /day (Utrogestan) Twins 4/11 (36.4%) RR 0.68 (95% CI 0.27-1.71)	Placebo Twins 7/13 (53.8%)	Not PO	?	?	+
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w 33/56 (58.9%) RR 0.82 (95% CI 0.59–1.14) p=0.56	Placebo 18/25 (72.0%)	Not PO	+	?	?
Caritis, 2009 USA SSTARS	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w 48/71 (67.6%) RR 1.06 (95% CI 0.83-1.36)	Placebo 40/63 (63.5%)	Not PO	?	?	?
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5%) Twins n=12 (1.5%)	Previous sPTB <37 w	Twins I: 8 C: 4	100 mg vaginal progesterone pessary/d Twins 4/8 (50%) RR 1.00 (95% CI 0.30-3.32)	Placebo Twins 2/4 (50%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Lim, 2011 The Netherlands AMPHIA	Twins and triplets+	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 C: 335	17-OHPC 250 mg im/w 80/336 (23.8%) RR 1.08 (95% CI 0.81-1.42)	Placebo 73/330 (22.1%)	Not PO	+	+	?
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w 93/325 (28.6%)* RR 1.05 (95% CI 0.82-1.34)	Placebo 90/330 (27.3%)*	PO *in original article PTB or fetal death <35 w (fetal death includes miscarriage, termination of pregnancy, and stillbirth) Unclear whether EPPPIC included only PTB and not IUFD.	+	?	+
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets I: 2 (5%) C: 1(2%)	I: 42 C: 42	90 mg progesterone vaginal gel 8%/d 8/42 (19.0%) RR 0.89 (95% CI 0.38-2.08)	Placebo 9/42 (21.4%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.1.3.a. Intervention progesterone
Outcome variable: Any preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Progesterone in comparison with other interventions									
Dang 2019 Vietnam (single centre)	Twins	Short TVS-CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 24/148 (16%) RR 0.73 (95% CI 0.46-1.18) p=0.24 Subgroup analysis TVS CL ≤28 mm n=47 10/47 (21%) RR 0.47 (95% CI 0.24-0.90) p=0.03	Vaginal progesterone 400 mg/d 33/149 (22%) Subgroup analysis TVS CL ≤28 mm n=35 16/35 (46%)	PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, aOR; adjusted odds ratio, aRR; adjusted relative risk, ART; assisted reproductive technology, BMI; body mass index, C; control, CL; cervical length, d; day, I; intervention, DA, diamniotic, DCDA; dichorionic diamniotic, FFN; fetal fibronectine, im; intramuscular, IUFD; intrauterine fetal death, MA; monoamniotic, MAR; medically assisted reproduction, MC; monochorionic, NNT; number needed to treat, PO; primary outcome, sPTB; spontaneous preterm birth, RR; risk ratio, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.3.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg vaginal micronized progesterone/d 3/41 (7%) RR 0.73 (95% CI 0.17-3.057) No p value	Placebo 4/39 (10%)	Not PO	+	?	-
Brizot, 2015 Brazil	Twins DCDA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d 35/189 (18.5%) OR 1.32 (95% CI 0.24-2.37) No p value	Placebo 28/191 (14.6%)	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66%, C:58% Prior PTB: I: 12%, C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 16/160 (10%) RR 0.9 (95% CI 0.4-1.9) p=0.72	Placebo (1 mL castor oil) 9/78 (11.5%)	Not PO	+	?	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 56/541 (10.4%)* OR 1.35 (95% CI 0.88-2.05) No p value	Placebo 44/538 (8.2%)*	PO sPTB 24-34 w	+	+	?
Rode, 2011 PREDICT Austria & Denmark	Twins	DA twins MC I:12.9% C: 16.6% MAR I:46.7% C:47.5%	I: 334 C: 343	200 mg progesterone pessary (Utrogestan)/d 42/334 (12.6%) OR 0.8 (95% CI 0.5-1.2) No p value	Placebo pessary 53/341 (15.5%)	Not PO	+	+	+
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 C: 125	200 mg vaginal progesterone /day (Utrogestan) 24/125 (19.2%) aRR 0.56 (0.32-0.91), p=0.02 RR adjusted for maternal age, BMI, smoking status, race, history of preterm birth, and cervical length at the time of randomisation.	Placebo 43/125 (34.4%)	PO	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.3.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 34 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centers)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 18/125 (14%) RD (rate in progesterone group minus the rate in pessary group) -0.01% (95% CI -8.84 to 8.83) p=0.99	200 mg vaginal progesterone/d 17 /118 (14%)	PO	+	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, BMI; body mass index, C; control, CL; cervical length, d; day, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, I; intervention, im; intramuscular, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, OR; odds ratio, PTB; preterm birth, RD; risk difference, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.4.a. Intervention progesterone
Outcome variable: Any preterm birth before 33 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/Twins / Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Randomised controlled trials									
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 21/235 (8.9%) RR 0.55 (95% CI 0.33-0.92) p=0.020	Placebo 36/223 (16.1%)	PO	?	?	+
Systematic reviews with individual patient meta-analysis (only articles with results not shown in original articles are included here) Assessment of Directness, Study limitations and Precision refer to the original articles and not to the subgroups presented below									
Romero, 2018	**Singletons**								
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0)	Twin pregnancy, previous sPTD, uterine malformation	Singletons with TVS CL ≤25 mm I: 4 C: 4	100 mg vaginal progesterone/d Singletons 0/4 (0%) RR 0.33 (95% CI 0.02-6.37)	Placebo Singletons 1/4 (25%)	Not PO 9.6% of all randomised singleton (8/83)	?	?	-
Fonseca, 2007 Brazil (multicenter inter-national, UK [5 centers], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	Singletons I: 114 C: 112	200 mg vaginal progesterone /day (Utrogestan) Singletons 19/114 (16.7%) RR 0.60 (95% CI 0.36-1.00)	Placebo Singletons 31/112 (27.7%)	Not PO 100% of all randomised singletons	?	?	+
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	Singletons with TVS CL ≤25 mm I:133 C:118	200 mg progesterone/day 29/133 (21.8%) RR 0.74 (95% CI 0.48-1.12)	Placebo 35/118 (29.7%)	Not PO 20.4% of all randomised singletons (251/1228)	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.4.a. Intervention progesterone
Outcome variable: Any preterm birth before 33 gestational weeks

* + No or minor problems
? Some problems
\- Major problems

Author, year Country Trial acronym	Singletons/Twins / Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	Singletons with TVS CL ≤25 mm I: 12 C: 19	90 mg vaginal progesterone gel 8%/d 1/12 (8.3%) RR 0.40 (95% CI 0.05-3.13)	Placebo 4/19 (21.1%)	Not PO 4.7% of all randomised singletons (31/659)	?	?	?
Romero, 2017	**Twins**								
Brizot, 2015 Brazil	Twins DA	MC I: 25%C: 19% Only naturally conceived, no history of PTB	Twins with TVS CL ≤25 mm I: 15 C: 6	200 mg vaginal natural progesterone/d 9/15 (60%) RR 0.90 (95% CI 0.45-1.81)	Placebo 4/6 (66.7%)	Not PO 5.4% of all randomised twins (21/390)	?	?	-
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0)	Twin pregnancy, previous sPTD, uterine malformation	Twins with TVS CL ≤25 mm I:5 C:2	100 mg vaginal progesterone/d 1/5 (20%) RR 0.51 (95% CI 0.17-1.50)	Placebo 1/2 (50%)	Not PO 10.4% of all randomised twins (7/67)	?	?	-
Fonseca, 2007 Brazil (Multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	Twins with TVS CL ≤15 mm I: 11 C: 13	200 mg vaginal progesterone /d (Utrogestan) 3/11 (27.3%) RR 0.51 (95% CI 0.17-1.50)	Placebo 7/13 (53.8%)	Not PO 100% of all randomised twins (24/24)	?	?	+
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	Twins with TVS CL ≤25 I: 7 C: 14	200 mg vaginal progesterone/d (pessary) 3/7 (42.9%) RR 1.20 (95% CI 0.40-3.63)	Placebo 5/14 (35.7%)	Not PO 3.1% of all randomised twins (21/677)	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.4.a. Intervention progesterone
Outcome variable: Any preterm birth before 33 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/Twins / Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	Twins with TVS CL ≤25 I:5 C:1	I1: 200 mg vaginal progesterone (pessary) /d or I2: 400 mg vaginal progesterone (pessary)/d 3/5 (60%) 0.78 (95% CI 0.27-2.22) I1 vs I2=NS	Placebo 1/1 (100%)	Not PO 2.1% of all randomised twins (6/290)	?	?	-
Romero, 2022 Updated IPD MA of Romero 2017	**Twins**								
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	Twins with TVS CL ≤25 I: 9 C: 7	600 mg vaginal progesterone/d 1/9 (11.1%) OR 0.13 (95% CI 0.02-0.84) No p value	Placebo 6/7 (85.7%)	Not PO	+	+	?

C; control, CL; cervical length, d; day. DA; diamniotic, DCDA; diamniotic dichorionic, FFN; fetal fibronectin, im; intramuscular, I; intervention, MAR; medically assisted reproductive medicine, MC; monochorionic, NS; not significant, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB, spontaneous preterm birth, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.5.a. Intervention progesterone
Outcome variable: Any preterm birth before 32 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 54/1116 (4.8%) RR 0.92 (95% CI 0.60-1.42) No p value	Placebo 30/574 (5.2%)	Not PO NB denominator more than in outcome <37 w	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 28/327 (8.6%) RR 0.88 (95% CI 0.54-1.43) No p value	Placebo (castor oil) 32/330 (9.7%)	Not PO	?	+	+
Jabeen, 2012 Pakistan	Singletons	Previous sPTB	I: 30 C: 30	17-OHPC 250 mg/w 4/30 (13.33%) No statistics	Placebo (inert oil) 7/30 (23.33%)	Not PO	?	-	-
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 35/306 (11.4%) RR 0.58 (95% CI 0.37-0.91) No p value	Placebo (castor oil) 30/153 (19.6%)	Not PO	?	?	?
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 31/309 (10.0%) OR 0.9 (95% CI 0.52-1.56) No p value	Placebo 34/302 (11.3%)	PO ≤32 w	?	?	?
Rai, 2009 India	Singletons	Previous sPTB	I: 75 C:75	200 micronized oral progesterone/d 2/74 (2.7%) No RR, OR or p value	Placebo 18/74 (24.3%)	Not PO	-	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg vaginal micronized progesterone/d 3/41 (7%) RR 0.58 (95% CI 0.14-2.30) No p value	Placebo 5/39 (13%)	Not PO	+	?	-
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w 18/194 (9.3%) RR 0.5 (95% CI 0.3-1.1) p=0.09	Placebo (castor oil) 15/94 (16.0%)	Not PO	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d 22/189 (11.6%) OR 1.34 (95% CI 0.65-2.80) No p value	Placebo 17/191 (8.9%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.5.a. Intervention progesterone
Outcome variable: Any preterm birth before 32 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 15/160 (9%) RR 1.8 (95% CI 0.6–5.3) p=0.32	Placebo (1 mL castor oil) 4/78 (5%)	Not PO	+	?	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 53/582 (9.1%)* OR 0.81 (95% CI 0.55-1.20) No p value 38/567 (6.7%)** OR 0.97 (95% CI 0.61-1.55) No p value	Placebo 65/587 (11.1%)* 39/561 (7.0%)**	Not PO *any birth after randomisation to 32 w **any birth 24-32 w	+	+	?
Rode, 2011 PREDICT Austria & Denmark	Twins	DA twins MC I:12.9% C: 16.6% MAR I:46.7% C:47.5%	I: 334 C: 343	200 mg progesterone pessary (Utrogestan)/d 24/334 (7.2%) OR 0.8 (95% CI 0.4-1.3) No p value	Placebo pessary 31/341 (9.1%)	Not PO	+	+	+
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w 55/325 (16.9%)* RR 1.2 (95% CI 0.8–1.7)	Placebo 48/330 (14.5%)*	*PTB or fetal death <32 weeks (fetal death includes miscarriage, termination of pregnancy, and stillbirth)	+	?	+
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C:96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d 3/97 (3.1%) I2: 400 mg vaginal progesterone (pessary)/d 7/97 (7.2%) I1 + I2: 10/194 (5.2%) I1 vs I2 vs C= NS I1+I2 vs C= NS I1 vs I2=NS	Placebo 6/96 (6.3%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.5.a. Intervention progesterone
Outcome variable: Any preterm birth before 32 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w 29/71 (41%) RR 1.4 (95% CI 0.8–2.2) No p value	Placebo 19/63 (30%)	PTB< 32 w or fetal loss Not PO	?	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w 19/56 (34%) RR 0.7 (95% CI 0.4–1.1) p=0.15	Placebo 13/25 (52%)	Not PO	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multiple pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 C: 335	17-OHPC 250 mg im/w 48/336 (14%) RR 1.37 (95% CI 0.91–2.05) No p value	Placebo 34/335 (10%)		+	+	?

Project: Prevention of preterm birth
Appendix 4.1.5.a. Intervention progesterone
Outcome variable: Any preterm birth before 32 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Keeler, 2009a USA	Singletons	Short TVS-CL ≤25 in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 15/42 (35.7%) RR 0.98 (95% CI 0.54-1.79) No p-value Post hoc analysis TVS CL ≤15 mm 7/22 (31.8%) RR 0.60 (95% CI 0.27-1.29) No p-value	17-OHPC 250 mg weekly 13/37 (35.1%) Post hoc analysis TVS CL ≤15 mm 8/15 (53.3%)	Not PO There was no indicated PTB i.e. any PTB=sPTB	+	?	-

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, d; day, DA; diamniotic. DCDA; dichorionic diamniotic, , DC; dichorionic, GA; gestational age, I; intervention, im; intramuscular, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, OR; odds ratio, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w: week

Project: Prevention of preterm birth
Appendix 4.1.5.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 32 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 38/1116 (3.4%) RR 0.88 (95% CI 0.52-1.48) No p value	Placebo 22/574 (3.8%)	Not PO NB Different numbers in denominator for different gestational week.	+	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg vaginal micronized progesterone/d 1/41 (2.4%) RR 0.33 (95% CI 0.035-2.99) No p value	Placebo 3/39 (7.7%)	Not PO	+	?	-
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 25/554 (4.5%)* OR 1.05 (95% CI 0.59-1.86) No p value	Placebo 24/546 (4.4%)*	Not PO *any birth 24-32 w	+	+	?
Other interventions in comparison with progesterone									
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 mm in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 15/42 (35.7%) RR 0.98 (95% CI 0.54-1.79) No p-value Post hoc analysis TVS CL ≤15 mm 7/22 (31.8%) RR 0.60 (95% CI 0.27-1.29) No p-value	17-OHPC 250 mg/w 13/37 (35.1%) Post hoc analysis TVS CL ≤15 mm 8/15 (53.3%)	Not PO There was no indicated PTB i.e. any PTB=sPTB	+	?	-

17-OHPC; 17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, d; day, C; control, CI; confidence interval, CL; cervical length, I; intervention, im; intramuscular, MC; monochorionic, NB; nota bene, sPTB; spontaneous preterm birth, OR; odds ratio, RR; risk ratio, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.6.a. Intervention progesterone
Outcome variable: Any preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	No. of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 15/327 (4.6%) RR 0.69 (95% CI 0.36-1.30) No p value	Placebo (castor oil) 22/330 (6.7%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 12/235 (5.1%) RR 0.50 (95% CI 0.25-0.97) p=0.036	Placebo 23/223 (10.3%)	Not PO	?	?	+
Hayashi, 2021 Japan TROPICAL	Singletons	Short TVS CL 25-<30 mm Previous PTB I: 11.9% C: 16.7%	I: 59 C: 60	200 mg vaginal progesterone/d 0/59 (0%) p=1.0 No RR	Placebo 1/60 (1.7%)	Not PO	?	?	-
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 10/309 (3.2%)* OR 1.07 (95% CI 0.38-2.96) No p value	Placebo 9/302 (3.0%)*	Not PO * ≤28 w	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 3/399 (1%) No statistics	Placebo 5/401 (1%)	Not PO	?	+	?
Rai, 2009 India	Singletons	Previous sPTB	I: 75 C:75	200 micronized oral progesterone/d 0/74 (0%) p=0.25	Placebo 3/74 (4.1%)	Not PO	-	?	?
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w 8/194 (4.1%) RR 0.5 (95% CI 0.2-1.3) p=0.13	Placebo (castor oil) 8/94 (8.5%)	Not PO	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d 10/189 (5.3%) OR 1.72 (95% CI 0.55-5.88) No p value	Placebo 6/191 (3.1%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.6.a. Intervention progesterone
Outcome variable: Any preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	No. of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C: 58% Prior PTB: I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 3/160 (2%) RR 1.5 (95% CI 0.2–14.0) p=1.0	Placebo (1 mL castor oil) 1/78 (1%)	Not PO	+	?	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 23/582 (4.0%)* OR 0.65 (95% CI 0.38-1.13) No p value 8/567 (1.4%)** OR 0.89 (95% CI 0.34-2.33) No p value	Placebo 35/587 (6.0%)* 9/561 (1.6%)**	Not PO *any birth after randomisation to 28 w **any birth 24-28 w	+	+	?
Rode, 2011 PREDICT Austria & Denmark	Twins	DA twins MC I:12.9% C: 16.6% MAR I:46.7% C:47.5%	I: 334 C: 343	200 mg progesterone pessary (Utrogestan)/d 9/334 (2.7%) OR 1.3 (95% CI 0.5-3.6)) No p value	Placebo pessary 7/341 (2.1%)	Not PO	+	+	+
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w 26/325 (8.0%)* RR 1.3 (95% CI 0.8-2.3) No p value	Placebo 20/330 (6.1%)*	Not PO *PTB or fetal death <28 w (fetal death includes miscarriage, termination of pregnancy, and stillbirth)	+	?	+

Project: Prevention of preterm birth
Appendix 4.1.6.a. Intervention progesterone
Outcome variable: Any preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	No. of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C:96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary)/d 1/97 (1.0%) I2: 400 mg vaginal progesterone (pessary)/d 3/97 (3.1%) I1 + I2: 4/194 (2.1%) I1 vs I2 vs C= NS I1+I2 vs C= NS I1 vs I2=NS	Placebo 1/96 (1.0%)	Not PO	?	?	-
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w 7/71 (10%)* RR 0.9 (95% CI 0.3-2.4) No p value	Placebo 7/63 (11%)*	Not PO *PTB <28 w or fetal loss	?	?	?
Combs, 2010	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w 9/56 (16%) RR 2.0 (95% CI 0.5-8.6) p=0.49	Placebo 2/25 (8%)	Not PO	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women C: 335 women	17-OHPC 250 mg im/w 19/336 (6%) RR 1.04 (95% CI 0.56-1.94) No p value	Placebo 18/332 (5%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.6.a. Intervention progesterone
Outcome variable: Any preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	No. of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (history of sPTB, second trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 10/42 (23.8%) RR 0.79 (0.34-1.88) No p-value Post hoc analysis TVS CL ≤15 mm 5/22 (22.7%) RR 0.68 (0.24-1.95) No p-value	17-OHPC 250 mg weekly 7/37 (18.9%) Post hoc analysis TVS CL ≤15 mm 5/15 (33.3%)	Not PO There was no indicated PTB i.e. any PTB=sPTB	+	?	-
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I: 150 C: 150	Arabin pessary 9/148 (6%) RR 1.29 (95% CI 0.50-3.38) p=0.62 Subgroup analysis TVS CL ≤28 mm n=47 4/47 (9%) RR 0.74 (95% CI 0.2-2.77) p=0.72	Vaginal progesterone 400 mg/d 7/149 (5%) Subgroup analysis TVS CL ≤28 mm n=35 4/35 (11%)	Not PO	?	?	?

17-OHPC; 17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, DCDA; dichorionic diamniotic, d: day, DA; diamniotic, DC; dichorionic, GA; gestational age, I; intervention, im; intramuscular, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, OR; odds ratio, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan. w; week

Project: Prevention of preterm birth
Appendix 4.1.6.b. Intervention progesterone
Outcome variable: Spontaneous preterm birth before 28 gestational weeks

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d 8/567 (1.4%)* OR 1.15 (95% CI 0.41-3.21) No p value	Placebo 7/559 (1.3%)*	Not PO *any birth 24-28 w	+	+	?
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 10/125 (8%) RD (rate in progesterone group minus the rate in pessary group) 0.37% (95% CI -6.38 to 7.12) p=0.91	200 mg vaginal progesterone/d 9 /118 (8%)	Not PO	+	?	?
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 mm in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 10/42 (23.8%) RR 0.79 (95% CI 0.34-1.88) No p value Post hoc analysis TVS CL ≤15 mm 5/22 (22.7%) RR 0.68 (95% CI 0.24-1.95) No p value	17-OHPC 250 mg/w 7/37 (18.9%) Post hoc analysis TVS CL ≤15 mm 5/15 (33.3%)	Not PO There was no indicated PTB i.e. any PTB=sPTB	+	?	-

17-OHPC; 17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CI; confidence interval, CL; cervical length, d; day, im; intramuscular, I; intervention, MC; monochorionic, OR; odds ratio, PTB; preterm birth, RD; risk difference, RR; risk ratio, sPTB; spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.7. Intervention progesterone
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Ali, 2020 Egypt	Singletons	Indication for cerclage: previous second trimester loss, sPTB (<34 w) or short cervix (<25 mm)	I: 121 C:121	400 mg vaginal progesterone (pessary)/d Mean ± SD: 37.88 ± 0.81 w n=121 p<0.001	Placebo Mean ± SD: 36.98 ± 1.20 w n=121	Not PO Progesterone was used as an adjuvant after cerclage NB PTB 28-34 weeks, with spontaneous abortion< 28 weeks = primary outcome was excluded	?	?	?
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d Mean ± SD: 35.4±2.7 w n=96 p=0.01	Placebo Mean ± SD: 33.9±2.9 w n=91	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesterone supp /d Mean ± SD: 36.5±3.8 w n=50 p=0.001	Placebo Mean ± SD: 33.6±4.5 w n=50	Not PO	-	?	-
Da Fonseca, 2003 Brazil	Singletons	Previous sPTB, prophylactic cerclage, uterine malformations	I: 81 C:76	100 mg vaginal progesterone/d Mean ± SD: 36 ±3.3 w n=72 p=0.029	Placebo Mean ± SD: 37±2.8 w n=70	Not PO	?	?	?
Glover, 2011 USA	Singletons	Previous singleton sPTB (<37 w)	I: 20 C:16	400 mg oral micronized progesterone/d Mean ± SD: 37.0±2.7 w n=19 p=0.3	Placebo Mean ± SD: 35.9±3.8 w n=14	Not PO In abstract: 35.9±2.6	+	?	-
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w Mean ± SD: 37.6±3.9 n=327 p=0.93	Placebo (castor oil) Mean ± SD: 37.4±4.3 n=330	Not PO	?	+	+

Project: Prevention of preterm birth
Appendix 4.1.7. Intervention progesterone
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Hayashi, 2021 Japan TROPICAL	Singletons	Short TVS CL 25-<30 mm Previous PTB I: 11.9% C: 16.7%	I: 59 C: 60	200 mg vaginal progesterone/d Median (range): 38.9 (36.4-41) w n=59 p=0.694	Placebo Median (range): 39.1 (23.7-41.6) w n=60	Not PO	?	?	–
Ibrahim, 2010 Egypt	Singletons	Previous PTB	I: 25 C: 25	17-OHPC 250 mg/w Mean ± SD: 37.47 ± 1.56 w n=25 p<0.001	Placebo (saline) Mean ± SD: 34.71 ± 2.49 n=25	Not PO	-	-	-
Jafarpour, 2020 Iran	Singletons	Previous PTB	I: 50 C: 50	17-OHPC 250 mg/w Mean ± SD: 35.90 (1.21) n=50 p=0.26	Routine prenatal care Mean ± SD: 35.3 (2.06) n=50	Not PO	?	?	-
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d Mean ± SD: 36.6 ±3.8 w n=309 NS	Placebo Mean ± SD: 36.6±4.2 w n=302	Not PO	?	?	?
Rai, 2009 India	Singletons	Previous sPTB	I: 75 C:75	200 micronized oral progesterone/d Mean ± SD: 36.1±2.66 w n=74 p<0.001	Placebo Mean ± SD: 34.0±3.25 w n=74	Not PO	-	?	?
Saghafi, 2011 Iran	Singletons	Previous PTB	I: 50 C: 50	17-OHPC 250 mg im/w Mean: 36.94 w n=50 p=0.011	No placebo Mean: 35.10 w n=50	Not PO Not stated but assumed to be only singletons No SD or range	-	-	-
Shadab, 2018 Pakistan	Singletons	Previous sPTB	I: 66 C: 66	17-OHPC 250 mg im/w Mean ± SD: 36.35±1.36 w n=66 No p value	Vitamin B im as placebo Mean ± SD: 34.51±3.33 w n=66	Not PO	-	-	-
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w Mean ± SD: 35.1±3.1 w n=194 p=0.21	Placebo (castor oil) Mean ± SD: 34.6±3.8 w n=94	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.7. Intervention progesterone
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16 C: 14	17-OHPC 250 mg im/w Mean ± SD: 33.9±4.1 n=16 p=0.19	Placebo Mean ± SD: 33.1±2.9 n=14	Not PO	?	?	-
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d Mean ± SD: 35.08±3.19 w n=189 No statistics	Placebo Mean ± SD: 35.55±2.85 w n=191	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w Mean ± SD: 35.3±2.5 w n=160 p=0.10	Placebo (1 mL castor oil) Mean ± SD: 35.9±2.3 w n=78	Not PO	+	?	?
Norman, 2009 UK (9 hospitals) STOPPIT	Twins	MC twins I: 46/247 C: 45/247 No MA twins	I: 247 C: 247	90 mg vaginal progesterone /day (Crinone) Mean (SD): 35.4 (3.5) w n=247 mean difference –0.3 (–0.9 to 0.3) w p=0.31	Placebo Mean (SD): 35.7 (3) w n=247	Not PO	+	+	?
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334 C: 343	200 mg vaginal progesterone/d (pessary) Mean ± SD: 252±19.6 d n=334 p=0.43	Placebo Mean ± SD: 251±19.1 d n=341	Not PO	+	+	+
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w Mean ± SD: 34.6±3.9 w n=325 No p value	Placebo Mean ± SD: 34.9±3.6 w n=330	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.1.7. Intervention progesterone
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d Mean ± SD: 36 ± 2.2 w n=97 I2: 400 mg vaginal progesterone (pessary)/d Mean ± SD: 36 ± 2.8 w n=97 I1 + I2: Mean ± SD: 36 ± 0.3 w n=194 No p value	Placebo Mean ± SD: 36 ± 2.6 w n=96	Not PO	?	?	-
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 C: 335	17-OHPC 250 mg im/w Mean ± SD: 35.4±3.6 w n=336 p=0.32	Placebo Mean ± SD: 35.7±3.8 w n=332	Not PO	+	+	?
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42 C: 42	90 mg vaginal progesterone gel 8%/d Median: 36+3 (IQR, 2+6) w n=42 Difference 1 day (95% CI 4 to -1 days) p=0.585	Placebo Median: 36+2 (IQR, 3+0) w n=42		+	?	+
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0)	Twin pregnancy, previous sPTD, uterine malformation	I: 84 C: 76	100 mg vaginal progesterone/d Singletons and twins Mean ± SD: 36w 6d ± 2w 3d n=80 p<0.05	Placebo Singletons and twins Mean ± SD: 35w 6d ± 3w 2d n=70	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.7. Intervention progesterone
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Caritis, 2009 USA SSTARS	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w Median: 32.4 (IQR, 30.0, 34.4) w n=71 p=0.527	Placebo Median: 33.0 (IQR, 31.6, 34.3) w n=63	Not PO	+	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w Mean ± SD: 31.9±4.1 w n=56 p=0.36	Placebo Mean ± SD: 31.8±2.9 w n=25	Not PO	+	?	?
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centers)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 37.3 w (no SD) n=125 p=0.71	200 mg vaginal progesterone/d 37.5 w (no SD) n=118	Not PO	+	?	?
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) Mean ± SD: 32.9±6.4 w n=42 p=0.96	17-OHPC 250 mg/w Mean ± SD: 33.0±5.9) w n=37	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.7. Intervention progesterone
Outcome variable: Gestational age at delivery

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dang 2019 Vietnam (single center)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary Median (range) 37 (35.5-37.5) w p=0.50 Subgroup analysis TVS CL ≤28 mm Median (range) 37 (35-37.5) w n=47 p=0.09	400 mg vaginal progesterone/d Median (range) 36.5 (34.3-37.5) w Subgroup analysis TVS CL ≤28 mm Median (range) 34.5 (32.8-36.8) w n=35	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, d; days, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, I; intervention, im; intramuscular, IQR; interquartile range, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, OR; odds ratio, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.8. Intervention progesterone
Outcome variable: Low birth weight (<2500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Singletons									
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 2/52 (3.8%) p=0.41	Placebo 4/47(8.5%)	Not PO LBW was not defined	?	-	-
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 29/96 (33.7%) p=0.003	Placebo 48/91(52.8%)	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesteron supp/d 20/50 (40 %) RR 1.65 (95% CI 1.11-2.45) p=0.009	Placebo 33/50 (66 %)	Not PO	-	?	-
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 72/323 (22.3%) RR 0.97 (95% CI 0.73-1.30) No p value	Placebo (castor oil) 75/328 (22.9%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 60/234 (25.6%) RR 0.83 (95% CI 0.62-1.11) p=0.213	Placebo 68/220 (30.9%)	Not PO	?	?	+
Hauth, 1983 USA	Singletons	Women from an active –duty military population	I: 80 C: 88	17-OHPC 1000 mg im/w 6/80 (7.5%) NS	Placebo (castor oil) 8/88 (9.1%)	Not PO (calculated from Table II)	-	-	-
Ibrahim, 2010 Egypt	Singletons	Previous PTB	I: 25 C: 25	17-OHPC 250 mg/w 5 /25(25%) p=0.04	Placebo (saline) 10/25 (40%)	Not PO	-	-	-
Jabeen, 2012 Pakistan	Singletons	Previous sPTB	I: 30 C: 30	17-OHPC 250 mg/w 5/30 (16.7%) p=0.739	Placebo (inert oil) 6/30 (20%)	Not PO	?	-	-

Project: Prevention of preterm birth
Appendix 4.1.8. Intervention progesterone
Outcome variable: Low birth weight (<2500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Jafarpour, 2020 Iran	Singletons	Previous PTB	I: 50 C: 50	17-OHPC 250 mg/w 14/50 (28%) RR 1.56 (95% CI 1.6-2.29) p=0.023 NB in text: 95% CI 1.06-2.29	Routine prenatal care 25/50 (50%)	Not PO	?	-	-
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 82/301 (27.2%) RR 0.66 (95% CI 0.51-0.87) No p value	Placebo (castor oil) 62/151 (41.1%)	Not PO	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 41/395 (10%) RR 0.9 (95% CI 0.6-1.3) No p value	Placebo 46/395 (12%)	Not PO	?	+	?
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 9/41 (22%) RR 1.07 (95% CI 0.46-2.48) No p value	Placebo 8/39 (21%)	Not PO	+	?	-
Multifetal pregnancies									
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2:1 I: 197 C:96 Analysed I:194 women/388 infants C: 94 women/188 infants	17-OHPC 250 mg im/w 241/383 (62.9%) RR 0.7 (95% CI 0.5-1.1) p=0.11	Placebo (castor oil) 127/182 (69.8%)	Not PO	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/390 C: 195/390	200 mg vaginal natural progesterone/d 234/354 (66.1%) OR 1.18 (95% CI 0.81-1.71) No p value	Placebo 235/375 (62.7%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.8. Intervention progesterone
Outcome variable: Low birth weight (<2500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160/320 C: 80/160 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 195/320 (61%) OR 1.9 (95% CI 1.2-3.1) p=0.009	Placebo (1 mL castor oil) 70/156 (45%)	Not PO	+	?	?
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) 306/659 (46.4%) OR 0.8 (95% CI 0.6-1.0) No p value	Placebo 357/677 (52.9%)	Not PO	+	+	+
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327/654 C: 334/668	17-OHPC 250 mg im/w 377/632 (60.0%) RR 0.9 (95% CI 0.8-1.0) No p value	Placebo 415/648 (64.0%)	Not PO	+	?	+
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98/196 I2: 98/196 C: 98/196	I1: 200 mg vaginal progesterone (pessary) /d I2: 400 mg vaginal progesterone (pessary)/d I1: 104/194 (53.6%) I2: 113/191 (59.2%) I1+I2: 217/385 (56.4%) Comparison between groups NS	Placebo 117/190 (61.6%)	Not PO	?	?	-
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71/213 C: 63/183	17-OHPC 250 mg im/w 191/212 /91%) RR 0.9 (95% CI 0.9-1.0) No p value	Placebo 175/183 (96%)	Not PO	?	?	?
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one	I: 336 women /681 infants (654 twins, 27 triplets) C: 335 women/	17-OHPC 250 mg im/w 363/681 (53%) RR 1.0. (95% CI 0.89–1.13) No p value	Placebo 355/674 (53%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.8. Intervention progesterone
Outcome variable: Low birth weight (<2500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
		quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	680 infants (652 twins, 24 triplets, 4 quads)						
Mixed singletons and twins									
Aboulghar 2012 Egypt	Mixed Singletons 215/306 (70.3%) DC twins 91/306 (29.7%)	ART pregnancies	Randomised I:161 C:152 Analysed I:161 (112 singletons, 49 sets of twins [98 twins]) C:145 (103 singletons, 42 sets of twins [84 twins])	400 mg vaginal natural progesterone/d Singletons 5/112 (4.5%) Twin pregnancies: 29/49 (59.2%) OR 1.63 (95% CI 0.6-1.9)	Placebo Singletons 11/103 (10.7%) Twin pregnancies 31/42 (73.8%)	Not PO NB denominator for twins is pregnancy level not fetal level	?	?	-
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women (114 singletons, 11 twin pregnancies)/136 infants C: 125 women (112 singletons, 13 twin pregnancies)/138 infants	200 mg vaginal progesterone /d (Utrogestan) 56/136 (41.2%) RR 0.96 (95% CI 0.69-1.26) p=0.81 aRR 0.97 (95% CI 0.68-1.29) p=0.85	Placebo 59/138 (42.8%)	Not PO No separate neonatal outcome for twins	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.8. Intervention progesterone
Outcome variable: Low birth weight (<2500 g)

* + No or minor problems
? Some problems
\- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Johnson, 1975, single centre, USA	Singletons and twins Only one twin pregnancy	Two spontaneous abortions immediately before this pregnancy or one preterm birth and one spontaneous abortion immediately before this pregnancy or two preterm births at any point.	50 randomised 43/50 analysed, 37 included in final analysis I:18 C:19	17-OHPC 250 mg im/w 4/18 (22.2%) No statistics	Placebo 11/19 (57.9%)	Not stated if PO Calculated from Figure 2	-	-	-

Project: Prevention of preterm birth
Appendix 4.1.8. Intervention progesterone
Outcome variable: Low birth weight (<2500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVSCL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 32/125 (26%) No RR p=0.38	200 mg vaginal progesterone/d 25 /118 (21%)	Not PO	+	?	?
Dang 2019 Vietnam (single center)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 143/296 (48%) RR 0.80 (95% CI 0.44-0.84) p<0.001 Subgroup analysis TVS CL ≤28 mm n=94 50/94 (53%) RR 0.73 (95% CI 0.22-0.82) p=0.02	Vaginal progesterone 400 mg/d 181/298 (61%) Subgroup analysis TVS CL ≤28 mm n=70 51/70 (73%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, aRR; adjusted risk ratio, ART; assisted reproductive technology, C; control, CL; cervical length, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction, MC; monochorionic, MCDA; monochorionic diamniotic, NNM; neonatal mortality, NS: not significant, OR; odds ratio, PO: primary outcome, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.9. Intervention progesterone
Outcome variable: Very low birth weight (<1500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Singletons									
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesterone supp /d 5/50 (10 %) RR 3.6 (95% CI 1.45-8.94) p=0.002	Placebo 18/50 (36 %)	Not PO	-	?	-
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 23/323 (7.1%) RR 0.81 (95% CI 0.48-1.36)	Placebo (castor oil) 29/328 (8.8%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 15/234 (6.4%) RR 0.47 (95% CI 0.26-0.85) p=0.010	Placebo 30/220 (13.6%)	Not PO	?	?	+
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 26/301 (8.6%) RR 0.62 (95% CI 0.36-1.07) No p value	Placebo (castor oil) 21/151 (13.9%)	Not PO	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 7/395 (2%) RR 1.0 (95% CI 0.4-2.8) No p value	Placebo 7/395 (2%)	Not PO	?	+	?
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 2/41 (5%) RR 0.46 (95% CI 0.081-2.62) No p value	Placebo 4/39 (11%)	Not PO	+	?	-
Twins									
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2.1 I: 197 C:96 Analysed I:194 women/388 infants C: 94 women/188 infants	17-OHPC 250 mg im/w 29/383 (7.6%) RR 0.5 (95% CI 0.3-0.9) p=0.01	Placebo (castor oil) 26/182 (14.3%)	Not PO PNM: IUFD after 24 w and neonatal deaths <28 d	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.9. Intervention progesterone
Outcome variable: Very low birth weight (<1500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/390 C: 195/390	200 mg vaginal natural progesterone/d 34/354 (9.6%) OR 0.98 (95% CI 0.53-1.81) No p value	Placebo 39/375 (10.4%)	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160/320 C: 80/160 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 28/320 (9%) OR 1.8 (95% CI 0.6-5.1) p=0.29	Placebo (1 mL castor oil) 8/156 (5%)	Not PO	+	?	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582/1164 C: 587/1174	600 mg vaginal progesterone/d Pregnancy level 51/569 (9.0%) OR 1.03 (95% CI 0.68-1.56) No p value Fetal level 75/1125 (6.7%) OR 0.93 (95% CI 0.65-1.32) No p value	Placebo Pregnancy level 50/565 (8.8%) Fetal level 76/1113 (6.8%)	Not PO	+	+	?
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) 36/659 (5.5%) OR 0.8 (95% CI 0.4-1.4) No p value	Placebo 48/677 (7.1%)	Not PO	+	+	+
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327/654 C: 334/668	17-OHPC 250 mg im/w 81/632 (12.9%) RR 2.0 (95% CI 1.0-3.9) No p value	Placebo 64/648 (9.9%)	Not PO	+	?	+
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98/196 I2: 98/196 C: 98/196	I1: 200 mg vaginal progesterone (pessary) /d I2: 400 mg vaginal progesterone (pessary)/d I1: 9/194 (4.6%) I2: 13/191 (6.8%) I1+I2: 22/385 (5.7%) Comparison between groups NS	Placebo 13/191 (6.8%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.9. Intervention progesterone
Outcome variable: Very low birth weight (<1500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71/213 C: 63/183	17-OHPC 250 mg im/w 91/212 (43%) RR 1.7 (95% CI 1.1-2.7) No p value	Placebo 46/183 (25%)	Not PO	?	?	?
Mixed singletons and twins									
Aboulghar 2012 Egypt	Mixed Singletons 215/306 (70.3%) DC twins 91/306 (29.7%)	ART pregnancies	Randomised I:161 C:152 Analysed I:161 (112 singletons, 49 sets of twins [98 twins]) C:145 (103 singletons, 42 sets of twins [84 twins])	400 mg vaginal natural progesterone/d Singletons 2/112 (1.8%) OR 1.8 (95% CI 0.16–20.76) Twins: 2/49 (4.3%) OR 0.25 (95% CI 0.049-1.34)	Placebo Singletons 1/103 (1,0%) Twins 6/42 (14.3%)	Not PO NB Denominator for twins are pregnancy level not fetal level	?	?	-
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women (114 singletons, 11 twin pregnancies)/136 infants C: 125 women (112 singletons, 13 twin pregnancies)/138 infants	200 mg vaginal progesterone /d (Utrogestan) 18/136 (13.2%) RR 0.68 (95% CI 0.36-1.21) p=0.20 aRR 0.74 (95% CI 0.36-1.37) p=0.35	Placebo 27/138 (19.6%)	Not PO No separate neonatal outcome for twins	?	?	+
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants (654 twins, 27 triplets) C: 335 women/ 680 infants (652 twins, 24 triplets, 4 quads)	17-OHPC 250 mg im/w 90/681 (13%) RR 1.25 (95% CI 0.83-1.90) No p value	Placebo 64/674 (9%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.9. Intervention progesterone
Outcome variable: Very low birth weight (<1500 g)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments Risk factor	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 10/125 (8%) No RR p=0.92	200 mg vaginal progesterone/d 10 /118 (8%)	Not PO	+	?	?
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 29/296 (10%) RR 1.17 (0.68-2.08) p=0.57 Subgroup analysis TVS CL ≤28 mm n=94 12/94 (13%) RR 0.74 (95% CI 0.30-1.68) p=0.51	400 mg vaginal progesterone/d 25/298 (8%) Subgroup analysis TVS CL ≤28 mm n=70 12/70 (17%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, aRR; adjusted risk ratio, ART; assisted reproductive technology, C; control, CL; cervical length, d; days, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction, MC; monochorionic, MCDA; monochorionic diamniotic, NNM; neonatal mortality, NS; not significant, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB; spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w IUFD 0/52	Placebo IUFD 1/47 (2.1%)	Not PO IUFD not defined PNM not reported	?	-	-
Ali, 2020 Egypt	Singletons	Indication for cerclage: previous second trimester loss, sPTD (<34 w) or short cervix TVS CL <25 mm	I: 121 C:121	400 mg vaginal progesterone (pessary)/d Abortion before 28 w 21/121 (17.4%) p=0.016	Placebo Abortion before 28 w 37/121 (30.6%)	PO abortion before 28 w Progesterone was used as an adjuvant after cerclage PNM not reported	?	?	?
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d Mid trimester abortion 7/103 (6.8%) p=0.46	Placebo Mid trimester abortion 11/102 (10.8%)	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups PNM not reported	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w IUFD 12/1124 (1.1%) RR 2.07 (95% CI 0.59-7.29) PNM 15/1128 (1.3%) No statistics	Placebo IUFD 3/571 (0.5%) PNM 4/578 (0.7%)	Not PO IUFD from 20+0 w Denominator is women pregnant from 20+0 w PNM defined as IUFD or NNM <28 d (calculated from Table 4)	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w Fetal loss/abortion <20 w 1/327 (0.3%) No statistics IUFD 4/327 (1.2%) RR 4.04 (95% CI 0.45-35.92) PNM 10/327 (3.1%) No statistics	Placebo (castor oil) Fetal loss/abortion <20 w 0/330 IUFD 1/330 (0.3%) PNM 9/330 (2.7%)	Not PO PNM defined as IUFD or NNM (calculated from Table 3) NNM not defined	?	+	+

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d IUFD 5/235 (2.1%) RR 0.79 (95% CI 0.25–2.57) p=0.700 PNM 8/235 (3.4%) RR 0.69 (95% CI 0.28-1.68) p=0.413	Placebo IUFD 6/223 (2.7%) PNM 11/223 (4.9%)	Not PO PNM: IUFD and NNM IUFD and NNM not defined	?	?	+
Hauth, 1983 USA	Singletons	Women from an active –duty military population	I: 80 C: 88	17-OHPC 1000 mg im/w IUFD 2/80 PNM 3/88 (3.8%) No statistics	Placebo (castor oil) IUFD 0/88 PNM 3/88 (3.4%)	Not PO IUFD or NNM not defined	-	-	-
Jabeen, 2012 Pakistan	Singletons	Previous sPTB	I: 30 C: 30	17-OHPC 250 mg/w PNM 2/30 (6.7%) p=0.228	Placebo (inert oil) PNM 5/30 (16.7%)	Not PO PNM not defined	?	-	-
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w IUFD 6/306 (2.0%) RR 1.50 (95% CI 0.31–7.34) NNM 8/306 (2.6%) RR 0.44 (95% CI 0.17–1.13) no p-values PNM 14/306 (4.6%) No statistics	Placebo (castor oil) IUFD 2/153 (1.3%) NNM 9/153 (5.9%) PNM 11/153 (7.2%)	Not PO IUFD or NNM not defined PNM calculated from IUFD+NNM in Table 3	?	?	?
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d IUFD 8/600 (1%) RR 1.14 (95% CI 0.41-3.17) p=0.8 NNM 1/600 (<1%) RR 0.17 (95% CI 0.06-0.49) p=0.0009 PNM 9/600 (1.5%) No statistics	Placebo IUFD 7/597 (1%) NNM 6/597 (1%) PNM 13/600 (2.2%)	Not PO PNM or NNM not defined PNM calculated from IUFD+NNM	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d IUFD <20 w 0/309 IUFD >20 w 5/309 (1.6%) OR 1.22 (95% CI 0.33- 4.61) No p value PNM 11/309 (3.6%) No statistics	Placebo IUFD <20 w 0/309 IUFD >20 w 4/302 (1.3%) PNM 11/302 (3.6%)	Not PO PNM: IUFD >20 and NNM <28 d Calculated from Table 2	?	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d PNM 1/41 (2%) RR 0.46 (95% CI 0.031–6.8) No p value	Placebo PNM 2/39 (5%)	Not PO PNM: IUFD (no IUFD occurred) and NNM before discharge	+	?	-
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised I: 197 C:96 Analysed I:194 women/388 infants C: 94 women/188 infants Randomised 2:1	17-OHPC 250 mg im/w PNM 17/388 (4.4%) OR 0.53 (95% CI 0.21-1.33) p=0.18	Placebo (castor oil) PNM 15/188 (8.0%)	Not PO PNM: IUFD after 24 w and neonatal deaths <28 d	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/390 C: 195/390	200 mg vaginal natural progesterone/d IUFD 8/378 (2.1%) OR 1.63 (95% CI 0.42-6.23) PNM 17/378 (4.5%) OR 1.33 (95% CI 0.53-3.34) no p values	Placebo IUFD 5/382 (1.3%) PNM 13/382 (3.4%)	Not PO PNM: IUFD and NNM IUFD not defined NNM death before discharge	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160/320 C: 80/160 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w IUFD/ miscarriage 0/320 PNM 0/320 p=0.03	Placebo (1 mL castor oil) IUFD/miscarriage 0/156 PNM 3/156 (1.9%)	Not PO PNM: IUFD/miscarriage and NNM NNM not defined	+	?	?

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Norman, 2009 UK (9 hospitals) STOPPIT	Twins	MC twins I: 46/247 C: 45/247 No MA twins	I: 247/494 C: 247/494	90 mg vaginal progesterone /day (Crinone) IUFD 6/494 (1.2%) p=0.52 NNM 8/494 (1.6%) p=0.59 PNM: 14/494 (2.8%) No statistics	Placebo IUFD 4/494 (0.8%) NNM 6/494 (1.2%) PNM: 10/494 (2.0%)	Not PO PNM (IUFD+ NNM) calculated from 7 Table IUFD and NNM not defined	+	+	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582/1164 C: 587/1174	600 mg vaginal progesterone/d Pregnancy level PNM 12/582 (2.1%) OR 1.41 (95% CI 0.58-3.39) Fetal level PNM 15/1164 (1.3%) OR 1.57 (95% CI 0.70-3.53)	Placebo Pregnancy level PNM 9/587 (1.5%) Fetal level PNM 10/1174 (0.9%)	Not PO PNM: IUFD and NNM IUFD and NNM not defined	+	+	?
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) Pregnancy level IUFD 2/334* (0.6%) OR 1.0 (95% CI 0.1–7.3) Infant death during delivery One infant 1/334 (0.3%) OR 1.0 (95% CI 0.1–16.4) Both infants 0/334 Fetal level (calculated) IUFD: 2/668 (0.3%) Infant death during delivery: 1/664 (0.2%) PNM: 10/664 (1.5%) No statistics	Placebo Pregnancy level IUFD 2/341* (0.6%) Infant death during delivery One infant 1/334 (0.3%) Both infants 1/334 (0.3%) Fetal level (calculated) IUFD: 2/682 (0.3%) Infant death during delivery: 3/678 (0.4%) PNM: 7/678 (1.0%)	Not PO IUFD not defined *only one fetus died PNM: IUFD and death during delivery and NNM <28 d PNM calculated from Table 3	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327/654 C: 334/668	17-OHPC 250 mg im/w Pregnancy level IUFD 12/325 (3.7)* RR 1.4 (95% CI 0.6-3.2) PNM 22/325** RR 1.5 (95% CI 0.8- 2.8) Fetal level IUFD 18/650 (2.8%) No statistics PNM 34/650 (5.2%) RR 1.5 (95% CI 0.8-2.8) No p value	Placebo Pregnancy level IUFD 9/330 (2.7%)* PNM 15/330** Fetal level IUFD 12/660 (1.8%) PNM 22/660 (3.3%)	Not PO *At least one fetus died **At least one fetus or neonate died IUFD includes miscarriage, termination of pregnancy, and stillbirth. PNM: IUFD or NNM NNM not defined Denominator for fetal level from flowchart and numbers from text	+	?	+
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98/196 I2: 98/196 C: 98/196	I1: 200 mg vaginal progesterone (pessary) /d I2: 400 mg vaginal progesterone (pessary)/d IUFD of co twin I1: 0/97 I2: 3/97 (3.1%) I1 + I2: 3/194 (1.5%) Comparison between groups: NS PNM I1: 0/194 I2: 8/191 (4.2%) I1+I2: 8/385 (2.1%) No statistics	Placebo IUFD of co twin 2/96 (2.1%) PNM 5/190 (2.6%)	Not PO IUFD occurred after 24 w NNM <28 d PNM calculated	?	?	-
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71/213 C: 63/189	17-OHPC 250 mg im/w IUFD 1/213 (0.5%) No statistics PNM 6/213 (2.8%) No statistics	Placebo IUFD 6/189 (3.2%) PNM 8/189 (4.2%)	Not PO PNM: IUFD and NNM NNM not defined IUFD included miscarriage, termination, or IUFD occurring anytime after randomisation PNM calculated	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Combs, 2010	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/168 fetuses C: 25 women/75 fetuses	17-OHPC 250 mg im/w IUFD 13/168 (8%) p=0.01 PNM 19/168 (11%) OR 4.7 (95% CI 1.0–22.0) p=0.05	Placebo IUFD 0/75 PNM 2/75 (3%)	Not PO PNM: IUFD, miscarriage and NMM NNM not defined	+	?	?
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42 women/86 infants C: 42 women/85 infants	90 mg vaginal progesterone gel 8%/d PNM 2/84* (2%) RR 1.98 (0.18-21.39) p>0.999 *2 unknown	Placebo PNM 1/85 (1%)	Not PO PNM: IUFD and NNM IUFD occurred after 20 w No NNM occurred	+	?	+
Aboulghar 2012 Egypt	Mixed Singletons 215/306 (70.3%) DC twins 91/306 (29.7%)	ART pregnancies	Randomised I:161 C:152 Analysed I:161 (112 singletons, 49 sets of twins [98 twins]) C:145 (103 singletons, 42 sets of twins [84 twins])	400 mg vaginal natural progesterone/d Singletons PNM 1/112 (0.9%) Twins: PNM 4/98 (4.1%) No statistics	Placebo Singletons PNM 5/103 (4.9%) Twins PNM 5/84 (6.0%)	Not PO PNM: IUFD + NNM Only one IUFD reported (in singletons, none in twins) NNM < 28 d PNM calculated from Tables 2 and 3	?	?	-
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d IUFD 4/406 (1.0%) p=0.749 PNM 5/406 (1.2%) Unadjusted RR 0.69 (95% CI 0.22–2.16) p=0.526	Placebo IUFD 5/393 (1.3%) PNM 7/393 (1.8%)	Not PO PNM: IUFD + NNM IUFD after trial entry and prior to birth NNM before discharge	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women (114 singletons, 11 twin pregnancies)/136 infants C: 125 women (112 singletons, 13 twin pregnancies)/138 infants	200 mg vaginal progesterone /d (Utrogestan) IUFD 1/136 (0.7%) p=0.98 PNM 3/136 (2.2%) No statistics	Placebo IUFD 1/138 (0.7%) PNM 8/138 (5.8%)	Not PO PNM: IUFD and NND PNM calculated from Table 2 IUFD and NND not defined	?	?	+
Johnson, 1975, single centre, USA	Singletons and twins Only one twin pregnancy	Two spontaneous abortions or one preterm birth and one spontaneous abortion immediately before this pregnancy or two preterm birth at any point.	50 randomised 43/50 analysed, 37 included in final analysis I:18 C:19	17-OHPC 250 mg im/w Fetal level PNM 0/18 p<0.05	Placebo Fetal level PNM 7*/26 (26.9%) *2 deaths in a twin pregnancy 5 IUFD and 2 NND	Not stated if PO PNM not defined NB the high PNM rate. *PNM from Table 1 in article, but number of pregnancies differs from number of pregnancies included in final analysis.	-	-	-
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 6/125 (5%) No RR p=0.35	200 mg vaginal progesterone/d 3/118 (3%)	Not PO PNM: fetal and neonatal death	+	?	?
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 5/42 (11.9%) No statistics	17-OHPC 250 mg/w 4/37 (10.8%)	Not PO PNM: any stillbirth or neonatal death during the study period	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.10. Intervention progesterone
Outcome variable: Perinatal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary Stillbirth 14/296 (5%) RR 1.08 (95% CI 0.50-2.36) p=0.85 NNM 7/296 (2%) RR 1.76 (95% CI 0.52-6.15 p=0.38 Subgroup analysis TVS CL ≤28 mm n=94 Stillbirth 4/94 (4%) RR 0.43 (95% CI 0.11-1.42) p=0.21 NNM 3/94 (3%) No statistics	400 mg vaginal progesterone/d Stillbirth 13/298 (4%) NNM 4/ 298 (1%) Subgroup analysis TVS CL ≤28 mm n=70 Stillbirth 7/70 (10%) NNM 0/94 (0%)	Not PO PNM: Stillbirths (>28 weeks) and neonatal mortality <28 days	?	?	?

17-OHPC; 17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, d. days, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, IUFD; intrauterine fetal death, NB nota bene; NNM; neonatal mortality, NR; not reported, OR; odds ratio, PNM; perinatal mortality, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.11. Intervention progesterone
Outcome variable: Neonatal mortality before 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 7/96 (7.3%) p<0.001	Placebo 23/91 (25.3%)	Not PO NNM not defined NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesterone supp/d 2/50 (4%) RR 4.0 (95% CI 0.89-17.91) p=0.056	Placebo 21/50 (42 %)	Not PO NNM not defined	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomized 2:1	17-OHPC 250 mg im/w 3/1112 (0.3%) RR 1.48 (95% CI 0.14-15.24) No p value	Placebo 1/568 (0.2%)	Not PO NNM <28 d Patients with missing data assumed not to have the outcome	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 6/327 (1.8%) RR 0.76 (95% CI 0.27-2.16) No p value	Placebo (castor oil) 8/330 (2.4%)	Not PO NNM not defined	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 3/235 (1.3%) RR 0.57 (95% CI 0.14-2.35) p=0.431	Placebo 5/223 (2.2%)	Not PO NNM not defined	?	?	+
Hauth, 1983 USA	Singletons	Women from an active duty military population	I: 80 C: 88	17-OHPC 1000 mg im/w 2/80 (2.5%) No statistics	Placebo (castor oil) 0/88	Not PO NNM not defined	-	-	-
Hayashi, 2021 Japan TROPICAL	Singletons	Short TVS CL 25-<30 mm Previous PTB I: 11.9% C: 16.7%	I: 59 C: 60	200 mg vaginal progesterone/d 0/59 (0%) p=1.0	Placebo 1/60 (1.7%)	Not PO Infant death	?	?	-
Ibrahim, 2010 Egypt	Singletons	Previous PTB	I: 25 C: 25	17-OHPC 250 mg/w 1 /25 (4%) p<0.05	Placebo (saline) 4/25 (16%)	Not PO NNM not defined	-	-	-

Project: Prevention of preterm birth
Appendix 4.1.11. Intervention progesterone
Outcome variable: Neonatal mortality before 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w 8/306 (2.6%) RR 0.44 (95% CI 0.17–1.13) no p-value	Placebo (castor oil) 9/153 (5.9%)	Not PO NNM not defined	?	?	?
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d 1/600 (<1%) RR 0.17 (95% CI 0.06-0.49) p=0.0009	Placebo 6/597 (1%)	Not PO NNM not defined	+	+	+
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 6/309 (1.9%) OR 0.87 (95% CI 0.29-2.60) No p value	Placebo 7/302 (2.3%)	Not PO NNM <28 d	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 14/388 (4%) RR 2.0 (95% CI 0.8- 4.9) No p value	Placebo 7/386 (2%)	Not PO 21 stillborns excluded and 5 infants with undocumented vital status at 28 days	?	+	?
Rai, 2009 India	Singletons	Previous sPTB	I: 75 C:75	200 micronized oral progesterone/d 3/74 (4.1%) No RR or OR p=0.190	Placebo 7/74 (9.5%)	Not PO NNM not defined	-	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 1/41 (2%) RR 0.46 (95% CI 0.031–6.8) No p value	Placebo 2/39 (5%)	Not PO NNM before discharge	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.11. Intervention progesterone
Outcome variable: Neonatal mortality before 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised I: 197 C:96 Analysed I:194 women/388 infants C: 94 women/188 infants Randomised 2:1	17-OHPC 250 mg im/w 5/388 (1.3%) RR 0.48 (95% CI 0.10–2.32) p=0.36	Placebo (castor oil) 5/188 (2.7%)	Not PO NNM <28 d	+	+	?
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16/32 C: 14/28	17-OHPC 250 mg im/w 2/32 (6%) p=0.359	Placebo 0/28	Not PO NNM not defined	?	?	-
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d 9/378 (2.4%) OR 1.14 (0.34-3.81) No p value	Placebo 8/382 (2.1%)	Not PO NNM before discharge	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160/320 C: 80/160 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 0/320 p=0.03	Placebo (1 mL castor oil) 3/156 (2%)	Not PO NNM not defined	+	?	?
Norman, 2009 UK (9 hospitals) STOPPIT	Twins	MC twins I: 46/247 C: 45/247 No MA twins	I: 247/494 C: 247494	90 mg vaginal progesterone /day (Crinone) 8/494 (1.6%) p=0.59	Placebo 6/494 (1.2%)	Not PO NNM not defined	+	+	?
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) 7/664 (1.0%) No statistics	Placebo 2/678 (0.3%)	Not PO NNM <28 d	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.11. Intervention progesterone
Outcome variable: Neonatal mortality before 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98/196 I2: 98/196 C: 98/196	I1: 200 mg vaginal progesterone (pessary) /d I2: 400 mg vaginal progesterone (pessary)/d I1: 0/194 I2: 5/191 (2.6%) I1+I2: 5/385 (1.3%) Comparison between groups: NS	Placebo 3/190 (1.6%)	Not PO NNM <28 d	?	?	-
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71/213 C: 63/183	17-OHPC 250 mg im/w 5/213 (2.3%) RR 2.2 (95% CI 0.4–12.4)	Placebo 2/183 (1.1%)	Not PO NNM not defined	?	?	?
Combs, 2010	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 women/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w 6/155 (4%) OR 1.5 (95% CI 0.3-8.1) p=0.66	Placebo 2/75 (3%)	Not PO NNM not defined	+	?	?
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42 women/86 infants C: 42 women/85 infants	90 mg vaginal progesterone gel 8%/d 0/86	Placebo 0/85	Not PO NNM not defined	+	?	+
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants (654 twins, 27 triplets) C: 335 women/ 680 infants (652 twins, 24 triplets, 4 quads)	17-OHPC 250 mg im/w 13/681 (2%) RR 0.60 (95% CI 0.25–1.43) No p value	Placebo 21/674 (3%)	Not PO NNM before discharge	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.11. Intervention progesterone
Outcome variable: Neonatal mortality before 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Aboulghar 2012 Egypt	Mixed Singletons 215/306 (70.3%) DC twins 91/306 (29.7%)	ART pregnancies	Randomised I:161 C:152 Analysed I:161 (112 singletons, 49 sets of twins [98 twins]) C:145 (103 singletons, 42 sets of twins [84 twins])	400 mg vaginal natural progesterone/d Singletons 1/112 (0.9%) No statistics Twins Pregnancy level 2/49 (4.1%) OR 0.31 (95% CI 0.05-1.71 Fetal level 4/98 (4.1%)	Placebo Singletons 4/103 (3.9%) Twins Pregnancy level 5/42 (11.9%) Fetal level 5/84 (6.0%)	Not PO NNM <28 d Fetal level calculated	?	?	-
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0%)	Twin pregnancy, previous sPTD, uterine malformation	I: 84 women C: 76 women	100 mg vaginal progesterone/d Singletons and twins 3/80* (3.8%) OR 1.15 (95% CI 0.2-5.9) (C vs I) p=0.867	Placebo Singletons and twins 3/70* (4.3%)	Not PO *Number of births with at least one NNM NNM not defined	?	?	-
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 women (390 singletons, 8 twin pregnancies)/ 406 infants C: 389 women (385 singletons, 4 twin pregnancies)/ 393 infants	100 mg vaginal progesterone pessary/d 1/406 (0.3%) p=0.619	Placebo 2/393 (0.5%)	Not PO NNM before discharge	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.11. Intervention progesterone
Outcome variable: Neonatal mortality before 28 days

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women (114 singletons, 11 twin pregnancies)/136 infants C: 125 women (112 singletons, 13 twin pregnancies)/138 infants	200 mg vaginal progesterone /day (Utrogestan) 2/136 (1.5%) RR 0.29 (95% CI 0.06-1.42) p=0.13 Adjusted RR 0.34 (95% CI 0.06-1.81) p=0.22 RR adjusted for maternal age, BMI, smoking status, race, history of preterm birth, and cervical length at the time of randomisation.	Placebo 7/138 (5.1%)	Not PO NNM not defined	?	?	+
Other interventions in comparison with progesterone									
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 7/296 (2%) RR 1.76 (95% CI 0.52-6.15 p=0.38 Subgroup analysis TVS CL ≤28 mm n=94 3/94 (3%) No statistics	Vaginal progesterone 400 mg/d 4/149 (1%) Subgroup analysis TVS CL ≤28 mm n=70 0/70 (0%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, BMI; body mass index, C; control, CL; cervical length, DC; dichorionic, DCDA; dichorionic diamniotic, GA; gestational age, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NNM; neonatal mortality, OR; odds ratio, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.12. Intervention progesterone
Outcome variable: Composite adverse neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 61/1093 (5.6%) RR 1.12 (95% CI 0.72-1.72) p=0.62	Placebo 28/559 (5.0%)	Not PO Patients with missing data assumed not to have the outcome Composite neonatal outcome: any of NNM, IVH 3-4, RDS, BPD, NEC, or proven sepsis	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 23/327 (7.0%) RR 0.77 (95% CI 0.46-1.30) No p value	Placebo (castor oil) 30/330 (9.1%)	Not PO Composite neonatal outcome: RDS, BPD, sepsis, NEC, IVH 3-4, PVL, ROP, IUFD or NNM	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 18/235 (7.7%) RR 0.57 (95% CI 0.33-0.99) p=0.043	Placebo 30/223 (13.5%)	Not PO Composite neonatal outcome: RDS, BPD, IVH 3-4, PVL, proven sepsis, NEC and PNM (IUFD or NNM)	?	?	+
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d 39/589 (7%) OR 0.62 (95% CI 0.41-1.07)* p=0.02? aOR 0.62 (95% CI (0.38-1.03) p=0.072 aOR adjusted for multiple primary outcomes using Bonferroni-Holm	Placebo 60/587 (10%)	PO (one of three) Composite neonatal outcome: Neonatal morbidity (BPD and/or brain injury on ultrasound scan) or NNM *corrected (in article 95% CI 0.41-0.94), no errata of p value Subgroup analyses for TVS CL and history of PTB, but without events	+	+	+
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2:1 I: 197 C:96 Analysed I:194 women/388 fetuses C: 94 women/188 fetuses	17-OHPC 250 mg im/w 74/388 (19.1%) OR 0.53 (95% CI 0.31-0.90) p=0.02	Placebo (castor oil) 58/188 (30.9%)	Not PO Composite neonatal outcome: RDS, pneumonia, proven sepsis, IVH (grade III-IV), NEC, PVL, ROP, PDA, seizures, and/or BPD	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.12. Intervention progesterone
Outcome variable: Composite adverse neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d 45/291 (15.5%) OR 1.01 (95% CI 0.58-1.75) No p value	Placebo 51/320 (15.9%)	Not PO Composite neonatal outcome: IVH, NEC, RDS, sepsis, and/or death before hospital discharge	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	Randomised 2:1 I: 160/320 C: 80/160	17-OHPC 250 mg (in 1 mL castor oil) im/w 46/320 (14%) OR 1.2 (95% CI 0.6-2.5) p=0.62	Placebo (1 mL castor oil) 19/155 (12%)	PO Composite neonatal morbidity: PNM (IUFD, NNM, miscarriage), RDS, BPD (use of oxygen therapy at 28 days of life), proven sepsis, pneumonia, IVH 3-4, PVL, NEC, ROP, or asphyxia	+	?	?
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98/196 I2:98/196 C: 98/196	I1: 200 mg vaginal progesterone (pessary) /d I2: 400 mg vaginal progesterone (pessary)/d Short-term morbidity I1: 24/194 (12.4%) I2: 31/191 (16.2%) I1+I2: 55/385 (14.3%) Long-term morbidity I1: 2/194 (1.0%) I2: 0 /191 I1+I2: 2/385 (0.5%) Comparison between groups: NS	Placebo Short-term morbidity 27/190 (14.2%) Long-term morbidity 2/190 (1.1%)	Not PO Short-term neonatal morbidity: RDS, pneumonia, sepsis, seizures, IVH 3-4, NEC, and/or PDA. Long-term neonatal morbidity: BPD, PVL and/or ROP	?	?	-
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 women/212 infants C: 63 women/183 infants	17-OHPC 250 mg im/w 78/212 (37%) RR 1.1 (95% CI 0.7-1.7) No p value	Placebo 65/183 (34%)	Not PO Composite neonatal outcome: NND, RDS, BPD, ROP, sepsis, NEC, IVH 3-4, and/or PVL	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.12. Intervention progesterone
Outcome variable: Composite adverse neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 women/168 (155 liveborn neonates) C: 25 women/75 (75 liveborn neonates)	17-OHPC 250 mg im/w 63/168 (38%) OR 0.9 (95% CI 0.4-2.0) p=0.71	Placebo 31/75 (41%)	PO Composite neonatal morbidity: PNM (IUFD, NNM, miscarriage), RDS, BPD (use of oxygen therapy at 28 days of life), proven sepsis, pneumonia, IVH 3-4, PVL, NEC, ROP, or asphyxia	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants (327 sets of twins, 9 sets of triplets) C: 335 women/ 680 infants (326 sets of twins, 8 sets of triplets, one quadruplet)	17-OHPC 250 mg im/w 110/681 (16%) RR 1.34 (95% CI 0.95-1.89) No p value	Placebo 80/674 (12%)	PO Composite severe RDS, BPD, IVH grade II B or worse, NEC, proven sepsis, and NNM before discharge from the hospital	+	+	?
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398/406 infants (390 singletons and 8 twin pregnancies) C: 389/393 infants (385 singletons and 4 twin pregnancies)	100 mg vaginal progesterone pessary/d 155/406 (38.2%) RR 0.99 (95% CI 0.82-1.18) p=0.887 aRR 0.98 (95% CI 0.82-1.17) p=0.798 aRR adjusted for GA at randomisation, GA of previous PTB, and reason for PTB	Placebo 152/393 (38.7%)	Not PO Composite neonatal outcome: PTB <37w, PNM, RDS, BPD, Apgar score <4, SGA (< 3rd centile), IVH, PVL, PDA, NEC, proven sepsis, and/or ROP	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24 sets, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women/136 infants (114 singletons, 22 twins) C: 125 women/138 infants (112 singletons, 26 twins)	200 mg vaginal progesterone /d (Utrogestan) 11/136 (8.1%) RR 0.59 (95% CI 0.26-1.25) p=0.17 aRR 0.57 (95% CI 0.23-1.31) p=0.19 aRR adjusted for maternal age, BMI, smoking status, race, history of PTB, and cervical length at the time of randomisation.	Placebo 19/138 (13.8%)	Not PO Composite neonatal outcome: RDS, IVH, NEC, and/or ROP	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.12. Intervention progesterone
Outcome variable: Composite adverse neonatal outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 24/125 (19%) No RR p=0.65	200 mg vaginal progesterone/d 20/118 (17%)	Not PO Composite adverse outcome included mechanical ventilation, IVH, RDS, ROP, NEC, NICU admissions	+	?	?
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (History of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) Mild 1/42 (2.3%) Severe 9/42 (21.4%) p=0.34 for any morbidity	17-OHPC 250 mg weekly Mild 5/37 (13.5%) Severe 7/37 (18.9%)	Not PO Mild morbidity defined as NICU admission without severe morbidity. Severe morbidity defined as life threatening morbidity including RDS requiring mechanic ventilation >24 h, IVH, sepsis, or NEC	+	?	-
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 55/296 (19%) RR 0.70 (95% CI 0.43-0.93) p=0.02 Subgroup analysis TVS CL ≤28 mm n=94 18/94 (19%) RR 0.38 (95% CI 0.12-0.47) p<0.001	400 mg vaginal progesterone /d 79/298 (27%) Subgroup analysis TVS CL ≤28 mm n=70 35/70 (50%)	Not PO Post hoc analysis Not defined, but PNM, RDS, BPD, IVH, NEC, sepsis, Apgar <7 at 5 min, NICU admissions were reported	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, aRR; adjusted risk ratio, aOR; adjusted odds ratio, ART; assisted reproductive technology, BMI; body mass index, BPD; bronchopulmonary dysplasia, C; control, CL; cervical length, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, im; intramuscular, h; hours, I; intervention, IUFD; intrauterine fetal death, IVH; intraventricular haemorrhage, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NEC; necrotizing enterocolitis, NNM; neonatal mortality, OR; odds ratio, PDA; patent ductus arteriosus, PTB; preterm birth, PVL; periventricular leucomalaci, RDS; respiratory distress syndrome, RR; risk ratio, ROP; retinopathy of prematurity, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.13. Intervention progesterone
Outcome variable: Respiratory distress syndrome (RDS)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations	Precision *
				Intervention	Control				
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 21/96 (21.8%) p=0.004 No RR	Placebo 39/91 (42.8%)	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesterone supp /d 10/50 (20%) RR 2.1 (95% CI 1.10-3.99) p=0.017 No RR	Placebo 21/50 (42%)	Not PO	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	Randomised 2:1I: 1130 C: 578	17-OHPC 250 mg im/w 54/1093 (4.9%) RR 1.06 (95% CI 0.67-1.68) No p value	Placebo 26/559 (4.7%)	Not PO Patients with missing data assumed not to have the outcome	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 13/320 (4.1%) RR 0.82 (95% CI 0.40-1.68) No p value	Placebo (castor oil) 16/323 (5.0%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 7/235 (3.0%) RR 0.39 (95% CI 0.17-0.92) p=0.026	Placebo 17/223 (7.6%)	Not PO ITT analysis set	?	?	+
Meis, 2003 USA	Singletons	Previous sPTB	Randomized 2:1I:310 C:153	17-OHPC 250 mg im/w 29/305 (9.5%) RR 0.63 (95% CI 0.38-1.05) No p value	Placebo (castor oil) 23/152 (15.1%)	Not PO	?	?	?
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 34/309 (11.0%) OR 0.91 (95% CI 0.56-1.50) No p value	Placebo 36/302 (11.9%)	Not PO	?	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 2/41 (5%) RR 0.92 (95% CI 0.14-6.21) No p value	Placebo 2/39 (6%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.13. Intervention progesterone
Outcome variable: Respiratory distress syndrome (RDS)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations	Precision *
				Intervention	Control				
Yemini, 1985 Israel	Singletons	Previous ≥2 PTB or ≥2 spontaneous miscarriages	I: 39 C: 40	17-OHPC 250 mg im/w 1/5 (20%) No statistics	Placebo 4/14 (28.6%)	Not PO All had cerclage Denominator = infants born < 36 w	-	-	-
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2:1 I: 197 C:96 Analysed I:194 women/388 fetuses C: 94 women/188 fetuses	17-OHPC 250 mg im/w 55/381 (14.4%) OR 0.55 (95% CI 0.31-0.98) p=0.04	Placebo (castor oil) 44/188 (23.4%)	Not PO	+	+	?
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16/32 C: 14/28	17-OHPC 250 mg im/w 10/32 (31%) p=0.838 No RR	Placebo 9/28 (32%)	Not PO	?	?	-
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d 39/296 (13.2%) OR 0.95 (95% CI 0.54-1.69) No p value	Placebo 44/321 (13.7%)	Not PO	?	?	-
Rode, 2011 Denmark and Austria PREDICT	Twins DA	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) 73/659 (11.1%) OR 1.1 (95% CI 0.7-1.7) No p values	Placebo 69/674 (10.2%)	Not PO	+	+	+
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	Randomised 2:1 I: 160/320 C: 80/160	17-OHPC 250 mg (in 1 mL castor oil) im/w 44/319 (14%) OR 1.2 (95% CI 0.6-2.6) p=0.64	Placebo (1 mL castor oil) 18/153 (12%)	Not PO	+	?	?
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 women/212 infants C: 63 women/183 infants	17-OHPC 250 mg im/w 65/212 (31%) RR 1.1 (95% CI 0.7-1.8)	Placebo 50/183 (27%)	Not PO	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.13. Intervention progesterone
Outcome variable: Respiratory distress syndrome (RDS)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations	Precision *
				Intervention	Control				
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w 44/155 (28%) OR 0.68 (95% CI 0.3-1.6) p=0.38	Placebo 28/75 (37%)	Not PO	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants (327 sets of twins, 9 sets of triplets) C: 335 women/ 680 infants (326 sets of twins, 8 sets of triplets, one quadruplet)	17-OHPC 250 mg im/w 82/681 (12%) RR 1.55 (95% CI 1.01-2.37) No p value	Placebo 51/674 (8%)	Not PO	+	+	?
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42/86 (40 sets of twins, 2 sets of triplets) C: 42/85 (40 sets of twins, one set of triplets)	90 mg progesterone vaginal gel 8%/d 15/86 (17%) Difference 0.68 (95% CI 0.38-1.22) p=0.264	Placebo 22/85 (26%)	Not PO	+	?	+
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d 42/402 (10.5%) RR 0.99 (95% CI 0.65-1.51) p=0.958 aRR 0.98 (95% CI 0.64-1.49) p=0.912	Placebo 41/388 (10.6%)	PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.13. Intervention progesterone
Outcome variable: Respiratory distress syndrome (RDS)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations	Precision *
				Intervention	Control				
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women/136 infants (114 singletons, 22 twins) C: 125 women/138 infants (112 singletons, 26 twins)	200 mg vaginal progesterone /day (Utrogestan) 11/136 (8.1%) RR 0.59 (95% CI 0.26-1.25) p=0.17 aRR 0.57 (95% CI 0.23-1.31) p=0.19 aRR adjusted for maternal age, BMI, smoking status, race, history of PTB, and cervical length at the time of randomisation.	Placebo 19/138 (13.8%)	Not PO	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.13. Intervention progesterone
Outcome variable: Respiratory distress syndrome (RDS)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 7/125 (6%) No RR p=0.81	200 mg vaginal progesterone/d 6/118 (5%)	Not PO	+	?	?
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 32/296 (11%) RR 0.63 (95 % 0.37-0.94) p=0.03 Subgroup analysis TVS CL ≤28 mm n=94 12/94 (13%) RR 0.43 (95% CI 0.15-0.75) p=0.01	400 mg vaginal progesterone /d 51/298 (17%) Subgroup analysis TVS CL ≤28 mm n=70 21/70 (30%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, aRR; adjusted risk ratio, ART; assisted reproductive technology, BMI; body mass index, C; control, CL; cervical length, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NB; nota bene, NNM; neonatal mortality, OR; odds ratio, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.14. Intervention progesterone
Outcome variable: Bronchopulmonary dysplasia (BPD)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	Randomised 2:1 I: 1130 C: 578	17-OHPC 250 mg im/w 6/1093 (0.5%) RR 3.02 (95% CI 0.38-24.1) No p value	Placebo 1/559 (0.2%)	Not PO Patients with missing data assumed not to have the outcome	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 3/320 (0.9%) RR 0.60 (95% CI 0.15-2.51) No p value	Placebo (castor oil) 5/322 (1.6%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 4/235 (1.7%) RR 0.76 (95% CI 0.21-2.79) p=0.678	Placebo 5/223 (2.2%)	Not PO	?	?	+
Meis, 2003 USA	Singletons	Previous sPTB	Randomized 2:1I:310 C:153	17-OHPC 250 mg im/w 4/305 (1.3%) RR 0.40 (95% CI 0.11-1.46) No p value	Placebo (castor oil) 5/152 (3.3%)	Not PO	?	?	?
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d 17/580 (3%) OR 0.94 (95% CI 0.49-1.78) p=0.84	Placebo 18/574 (3%)	Not PO	+	+	+
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 0/41 NA No p value	Placebo 1/39 (3%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.14. Intervention progesterone
Outcome variable: Bronchopulmonary dysplasia (BPD)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2:1 I: 197 C:96 Analysed I:194 women/388 fetuses C: 94 women/188 fetuses	17-OHPC 250 mg im/w 6/385 (1.6%) OR 0.31 (95% CI 0.08-1.23) p=0.10	Placebo (castor oil) 9/188 (4.8%)	Not PO	+	+	?
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	Randomised 2:1 I: 160/320 C: 80/160	17-OHPC 250 mg (in 1 mL castor oil) im/w 9/308 (3%) OR NA p=0.03	Placebo (1 mL castor oil) 0/150	Not PO In article defined as oxygen use at 28 d of life	+	?	?
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 women/212 infants C: 63 women/183 infants	17-OHPC 250 mg im/w 15/212 (7%) RR 0.8 (95% CI 0.3-2.0) No p value	Placebo 17/183 (9%)	Not PO	?	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w 11/153 (7%) OR 0.63 (95% CI 0.2-2.5) p=0.51	Placebo 7/70 (10%)	Not PO In article defined as oxygen use at 28 d of life	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants (327 sets of twins, 9 sets of triplets) C: 335 women/ 680 infants (326 sets of twins, 8 sets of triplets, one quadruplet)	17-OHPC 250 mg im/w 16/681 (2%) RR 1.68 (95% CI 0.64–4.39)	Placebo 9/674 (1%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.14. Intervention progesterone
Outcome variable: Bronchopulmonary dysplasia (BPD)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42/86 (40 sets of twins, 2 sets of triplets) C: 42/85 (40 sets of twins, one set of triplets)	90 mg vaginal progesterone gel 8%/d 7/86 (8%) Difference 0.85 (95% CI 0.32-2.25) p=0.792	Placebo 8/85 (9%)	Not PO	+	?	+
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d 10/402 (2.5%) RR 1.38 (95% CI 0.49–3.87) p=0.542	Placebo 7/388 (1.8%)	Not PO Chronic lung disease defined as BPD	+	+	?
Other interventions in comparison with progesterone									
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 0/296 (0%) No statistics Subgroup analysis TVS CL ≤28 mm n=94 0/94 (%)	400 mg vaginal progesterone/d 0/298 (0%) Subgroup analysis TVS CL ≤28 mm n=70 0/70 (0%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, BPD; bronchopulmonary dysplasia, C; control, CL; cervical length, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NA; not applicable, NEC; necrotising enterocolitis, NNM; neonatal mortality, OR; odds ratio, PO; primary outcome PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; weeks

Project: Prevention of preterm birth
Appendix 4.1.15. Intervention progesterone
Outcome variable: Intraventricular haemorrhage (IVH)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d ICH (not defined) 8/96 (8.3%) p=0.55 No RR	Placebo ICH (not defined) 11/91 (12%)	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesteron supp/d IVH (grade not defined) 5/50 (10%) RR 2.0 (95% CI 0.74-5.43) p=0.161	Placebo IVH (grade not defined) 10/50 (20%)	Not PO	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w IVH 3-4 2/1093 (0.2%) RR 0.99 (95% CI 0.09-10.52) No p value	Placebo IVH 3-4 1/559 (0.2%)	Not PO Patients with missing data assumed not to have the outcome	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w IVH 3-4 2/320 (0.6%) RR 2.01 (95% CI 0.18-22.08) No p value	Placebo (castor oil) IVH 3-4 1/322 (0.3%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d IVH 3-4 0/235 (0.0) 0.32 (0.01-7.73)* p=0.305 No RR	Placebo IVH 3-4 1/223 (0.5%)	Not PO *Based on Logit estimator with continuity correction	?	?	+
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w IVH 3-4 2/305 (0.7%) NA Any IVH 4/305 (1.3%) RR 0.25 (95% CI 0.08-0.82) No p value	Placebo (castor oil) IVH 3-4 0/153 Any IVH 8/153 (5.2%)	Not PO CI corrected (from incorrect value in article)	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.15. Intervention progesterone
Outcome variable: Intraventricular haemorrhage (IVH)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d Brain injury on ultrasound scan* 18/584 (3%) OR 0.50 (95% CI 0.31-0.84) p=0.008 IVH (grade not defined) 7/584 (1.2%) No statistics	Placebo Brain injury on ultrasound scan* 34/574 (6%) IVH (grade not defined) 13/574 (2.3%)	Not PO *any IVH, parenchymal cystic or hemorrhagic lesion, persistent ventriculomegaly	+	+	+
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d IVH 1-4 6/309 (1.9%) OR 1.18 (95% CI 0.36 to 3.90) No p value IVH 3-4 1/309 (0.3%) No statistics	Placebo IVH 1-4 5/302 (1.6%) IVH 3-4 1/302 (0.3%)	Not PO	?	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d IVH 2-4 0/41 NA	Placebo IVH 2-4 0/39	Not PO	+	?	-
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16/32 C: 14/28	17-OHPC 250 mg im/w IVH (grade not defined) 3/32 (9%) p=0.851 No RR	Placebo IVH (grade not defined) 4/28 (14%)	Not PO	?	?	-
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d IVH (grade not defined) 4/292 (1.4%) OR 2.20 (95% CI 0.40-12.06) No p value	Placebo IVH (grade not defined) 2/320 (0.6%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.15. Intervention progesterone
Outcome variable: Intraventricular haemorrhage (IVH)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160/320 C: 80/160 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w IVH 3-4 3/316 (1%) OR NA p=0.55	Placebo (1 mL castor oil) IVH 3-4 0/152	Not PO	+	?	?
Rode, 2011 Denmark and Austria PREDICT	Twins DA	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) IVH (grade not defined) 10/659 (1.5%) OR 1.7 (95% CI 0.5-5.6) No p value	Placebo IVH (grade not defined) 6/674 (0.9%)	Not PO	+	+	+
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 women/212 infants C: 63 women/183 infants	17-OHPC 250 mg im/w IVH 3-4 2/212 (0.9%) RR 0.4 (95% CI 0.0-3.8) No p value	Placebo IVH 3-4 4/183 (2%)	Not PO	?	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w IVH 3-4 4/150 (3%) OR 0.7 (95% CI 0.1-3.4) p=0.63	Placebo IVH 3-4 3/75 (4%)	Not PO	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multiple pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants(327 sets of twins, 9 sets of triplets) C: 335 women/ 680 infants (326 sets of twins, 8 sets of triplets, one quadruplet)	17-OHPC 250 mg im/w IVH grade 2B or worse 4/681 (1%) RR 1.98 (95% CI 0.37-10.7) No p value	Placebo IVH grade 2B or worse 2/674 (0%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.15. Intervention progesterone
Outcome variable: Intraventricular haemorrhage (IVH)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42/86 (40 sets of twins, 2 sets of triplets) C: 42/85 (40 sets of twins, one set of triplets)	90 mg progesterone vaginal gel 8%/d IVH 3-4 3/86 (3%) Difference 2.93 (95% CI 0.31-27.58) p=0.621	Placebo IVH 3-4 1/85 (1%)	Not PO	+	?	+
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d Any IVH 9/402 (2.2%) RR 0.97 (95% CI 0.39-2.41) p=0.939 IVH 3-4 1/402 (0.3%) p=1.0 RR NA	Placebo Any IVH 9/388 (2.3%) IVH 3-4 1/388 (0.3%)	Not PO	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women/136 infants (114 singletons, 22 twins) C: 125 women/138 infants (112 singletons, 26 twins)	200 mg vaginal progesterone/d (Utrogestan) Any IVH 1/136 (0.7%) RR 0.51 (95% CI 0.05-5.30) p=0.58 aRR 0.33 (95% CI 0.01-8.84) p=0.52 aRR adjusted for maternal age, BMI, smoking status, race, history of PTB, and cervical length at the time of randomisation.	Placebo Any IVH 2/138 (1.4%)	Not PO IVH was grade 2 in all infants	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.15. Intervention progesterone
Outcome variable: Intraventricular haemorrhage (IVH)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 0/125 (0%) No RR p=0.31	200 mg vaginal progesterone/d 1/118 (0.9%)	Not PO	+	?	?
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 3/296 (1%) RR 1.51 (95% CI 0.25-9.14) p=0.69 Subgroup analysis TVS CL ≤28 mm n=94 3/94 (3%) RR 2.23 (95% CI 0.23-22.34) p=0.64	400 mg vaginal progesterone/d 2/298 (1%) Subgroup analysis TVS CL ≤28 mm n=70 1/70 (1%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, BMI; body mass index, C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, DCDA; dichorionic diamniotic, DC; dichorionic, im; intramuscular, I; intervention, ICH; intracranial haemorrhage, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NA; not applicable, OR; odds ratio, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.16. Intervention progesterone
Outcome variable: Necrotizing enterocolitis (NEC)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 5/96 (5.2%) p=0.36	Placebo 9/91 (9.8%)	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesterone supp/d 4/50 (8%) RR 2.25 (95% CI 0.74-6.83) p=0.137	Placebo 9/50 (18%)	Not PO	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	Randomised 2:1I: 1130 C: 578	17-OHPC 250 mg im/w 2/1093 (0.2%) RR 0.5 (95% CI 0.07-3.40) No p value	Placebo 2/559 (0.4%)	Not PO Patients with missing data assumed not to have the outcome	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w NEC grade II-III 2/320 (0.6%) RR 0.40 (95% CI 0.08-2.06) No p value	Placebo (castor oil) NEC grade II-III 5/322 (1.6%)	Not PO NEC II-III	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d 5/235 (2.1%) RR 1.19 (95% CI 0.32-4.36) p=0.797	Placebo 4/223 (1.8%)	Not PO ITT analysis set	?	?	+
Majhi, 2009 India	Singletons	Previous sPTB	I: 50 C: 50	100 mg vaginal progesterone/d 0/50 p=0.31	No placebo 1/50 (2%)	Not PO	?	?	?
Meis, 2003 USA	Singletons	Previous sPTB	Randomised 2:1 I:310 C:153	17-OHPC 250 mg im/w 0/305 No p-value	Placebo (castor oil) 4/152 (2.6%)	Not PO	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.16. Intervention progesterone
Outcome variable: Necrotizing enterocolitis (NEC)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d Suspected or confirmed NEC 18/581 (3%) OR 1.37 (95% CI 0.76-2.45) p=0.29	Placebo Suspected or confirmed NEC 13/574 (2%)	Not PO	+	+	+
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 3/309 (1.0%) OR 0.58 (95% CI 0.14-2.46) No p value	Placebo 5/302 (1.7%)	Not PO	?	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d NEC >stage 1 0/41 NA No p value	Placebo NEC >stage 1 0/39	Not PO	+	?	-
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2:1 I: 197 C:96 Analysed I:194 women/388 fetuses C: 94 women/188 fetuses	17-OHPC 250 mg im/w 4/386 (1.0%) OR 0.32 (95% CI 0.06–1.57) p=0.16	Placebo (castor oil) 6/188 (3.2%)	Not PO	+	+	?
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16/32 C: 14/28	17-OHPC 250 mg im/w 1/32 (3%) p=0.946	Placebo 0/28	Not PO	?	?	-
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d 1/293 (0.3%) OR 0.54 (95% CI 0.05-6.02)	Placebo 2/320 (0.6%)	Not PO	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.16. Intervention progesterone
Outcome variable: Necrotizing enterocolitis (NEC)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	Randomised 2:1 I: 160/320 C: 80/160	17-OHPC 250 mg (in 1 mL castor oil) im/w 0/315 OR NA	Placebo (1 mL castor oil) 0/152	Not PO	+	?	?
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 women/212 infants C: 63 women/183 infants	17-OHPC 250 mg im/w 2/212 (0.9%) RR 0.3 (95% CI 0.0-3.1)	Placebo 5/183 (3%)	Not PO	?	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w NEC requiring surgery 8/154 (5%) OR 1.4 (95% CI 0.2-7.6) p=0.73	Placebo NEC requiring surgery 3/75 (4%)	Not PO	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants (327 sets of twins, 9 sets of triplets) C: 335 women/ 680 infants (326 sets of twins, 8 sets of triplets, one quadruplet)	17-OHPC 250 mg im/w 8/681 (1%) RR 1.59 (95% CI 0.50-5.06)	Placebo 5/674 (1%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.16. Intervention progesterone
Outcome variable: Necrotizing enterocolitis (NEC)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rode, 2011 Denmark and Austria PREDICT	Twins DA	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) 1/659 (0.2%) OR 0.5 (95% CI 0.0-5.6) No p values	Placebo 2/674 (0.3%)	Not PO	+	+	+
Wood, 2012 Canada	Twins and triplets	ART I: 55% C: 60% Triplets: I: 2 (5%) C: 1(2%)	I: 42/86 (40 sets of twins, 2 sets of triplets) C: 42/85 (40 sets of twins, one set of triplets)	90 mg vaginal progesterone gel 8%/d 1/86 (1%) Difference 0.49 (95% CI 0.05-5.28) p=0.618	Placebo 2/85 (2%)	Not PO	+	?	+
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d 2/402 (0.5%) p=1.0 RR NA	Placebo 2/388 (0.5%)	Not PO	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women/136 infants (114 singletons, 22 twins) C: 125 women/138 infants (112 singletons, 26 twins)	200 mg vaginal progesterone /day (Utrogestan) 0/136 Statistics NA	Placebo 1/138 (0.7%)	Not PO	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.16. Intervention progesterone
Outcome variable: Necrotizing enterocolitis (NEC)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 2/125 (1.7%) No RR p=0.16	200 mg vaginal progesterone/d 0/118 (0%)	Not PO	+	?	?
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 8/296 (3%) RR 0.45 (95% CI 0.18-1.01) p=0.07 Subgroup analysis TVS CL ≤28 mm n=94 4/94 (4%) RR 0.43 (95% CI 0.11-1.42) p=0.21	400 mg vaginal progesterone/d 18/298 (6%) Subgroup analysis TVS CL ≤28 mm n=70 7/70 (10%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NEC; necrotizing enterocolitis, NNM; neonatal mortality, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.17. Intervention progesterone
Outcome variable: Neonatal sepsis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w Proven sepsis 5/1093 (0.5%) RR 0.84 (95% CI 0.20-3.56) No p value	Placebo Proven sepsis 3/559 (0.5%)	Not PO Patients with missing data assumed not to have the outcome	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w Early onset sepsis 3/320 (0.9%) RR 0.27 (95% CI 0.08-0.97) No p value	Placebo (castor oil) Early onset sepsis 11/322 (3.4%)	Not PO	?	+	+
Hassan, 2011 USA + 9 other countries PREGNANT	Singletons	Short TVS CL 10-20 mm (all) Previous PTB 16%	I: 236 C: 229	90 mg vaginal progesterone gel 8%/d Proven sepsis 7/235 (3.0%) RR 1.11 (95% CI 0.38–3.24) p=0.853	Placebo Proven sepsis 6/223 (2.7%)	Not PO	?	?	+
Majhi, 2009 India	Singletons	Previous sPTB	I: 50 C: 50	100 mg vaginal progesterone/d 0/50 p=0.16	No placebo 3/50 (6%)	Not PO	?	?	?
Meis, 2003 USA	Singletons	Previous sPTB	Randomised 2:1I:310 C:153	17-OHPC 250 mg im/w Proven sepsis 9/305 (3.0%) RR 1.12 (95% CI 0.35-3.58) No p value	Placebo (castor oil) Proven sepsis 4/152 (2.6%)	Not PO	?	?	?
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d Neonatal infection (positive blood or CNS culture) 44/537 (8%) OR 1.22 (95% CI 0.79-1.88) p=0.36	Placebo Neonatal infection (positive blood or CNS culture) 36/573 (6%)	Not PO	+	+	+
Van Os, 2015 The Netherlands TRIPLE P	Singletons	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d Proven sepsis 0/41 NA	Placebo Proven sepsis 0/39	Not PO	+	?	-
Yemini, 1985 Israel	Singletons	Previous ≥2 PTB or ≥2 spontaneous miscarriages	I: 39 C: 40	17-OHPC 250 mg im/w 1/5 (20%) No statistics	Placebo 2/14 (14.3%)	Not PO All had cerclage Denominator = infants born < 36 w	-	-	-

Project: Prevention of preterm birth
Appendix 4.1.17. Intervention progesterone
Outcome variable: Neonatal sepsis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2:1 I: 197 C:96 Analysed I:194 women/ 388 fetuses C: 94 women/ 188 fetuses	17-OHPC 250 mg im/w Proven sepsis 13/384 (3.4%) OR 0.24 (95% CI 0.10-0.57) p=0.00	Placebo (castor oil) Proven sepsis 24/188 (12.8%)	Not PO	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d 15/291 (5.2%) OR 2.16 (95% CI 0.87-5.33) No p value	Placebo 8/320 (2.5%)	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	Randomised 2:1 I: 160/320 C: 8/160	17-OHPC 250 mg (in 1 mL castor oil) im/w Proven sepsis 3/319 (1%) OR 1.5 (95% CI 0.1-16.8) p=0.77	Placebo (1 mL castor oil) Proven sepsis 1/154 (1%)	Not PO	+	?	?
Rode, 2011 Denmark and Austria PREDICT	Twins DA	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) Septicemia 20/659 (3.0%) OR 1.1 (95% CI 0.5-2.4) No p values	Placebo Septicemia 18/674 (2.7%)	Not PO	+	+	+
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 women/212 infants C: 63 women/183 infants	17-OHPC 250 mg im/w Proven sepsis 20/212 (9%) RR 1.3 (95% CI 0.6–3.0) No p value	Placebo Proven sepsis 13/183 (7%)	Not PO	?	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w Proven sepsis 4/154 (3%) OR 0.49 (95% CI 0.1-2.2) p=0.36	Placebo Proven sepsis 4/75 (5%)	Not PO	+	?	?

Project: Prevention of preterm birth
Appendix 4.1.17. Intervention progesterone
Outcome variable: Neonatal sepsis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women /681 infants (327 sets of twins, 9 sets of triplets) C: 335 women/ 680 infants (326 sets of twins, 8 sets of triplets, one quadruplet)	17-OHPC 250 mg im/w Proven sepsis 23/681 (3%) RR 2.06 (95% CI 0.91-4.66)	Placebo Proven sepsis 11/674 (2%)	Not PO	+	+	?
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies)/ 406 infants C: 389 (385 singletons and 4 twin pregnancies)/ 393 infants	100 mg vaginal progesterone pessary/d Proven early sepsis 0/402 (0%) p=0.24 RR NA	Placebo Proven early sepsis 2/388 (0.5%)	Not PO	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women/136 infants (114 singletons, 22 twins) C: 125 women/138 infants (112 singletons, 26 twins)	200 mg vaginal progesterone /day (Utrogestan) Treatment for proved or suspected sepsis 3/136 (2.2%) RR 0.28 (95% CI 0.07-1.01) p=0.05 aRR 0.29 (95% CI 0.07-1.10) p=0.07 aRR adjusted for maternal age, BMI, smoking status, race, history of PTB, and TVS CL at the time of	Placebo Treatment for proved or suspected sepsis 11/138 (8.0%)	Not PO	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.17. Intervention progesterone
Outcome variable: Neonatal sepsis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 17/296 (6%) RR 0.52 (95% CI 0.27-0.90) p=0.03 Subgroup analysis TVS CL ≤28 mm n=94 6/94 (6%) RR 0.30 (95% CI 0.09-0.68) p=0.01	400 mg vaginal progesterone/d 33/298 (11%) Subgroup analysis TVS CL ≤28 mm n=70 15/70 (21%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, BMI; body mass index, C; control, CL; cervical length, d; day, DA; diamniotic, DCDA; dichorionic diamniotic, DC; dichorionic, FFN; fetal fibronectin, im; intramuscular, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NA; not applicable, NEC; necrotizing enterocolitis, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.18. Intervention progesterone
Outcome variable: Retinopathy of prematurity

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	Randomised 2:1I: 1130 C: 578	17-OHPC 250 mg im/w 5/1093 (0.5%) RR 0.37 (95% CI (0.12-1.16) No p value	Placebo 7/559 (1.3%)	Not PO Patients with missing data assumed not to have the outcome	+	?	?
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w ROP grade 3-4 1/320 (0.3%) RR 0.34 (95% CI 0.04-3.21) No p value	Placebo (castor oil) ROP grade 3-4 3/322 (0.9%)	Not PO ROP 3-4	?	+	+
Meis, 2003 USA	Singletons	Previous sPTB	Randomised 2:1 I:310 C:153	17-OHPC 250 mg im/w 5/305 (1.6%) RR 0.50 (95% CI 0.15-1.70) No p value	Placebo (castor oil) 5/152 (3.3%)	Not PO	?	?	?
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Randomised 2:1 I: 197 C:96 Analysed I:194 women/388 fetuses C: 94 women/188 fetuses	17-OHPC 250 mg im/w 4/379 (1.1%) OR 0.21 (95% CI 0.05-0.96) p=0.04	Placebo (castor oil) 9/186 (4.6%)	Not PO	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d 6/292 (2.1%) OR 1.27 (95% CI 0.32-5.00) No p value	Placebo 6/320 (1.9%)	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	Randomised 2:1 I: 160/320 C: 80/160	17-OHPC 250 mg (in 1 mL castor oil) im/w 2/308 (0.6%) RR/OR NA p=1.0	Placebo (1 mL castor oil) 0/145	Not PO	+	?	?
Rode, 2011 Denmark and Austria PREDICT	Twins DA	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) 4/659 (0.6%) OR 1.0 (95% CI 0.2–4.8) No p value	Placebo 4/674 (0.6%)	Not PO	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.18. Intervention progesterone
Outcome variable: Retinopathy of prematurity

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Caritis, 2009 USA	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 women/212 infants C: 63 women/183 infants	17-OHPC 250 mg im/w Severe ROP ≥grade 3 0/212 RR/OR NA	Placebo Severe ROP ≥grade 3 0/183	Not PO	?	?	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w 4/145 (3%) OR 0.4 (95% CI 0.1-3.0) p=0.39	Placebo 4/62 (6.5%)	Not PO	+	?	?
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d 12/401 (3.0%) RR 1.28 (95% CI 0.51-3.26) p=0.600	Placebo 9/386 (2.3%)	Not PO	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women/136 infants (114 singletons, 22 twins) C: 125 women/138 infants (112 singletons, 26 twins)	200 mg vaginal progesterone /day (Utrogestan) 2/136 (1.5%) Statistics NA	Placebo 0/138	Not PO	?	?	+
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 2/125 (1.7%) No RR p=0.58	200 mg vaginal progesterone/d 1/118 (0.9%)	Not PO	+	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, DCDA; dichorionic diamniotic, DA; diamniotic, DC; dichorionic, GA; gestational age, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NA; not applicable, NEC; necrotizing enterocolitis, NNM; neonatal mortality, OR; odds ratio, PTB; preterm birth, ROP; retinopathy of prematurity; RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.19. Intervention progesterone
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 5/52 (9.6%)* No RR p=0.24	Placebo 9/47 (19.1%)*	Not PO *Figures from article text. In Table IV: NICU admission 47/52 (90.4%) and 38/47 (80.9 %) p=0.24	?	-	-
Ali, 2020 Egypt	Singletons	Indication for cerclage: previous second trimester loss, sPTD (<34 w) or short cervix (<25 mm)	I: 121 C:121	MacDonald cerclage + 400 mg vaginal progesterone (pessary)/d 8/100* (8.0%) No RR p=0.044	MacDonald cerclage +Placebo 15/84* (17.9%)	Not PO *Denominator includes only those women who completed the study period; excludes those who stopped treatment before 28 wk, those who were lost to follow-up, and those who had an abortion before 28 w (21/121 and 37/121) NB discrepancy with data in Table 2 8.5% and 20%, respectively	?	?	?
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 22/96 (22.9%) p<0.001 No RR Duration of NICU stay, mean (SD) 15.4±5.5 days p=0.008	Placebo 42/91 (46.2%) Duration of NICU stay, mean (SD) 19.5±5.8 days	Not PO Neonatal outcomes not defined NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Azargoon, 2016 Iran	Singletons	Previous PTB (<37 w), uterine malformations	I: 51 C: 52	400 mg vaginal progesterone supp /d 13/50 (26 %) RR 2.08 (95% CI 1.22-3.54) p=0.004 Duration of NICU stay, mean (SD) 11.6±5.8 days p=0.53	Placebo 27/50 (54 %) Duration of NICU stay, mean (SD) 10.4±6.1 days	Not PO	-	?	-

Project: Prevention of preterm birth
Appendix 4.1.19. Intervention progesterone
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	Randomised 2:1 I: 1130 C: 578	17-OHPC 250 mg im/w 137/1093 (12.5%) RR 1.21 95% CI 0.90-1.62) No p value Duration of NICU stay* Mean (SD) 18.6±20.4 d n=137 No statistics	Placebo 58/559 (10.4%) Duration of NICU stay* Mean (SD) 23.3±24.5 d n=58	Not PO Patients with missing data assumed not to have the outcome * of those admitted to NICU	+	?	?
Glover, 2011 USA	Singletons	Previous singleton sPTB (<37 w)	I: 20 C:16	400 mg oral micronized progesterone/d Duration of NICU stay Mean (SD) 6.5±10.5 d n=19 p=0.12	Placebo Duration of NICU stay Mean (SD) 7.5±9.0 d n=14	Not PO	+	?	-
Grobman, 2012 USA SCAN	Singletons	Nulliparous with short TVS CL <30 mm	I: 327 C: 330	17-OHPC 250 mg im/w 63/322 (19.6%) RR 0.93 (95% CI 0.69–1.27) No p value Duration of NICU stay Median (IQR) 17 (6.0-43.0) d n=327?* p=0.61	Placebo (castor oil) 69/329 (21.0%) Duration of NICU stay Median (IQR) 15.5 (6.0-57.5) d n=330?*	Not PO *Denominator unclear	?	+	+
Ibrahim, 2010 Egypt	Singletons	Previous PTB	I: 25 C: 25	17-OHPC 250 mg/w 3/25 (12%) p=0.03 No RR	Placebo (saline) 9/25 (36%)	Not PO	-	-	-
Jabeen, 2012 Pakistan	Singletons	Previous sPTB	I: 30 C: 30	17-OHPC 250 mg/w 7/30 (23.3%) p=0.559	Placebo (inert oil) 9/30 (30%)	Not PO	?	-	-
Majhi, 2009 India	Singletons	Previous sPTB	I: 50 C: 50	100 mg vaginal progesterone/d 0/50 p=0.12	No placebo 4/50 (8%)		?	?	?

Project: Prevention of preterm birth
Appendix 4.1.19. Intervention progesterone
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d Intensive care Mean (SD) 1.9 (8.1) d n=580 High dependency care Mean (SD) 2.1 (10.4) d n=580 Special care Mean (SD) 2.9 (8.3) d n=581	Placebo Intensive care Mean (SD) 1.8 (7.3) d n=569 High dependency care Mean (SD) 2.2 (8.4) d n=569 Special care Mean (SD) 4.2 (10.6) d n=570	Not PO	+	+	+
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 54/309 (17.5%) OR 0.75 (95% CI 0.51-1.11) No p value Duration of NICU stay Mean (SD)14.2 (16.6) d n=54 Mean difference −6.2 (−15.2 to 2.8) d	Placebo 65/302 (21.5%) Duration of NICU stay Mean (SD) 20.5 (30.7) d n=65	Not PO	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 29/389 (7%) RR 1.2 (95% CI 0.7-2.0) No p value	Placebo 24/390 (6%)	Not PO 21 stillborns excluded	?	+	?
Rai, 2009 India	Singletons	Previous sPTB	I: 75 C:75	200 micronized oral progesterone/d 10/74 (13.5%) p<0.001 No RR or OR	Placebo 38/74 (51.4%)	Not PO	-	?	?
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized vaginal progesterone/d 3/41 (7%) RR 0.53 (95% CI 0.12–2.25) No p value Duration of NICU stay Median (IQR) 3 (1.5–5.5) d n=3 Median difference (95% CI -5.0 (-27–0.15)	Placebo 5/39 (13%) Duration of NICU stay Median (IQR) 8 (7–31) d n=5	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.19. Intervention progesterone
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	Analysed I:194 women/388 fetuses C: 94 women/188 fetuses Randomised 2:1	17-OHPC 250 mg im/w Only hospital stay not NICU Mean (SD) 9 (17) days n=376 p=0.15	Placebo (castor oil) Only hospital stay not NICU Mean (SD) 13 (17) days n=178	Not PO	+	+	?
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16/32 C: 14/28	17-OHPC 250 mg im/w Mean (SD) NICU stay 18.4 (65.8) d n=32 p=0.155	Placebo Mean (SD) NICU stay 17.3 (29.8) d n=28	Not PO	?	?	-
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195/378 C: 195/382	200 mg vaginal natural progesterone/d 88/344 (25.6%) OR 1.06 (95% CI 0.68-1.67) No p value	Placebo 89/364 (24.5%)	Not PO	?	?	-
Norman, 2009 UK (9 hospitals) STOPPIT	Twins	MC twins I: 46/247 C: 45/247 No MA twins	I: 247/494 C: 247494	90 mg vaginal progesterone /day (Crinone) 167/494 (33.8%) OR 1.08 (95% CI 0.76-1.54) p=0.65 Mean (SD) NICU stay 7.5 (19.9) d n=494 (all) Mean difference 1.5 (–1.9 -5.0) p=0.38 Mean (SD) NICU stay 26.9 (33.5) n=167 (those admitted NICU) Mean difference 3.3 (–5.3-11.9) p=0.45	Placebo 158/494 (32.0%) Mean (SD) NICU stay 8.7 (23.1) d n=494 (all) Mean (SD) NICU stay 23.6 (29.5) d n=158 (those admitted NICU)	Not PO	+	+	?
Rode, 2011 Denmark and Austria PREDICT	Twins DA	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg vaginal progesterone/d (pessary) 307/664 (46.2%) OR 0.8 (95% CI 0.6–1.1) No p values	Placebo 354/678 (52.2%)	Not PO	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.19. Intervention progesterone
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Serra, 2013 Spain	Twins DCDA	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98/196 I2: 98/196 C: 98/196	I1: 200 mg vaginal progesterone (pessary) /d I2: 400 mg vaginal progesterone (pessary)/d I1: 21/194 (10.8%) I2: 19/191 (9.9%) I1+I2: 40/385 (10.4%) Comparison between groups: NS	Placebo 28/190 (14.7%)	Not PO	?	?	-
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56/155 liveborn neonates C: 25 women/75 liveborn neonates	17-OHPC 250 mg im/w Mean (SD) NICU 16.0 (23.2) d Intermediate stay 9.3 (12.5) d No statistics	Placebo Mean (SD) NICU 18.8 (30.1) d Intermediate stay 17.3 (17.8) d	Not PO Denominator unclear if pregnancies or neonates	+	?	?
Lim, 2011 The Netherlands AMPHIA	Multiple pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 /681 (327 sets of twins, 9 sets of triplets) C: 335 women/ 680 (326 sets of twins, 8 sets of triplets, one quadruplet)	17-OHPC 250 mg im/w 153/681 (22%) RR 1.29 (95% CI 0.97–1.72) No p value	Placebo 116/674 (16%)	Not PO	+	+	?
Aboulghar 2012 Egypt	Mixed Singletons 215/306 (70.3%) DC twins 91/306 (29.7%)	ART pregnancies	Randomised I:161 C:152 Analysed I:161 (112 singletons, 49 sets of twins) C:145 (103 singletons, 42 sets of twins)	400 mg vaginal natural progesterone/d Singletons 13/112 (11.6%) OR 1.8 (95% CI 0.68-4.7) No p value Twin pregnancies* 6/49 (12.2%) OR 0.39 (95% CI 0.1-1.1) No p value	Placebo Singletons 7/103 (6.8%) Twin pregnancies* 11/42 (26.2%)	Not PO *Only reported on pregnancy level	?	?	-

Project: Prevention of preterm birth
Appendix 4.1.19. Intervention progesterone
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0)	Twin pregnancy, previous sPTD, uterine malformation	I: 84 C: 76 Analysed I: 80/119 C: 70/98	100 mg vaginal progesterone/d Singletons and twins 13/80* (16.3%) C vs I OR: 3.04 (95% CI 1.41-6.54) p=0.004	Placebo Singletons and twins 26/80* (37.1%)	Not PO *Number of births with at least one neonate admitted to NICU	?	?	-
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d 68/402 (16.9%) RR 0.92 (95% CI 0.68-1.27) p=0.624 aRR 0.92 (95% CI 0.67-1.25) p=0.591 aRR adjusted for GA at randomisation, GA of previous PTB, and reason for PTB	Placebo 71/388 (18.3%)	Not PO	+	+	?
Fonseca, 2007 Brazil (multicentre inter-national, UK [5 centres], Chile, Brazil, Greece)	Mixed Singletons (226, 90%) Twins (24, 10%, all DA)	Short TVS CL ≤15 mm	I: 125 women/136 infants (114 singletons, 22 twins) C: 125 women/138 infants (112 singletons, 26 twins)	200 mg vaginal progesterone /day (Utrogestan) 33/136 (24.3%) RR 0.80 (95% CI 0.49-1.21) p=0.30 aRR 0.80 (95% CI 0.47-1.24) p=0.34 aRR adjusted for maternal age, BMI, smoking status, race, history of PTB, and CL at the time of randomisation.	Placebo 42/138 (30.4%)	Not PO	?	?	+

Project: Prevention of preterm birth
Appendix 4.1.19. Intervention progesterone
Outcome variable: Admittance to neonatal intensive care unit (NICU)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 14/125 (12%) No RR p=0.90	200 mg vaginal progesterone/d 14/118 (12%)	Not PO	+	?	?
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 39/296 (13%) RR 0.59 (95% CI 0.35-0.82) p=0.01 Subgroup analysis TVS CL ≤28 mm n=94 14/94 (15%) RR 0.37 (95% CI 0.12-0.55) p<0.001	400 mg vaginal progesterone mg/d 66/298 (22%) Subgroup analysis TVS CL ≤28 mm n=70 28/70 (40%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, aRR; adjusted risk ratio, ART; assisted reproductive technology, BMI; body mass index, C; control, CL; cervical length, DA; diamniotic, DC; dichorionic, DCDA; dichorionic, diamniotic GA; gestational age, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NICU; neonatal intensive care unit, NNM; neonatal mortality, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, SD; standard deviation, sPTB: spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.20. Intervention progesterone
Outcome variable: Long-term child outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cuijpers, 2021 The Netherlands TRIPLE P follow up (Van Os 2015)	Singletons	Short TVS CL ≤30 mm at 18-22 w	Randomised I: 41 C: 39 Follow up at 2 years I: 29 C: 30	200 mg micronized progesterone/d (Utrogestan pessary) Bayley-III cognitive score Mean (SD) 101.6 (9.7) n=28 Mean difference -3.4 (95% CI -9.3-2.6) p=0.29 Bayley-III motor score Mean (SD) 102.4 (10.9) n=28 Mean difference -4.9 (95% CI -11.2-1.4) p=0.13 Abnormal ASQ 5/27 (19%) RR (95% CI 0.33 to 3.06) p=1.00 Abnormal CBCL 1/27 (4%) RR 0.22 (95% CI 0.02 to 2.12) p=0.35 Death or abnormal developmental outcome Complete case analysis 6/41 (15%) RR 0.78 (95% CI 0.24-2.58) p=0.69 With multiple imputed data 14.4/41 (35%) RR 1.00 (95% CI 0.50-1.98) p=0.99	Placebo pessary Bayley-III cognitive score Mean (SD) 105.0 (12.5) n=29 Bayley-III motor score Mean (SD) 107.3 (12.6) n=29 Abnormal ASQ 5/27 (19%) Abnormal CBCL 4/27 (15%) Death or abnormal developmental outcome Complete case analysis 7/39 (18%) With multiple imputed data 13.7/39 (35%)	Not PO 2 year corrected year infant follow up No difference in physical (including genital and neurological examination) behavioral and health related outcomes Median (IQR) age at follow up at 25 (23-27) months of age in both groups Abnormal ASQ score: 1 SD below normative mean on two or more domains, or as score of 2 SD below normative mean on at least one domain Abnormal CBCL: score in the clinical range (> 97th percentile) Complete case analysis or with multiple imputed data includes all randomized infants	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.20. Intervention progesterone
Outcome variable: Long-term child outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	Randomised I: 618 C: 610	200 mg vaginal progesterone/d Cognitive composite score at 2 years* Mean (SD) 97.3 (17.9) n=430 Median (IQR) weeks at assessment 110.4 (104.0-121.5) Mean difference -0.48 (95% CI -2.77-1.81) p=0.68 Adj. mean difference -0.48 (95% CI -2.77-1.81) p=0.68	Placebo Cognitive composite score at 2 years* Mean (SD) 97.7 (17.5) n=439 Median (IQR) weeks at assessment 111.6 (104.6-122.2)	PO (one of three) *Bayley-III cognitive composite score at 22-26 months of chronological age. Scores were imputed for deaths	+	+	+
Northen, 2007 USA (follow-up of Meis 2003)	Singletons	Previous PTB	463 women in original study, I: 310 C: 153 348 children were potentially eligible for follow-up I: 194 C: 84	17-OHPC 250 mg im weekly ASQ Scored below cut off on at least one area at mean age 48 months 53/193 (27.5%) p=0.92 NS overall or in individual domains Preschool Activities Inventory Mean score boys 66.5 p=0.3 Mean score girls 32 p=0.5 NS difference in growth or physical abnormalities, including genital malformations	Placebo ASQ Scored below cut off on at least one area at mean age 48 months 23/82 (28%) Preschool Activities Inventory Mean score boys 67.3 Mean score girls 33	Not PO	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.20. Intervention progesterone
Outcome variable: Long-term child outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Norman, 2018 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM HTA-report	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	Randomised I: 618 C: 610	200 mg vaginal progesterone/d Cognitive composite score at 2 years* Mean (SD) 99.7 (14.7) n=410 Mean difference -0.04 (95% CI -0.26-0.19)	Placebo Cognitive composite score at 2 years* Mean (SD) 99.5 (14.7) n=423	PO (one of three) *Bayley-III cognitive composite score at 22-26 months of chronological age. Denominator is children alive at 2 years	+	+	+
Simons, 2021 Systematic review	7 RCTs (based on 5 RCTs) with singletons (n=3) and multifetal pregnancies (n=4)	Children born to women who received progesterone treatment for any indication during pregnancy	4222 children aged 6 m to 8 years	Singletons exposed to progesterone Mean (SD) composite Bailey score at 2 years 99.7 (14.7) n=438 (2 RCTs) Mean standardized difference -0.04 (95% CI -0.26 to 0.19)	Singletons exposed to placebo Mean (SD) composite Bailey score at 2 years 99.5 (14.7) n=452 (2 RCTs)	MA based two RCTs, unpublished data from one RCT, Cuijpers et al., 2020 and published data from one RCT, Norman et al., 2018	+	?	+
McNamara, 2015 UK STOPPIT follow up (Norman 2009)	Twins	MC twins I: 46/247 C: 45/247 No MA twins	I: 247/494 C: 247494	90 mg vaginal progesterone /day (Crinone) Delayed development CDI score (≥30% below age range) 42/140 (30%) 0.87 (95% CI 0.46–1.63) p=0.66 Borderline/delayed development CDI score (≥25% below age range) 60/140 (43%) OR 0.67 (95% CI 0.35–1.28) p=0.23	Placebo Delayed development CDI score (≥30% below age range) 65/184 (35%) Borderline/delayed development CDI score (≥25% below age range) 104/184 (57%)	Not PO No evidence of difference in general health status assessed with Health Utilities Index	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.20. Intervention progesterone
Outcome variable: Long-term child outcome

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments/definitions	Directness *	Study limitations *	Precision *
				Intervention	Control				
Rode, 2011 Denmark and Austria PREDIT	Twins DA	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334/668 C: 343/686	200 mg micronized vaginal progesterone (Utrogestan pessary) Mean (SD) ASQ score at 6 m 215 (37.5) n=517* (78.8%) p=0.45 Mean (SD) ASQ score at 18 m 193 (42.6) n=505* (76.8%) p=0.89 ASQ <115 3.8%	Placebo pessary Mean (SD) ASQ score at 6 m 218 (36.7) n=533* (79.7%) Mean (SD) ASQ score at 18 m 194 (40.6) n=486* (72.8%) ASQ <115 3.7%	Not PO *Numbers calculated, only % in article	+	+	+
Vedel, 2016 Denmark PREDICT follow up, Rode 2011	Twins DA	Fertility treatment I: 50.0% C: 47.2%	Randomised I: 114 C: 106 women returned ASQ for at least one child I: 492 children C: 497 children (register data) I: 225 children C: 212 children (ASQ data)	200 mg micronized vaginal progesterone (Utrogestan pessary) Total ASQ score Mean (SD) 269 (28.2) n=225 p=0.03 Gross motor skill 54.6 (7.6) p=0.03 NS difference for the other 4 domains Total score <10th percentile 14/225 (6.2%) OR 0.47 (95% CI 0.21-1.06) No difference for the 5 different domains <10th centile Age at completion, mean (SD) 56.9 (6.0) months p=0.76	Placebo pessary Total ASQ score Mean (SD) 261.7 (31.4) n=212 Gross motor skill 52.5 (9.6) Total score <10th percentile 26/212 (12.3%) Age at completion, mean (SD) 57.1 (6.1) months	No difference in hospital admissions, length of hospital stay and no overall difference in the rate of different diagnoses. ASQ (5 domains) assessed at 4 or 5 years of age (max score total 300 points, each domain [gross motor, fine motor, communication, problem solving, personal /social skills] max 60 points)	+	?	?

17-OHPC; 17-α-hydroxyprogesterone caproate, aRR; adjusted risk ratio, ASQ; Age and Stages Questionnaire, C; control, CBCL; child behaviour checklist, CDI; child development inventory score categorization, CL; cervical length, DA; diamniotic, HTA; Health Technology Assessment, I; intervention, IQR; interquartile range, m; months, MC; monochorionic, NS; not significant, OR; odds ratio, PTB; preterm birth, RCT; randomised controlled trial, RR; risk ratio, ROP; retinopathy of prematurity, SD; standard deviation, sPTB, spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.21 Intervention progesterone
Outcome variable: Maternal mortality

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Price, 2021 Zambia	Singletons	HIV	I: 399 C: 401	17-OHPC 250 mg im/w 0/399 (0%) No statistics	Placebo 1/401 (<1%)	Not PO	?	+	?
Other interventions in comparison with progesterone									
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary 0/148 (0%) No statistics	400 mg vaginal progesterone /d 0/149 (0%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, C; control, CL; cervical length, HIV; human immunodeficiency virus, im; intramuscular, I; intervention, PO; primary outcome, TVS; transvaginal scan, w; week

Project: Prevention of preterm birth
Appendix 4.1.22. Intervention progesterone
Outcome variable: Maternal morbidity, hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, eclampsia)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 8/52 (15.4%) No statistics	Placebo 1/47 (2.1%)	Not PO No definition of hypertension	?	-	-
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d GH 3/96 (3.1%) p=0.66	Placebo GH 2/91 (2.2%)	Not PO OBS critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB: High cerclage rates in both groups	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w PE 47/1130 (4.2%) RR 0.86 (95% CI 0.51-1.46) No p value	Placebo PE 30/578 (5.2%)	Not PO	+	?	?
Hauth, 1983 USA	Singletons	Women from an active duty military population	I: 80 C: 88	17-OHPC 1000mg im/w PIH 10/80 (12.5%) NS No p value, OR or RR	Placebo (castor oil) PIH 12/88 (13.6%)	Not PO	-	-	-
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg progesterone/day GH 23/593 (4%) PE 10/593 (2%) Eclampsia 0/593 No statistics	Placebo GH 24/590 (4%) PE 11/590 (2%) Eclampsia 1/590 (<1%)	Not PO	+	+	+
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w PIH 13/399 (3%) RR 2.2 (95% CI 0.8-5.7) PE 6/399 (2%) RR 0.7 (95% CI 0.2-1.9) Eclampsia 0/399 (0%) No RR. No p values	Placebo PIH 6/401 (2%) PE 9/401 (2%) Eclampsia 1/401 (< 1%)	Not PO	?	+	?

Project: Prevention of preterm birth
Appendix 4.1.22. Intervention progesterone
Outcome variable: Maternal morbidity, hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, eclampsia)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w HDP 16/194 (8.2%) OR 1.0 (95% CI 0.4–2.8) p=0.51	Placebo (castor oil) 7/94 (7.4%)	Not PO	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d PE 24/188 (12.8%) OR 0.85 (95% CI 0.45-1.60) No p value	Placebo PE 28/190 (14.7%)	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w GH/PE 40/160 (25%) OR 1.40 (0.72-2.73) p=0.41	Placebo (1 mL castor oil) GH/PE 15/78 (19%)	Not PO	+	?	?
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d PE 3/596 Eclampsia 0/596 No statistics	Placebo PE 0/598 Eclampsia 1/598	Not PO PE >5 d hospitalisation Eclampsia >10 d hospitalisation	+	+	?
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334 C: 343	200 mg vaginal progesterone/d (pessary) PE 27/332 (8.1%) OR 0.9 (95% CI 0.5-1.5) No p values	Placebo PE 30/341 (8.8%)	Not PO	+	+	+
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w HDP 66/325 (20.3%) RR 1.2 (95% CI 0.9-1.7) No p values	Placebo HDP 55/330 (16.7%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.1.22. Intervention progesterone
Outcome variable: Maternal morbidity, hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, eclampsia)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d HDP 5/97 (5.2%) I2: 400 mg vaginal progesterone (pessary)/d HDP 6/97 (6.2%) HDP I1 + I2: 11/194 (5.7%) I1, I2, C= NS I1+I2 vs C= NS I1 vs I2=NS	Placebo HDP 3/96 (3.1%)	Not PO	?	?	-
Lim, 2011 The Netherlands AMPHIA	Multiple pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women C: 335 women	17-OHPC 250 mg im/w HDP 54/336 (16%) RR 0.93 (95% CI 0.67-1.30) No p value	Placebo HDP 57/335 (17%)	Not PO	+	+	?
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d PE 12/398 (3.0%) RR 1.47 (95% CI 0.61-3.55) p=0.396	Placebo PE 8/389 (2.1%)	Not PO	+	+	?
Caritis, 2009 USA SSTARS	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w GH/PE 15/71 (21%) RR 0.7 (95% CI 0.4-1.3) No p value	Placebo GH/PE 18/63 (29%)	Not PO	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.22. Intervention progesterone
Outcome variable: Maternal morbidity, hypertensive disorders in pregnancy (gestational hypertension, preeclampsia, eclampsia)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Combs, 2010	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w GH/PE 8/56 (14%) RR 0.43 (95% CI 0.12-1.62) p=0.21	Placebo GH/PE 7/25 (28%)	Not PO	+	?	?
Other interventions in comparison with progesterone									
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary HDP 16/148 (10.8%) RR 0.81 (95% CI 0.43-1.49) p=0.59 Eclampsia/HELLP 1/148 (0.7%) RR 0.34 (95% CI 0.04-3.19) p=0.62	400 mg vaginal progesterone/d HDP 20/149 (13.4%) Eclampsia/HELLP 3/148 (2%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, aRR; adjusted relative risk, ART; assisted reproductive technology, C; control, CL; cervical length, DA; diamniotic, DC; dichorionic, DCDA; dichorionic diamniotic, GA; gestational age, GH; gestational hypertension, HDP; hypertensive disorder of pregnancy, HELLP; hemolysis elevated liver enzymes low platelets, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NA; not applicable, OR; odds ratio, PE; preeclampisa, PIH; pregnancy induced hypertension, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.23. Intervention progesterone
Outcome variable: Maternal morbidity, gestational diabetes mellitus (GDM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 11/52 (21.2%) No statistics	Placebo 6/47 (12.8%)	Not PO	?	-	-
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 1/96 (1.0%) p=0.51	Placebo 2/91 (2.2%)	Not PO OBS critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w 35/1130 (3.1%) RR 0.91 (95% CI 0.54-1.54) No p value	Placebo 21/578 (3.6%)	Not PO	+	?	?
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg progesterone/day 27/593 (5%) No statistics	Placebo 37/590 (6%)	Not PO	+	+	+
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w 13/194 (6.7%) OR 1.0 (95% CI 0.3-2.3) p=0.51	Placebo (castor oil) 7/94 (7.4%)	Not PO	+	+	?
Brizot, 2015 Brazil	Twins DA	MC 25% (I) and 19% (C) Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d 12/188 (6.4%) OR 0.79 (95% CI 0.33-1.88) No p value	Placebo 15/190 (7.9%)	Not PO	?	?	-
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART, I: 66% C:58% Prior PTB, I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w 21/160 (13%) OR 1.30 (95% CI 0.55-3.09) p=0.67	Placebo (1 mL castor oil) 8/78 (10%)	Not PO	+	?	?

Project: Prevention of preterm birth
Appendix 4.1.23. Intervention progesterone
Outcome variable: Maternal morbidity, gestational diabetes mellitus (GDM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334 C: 343	200 mg vaginal progesterone/d (pessary) 16/332 (4.8%) OR 1.4 (95% CI 0.6-3.0) No p values	Placebo 12/341 (3.5%)	Not PO	+	+	+
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C:96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d 2/97 (2.1%) I2: 400 mg vaginal progesterone (pessary)/d 4/97 (4.1%) I1 + I2: 6/194 (3.1%) I1, I2, C= NS I1+I2 vs C= NS I1 vs I2=NS	Placebo 5/96 (5.2%)	Not PO	?	?	-
Lim, 2011 The Netherlands AMPHIA	Multiple pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women C: 335 women	17-OHPC 250 mg im/w 7/336 (2%) RR 0.99 (95% CI 0.35-2.78) No p value	Placebo 7/332 (2%)	Not PO	+	+	?
Combs, 2010 USA	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w 9/55 (16%) RR 1.43 (95% CI 0.31-9.01) p=0.77	Placebo 3/25 (12%)	Not PO	+	?	?

Project: Prevention of preterm birth
Appendix 4.1.23. Intervention progesterone
Outcome variable: Maternal morbidity, gestational diabetes mellitus (GDM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Gyamfi, 2009 Secondary analysis of Meis, 2003 (singletons) and Rouse, 2007 (twins) USA	Mixed singletons and twins	Singletons: Women with previous sPTB Twins: Unselected DA twins	Singleton I: 293 C: 148 Twins: I: 323 C: 330	17-OHPC 250 mg im/w Singletons 17*/293 (5.8%) RR 1.23 (95% CI 0.52-2.89) p=0.64 Twins 24*/323 (7.4%) RR 0.98 (95% CI 0.57-1.68) p=0.94	Placebo Singletons 7*/148 (4.7%) Twins 25*/330 (7.6%)	Not PO *Numbers calculated from percentages in article	Meis, 2003 ? Rouse, 2007 +	? ?	? +

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, DA; diamniotic, DC; dichorionic, DCDA; dichorionic diamniotic, FFN; fetal fibronectin, GA; gestational age, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.24. Intervention progesterone
Outcome variable: Maternal morbidity, cholestasis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d Elevated liver enzymes 0/96	Placebo Elevated liver enzymes 0/91	Not PO OBS critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results OBS High rates of cerclage in both groups	-	?	-
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg vaginal progesterone/d Cholestasis 4/593 (1%) No statistics	Placebo Cholestasis 6/589 (1%)	Not PO	+	+	+
Brizot, 2015 Brazil	Twins DA	MC I: 25% C: 19% Only naturally conceived, no history of PTB	I: 195 C: 195	200 mg vaginal natural progesterone/d Elevated liver enzymes 0/188 NA No p value	Placebo Elevated liver enzymes 2/190 (1.0%)	Not PO	?	?	-
Rehal, 2021 UK (+5 other European countries)	Twins	MC I: 23% C: 23% ART I: 34% C: 35%	I: 582 C: 587	600 mg vaginal progesterone/d Cholestasis 0/596 Elevated liver enzymes 1/596 No statistics	Placebo Cholestasis 1/598 Elevated liver enzymes 1/598	Not PO Cholestasis > 2 days hospitalisation	+	+	?
Rode, 2011 Denmark and Austria PREDICT	Twins (DA)	MC I: 43/334 (12.9%) C: 57/343 (16.6%)	I: 334 C: 343	200 mg vaginal progesterone/d (pessary) Elevated liver enzymes 11/332 (3.3%) OR 0.4 (95% CI 0.2-0.9) No p value	Placebo Elevated liver enzymes 25/341 (7.3%)	Not PO	+	+	+

Project: Prevention of preterm birth
Appendix 4.1.24. Intervention progesterone
Outcome variable: Maternal morbidity, cholestasis

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d Cholestasis 1/97 (1.0%) I2: 400 mg vaginal progesterone (pessary)/d Cholestasis 5/97 (5.2%) I1 + I2: Cholestasis 6/194 (3.1%) I1, I2, C=NS I1+I2 vs C=NS I1 vs I2=NS	Placebo Cholestasis 0/96	Not PO	?	?	-

17-OHPC;17-α-hydroxyprogesterone caproate, ART; assisted reproductive technology, C; control, CL; cervical length, DA; diamniotic, DC; dichorionic, DCDA; dichorionic diamniotic, FFN: fetal fibronectine, GA; gestational age, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NS; not significant, OR; odds ratio, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.25 Intervention progesterone
Outcome variable: Maternal morbidity, infections including chorioamnionits

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d CA 9/96 (9.3%) p=0.55 PP sepsis 4/96 (4.1%) p=0.13	Placebo CA 12/91 (13.1%) PP sepsis 10/91 (0.9%)	Not PO OBS critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB: High rates of cerclage in both groups	-	?	-
Blackwell, 2020 USA PROLONG	Singletons	Previous singleton sPTB	I: 1130 C: 578 Randomised 2:1	17-OHPC 250 mg im/w CA 9/1130 (0.8%) RR 2.24 (95% CI 0.48-10.41) No p value	Placebo CA 2/578 (0.3%)	Not PO	+	?	?
Meis, 2003 USA	Singletons	Previous sPTB	I:310 C:153 Randomised 2:1	17-OHPC 250 mg im/w CA 11/306 (3.6%) RR 1.09 (95% CI 0.39-3.09) No p value	Placebo (castor oil) CA 5/153(3.3%)	Not PO	?	?	?
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg progesterone/day CA 9/83 (11%) No statistics	Placebo CA 10/84 (12%)	Not PO Infectious morbidity: antibiotics during delivery, and histology CA based on placenta examination.	+	+	+
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w CA 1/399 (<1%) No statistics	Placebo CA 0/401 (0%)	Not PO	?	+	?
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 1/41 (12%) RR 1.1 (95% CI 0.083-15) No p value	Placebo 1/39 (11%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.25 Intervention progesterone
Outcome variable: Maternal morbidity, infections including chorioamnionits

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Combs, 2011 USA	Twins DCDA	20% fetal reduction ART I: 66% C:58% Prior PTB: I: 12% C: 13%	I: 160 C: 80 Randomised 2:1	17-OHPC 250 mg (in 1 mL castor oil) im/w CA 3/158 (2%) p=0.55 Sepsis 0/155 NA PP endometritis 0/155 NA	Placebo (1 mL castor oil) CA 0/78 Sepsis 0/78 PP endometritis 0/78	Not PO	+	?	?
Norman, 2009 UK (9 hospitals) STOPPIT	Twins	MC twins I: 46/247 C: 45/247 No MA twins	I: 247 C: 247	90 mg vaginal progesterone /day (Crinone) CA or intrauterine infection 0 No denominator	Placebo CA or intrauterine infection 0 No denominator	Not PO	+	+	?
Rouse, 2007 USA SSTARS	Twins (DA)	MC I: 59/327 (18%) C: 57/334 (17.1%)	I: 327 C: 334	17-OHPC 250 mg im/w CA 6/324 (1.9%) RR 1.0 (95% CI 0.3-3.1) No p value	Placebo CA 6/330 (1.8%)	Not PO	+	?	+
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women C: 335 women	17-OHPC 250 mg im/w CA 20/336 (6%) RR 1.30 (95% CI 0.68-2.49) No p value	Placebo CA 15/332(5%)	Not PO CA as determined with placenta histology	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.25 Intervention progesterone
Outcome variable: Maternal morbidity, infections including chorioamnionits

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d CA 19/398 (4.8%) RR 1.43 (95% CI 0.72-2.85) p=0.312 aRR 1.49 (95% CI 0.75–2.98) adjusted p=0.253 Adjusted for GA at randomisation, GA of previous PTB, and reason for previous PTB	Placebo CA 13/389 (3.3%)	Not PO CA treated with antibiotics	+	+	?
Caritis, 2009 USA SSTARS	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w CA 1/71 (1%) NA	Placebo CA 0/63		?	?	?
Combs, 2010	Triplets	Trichorionic triamniotic triplets MAR I: 90% C: 84%	I: 56 C: 25	17-OHPC 250 mg im/w CA 5/56 (9%) RR 1.13 (95% CI 0.17-12.65) p>0.99 Sepsis 1/56 (2%) p>0.99 PP endometritis 2/56 (4%) p>0.99	Placebo CA 2/25 (8%) Sepsis 0/25 PP endometritis 0/25	Not PO	+	?	?

Project: Prevention of preterm birth
Appendix 4.1.25 Intervention progesterone
Outcome variable: Maternal morbidity, infections including chorioamnionits

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention Progesterone	Control Placebo				
Other interventions in comparison with progesterone									
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 mm in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) CA 12/42 (28.6%) RR 0.76 (95% CI 0.35-1.65) No p value	17-OHPC 250 mg weekly CA 8/37 (21.6%)	Not PO	+	?	-
Dang 2019 Vietnam (single centre)	Twins	Short TVS CL ≤38 mm (women with history of cervical surgery excluded)	I:150 C: 150	Arabin pessary ABU treated with antibiotics 14/148 (9.5%) RR 1.17 (95% CI 0.56-2.45) p=0.69 CA 0/148 (0%) No statistics Genital tract infection 5/148 (3.4) RR 0.72 (95% CI 0.23-2.21) p=0.77	400 mg vaginal progesterone /d ABU treated with antibiotics 12/149 (8.1%) CA 0/148 (0%) Genital tract infection 7 /149 (4.7%)	Not PO	?	?	?

17-OHPC;17-α-hydroxyprogesterone caproate, ABU; asymptomatic bacteriuria, aRR, adjusted relative risk, ART; assisted reproductive technology, C; control, CA; chorioamnionitis, CL; cervical length, DA; diamniotic, DC; dichorionic, DCDA; dichorionic diamniotic, GA; gestational age, I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NB; nota bene, OR; odds ratio, PP; postpartum, PTB; preterm birth, RR; risk ratio, sPTB: spontaneous preterm birth, TVS; transvaginal scan

Project: Prevention of preterm birth
Appendix 4.1.26 Intervention progesterone
Outcome variable: Maternal morbidity, preterm prelabour rupture of membranes (PPROM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Aflatoonian, 2013 Iran	Singletons	ART pregnancies	I: 52 C: 47	17-OHPC 250 mg im/w 4/52 (7.7%) No statistics	Placebo 2/47 (4.3%)	Not PO	?	-	-
Ashoush, 2017 Egypt	Singletons	Previous sPTB (<37 w)	I: 106 C: 106	400 mg oral progesterone/d 36/96 (37.5%) p=0.27	Placebo 40/91 (44.0%)	Not PO NB critical comment to article by Katsanevakis, Mol and Thornton concerning recruitment and results NB High rates of cerclage in both groups	-	?	-
Norman, 2016 UK (UK 65 hospitals, Sweden 1 hospital) OPPTIMUM	Singletons	FFN pos group: Any of previous PTB, second trimester loss, cervical surgery FFN neg group: previous sPTB <34 w or short TVS CL ≤25 mm	I: 618 C: 610	200 mg progesterone/day 65/593 (11%) No statistics	Placebo 72/590 (12%)	Not PO	+	+	+
O'Brien 2007 USA (+4 other countries)	Singletons	Previous sPTB	I: 332 C: 327	90 mg vaginal progesterone gel 8%/d 37/309 (12.0%) 0.95 (95%CI 0.58-1.53) No p value	Placebo 38/302 (12.6%)	Not PO	?	?	?
Price, 2021 Zambia	Singletons	HIV	I: 399 C:401	17-OHPC 250 mg/w 5/399 (1%) RR 0.7 (95% CI 0.2-2.2) No p value	Placebo 7/401 (2%)	Not PO	?	+	?
Van Os, 2015 The Netherlands TRIPLE P	Singleton	Short TVS CL ≤30 mm, no previous PTB	I: 41 C: 39	200 mg micronized progesterone vaginal/d 3/41 (7%) RR 0.59 (95% CI 0.15–2.3) No p value	Placebo 5/39 (13%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.1.26 Intervention progesterone
Outcome variable: Maternal morbidity, preterm prelabour rupture of membranes (PPROM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Awwad, 2015 Libanon PROGESTWIN	Twins, unselected	ART 75% MC 17%	I:197 C: 96 Randomised 2:1	17-OHPC 250 mg im/w 6/131 (4.6%) OR 1.3 (95% CI 0.2–6.6) p=0.55	Placebo (castor oil) 2/56 (3.6%)	Not PO	+	+	?
Briery, 2009 USA	Twins, unselected	1/3 previous PTB	I: 16 C: 14	17-OHPC 250 mg im/w 1/16 (6%) p=0.525	Placebo 1/14 (7%)	Not PO Numbers for PTB <37 w calculated from table 2	?	?	-
Serra, 2013 Spain	Twins (DCDA)	MAR I1: 92/96 (95.8%) I2: 94/97 (96.9%) C: 96/97 (99.0%)	I1: 98 I2:98 C: 98	I1: 200 mg vaginal progesterone (pessary) /d 4/97 (4.1%) I2: 400 mg vaginal progesterone (pessary)/d 1/97 (1.0%) I1 + I2: 5/194 (2.6%) I1 vs I2 vs C= NS I1+I2 vs C= NS I1 vs I2=NS	Placebo 3/96 (3.1%)	Not PO	?	?	-
Lim, 2011 The Netherlands AMPHIA	Multifetal pregnancies	Triplets/+ I: 9 (3%) C: 9 (3%) (incl.one quadruplet) MC I: 57 (17%) C: 57 (17%) Fertility treatment I: 140 (42%) C: 120 (36%)	I: 336 women C: 335 women	17-OHPC 250 mg im/w 34/336 (10%) RR 1.22 (95% CI 0.76-1.96) No p value	Placebo 28/332(8%)	Not PO	+	+	?

Project: Prevention of preterm birth
Appendix 4.1.26 Intervention progesterone
Outcome variable: Maternal morbidity, preterm prelabour rupture of membranes (PPROM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Cetingoz, 2011 Turkey	Mixed Singletons I: 41/80 (51.3%) C: 42/70 (60%) Twins I: 39/80 (48.7%) C: 28/70 (40.0)	Twin pregnancy, previous sPTD, uterine malformation	I: 84 C: 76	100 mg vaginal progesterone/d Singletons and twins 3/80 (3.8%) p>0.05	Placebo Singletons and twins 2/70 (2.9%)	Not PO No data for singletons and twins. respectively	?	?	-
Crowther, 2017 Australia PROGRESS	Mixed Singletons n=775 (98.5% Twins n=12 (1.5%)	Previous sPTD <37 w	I: 398 (390 singletons and 8 twin pregnancies) 406 infants C: 389 (385 singletons and 4 twin pregnancies) 393 infants	100 mg vaginal progesterone pessary/d 51/398 (12.8%) RR 1.13 (95% CI 0.78-1.65) p=0.518 aRR 1.14 (95% CI 0.78-1.66) adjusted p=0.500 Adjusted for GA at randomisation, GA of previous PTB, and reason for previous PTB	Placebo 44/389 (11.3%)	Not PO	+	+	?
Caritis, 2009 USA SSTARS	Triplets	30% DC or unknown chorionicity ART: 70%	I: 71 C: 63	17-OHPC 250 mg im/w 6/71 (8%) RR 0.8 (95% CI 0.3-2.1) No p value	Placebo 7/63 (11%)	Not PO	?	?	?

Project: Prevention of preterm birth
Appendix 4.1.26 Intervention progesterone
Outcome variable: Maternal morbidity, preterm prelabour rupture of membranes (PPROM)

* + No or minor problems
? Some problems
- Major problems

Author, year Country Trial acronym	Singletons/ Twins/ Triplets	Risk factor	Number of randomised patients n=	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention	Control				
Other interventions in comparison with progesterone									
Keeler, 2009a USA	Singletons	Short TVS CL ≤25 in women with risk factors for PTB (history of sPTB, second-trimester pregnancy loss, previous cervical surgery or uterine anomaly)	I: 42 C: 37	Cerclage (MacDonald) 13/42 (32.5%) RR 1.14 (95% CI 0.61-2.12) No p-value	17-OHPC 250 mg weekly 13/37 (37.1%)	Not PO	+	?	-
Cruz-Melguizo, 2018 Spain (27 centres)	Singletons	Short TVS CL ≤25 mm (women with cervical surgery and ≥3 previous PTBs were excluded)	I: 125 C: 118	Pessary 12/125 (10%) RD 0.28 (95% CI -7.08 to 7.64) p=0.94	200 mg vaginal progesterone/d 11/118 (9%)	Not PO	+	?	?

17-OHPC; 17-α-hydroxyprogesterone caproate, aRR; adjusted risk ratio, ART; assisted reproductive technology, C; control, CL; cervical length, DA; diamniotic, DC; dichorionic, DCDA; dichorionic diamniotic, GA; gestational age, HIV; human immunodeficiency virus I; intervention, IUFD; intrauterine fetal death, MAR; medically assisted reproduction; MC; monochorionic, MCDA; monochorionic diamniotic, NS; not significant, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, RD; risk difference, sPTB: spontaneous preterm birth, TVS; transvaginal scan