Region Västra Götaland, HTA-centrum
Regional activity-based HTA [Verksamhetsbaserad HTA]
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Results section 8.3

Comparison pessary vs no pessary

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

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Table of contents

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

Results in singleton pregnancies

Included studies

Seven RCTs reporting on singleton pregnancies were included (Appendix 2). All trials were considered to have low risk of bias (Table 1). No systematic reviews contributed to the meta-analyses. In total, 2873/2951 women/babies were included in the analyses. One trial included both singleton (92.4%) and twin (7.6%) pregnancies (Pacagnella et al., 2022). For this trial, the outcomes any preterm birth <37, 34, 32, 28 gestational weeks were reported separately for singletons and twins. For all other outcomes singleton and twin pregnancies were mixed but reported as singleton outcomes.

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

Singleton pregnancies		**Multifetal pregnancies**		**Mixed singleton and multifetal**	
Dugoff, 2018	Low	Berghella, 2017a	Low	Pacagnella, 2022	Low
Goya, 2012	Low	Goya, 2016	Low		
Hui, 2013	Low	Liem, 2013a	Low		
Karbasian, 2016	Low	Nicolaides, 2016a	Low		
Nicolaides, 2016b	Low	Norman, 2021	Low		
Saccone, 2017c	Low				

Setting

The included trials were conducted in several different countries, including the USA, China, Iran, Brazil, Italy and Spain. In addition, there was one British study with cohorts from nine different countries (England, Slovenia, Portugal, Chile, Australia, Italy, Albania, Germany, and Belgium, 16 hospitals).

Population

All trials included asymptomatic women with the specific risk factor for preterm birth, short cervical length. The cut off for inclusion was cervical length ≤25 mm in all trials except for one that used ≤30 mm (Pacagnella et al., 2022).

Intervention

Women were randomised between the gestational weeks 18+0 and 23+6 and the pessary was inserted shortly after randomisation. In all trials, the pessary was removed at 36 or 37 gestational weeks. In case of bleeding, contractions, PPROM, or other complications, the pessary was removed earlier. In two trials it was not stated whether the pessary was removed or not at PPROM (Goya et al., 2012; Saccone et al., 2017c). Two trials compared pessary and progesterone with vaginal progesterone (Karbasian et al., 2016; Pacagnella et al., 2022). The remaining trials compared pessary with no pessary. In one of the trials, a vaginal examination was performed in the control group to simulate pessary insertion (Hui et al., 2013). If the cervical length was ≤20 mm (Dugoff et al., 2018; Saccone et al., 2017c) or ≤15 mm (Nicolaides et al., 2016b), vaginal progesterone was recommended in addition. Blinding was otherwise not feasible due to the nature of the intervention. The Arabin pessary was used in five trials, the Biotech cup in one trial (Dugoff et al., 2018), and the Ingamed pessary in one trial (Pacagnella et al., 2022). The Arabin pessary is from Germany, the Biotech cup is available in the United States, and the Ingamed in Brazil. They are all very similar.

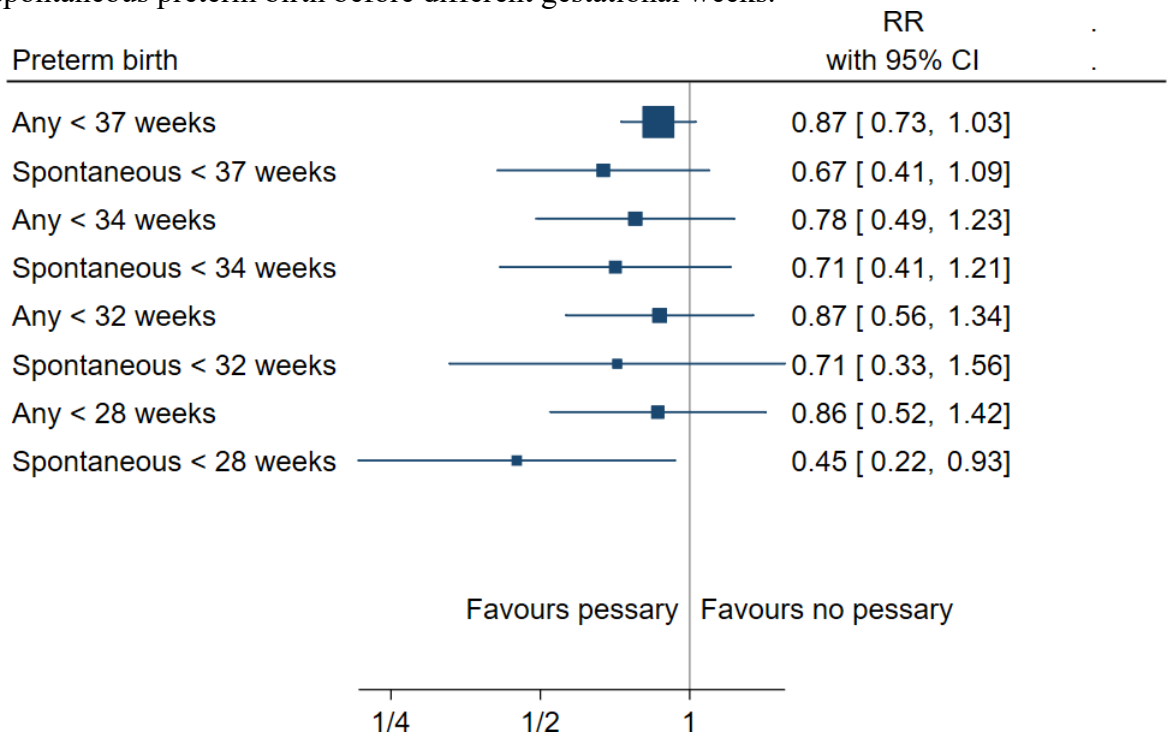
Directness, study limitations, and precision
A number of the included trials had some problems with directness; due to ethnicity (a high proportion of Afro-American women) (Dugoff et al., 2018), an unusually high incidence of preterm birth in the control group (Goya et al., 2012), 7.6% twins in one trial (Pacagnella et al., 2022), or a screening process that was not clearly described (Saccone et al., 2017c). The risk of bias in the individual studies is 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 4.3. All trials were limited by lack of blinding. However, blinding of participants and personnel was not feasible. Hence, all the included trials were classified as having low risk of bias. Trials were generally underpowered for outcomes such as neonatal mortality and morbidity, and maternal morbidity since these were not primary outcomes, except in the trial by Pacagnella et al. (2022).
Furthermore, two trials were stopped early, affecting precision. The reasons were, a competing trial, and a lower enrollment than expected, respectively (Nicolaides et al., 2016b; Dugoff et al., 2018).

Results per outcome

Preterm birth in singletons across gestational weeks

Meta-analyses of trials reporting any preterm birth or spontaneous preterm birth (<37, <34, <32, and <28 gestational weeks), are presented below. Figure 1 presents the pooled estimates from the meta-analyses of the trials with low risk of bias, for any type of pessary and short cervical length as a risk factor for preterm birth.

Figure 1. Summary graph of pooled estimates from meta-analyses comparing pessary and no pessary in women with a singleton pregnancy and short cervical length, regarding the outcomes any and spontaneous preterm birth before different gestational weeks.



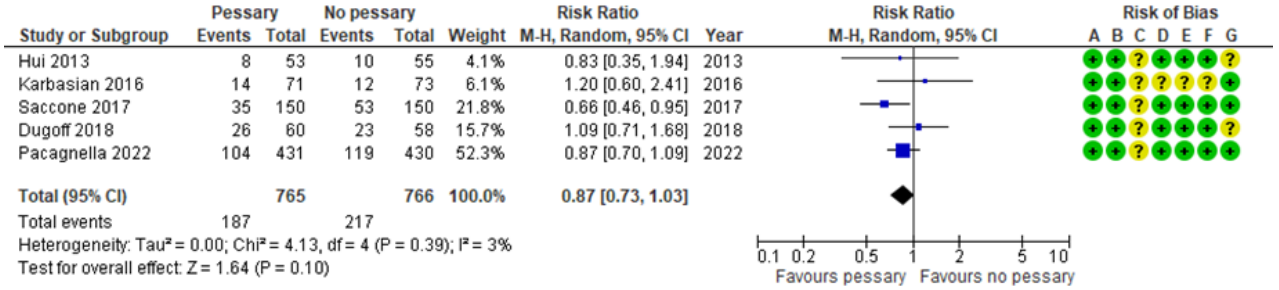
All pooled estimates (RR) were below 1.0, ranging from 0.45 to 0.87, although there were generally no significant differences in rate of preterm birth across gestational weeks, comparing pessary with no pessary in women with short cervical length.

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 4.3.1.a and figure 2)
A meta-analysis of five trials, including 1531 women, showed no difference in the rate of any preterm birth, RR 0.87 (95% CI 0.73 to 1.03). The crude event rate across trials was 28.3% without pessary. The pooled weighted RD was -3.7% percentage points (95% CI -8.5 to 1.0).

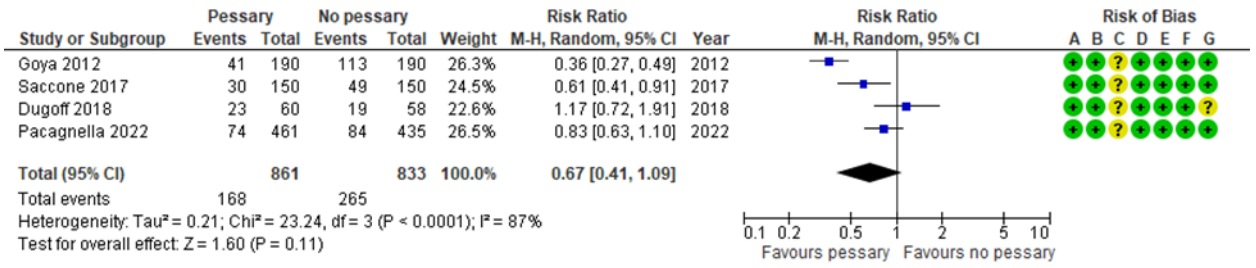
Figure 2. Outcome: Any preterm birth <37 weeks.



Conclusion: Pessary compared with no pessary probably results in no difference in the risk of any preterm birth before 37 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <37 weeks (Appendix 4.3.1.b and Figure 3)
A meta-analysis of four trials, including 1694 women, showed no difference in the rate of spontaneous preterm birth, RR 0.67 (95% CI 0.41 to 1.09). The crude event rate across trials was 31.8% without pessary. The pooled weighted RD was -12.6% percentage points (95% CI -30.6 to 5.4).

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



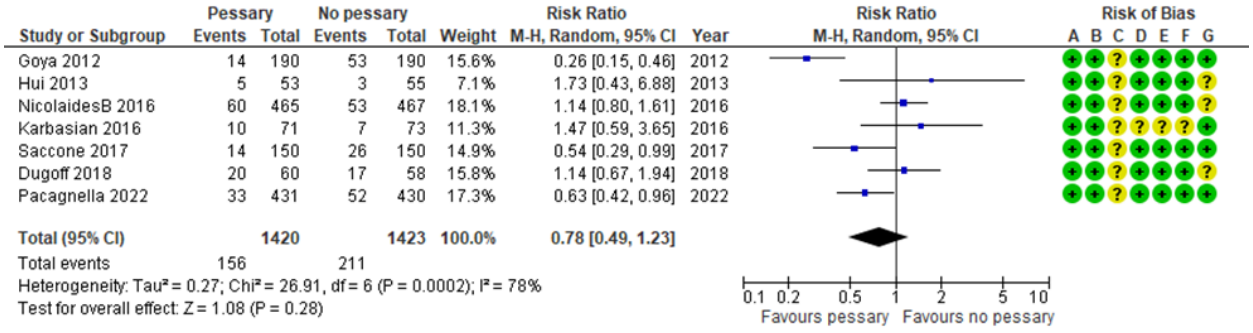
Conclusion: Pessary compared with no pessary may result in no difference in the risk of spontaneous preterm birth before 37 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Any preterm birth <35 weeks
No trial reported spontaneous preterm birth <35 weeks.

Spontaneous preterm birth <35 weeks
No trial reported spontaneous preterm birth <35 weeks.

Any preterm birth <34 weeks (Appendix 4.3.2.a and Figure 4)
A meta-analysis of seven trials, including 2843 women, showed no difference in the rate of any preterm birth, RR 0.78 (95% CI 0.49 to 1.23). The crude event rate across trials was 14.8% without pessary. The pooled weighted RD was -3.5 % percentage points (95% CI -9.7 to 2.8).

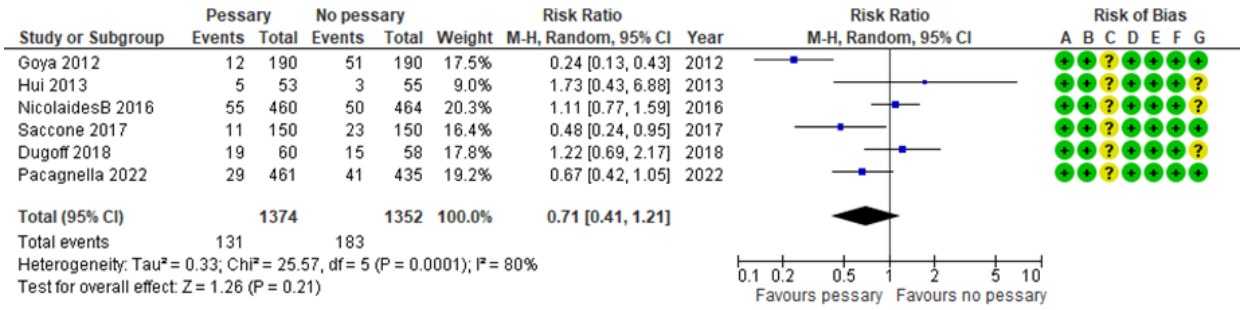
Figure 4. Outcome: Any preterm birth <34 weeks.



Conclusion: Pessary compared with no pessary may result in no difference in the risk of any preterm birth before 34 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <34 weeks (Appendix 4.3.2.b and Figure 5)
A meta-analysis of six trials, including 2726 women, showed no difference in the rate of spontaneous preterm birth, RR 0.71 (95% CI 0.41 to 1.21). The crude event rate across trials was 13.5% without pessary. The pooled weighted RD was -4.3 % percentage points (95% CI (-10.8 to 2.3).

Figure 5. Outcome: Spontaneous preterm birth <34 weeks.



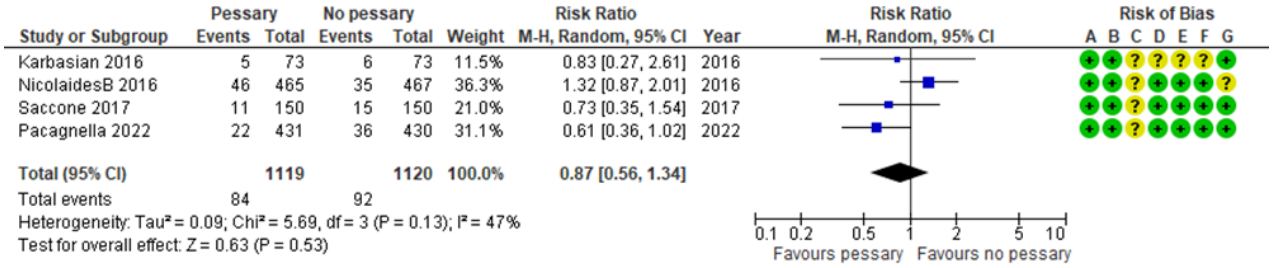
Conclusion: Pessary compared with no pessary may result in no difference in spontaneous preterm birth before 34 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Any preterm birth <33 weeks
No trial reported any preterm birth <33 weeks.

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

Any preterm birth <32 weeks (Appendix 4.3.3.a and Figure 6)
A meta-analysis of four trials, including 2239 women, showed no difference in the rate of any preterm birth, RR 0.87 (95% CI 0.56 to 1.34). The crude event rate across trials was 8.2% without pessary. The pooled weighted RD was -1.0 % percentage points (95% CI -4.3 to 2.3).

Figure 6. Outcome: Any preterm birth <32 weeks.

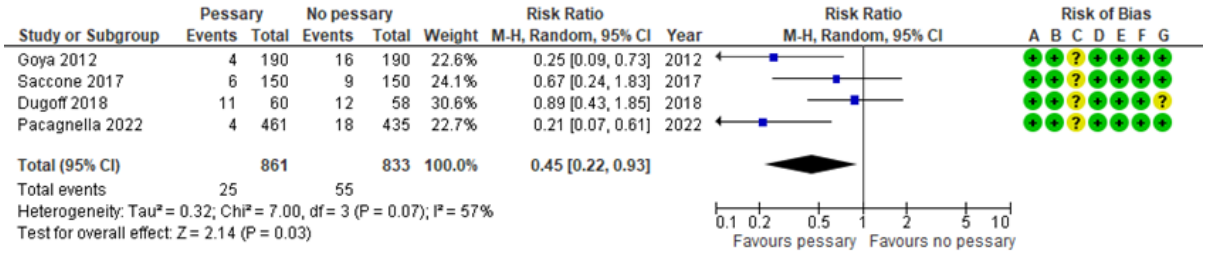


Conclusion: Pessary compared with no pessary may result in no difference in the risk of any preterm birth before 32 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <32 weeks (Appendix 4.3.3.b)
One trial, including 300 women, showed no difference in the rate of spontaneous preterm birth; RR 0.71 (95% CI 0.33 to 1.56). The crude event rate across trials was 9.3% without pessary. The pooled weighted RD was -2.7 % percentage points (95% CI -8.8 to 3.5).
Conclusion: Pessary compared with no pessary may result in no difference in the risk of spontaneous preterm birth before 32 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Any preterm birth <28 weeks (Appendix 4.3.4.a and Figure 7)
A meta-analysis of five trials, including 2319 women, showed no difference in the rate of any preterm birth, RR 0.86 (95% CI 0.52 to 1.42). The crude event rate across trials was 5.1% without pessary. The pooled weighted RD was -0.6 % percentage points (95% CI -3.1 to 1.9).

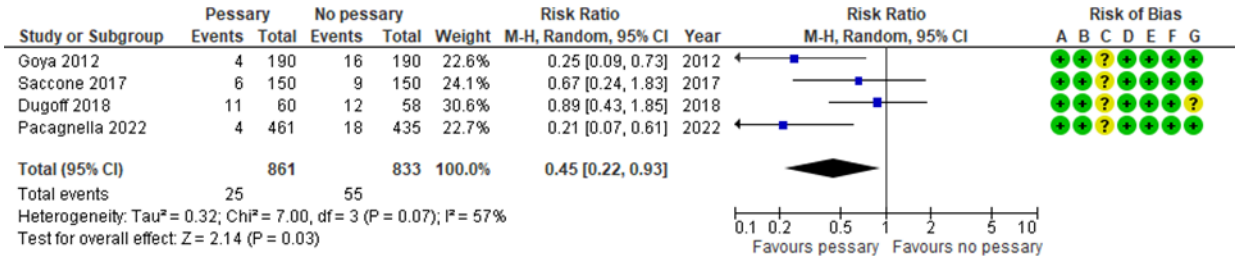
Figure 7. Outcome: Any preterm birth <28 weeks.



Conclusion: Pessary compared with no pessary may result in no difference in the risk of any preterm birth before 28 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <28 weeks (Appendix 4.3.4.b and Figure 8)
A meta-analysis of four trials, including 1694 women, showed a significant difference in the rate of spontaneous preterm birth, RR 0.45 (95% CI 0.22 to 0.93). The crude event rate across trials was 6.6% without pessary. The pooled weighted RD was -3.6 % percentage points (95% CI -5.3 to -1.8).

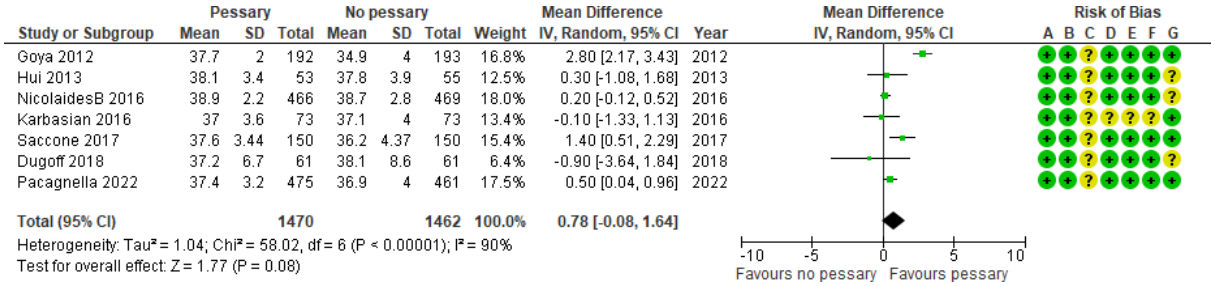
Figure 8. Outcome: Spontaneous preterm birth <28 weeks.



Conclusion: Pessary compared with no pessary may reduce the risk of spontaneous preterm birth before 28 gestational weeks, in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Gestational age in singletons (Appendix 4.3.5 and Figure 9)
A meta-analysis of seven trials, including 2932 women showed no mean difference in gestational age, 0.78 (-0.08 to 1.64) weeks, corresponding to approximately 5.5 days longer (0.5 day less to 11.5 days longer) gestational length in the pessary group.

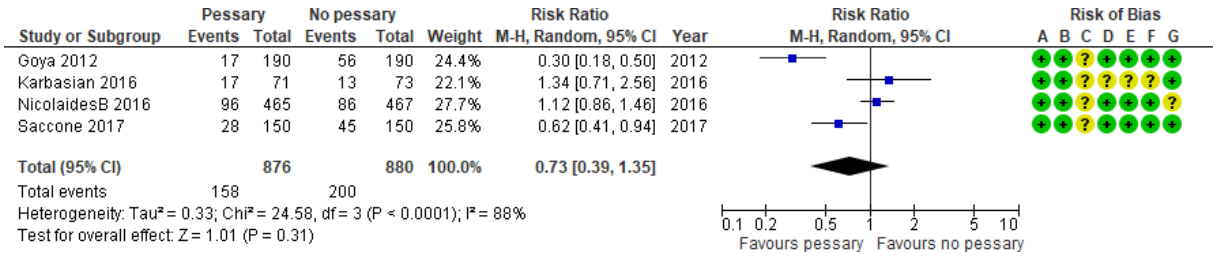
Figure 9. Outcome: Gestational age at delivery (weeks).



Conclusion: Pessary compared with no pessary probably results in no difference in gestational age at delivery, in women with a singleton pregnancy and short cervical length (GRADE⊕⊕⊕◯).

Low birth weight in singletons (Appendix 4.3.6 and Figure 10)
A meta-analysis of four trials, including 1756 women with a singleton pregnancy, showed no difference in the rate of low birth weight, RR 0.73 (95% CI 0.39 to 1.35). The crude event rate across trials was 25.6% without pessary. The pooled weighted RD was -6.2% percentage points (95% CI -18.8 to 6.4

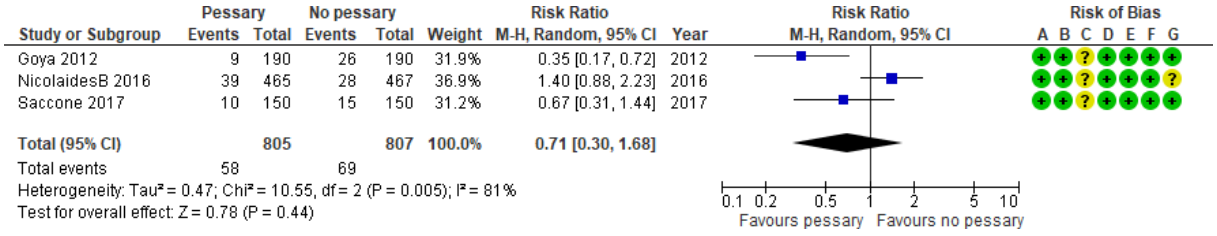
Figure 10. Outcome: Low birth weight (<2500 g).



Conclusion: Pessary compared with no pessary may result in no difference in the risk of low birth weight (<2500 g), in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Very low birth weight in singletons (Appendix 4.3.7 and Figure 11)
A meta-analysis of three trials, including 1612 women with a singleton pregnancy, showed no difference in the rate of low birth weight, RR 0.71 (95% CI 0.30 to 1.68). The crude event rate across trials was 8.6% without pessary. The pooled weighted RD was -3.0 % percentage points (95% CI -10.1 to 4.1).

Figure 11. Outcome: Very low birth weight (<1500 g).

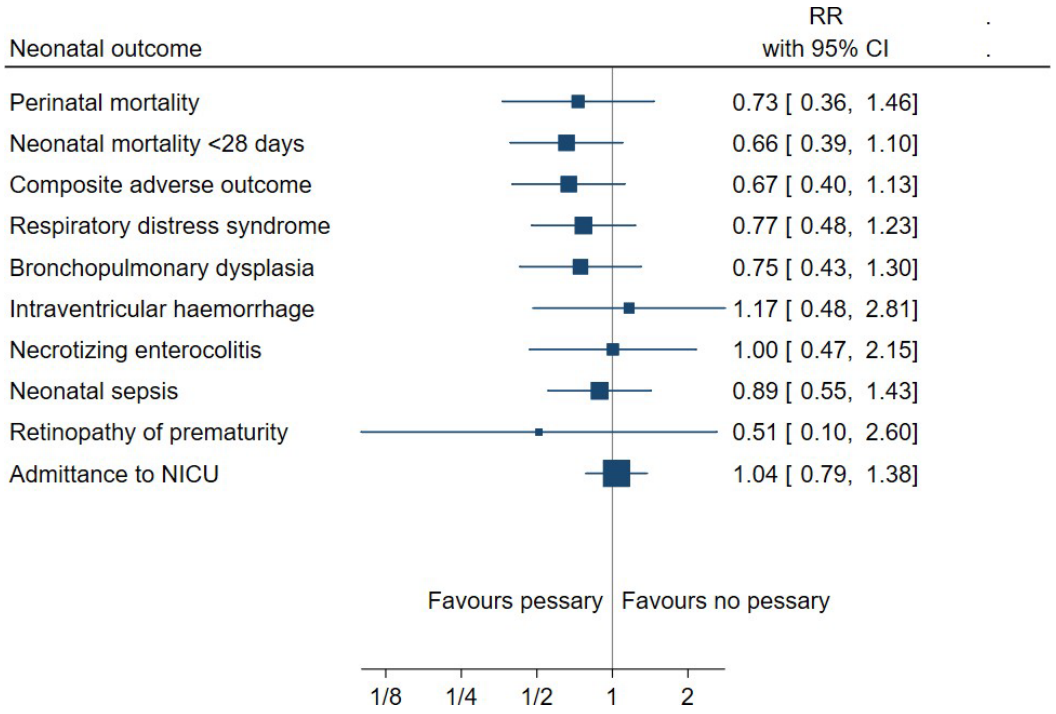


Conclusion: Pessary compared with no pessary may result in no difference in the risk of very low birth weight (<1500 g), in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Mortality and morbidity in neonates from singleton pregnancies

Meta-analyses of perinatal mortality, neonatal mortality <28 days and morbidity in singletons are presented below. Figure 12 presents the pooled estimates from the meta-analyses of the trials with low risk of bias, for any type of pessary and short cervical length as a risk factor for preterm birth.

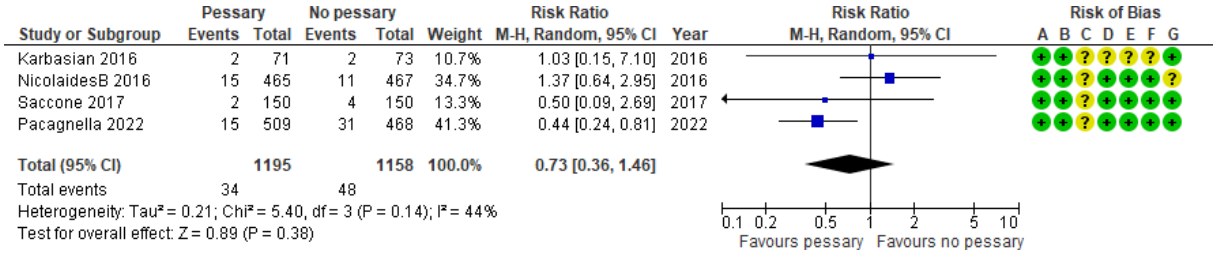
Figure 12. Summary graph of pooled estimates from meta-analyses comparing pessary and no pessary in women with short cervical length and singleton pregnancies, regarding neonatal outcomes.



The pooled estimates (RR) ranged from 0.51 to 1.17 for perinatal mortality and neonatal outcomes, showing no difference when comparing pessary with no pessary in women with short cervical length. However, the majority of the pooled estimates were below 1.0.

Perinatal mortality (Appendix 4.3.8 and Figure 13)
A meta-analysis of four trials, including 2353 neonates showed no difference in the rate of perinatal mortality, RR 0.73 (95% CI 0.36 to 1.46). The crude event rate across trials was 4.1% without pessary. The pooled weighted RD was -1.1 % percentage points (95% CI -3.5 to 1.3).

Figure 13. Outcome: Perinatal mortality.

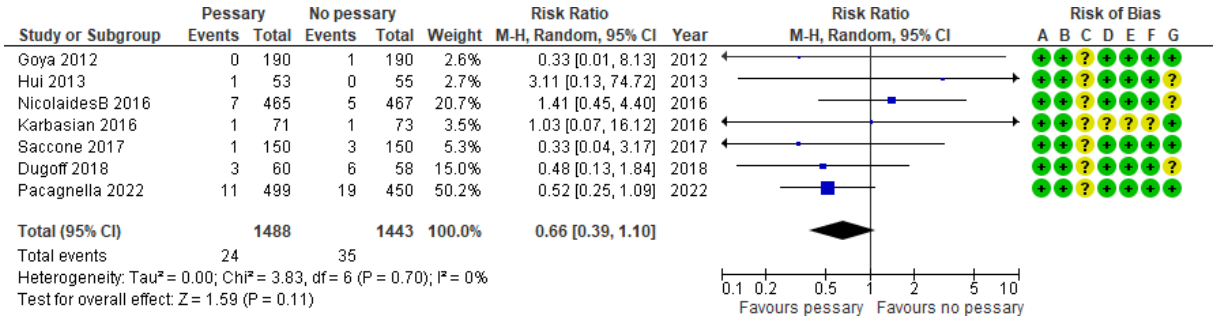


Conclusion: Pessary compared with no pessary may result in no difference in perinatal mortality in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

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

Neonatal mortality < 28 days (Appendix 4.3.9 and Figure 14)
A meta-analysis of seven trials, including 2931 women with a singleton pregnancy, showed no difference in the rate of neonatal mortality <28 days, RR 0.66 (95% CI 0.39 to 1.10). The crude event rate across trials was 2.4% without pessary. The pooled weighted RD was -0.5 % percentage points (95% CI -1.4 to 0.5).

Figure 14. Outcome: Neonatal mortality <28 days.

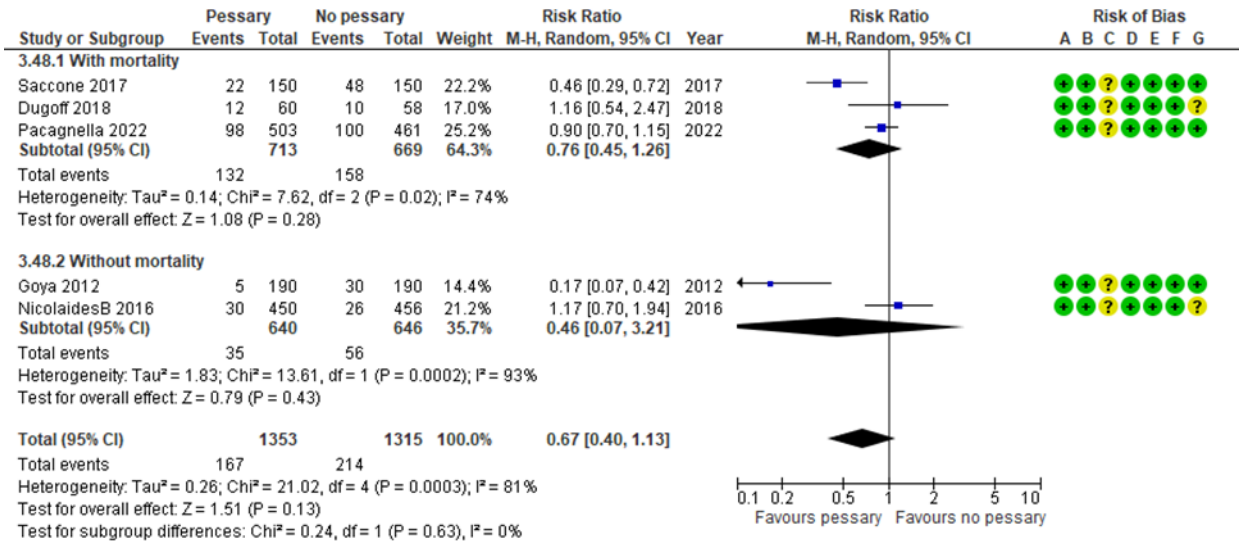


Conclusion: Pessary compared with no pessary may result in no difference in neonatal mortality <28 days, in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Composite adverse neonatal outcome (Appendix 4.3.10 and Figure 15)
A meta-analysis of five trials, including 2668 neonates showed no difference in the rate of composite neonatal morbidity, RR 0.67 (95% CI 0.40 to 1.13). The crude event rate across trials was 16.3% without pessary. The pooled weighted RD was -5.9 % percentage points
(95% CI -13.2 to 1.4).

A sensitivity analysis of two trials with low risk of bias, including 1286 neonates showed no difference in the rate of composite neonatal morbidity when excluding trials including neonatal mortality, RR of 0.46 (95% CI 0.07 to 3.21).
The composite adverse neonatal outcome included any of intrauterine fetal death, neonatal death, intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, respiratory distress syndrome, retinopathy of prematurity, or confirmed sepsis.

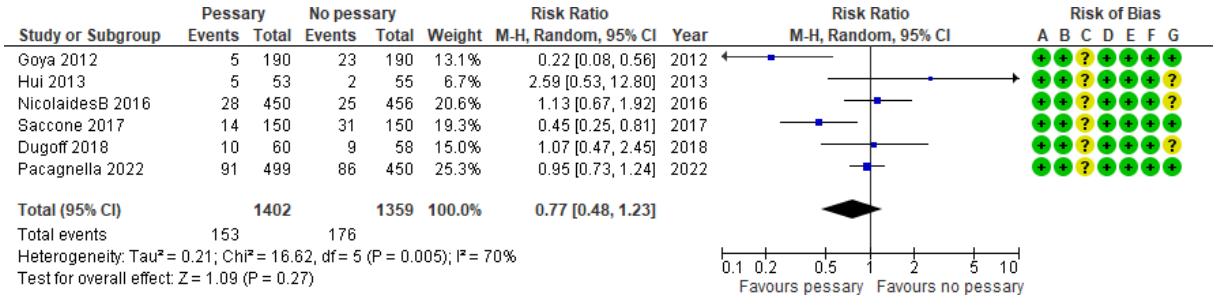
Figure 15. Outcome: Composite adverse neonatal outcome with or without mortality.



Conclusion: Pessary, compared with no pessary may result in no difference in a composite adverse neonatal outcome in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Respiratory distress syndrome (RDS) (Appendix 4.3.11 and Figure 16)
A meta-analysis of six trials, including 2761 neonates showed no difference in the rate of RDS, RR of 0.77 (95% CI 0.48 to 1.23). The crude event rate across trials was 13.0% without pessary. The pooled weighted RD was -2.7 % percentage points (95% CI -7.7 to 2.2).

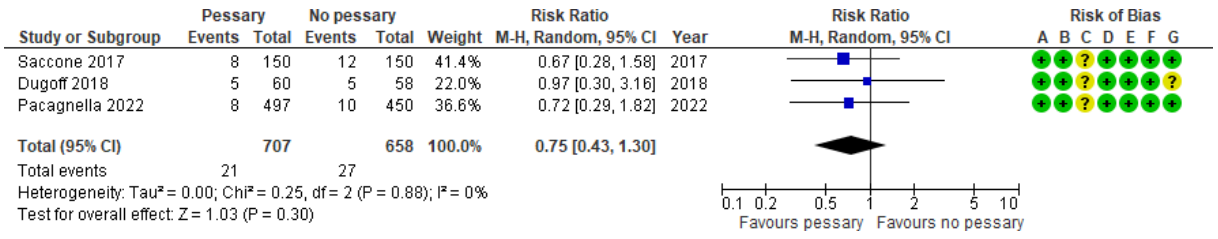
Figure 16. Outcome: Respiratory distress syndrome.



Conclusion: Pessary, compared with no pessary may result in no difference in RDS in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Bronchopulmonary dysplasia (BPD) (Appendix 4.3.12 and Figure 17)
A meta-analysis of three trials, including 1365 neonates showed no difference in the rate of BPD, RR of 0.75 (95% CI 0.43 to 1.30). The crude event rate across trials was 4.1% without pessary. The pooled weighted RD was -0.8 % percentage points (95% CI -2.4 to 0.9).

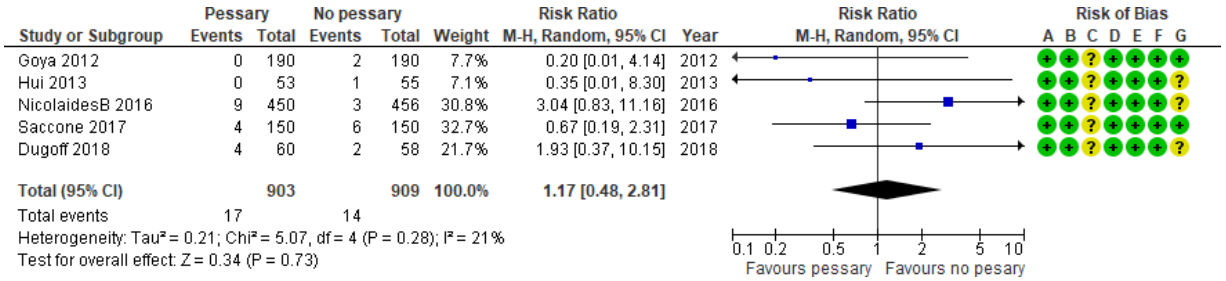
Figure 17. Outcome: Bronchopulmonary dysplasia.



Conclusion: Pessary, compared with no pessary may result in no difference in BPD in singletons from women short cervical length (GRADE ⊕⊕◯◯).

Intraventricular hemorrhage (IVH) (Appendix 4.3.13 and Figure 18)
A meta-analysis of five trials, including 1812 women showed no difference in the rate of IVH, RR 1.17 (95% CI 0.48 to 2.81). The crude event rate across trials was 1.5% without pessary. The pooled weighted RD was -0.0 % percentage points (95% CI -1.6 to 1.5).

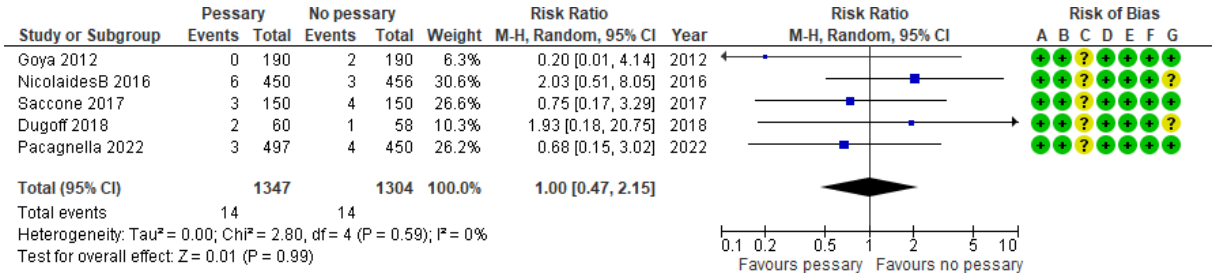
Figure 18. Outcome: Intraventricular haemorrhage.



Conclusion: Pessary, compared with no pessary may result in no difference in IVH in singletons from women short cervical length (GRADE ⊕⊕◯◯).

Necrotizing enterocolitis (NEC) (Appendix 4.3.14 and Figure 19)
A meta-analysis of five trials, including 2651 neonates showed no difference in the rate of NEC, RR 1.00 (95% CI 0.47 to 2.15). The crude event rate across trials was 1.1% without pessary. The pooled weighted RD was -0.1 % percentage points (95% CI -0.8 to 0.6).

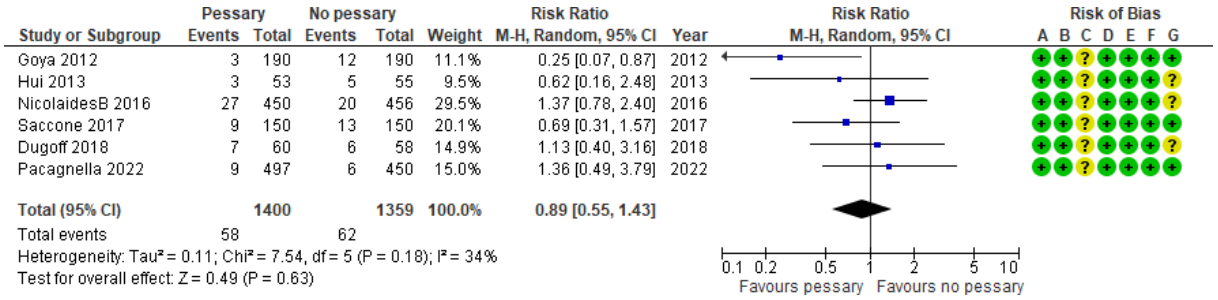
Figure 19. Outcome: Necrotizing enterocolitis.



Conclusion: Pessary, compared with no pessary may result in no difference in NEC in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Neonatal sepsis (Appendix 4.3.15 and Figure 20)
A meta-analysis of six trials, including 2759 neonates showed no difference in the rate of neonatal sepsis, RR 0.89 (95% CI 0.55 to 1.43). The crude event rate across trials was 4.6% without pessary. The pooled weighted RD was -0.7 % percentage points (95% CI -2.9 to 1.5).

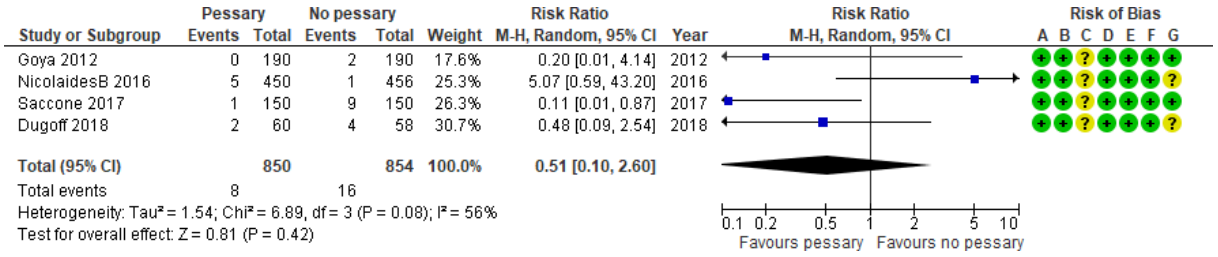
Figure 20. Outcome: Neonatal sepsis.



Conclusion: Pessary, compared with no pessary may result in no difference in neonatal sepsis in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Retinopathy of prematurity (ROP) (Appendix 4.3.16 and figure 21)
A meta-analysis of four trials, including 1704 neonates showed no difference in the rate of ROP, 0.51 (95% CI 0.10 to 2.60). The crude event rate across trials was 1.9% without pessary. The pooled weighted RD was -1.6 % percentage points (95% CI -4.5 to 1.4).

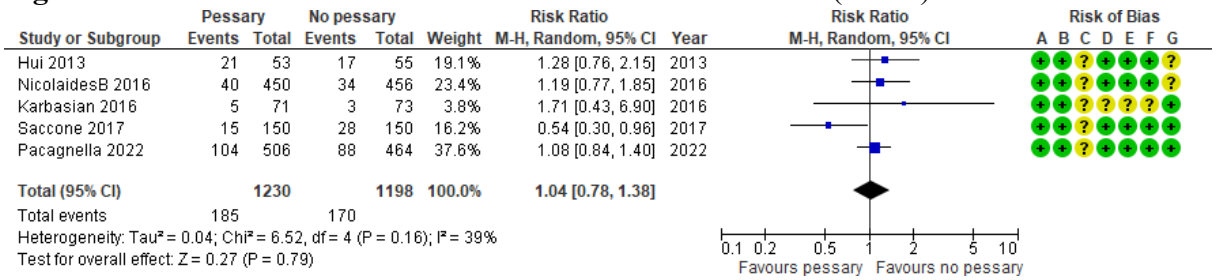
Figure 21. Outcome: Retinopathy of prematurity.



Conclusion: Pessary, compared with no pessary may result in no difference in ROP in singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Admittance to neonatal intensive care unit (Appendix 4.3.17 and Figure 22)
A meta-analysis of five trials, including 2428 neonates showed no difference in the rate of NICU admission, RR 1.04 (95% CI 0.78 to 1.38). The crude event rate across trials was 14.2% without pessary. The pooled weighted RD was 0.4 % percentage points (95% CI -3.4 to 4.2).

Figure 22. Outcome: Admittance to neonatal intensive care unit (NICU).

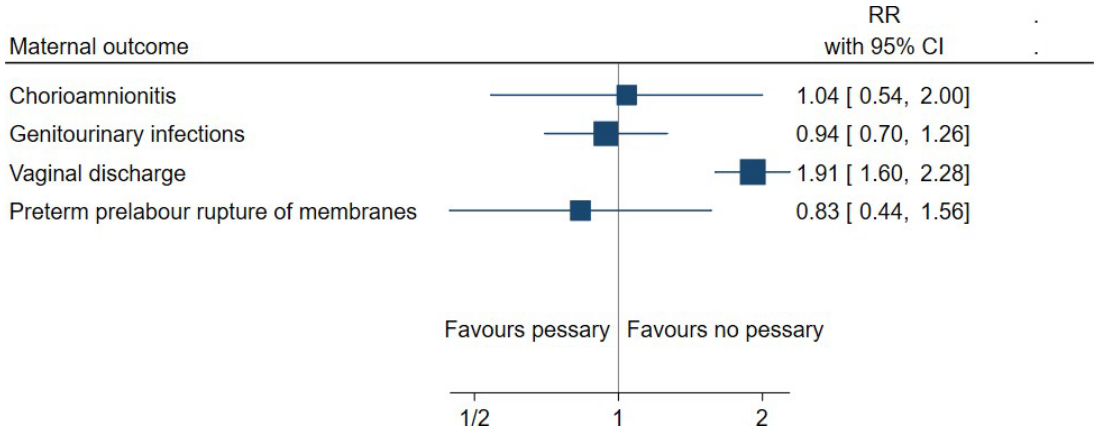


Conclusion: Pessary, compared with no pessary may result in no difference in admittance to NICU for singletons from women with short cervical length (GRADE ⊕⊕◯◯).

Long-term child outcomes in singletons
No trial reported on long term child outcome in singleton pregnancies.

Mortality and morbidity in women with singleton pregnancies
Meta-analyses of trials reporting maternal morbidity in women with a singleton pregnancy are presented below. Figure 23 presents the pooled estimates from the meta-analyses of the trials with low risk of bias, for any type of pessary and short cervical length as a risk factor for preterm birth.

Figure 23. Summary graph of pooled estimates from meta-analyses comparing pessary and no pessary in singleton pregnancies, regarding maternal outcomes. Different handling of pessaries is represented in this graph.



Maternal mortality <28d
No trial reported maternal mortality <28d.

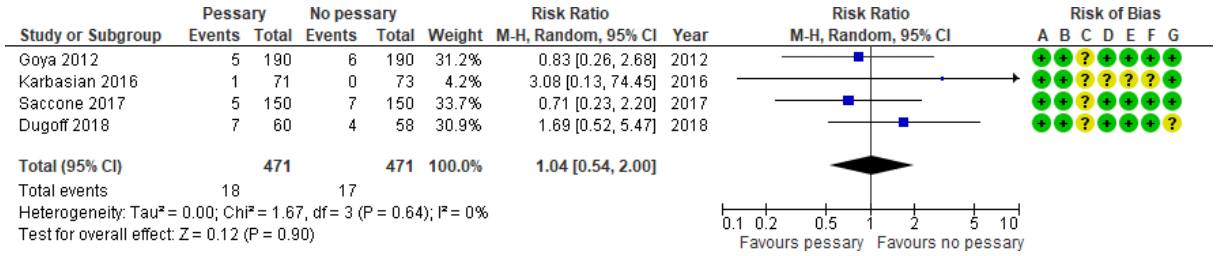
Hypertensive disorders in pregnancy
No trial reported hypertensive disorders in pregnancy.

Gestational diabetes mellitus
No trial reported gestational diabetes mellitus.

Cholestasis of pregnancy
No trial reported cholestasis of pregnancy.

Chorioamnionitis (Appendix 4.3.21 and Figure 24)
A meta-analysis of four trials, including 942 women showed no difference in the rate of chorioamnionitis, RR 1.04 (95% CI 0.54 to 2.00). The crude event rate across trials was 3.6% without pessary. The pooled weighted RD was 0.1 % percentage points (95% CI -2.0 to 2.3).

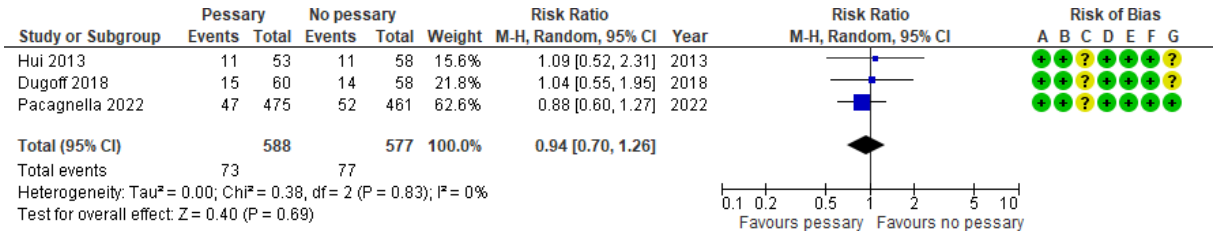
Figure 24. Outcome: Chorioamnionitis.



Conclusion: Pessary, compared with no pessary may result in no difference in chorioamnionitis in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Genitourinary infections (Appendix 4.3.22 and Figure 25)
A meta-analysis of three trials, including 1165 women showed no difference in the rate of genitourinary infections, RR 0.94 (95% CI 0.70 to 1.26). The crude event rate across trials was 13.3% without pessary. The pooled weighted RD was -1.1 % percentage points (95% CI -4.8 to 2.6).

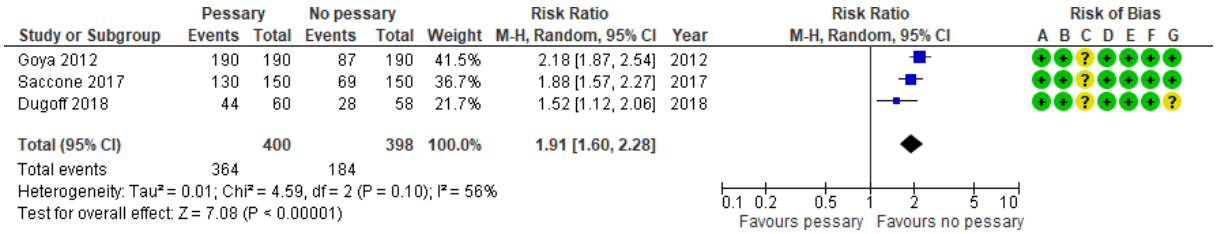
Figure 25. Outcome: Genitourinary infection.



Conclusion: Pessary, compared with no pessary may result in no difference in genitourinary infections in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Vaginal discharge (Appendix 4.3.23 and Figure 26)
A meta-analysis of three trials, including 798 women showed an increase in the frequency of vaginal discharge, RR 1.91 (95% CI 1.60 to 2.28). The crude event rate across trials was 46.2% without pessary. The pooled weighted RD was 41.5 % percentage points (95% CI 26.3 to 56.8).

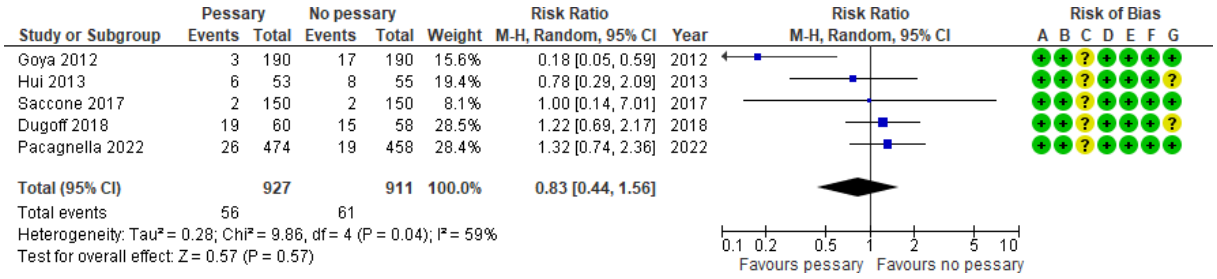
Figure 26. Outcome: Vaginal discharge.



Conclusion: Pessary, compared with no pessary probably increases the risk of vaginal discharge in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕⊕◯).

Preterm prelabour rupture of the membranes (PPROM) (Appendix 4.3.24 and Figure 27)
A meta-analysis of five trials, including 1838 women showed no difference in the rate of PPROM, RR 0.83 (95% CI 0.44 to 1.56). The crude event rate across trials was 6.7% without pessary. The pooled weighted RD was -1.4 % percentage points (95% CI -5.1 to 2.3).

Figure 27. Outcome: Preterm prelabour rupture of membranes.



Conclusion: Pessary, compared with no pessary may result in no difference in PPROM in women with a singleton pregnancy and short cervical length (GRADE ⊕⊕◯◯).

Results in multifetal pregnancies

Included studies

In total, seven publications of five RCTs were included, with two long-term follow-up reports (van't Hooft et al., 2018; Simons et al., 2019) (Appendix 2). All trials were considered to have low risk of bias (Table 1). No systematic reviews contributed to the meta-analysis. One trial included both twins (98%) and triplets (2%) (Liem et al., 2013a). Another trial, including both singleton and twin pregnancies (7.6%), contributed with data on twin pregnancies (Pacagnella et al., 2022). In total, 2913/6042 number of women/newborns were included in the analyses.

Setting

The included trials were conducted in the USA, Spain, the Netherlands and the United Kingdom, including one British study with cohorts from 12 different countries.

Population

All trials included asymptomatic women with a multifetal pregnancy with or without additional risk factors. Three articles included only women with short cervical length ≤25 mm (Goya et al., 2016), ≤30 mm (Berghella et al., 2017a), ≤35 mm (Norman et al., 2021). One trial had a subgroup with women with cervical length ≤38 mm (Liem et al., 2013a).

Intervention

All seven publications (five trials) compared pessary with no pessary. Women were randomised between the gestational weeks 16+0 and 27+6 and the pessary was inserted shortly after randomisation. In all trials, the pessary was removed at 36 or 37 gestational weeks. In the case of bleeding, contractions, PPROM, or other complications, the pessary was removed earlier. In Goya et al., 2016 women were controlled once a month with TVS and a clinical questionnaire to confirm the correct placement of the pessary and CL. The pessary was not removed at PPROM, but the women were instead followed up at the hospital, and the pessary was removed in case of chorioamnionitis or start of labour. Blinding was not feasible due to the nature of the intervention. The Arabin pessary was used in five trials and the Biotech cup in one trial (Berghella et al., 2017a).

Directness, study limitations, and precision

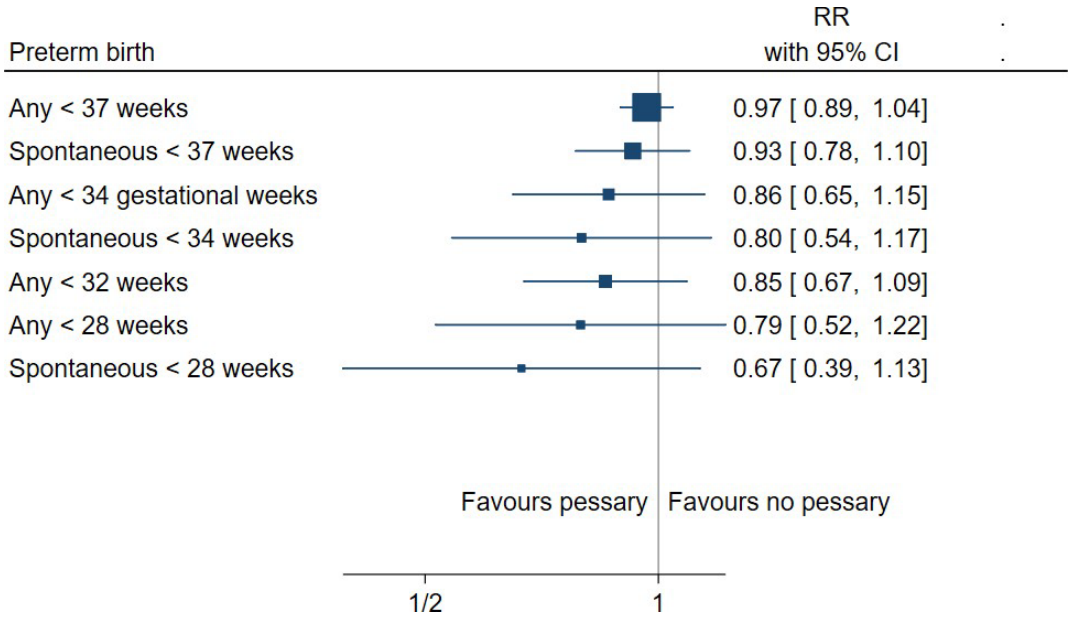
The five trials and the two reports included showed no major problem with directness. The risk of bias in the individual studies was presented graphically in colour within the forest plots (legends in Table 2), and as an overall judgement of study limitations in the outcome tables in Appendix 4.3. All trials were limited by lack of blinding since blinding participants and personnel was not feasible. It is also noted that the two reports on long-term outcomes had a significant loss to follow-up which may have affected the results.

Follow-up rate was 45% (Simons et al., 2019) and 83% (van't Hooft et al., 2018). However, all original trials were considered having low risk of bias. The studies were generally underpowered for outcomes such as neonatal mortality and morbidity and maternal morbidity.

Preterm birth in multifetal pregnancies across gestational weeks

Meta-analyses of trials reporting any or spontaneous preterm birth (<37, <34, <32, and <28 gestational weeks), are presented below.
Figure 28 presents the pooled estimates from the meta-analyses of the trials with low risk of bias, for any type of pessary in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth.

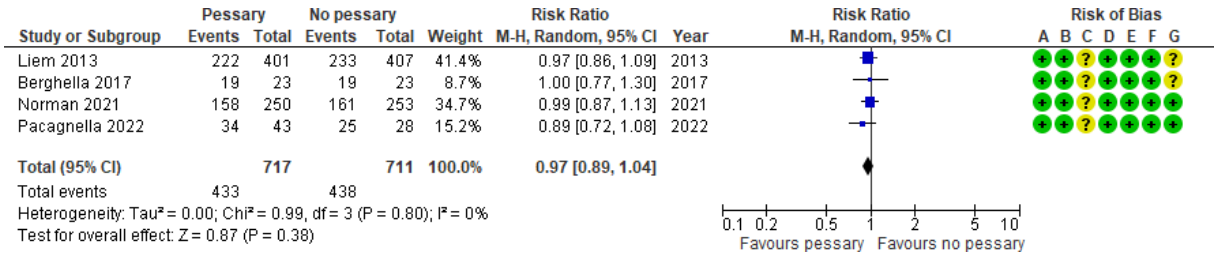
Fig 28. Summary graph of pooled estimates from meta-analyses comparing pessary and placebo in women with a multifetal pregnancy with or without additional risk factor(s), regarding the outcomes any and spontaneous preterm birth before different gestational weeks.



The pooled estimates (RR) ranged from 0.67 to 0.97 across the span of gestational weeks, comparing pessary with no pessary in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth. No significant difference was seen regarding preterm birth. However, all pooled estimates were below 1.0.

Any preterm birth <37 weeks (Appendix 4.3.1.a and Figure 29)
A meta-analysis of four trials, including 1428 women, showed no difference in the rate of any preterm birth, RR 0.97 (95% CI 0.89 to 1.04). The crude event rate across trials was 58.6% without pessary. The pooled weighted RD was -2.0% percentage points (95% CI -7.0 to 2.9).

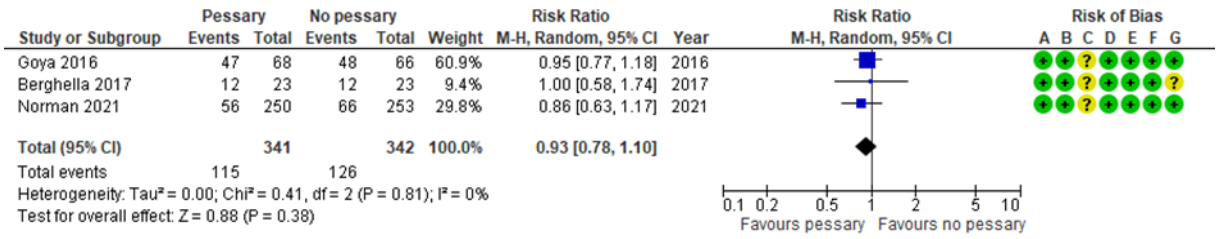
Figure 29. Outcome: Any preterm birth <37 weeks.



Conclusion: Pessary compared with no pessary probably results in no difference in the risk of any preterm birth before 37 gestational weeks in women with a multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous preterm birth <37 weeks (Appendix 4.3.1.b and Figure 30)
A meta-analysis of three trials, including 683 women with short cervical length, showed no difference in the rate of spontaneous preterm birth, RR 0.93 (95% CI 0.78 to 1.10). The crude event rate across trials was 67.4% without pessary. The pooled weighted RD was -3.5 % percentage points (95% CI-10.0 to 3.1).

Figure 30. Outcome: Spontaneous preterm birth <37 weeks.



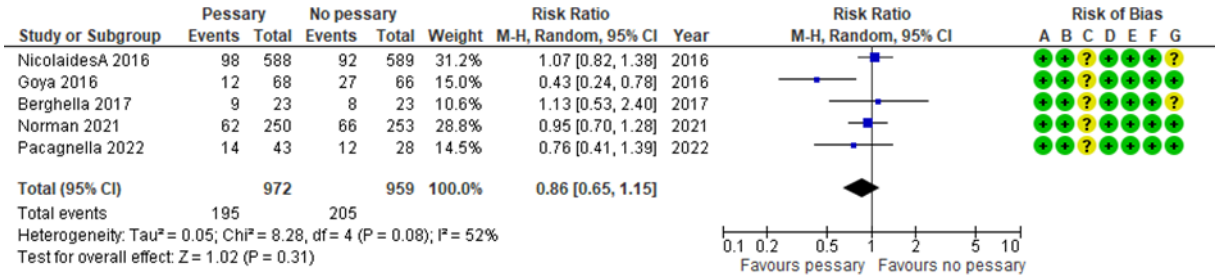
Conclusion: Pessary compared with no pessary probably results in no difference in the risk of spontaneous preterm birth before 37 gestational weeks in women with a twin pregnancy and short cervical length (GRADE ⊕⊕⊕◯).

Any preterm birth <35 weeks
No trial reported spontaneous preterm birth <35 weeks.

Spontaneous preterm birth <35 weeks
No trial reported spontaneous preterm birth <35 weeks.

Any preterm birth <34 weeks (Appendix 4.3.2.a and Figure 31)
A meta-analysis of five trials, including 1931 women, showed no difference in the rate of any preterm birth, RR 0.86 (95% CI 0.65 to 1.15). The crude event rate across trials was 18.7% without pessary. The pooled weighted RD was -4.7 % percentage points (95% CI -12.8 to 3.5).

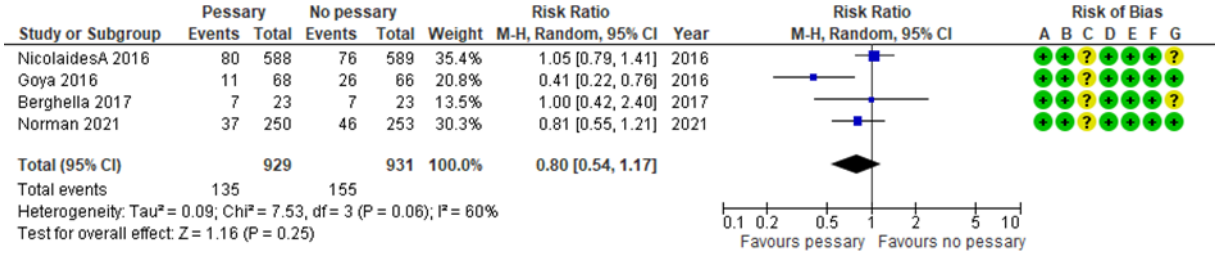
Figure 31. Outcome: Any preterm birth <34 weeks.



Conclusion: Pessary compared with no pessary may result in no difference in the risk of any preterm birth before 34 gestational weeks, in women with a twin pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Spontaneous preterm birth <34 weeks (Appendix 4.3.2.b and Figure 32)
A meta-analysis of four trials, including 1860 women, showed no difference in the rate of spontaneous preterm birth RR 0.80 (95% CI 0.54 to 1.17). The crude event rate across trials was 16.1% without pessary. The pooled weighted RD was -5.2 % percentage points (95% CI -13.5 to 3.2).

Figure 32. Outcome: Spontaneous preterm birth <34 weeks.



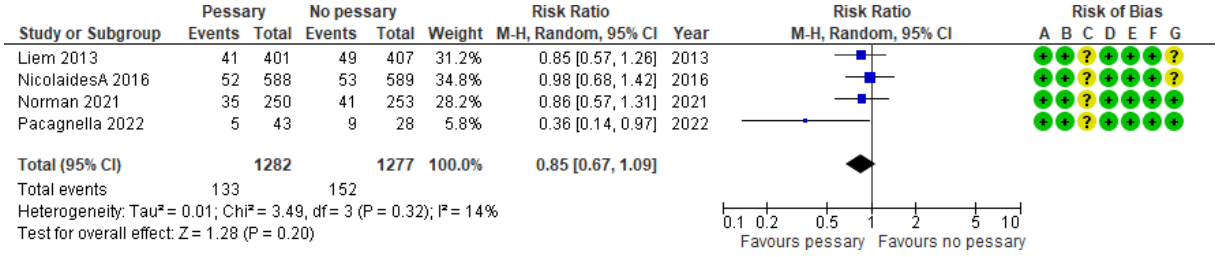
Conclusion: Pessary compared with no pessary may result in no difference in the risk of spontaneous preterm birth before 34 gestational weeks, in women with a twin pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Any preterm birth <33 weeks
No trial reported any preterm birth <33 weeks.

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

Any preterm birth <32 weeks (Appendix 4.3.3.a and Figure 33)
A meta-analysis of four trials, including 2559 women, showed no difference in the rate of any preterm birth, RR 0.85 (95% CI 0.67 to 1.09). The crude event rate across trials was 10.2% without pessary. The pooled weighted RD was -1.6 % percentage points (95% CI -4.9 to 1.

Figure 33. Outcome: Any preterm birth <32 weeks



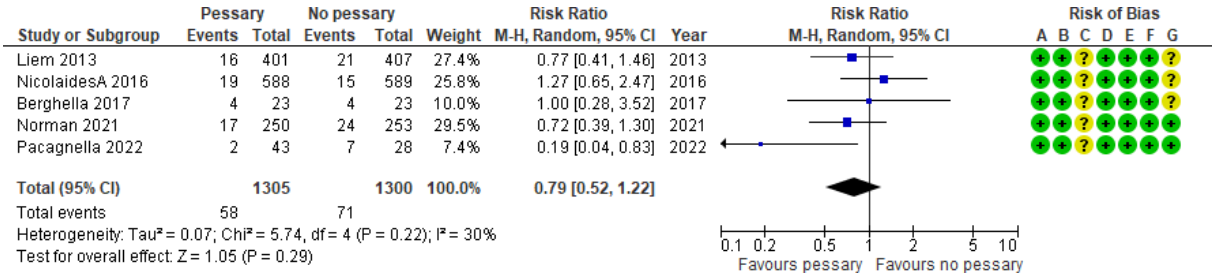
Conclusion: Pessary compared with no pessary probably results in no difference in the risk of any preterm birth before 32 gestational weeks, in women with a multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Spontaneous birth <32 weeks
One trial (Norman et al., 2021), including 503 women, showed no difference in the rate of spontaneous preterm birth; RR 0.82 (0.51 to 1.33). The crude event rate was 12.6 % without pessary.

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

Any preterm birth <28 weeks (Appendix 4.3.4.a and Figure 34)
A meta-analysis of five trials, including 2605 women, showed no difference in the rate of any preterm birth, RR 0.79 (95% CI 0.52 to 1.22). The crude event rate across trials was 3.9% without pessary. The pooled weighted RD was -1.3 % percentage points (95% CI -4.3 to 1.7).

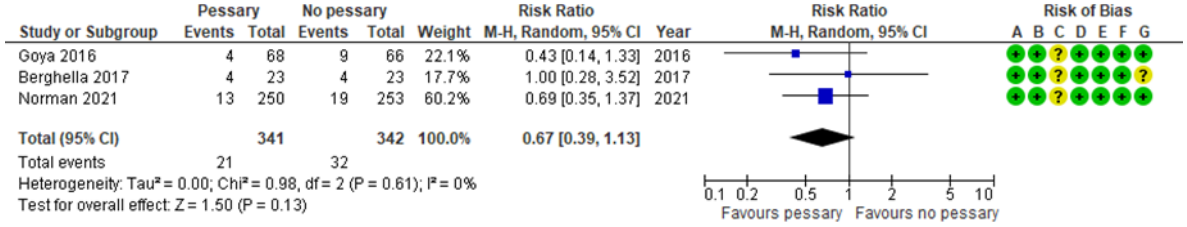
Figure 34. Outcome: Any preterm birth <28 weeks.



Conclusion: Pessary compared with no pessary may result in no difference in the risk of any preterm birth before 28 gestational weeks, in women with a multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Spontaneous birth <28 weeks (Appendix 4.3.4.b and Figure 35)
A meta-analysis of three trials, including 683 women with short cervical length, showed no difference in the rate of spontaneous preterm birth, RR 0.67 (95% CI 0.39 to 1.13). The crude event rate across trials was 14.6% without pessary. The pooled weighted RD was -3.1 % percentage points (95% CI -6.9 to 0.8).

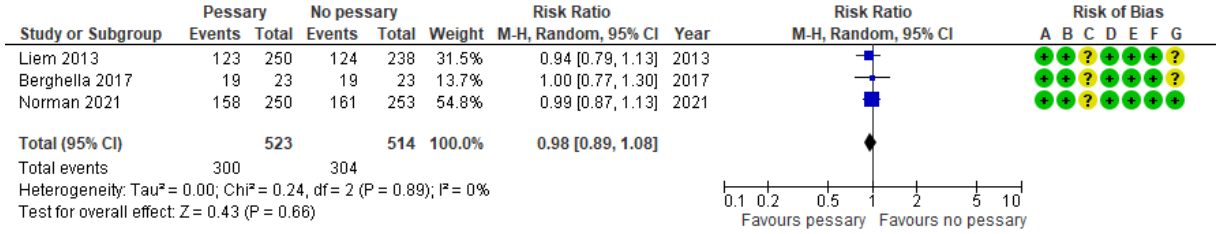
Figure 35. Outcome: Spontaneous preterm birth <28 weeks.



Conclusion: Pessary compared with no pessary may result in no difference in the risk of spontaneous preterm birth before 28 gestational weeks in twins and short cervical length (GRADE ⊕⊕◯◯).

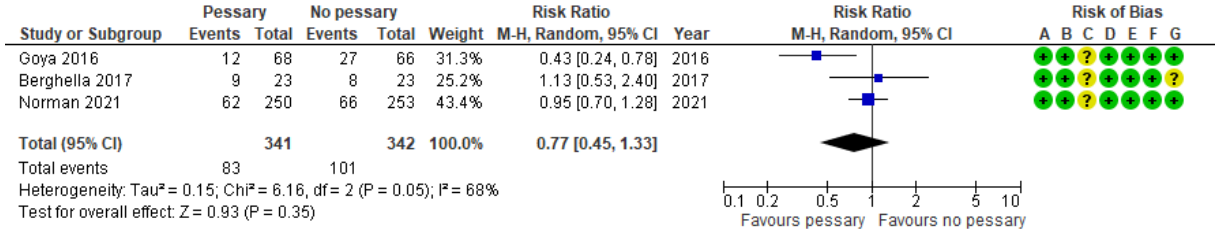
Subgroup analyses (Appendix 4.3.1.a, Appendix 4.3.2.a, Figure 36 and 37)
Pre-specified subgroup analyses according to risk factors, of which only short cervical length was applicable, were conducted.

Figure 36. Outcome: Any preterm birth <37 weeks according to the risk factor short cervical length.



Cut-off cervical length: Liem 2013a ≤38 mm, Berghella 2017a <30 mm, Norman 2021 <35 mm.

Figure 37. Outcome: Any preterm birth <34 weeks according to the risk factor short cervical length.

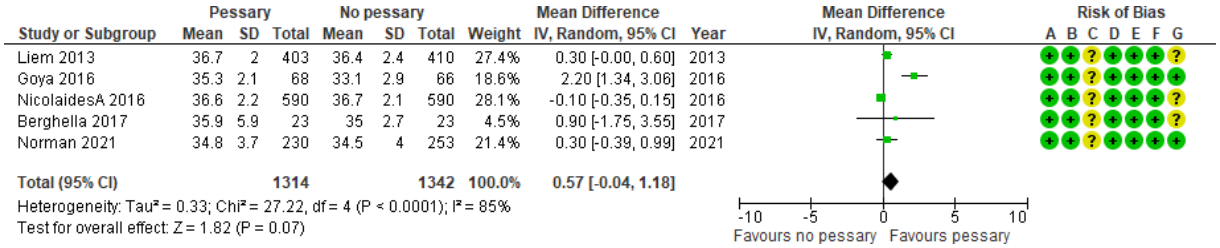


Cut-off cervical length: Goya 2016 ≤25 mm, Berghella 2017a <30 mm, Norman 2021 <35 mm.

Exploratory subgroup analyses according to the specific risk factor short cervical length did not demonstrate any benefit from pessary.

Gestational age in multifetal pregnancies (Appendix 4.3.5 and figure 38)
A meta-analysis of five trials, including 2656 women showed no mean difference in gestational age, 0.57 (-0.04 to 1.18) weeks, corresponding to approximately four days longer (0.3 day less to eight days longer) gestational length in the pessary group.

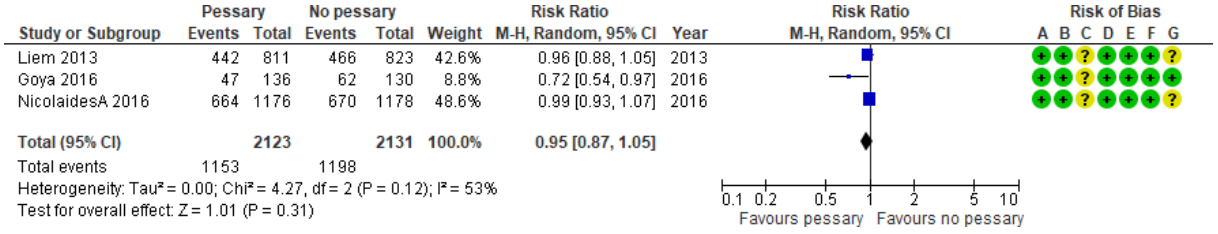
Figure 38. Outcome: Gestational age at delivery (weeks).



Conclusion: Pessary compared with no pessary probably results in no difference in length of gestation in women with a multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Low birth weight in multifetal pregnancies (Appendix 4.3.6 and Figure 39)
A meta-analysis of three trials, including 4254 women showed no difference in the rate of low birth weight, RR 0.95 (95% CI 0.87 to 1.05). The crude event rate across trials was 56.2% without pessary. The pooled weighted RD was -2.8 % percentage points (95% CI -7.6 to 2.0).

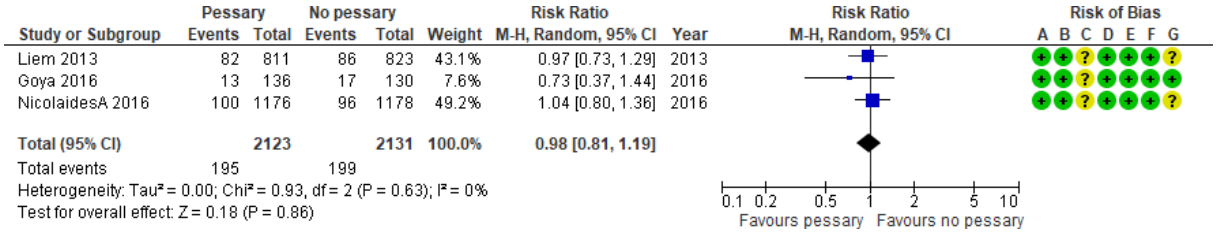
Figure 39. Outcome: Low birth weight (<2500 g).



Conclusion: Pessary compared with no pessary probably results in no difference in the risk of low birth weight (<2500g) in neonates from a twin pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Very low birth weight in multifetal pregnancies (Appendix 4.3.7 and Figure 40)
A meta-analysis of three trials, including 4254 women showed no difference in the rate of low birth weight, RR 0.98 (95% CI 0.81 to 1.19). The crude event rate across trials was 9.3% without pessary. The pooled weighted RD was -0.1 % percentage points (95% CI -1.8 to 1.7).

Figure 40. Outcome: Very low birth weight (<1500 g).

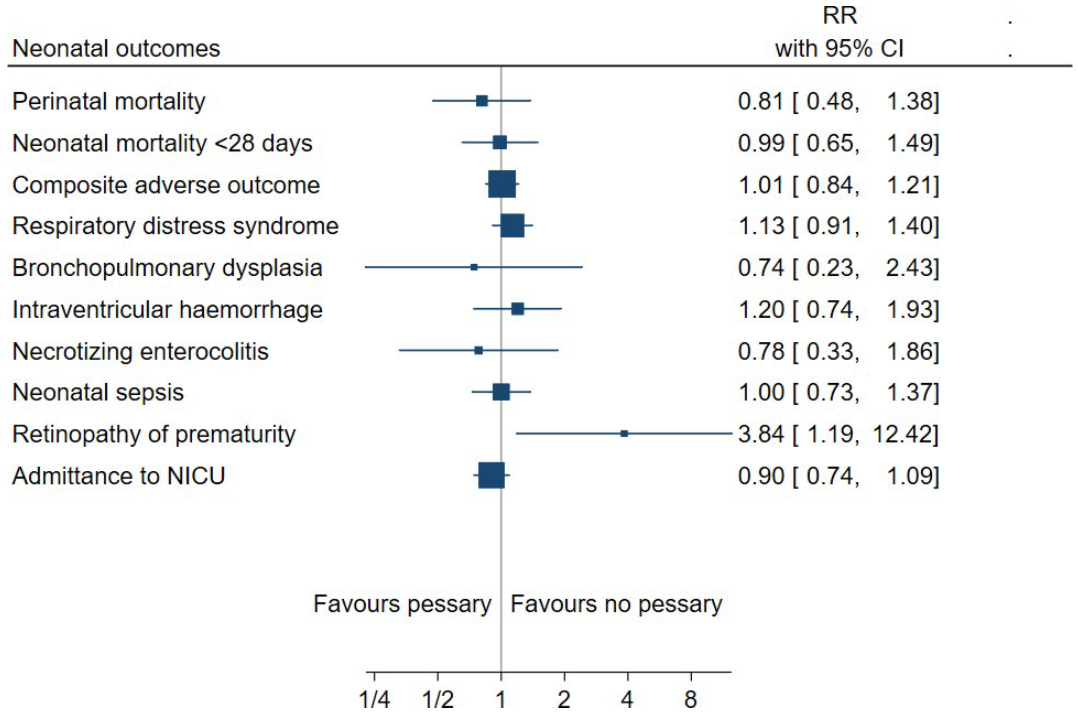


Conclusion: Pessary compared with no pessary probably results in no difference in the risk of very low birth weight (<1500g) in neonates from a twin pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Mortality and morbidity in neonates from multifetal pregnancies

Meta-analyses of perinatal mortality, neonatal mortality <28 days and morbidity in multifetal pregnancies are presented below. Figure 41 presents the pooled estimates from the meta-analyses of the trials with low risk of bias, for any type of pessary in a multifetal pregnancy with or without additional maternal risk factor(s) for preterm birth.

Figure 41. Summary graph of pooled estimates from meta-analyses comparing pessary and no pessary in neonates from women with a multifetal pregnancy with or without any additional risk factor(s), regarding neonatal outcomes.

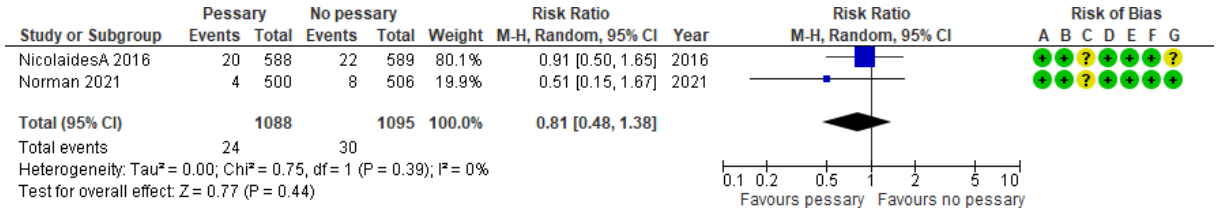


The pooled estimates ranged from 0.74 to 3.84, comparing pessary with no pessary in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth. In general, there were no difference in perinatal mortality and neonatal outcomes, and the majority of all pooled estimates were around 1.0.

Perinatal mortality (Appendix 4.3.8 and Figure 42)

A meta-analysis of two trials, including 2183 neonates, showed no difference in the rate of perinatal mortality, RR 0.81 (95% CI 0.48 to 1.38). The definition of perinatal mortality includes intrauterine death and neonatal mortality. Intrauterine death and neonatal mortality were not defined in Nicolaides et al. (2016a), but in Norman et al. (2021) defined as fetal and neonatal death within 28 days. The crude event rate across trials was 2.7% without pessary. The pooled weighted RD was -0.7 % percentage points (95% CI -1.8 to 0.5).

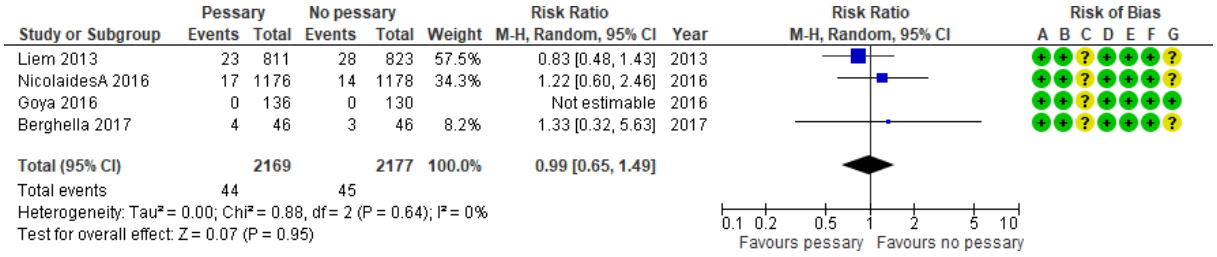
Figure 42. Outcome: Perinatal mortality.



Conclusion:Pessary compared with no pessary may result in no difference in perinatal mortality in perinates from a twin pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Neonatal mortality (Appendix 4.3.9 and Figure 43)
A meta-analysis of four trials, including 4346 neonates, showed no difference in the rate of neonatal mortality <28 days, RR 0.99 (95% CI 0.65 to 1.49). The crude event rate across trials was 2.1% without pessary. The pooled weighted RD was 0.1 % percentage points (95% CI -0.6 to 0.8).

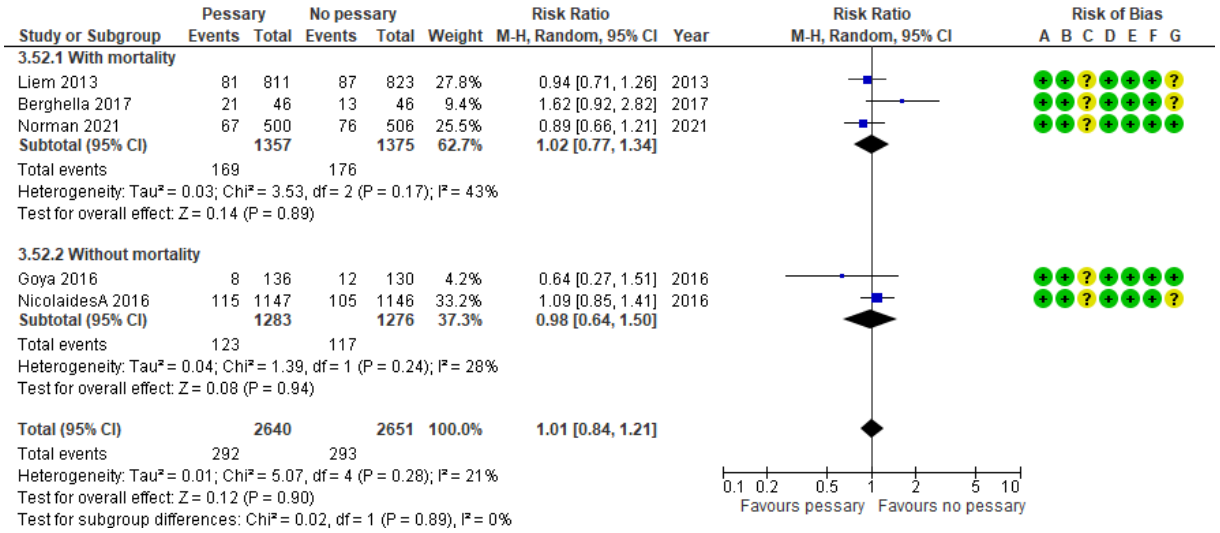
Figure 43. Outcome: Neonatal mortality <28 days.



Conclusion: Pessary compared to no pessary may result in no difference in neonatal mortality <28 days in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Composite adverse neonatal outcome (Appendix 4.3.10 and figure 44)
A meta-analysis of five trials, including 5291 neonates showed no difference in the rate of composite neonatal morbidity, RR 1.01 (95% CI 0.84 to 1.21). The crude event rate across trials was 10.1% without pessary. The pooled weighted RD was -0.3 % percentage points (95% CI -2.4 to 1.9).
A sensitivity analysis of two trials with low risk of bias, including 2559 neonates showed no difference in the rate of composite adverse neonatal morbidity when excluding trials including neonatal mortality, RR of 0.98 (95% CI 0.64 to 1.50).
The composite adverse neonatal outcome included any of intrauterine fetal death, neonatal death, intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, respiratory distress syndrome, retinopathy of prematurity, or confirmed sepsis.

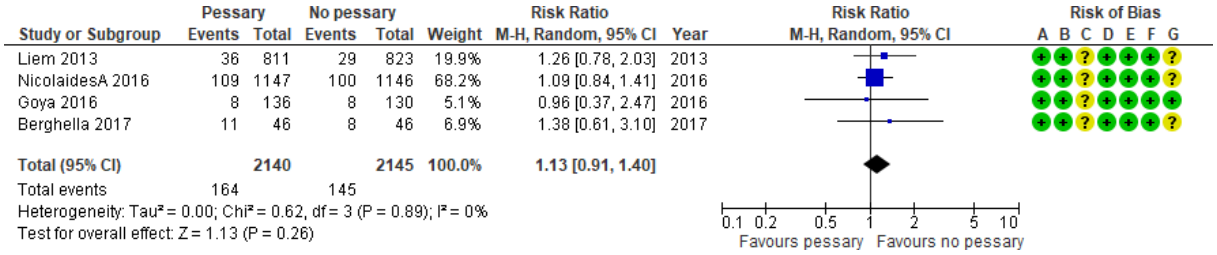
Figure 44. Outcome: Composite adverse neonatal outcome with or without mortality.



Conclusion: Pessary, compared with no pessary probably results in no difference in a composite adverse neonatal outcome in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Respiratory distress syndrome (RDS) (Appendix 4.3.11 and figure 45)
A meta-analysis of four trials, including 4285 neonates showed no difference in the rate of RDS, RR of 1.13 (95% CI 0.91 to 1.40). The crude event rate across trials was 6.8% without pessary. The pooled weighted RD was 0.8 % percentage points (95% CI -0.6 to 2.3).

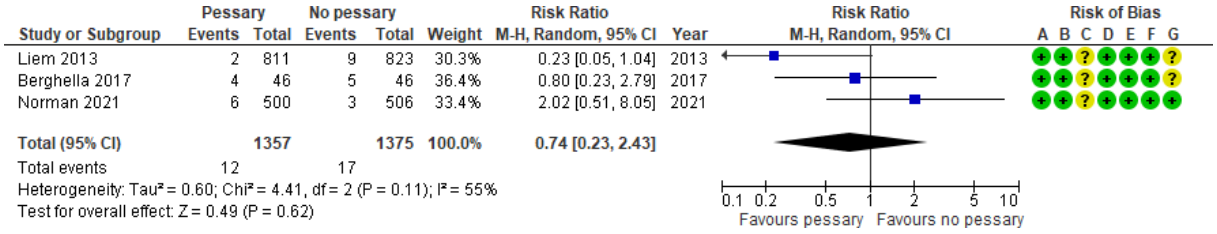
Figure 45. Outcome: Respiratory distress syndrome



Conclusion: Pessary, compared with no pessary probably results in no difference in RDS in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Bronchopulmonary dysplasia (BPD) (Appendix 4.3.12 and figure 46)
A meta-analysis of three trials, including 2732 neonates showed no difference in the rate of BPD, RR of 0.74 (95% CI 0.23 to 2.43). The crude event rate across trials was 1.6% without pessary. The pooled weighted RD was -0.2 % percentage points (95% CI -1.5 to 1.0).

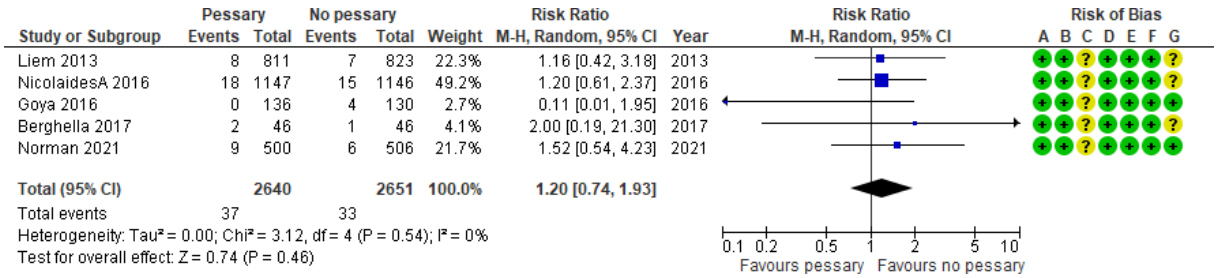
Figure 46. Outcome: Bronchopulmonary dysplasia.



Conclusion: Pessary, compared with no pessary may result in no difference in BPD in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE⊕⊕◯◯).

Intraventricular hemorrhage (IVH) (Appendix 4.3.13 and Figure 47)
A meta-analysis of five trials, including 5291 women showed no difference in the rate of IVH, RR 1.20 (0.74 to 1.93). The crude event rate across trials was 1.3% without pessary. The pooled weighted RD was 0.2 % percentage points (95% CI -0.5 to 0.8).

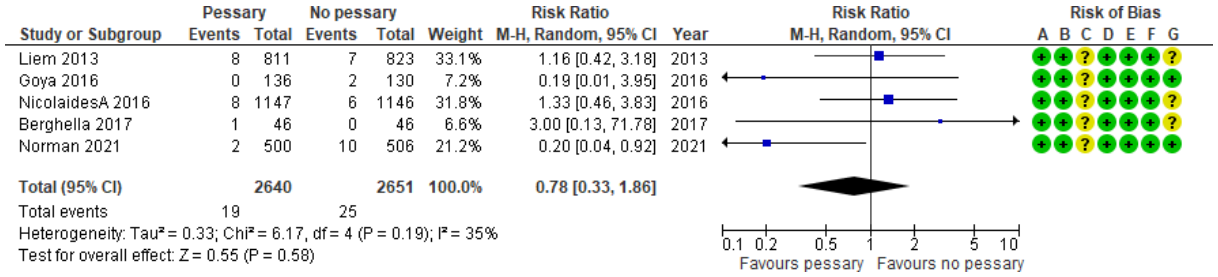
Figure 47. Outcome: Intraventricular haemorrhage.



Conclusion: Pessary, compared with no pessary may result in no difference in IVH in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Necrotizing enterocolitis (NEC) (Appendix 4.3.14 and Figure 48)
A meta-analysis of five trials, including 5291 neonates showed no difference in the rate of NEC, RR 0.78 (95% CI 0.33 to 1.86). The crude event rate across trials was 0.7% without pessary. The pooled weighted RD was -0.3 % percentage points (95% CI -1.2 to 0.5).

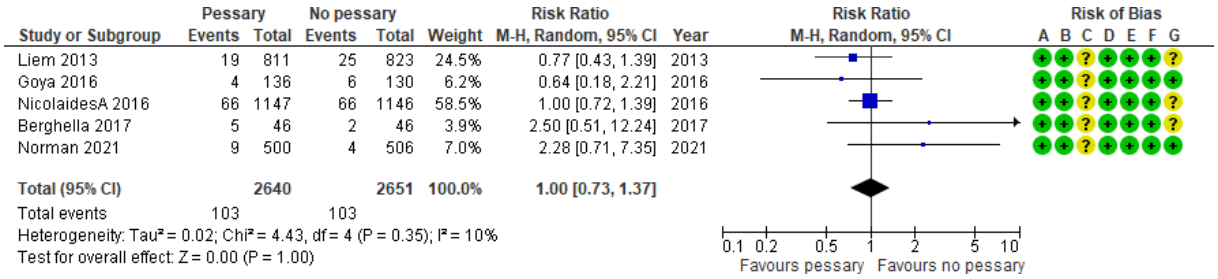
Figure 48. Outcome: Necrotizing enterocolitis.



Conclusion: Pessary, compared with no pessary may result in no difference in the rate of NEC in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Neonatal sepsis (Appendix 4.3.15 and figure 49)
A meta-analysis of five trials, including 5291 neonates showed no difference in the rate of neonatal sepsis, RR 1.00 (95% CI 0.73 to 1.37). The crude event rate across trials was 4.6% without pessary. The pooled weighted RD was 0.1 % percentage points (95% CI -0.9 to 1.2).

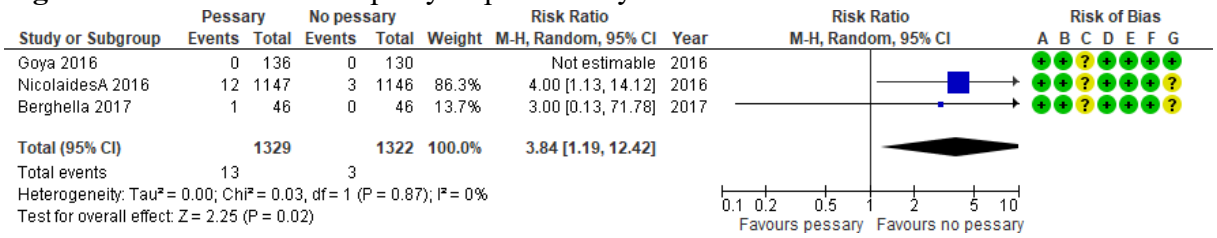
Figure 49. Outcome: Neonatal sepsis.



Conclusion: Pessary, compared with no pessary probably result in no difference in neonatal sepsis in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Retinopathy of prematurity (ROP) (Appendix 4.3.16 and Figure 50)
A meta-analysis of three trials, including 2651 neonates showed an increase in the rate of ROP in pessary users, 3.84 (95% CI 1.19 to 12.42). The crude event rate across trials was 0.2% without pessary. The pooled weighted RD was 0.7 % percentage points (95% CI 0.1 to 1.3). Very serious imprecision affected certainty of evidence.

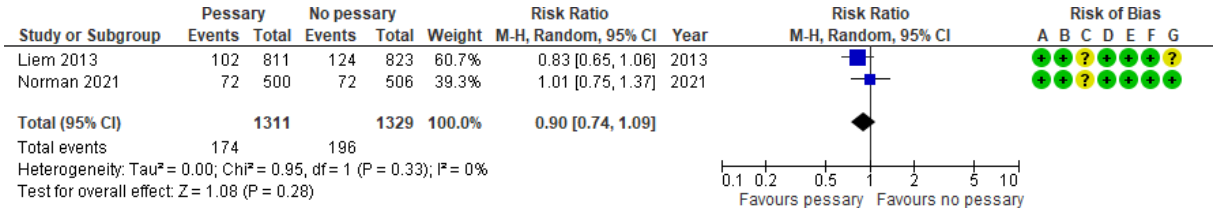
Figure 50. Outcome: Retinopathy of prematurity.



Conclusion: It is uncertain whether pessary increases the risk of ROP in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕◯◯◯).

Admittance to neonatal intensive care unit (NICU) (Appendix 4.3.17 and Figure 51)
A meta-analysis of two trials, including 2640 neonates showed no difference in the rate of NICU admission, RR 0.90 (95% CI 0.74 to 1.09). The crude event rate across trials was 15.1% without pessary. The pooled weighted RD was -1.5 % percentage points (95% CI -4.1 to 1.2).

Figure 51. Outcome: Admittance to neonatal intensive care unit (NICU).

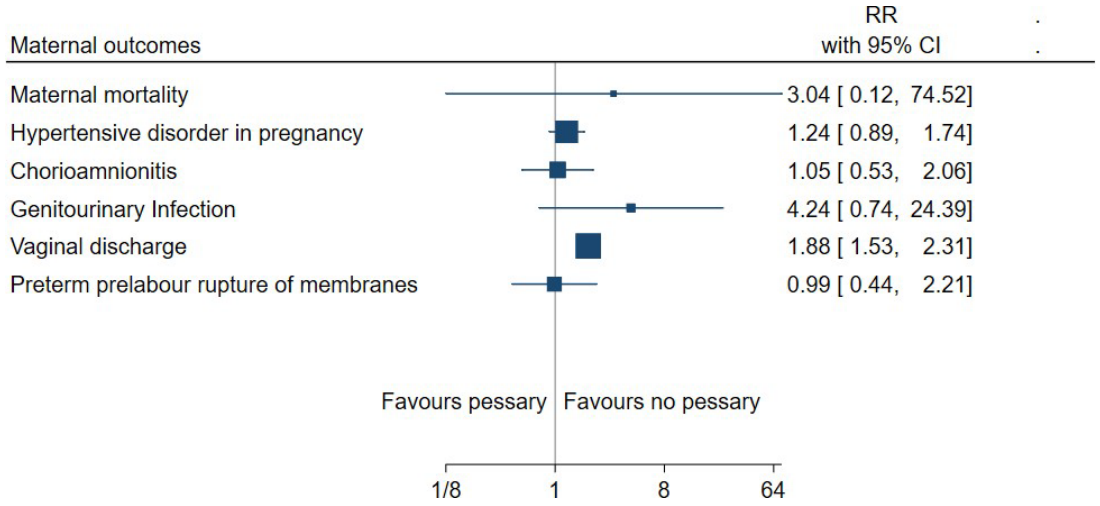


Conclusion: Pessary, compared with no pessary probably results in no difference in admittance to NICU in neonates from a multifetal pregnancy, not considering additional maternal risk factor(s) for preterm birth (GRADE ⊕⊕⊕◯).

Long-term child outcomes in multifetal (Appendix 4.3.18)
Two articles (714 children) examined long-term child outcome in twins and triplets (Van`t Hooft et al., 2018, Simons et al., 2019). Both articles are a follow up of the ProTWIN trial (Liem et al., 2013). Follow-up rate was 45% (Simons et al., 2019) and 83% (van 't Hooft et al., 2018). A meta-analysis was not feasible due to different outcomes. Van´t Hooft et al. showed no difference in neurodevelopment assessed by the Bayley-III Cognitive Composite score at 3 years, neither were there any differences in cognitive, language or motor development. Simons et al. (2019) concluded no improvement in development, behavioral, or physical outcomes of surviving children after four years.

Mortality and morbidity in women with multifetal pregnancies
Meta-analyses of trials reporting maternal mortality and morbidity in women with a multifetal pregnancy are presented below. Figure 52 presents the pooled estimates from meta-analyses of trials with low risk of bias, for any type of pessary in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth.

Figure 52. Summary graph of pooled estimates from meta-analyses comparing pessary and no pessary in women with a multifetal pregnancy with or without additional risk factor(s), regarding maternal outcomes.



The pooled estimates (RR) ranged from 0.99 to 4.24, comparing pessary with no pessary in women with a multifetal pregnancy with or without additional risk factor(s) for preterm birth. Pessary increased the rate of vaginal discharge, but for other maternal outcomes, there was no significant difference.

Maternal mortality <28 d (Appendix 4.3.19)
One trial from the Netherlands reported one maternal death in the intervention group (1/401). The treatment was a cerclage instead of a pessary, and death occurred later due to chorioamnionitis.

Hypertensive disorders in pregnancy (HDP) (Appendix 4.3.20)

One trial, including 808 women showed no difference in the rate of HDP, RR 1.24 (95% CI 0.89 to 1.74). The crude event rate across trials was 13.0% without pessary. The RD was 3.2 % percentage points (95% CI -1.7 to 8.1).

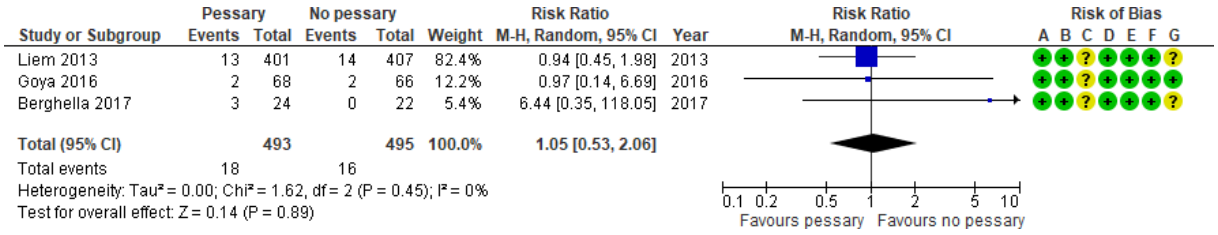
Conclusion: Pessary, compared with no pessary may result in no difference in HDP in women with a multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Gestational diabetes mellitus
No trial reported gestational diabetes mellitus.

Cholestasis of pregnancy
No trial reported cholestasis of pregnancy.

Chorioamnionitis (Appendix 4.3.21 and Figure 53)
A meta-analysis of three trials, including 988 women showed no difference in the rate of chorioamnionitis, RR 1.05 (95% CI 0.53 to 2.06). The crude event rate across trials was 3.2% without pessary. The pooled weighted RD was 0.6 % percentage points (95% CI -3.1 to 4.2).

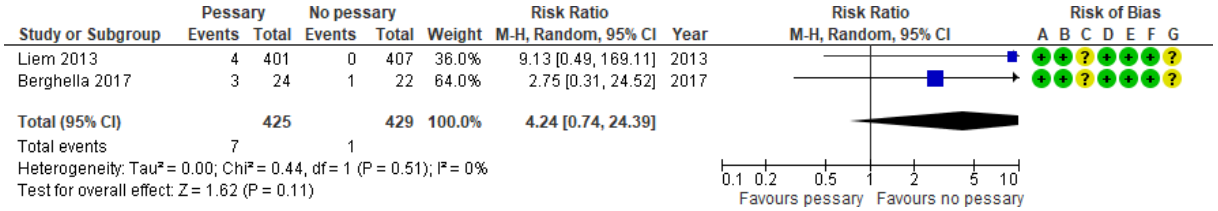
Figure 53. Outcome: Chorioamnionitis.



Conclusion: Pessary, compared with no pessary may result in no difference in chorioamnionitis in women with multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Genitourinary infections (Appendix 4.3.22 and Figure 54)
A meta-analysis of two trials, including 854 women showed no difference in the rate of genitourinary infections, RR 4.24 (95% CI 0.74 to 24.39). The crude event rate across trials was 0.2% without pessary. The pooled weighted RD was 1.4 % percentage points (95% CI -2.5 to 5.4).

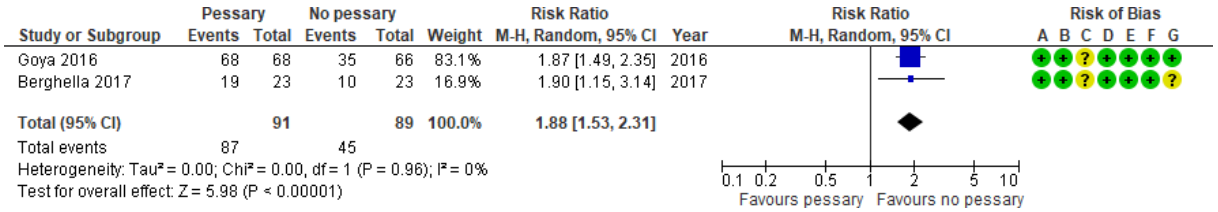
Figure 54. Outcome: Genitourinary infection.



Conclusion: Its uncertain whether pessary, compared with no pessary results in any difference in genitourinary infections in women with multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕◯◯◯).

Vaginal discharge (Appendix 4.3.23 and Figure 55)
A meta-analysis of two trials, including 180 women showed an increased rate of vaginal discharge, RR 1.88 (95% CI 1.53 to 2.31). The crude event rate across trials was 50.6% without pessary. The pooled weighted risk RD was 45.5 % percentage points (95% CI 34.6 to 56.5).

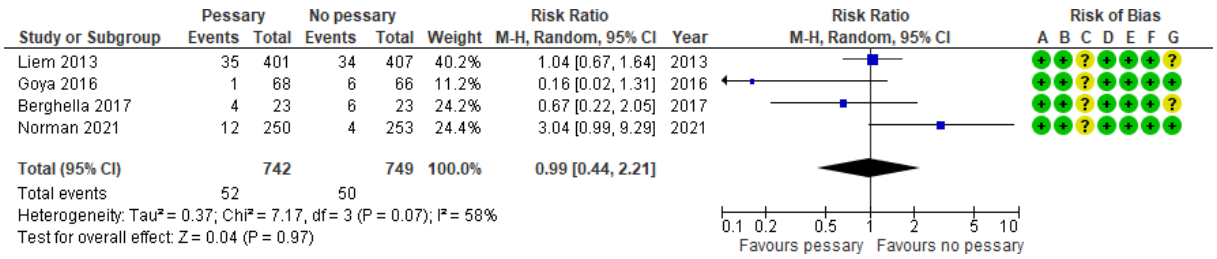
Figure 55. Outcome: Vaginal discharge.



Conclusion: Pessary, compared with no pessary probably increases the risk of vaginal discharge in women with a twin pregnancy, not considering additional risk factor(s) for preterm birth (GRADE⊕⊕⊕◯).

Preterm prelabour rupture of the membranes (PPROM) (Appendix 4.3.24 and Figure 56)
A meta-analysis of four trials, including 1491 women showed no difference in the rate of PPROM, RR 0.99 (95% CI 0.44 to 2.21). The crude event rate across trials was 9.3% without pessary. The pooled weighted risk RD was -0.6 % percentage points (95% CI -5.3 to 4.2).

Figure 56. Outcome: Preterm prelabour rupture of membranes.



Conclusion: Pessary, compared with no pessary may result in no difference in PPROM in women with a multifetal pregnancy, not considering additional risk factor(s) for preterm birth (GRADE ⊕⊕◯◯).

Project: Prevention of preterm birth
Appendix 4.3.1.a. Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singletons	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 26/60 (43.3%) RR 1.09 (95% CI 0.71-1.68) p=0.71	No pessary 23/58 (39.7%)	PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) 8/53 (15.1%) RR 0.96 (95% CI 0.81-1.14) p=0.67	Digital examination at entry to simulate pessary insertion 10/55 (18.2%)	Not PO	+	?	-
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary (Arabin)+vaginal progesterone 14/71 (19.7%) p=0.6	Vaginal progesterone 12/73 (16.4%)	PO	+	?	-
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Singletons 104/431 (24.1%) RR 0.87 (95% CI 0.70-1.09) p= 0.24 Multifetal 34/43 (79.1%) RR 0.89 (95%CI 0.72-1.08) p= 0.24	Vaginal progesterone Singletons 119/430 (27.7%) Multifetal 25/28 (89.3%)	Not PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C:150	Pessary (Arabin) 35/150 (23.3%) RR 0.66 (95% CI 0.46-0.95) p=0.03	Standard care 53/150 (35.3%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?

Project: Prevention of preterm birth
Appendix 4.3.1.a. Intervention pessary
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				
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm DCDA 78% MCDA 22% Previous PTB 0 vs 13%	46 I: 23 C: 23	Pessary (Bioteque cup) 19/23 (83%) RR 1.00 (95% CI 0.76-2.30) p=1.00	No pessary 19/23 (83%)	Not PO	+	?	-
Liem 2013a The Netherlands ProTWIN	Twins Triplets (2%)	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24% Previous PTB 7 vs 6%	813 I: 403 C: 410	Pessary (Arabin) 222/401 (55%) RR 0.94 (95% CI 0.87-1.07) No p-value	Standard care 233/407 (57%)	Not PO I: 5 cerclage C: 0 cerclage	+	?	?
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL<35mm	503 I: 250 C: 253	Pessary (Arabin) 158/250 (63.2%) OR 0.95 (95% CI 0.57-1.58) p=0.79	Standard care 161/253 (63.6%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic , I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.1.b. Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 23/60 (38.3%) RR 1.17 (95% CI 0.72-1.91) p=0.59	No pessary 19/58 (32.8%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 41/190 (22%) OR 0.19 (95% CI 0.12-0.30) p=<0.0001	Standard care 113/190 (59%)	Not PO	?	?	+
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone 74/461 (16.1%) RR 0.85 (95% CI 0.64-1.13)	Vaginal progesterone 84/435 (19.3%)	PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 30/150 (20.0%) RR 0.61 (95% CI 0.41-0.91) p=0.02	Standard care 49/150 (32.7%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm DCDA 78% MCDA 22% Previous PTB 0 vs 13%	46 I: 23 C: 23	Pessary (Bioteque cup) 12/23 (52%) RR 1.00 (95% CI 0.58-1.74) p=1.00	No pessary 12/23 (52%)	Not PO	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 47/68 (69.1%) RR 0.95 (95% CI 0.76-1.18) No p-value	Standard care 48/66 (72.7%)	Not PO	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL<35mm	503 I: 250 C: 253	Pessary (Arabin) 56/250 (22.4%) OR 0.81 (95% CI 0.47-1.41) p=0.32	Standard care 66/253 (26.1%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic , I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.2.a. Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 20/60 (33.3%) RR 1.14 (95% CI 0.67-1.94) p=0.69	No pessary 17/58 (29.3%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 14/190 (7%) OR 0.21 (95% CI 0.10-0.40) p<0.0001	Standard care 53/190 (28%)	Not PO	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm Previous PTB 5.7 vs 10.9%	108 I: 53 C: 55	Pessary (Arabin) 5/53 (9.4%) RR 1.04 (95% CI 0.94-1.12) p=0.46	Digital examination at entry to simulate pessary insertion 3/55 (5.5%)	PO	+	?	-
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary (Arabin)+vaginal progesterone 10/71 (14.1%) No p-value	Vaginal progesterone 7/73 (9.6%)	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm Previous PTB 15.1 vs 18%	935 I: 466 C: 469	Pessary (Arabin) 60/465 (12.9%) OR 1.16 (95% CI 0.78-1.72) p=0.47	Standard care 53/467 (11.3%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Singletons 33/431 (7.7%) RR 0.63 (95% CI 0.42-0.96) p= 0.03 Multifetal 14/43 (32.6%) RR 0.76 (95%CI 0.41-1.39) p= 0.43	Vaginal progesterone Singletons 52/430 (12.1%) Multifetal 12/28 (42.9%)	Not PO	?	?	?

Project: Prevention of preterm birth
Appendix 4.3.2.a. Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 14/150 (9.3%) RR 0.54 (95% CI 0.29-0.99) p=0.04	Standard care 26/150 (17.3%)	Not PO If CL <20mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm DCDA 78% MCDA22% Previous PTB 0 vs 13%	46 I: 23 C: 23	Pessary (Bioteque cup) 9/23 (39%) RR 1.13 (95% CI 0.53-2.40) p=1.00	No pessary 8/23 (35%)	Not PO	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 12/68 (17.6%) RR 0.43 (95% CI 0.24-0.78) p=0.002	Standard care 27/66 (40.9%)	Not PO	+	?	+
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8% Previous PTB 8.8 vs 14.3%	1180 I: 590 C: 590	Pessary (Arabin) 98/588 (16.7%) RR 1.067 (95% CI 0.822-1.385) No p-value	Standard care 92/589 (15.6%)	Not PO	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL<35mm	503 I: 250 C: 253	Pessary (Arabin) 62/250 (24.8%) OR 0.90 (95% CI 0.52-1.57) p=0.64	Standard care 66/253 (26.1%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.2.b. Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 19/60 (31.7%) RR 1.22 (95% CI 0.69-2.17) p=0.55	No pessary 15/58 (25.9%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 12/190 (6%) OR 0.18 (95% CI 0.08-0.37) p<0.0001	Standard care 51/190 (27%)	PO	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm Previous PTB 5.7 vs 10.9%	108 I: 53 C: 55	Pessary (Arabin) 5/53 (9.4%) RR 1.04 (95% CI 0.94-1.12) p=0.46	Digital examination at entry to simulate pessary insertion 3/55 (5.5%)	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm Previous PTB 15.1 vs 18%	935 I: 466 C: 469	Pessary (Arabin) 55/460 (12.0%) OR 1.12 (95% CI 0.75-1.69) p= 0.57	Standard care 50/464 (10.8)	PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone 29/461 (6.3%) RR 0.68 (95% CI 0.43-1.08) No p-value	Vaginal progesterone 41/435 (9.4%)	PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 11/150 (7.3%) RR 0.48 (95% CI 0.24-0.95) p=0.04	Standard care 23/150 (15.3%)	PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm DCDA 78% MCDA 22% Previous PTB 0 vs 13%	46 I: 23 C: 23	Pessary (Bioteque cup) 7/23 (30%) RR 1.0 (95%CI 0.42-2.40) p=1.0	No pessary 7/23 (30%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.3.2.b. Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 11/68 (16.2%) RR 0.41 (95% CI 0.22-0.76) p= 0.003	Standard care 26/66 (39.4%)	PO	+	?	+
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8% Previous PTB 8.8 vs 14.3%	1180 I: 590 C: 590	Pessary (Arabin) 80/588 (13.6%) RR 1.054 (95% CI 0.787-1.413) No p-value	Standard care 76/589 (12.9%)	PO	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL<35mm	503 I: 250 C: 253	Pessary (Arabin) 37/250 (14.8%) OR 0.77 (95% CI 0.40-1.47) p=0.30	Standard care 46/253 (18.2%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.3.a. Intervention pessary
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				
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary (Arabin)+vaginal progesterone 5/73 (6.8%)	Vaginal progesterone 6/73 (8.2%)	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm Previous PTB 15.1 vs 18%	935 I: 466 C: 469	Pessary (Arabin) 46/465 (9.9%) OR 1.36 (95% CI 0.86-2.15) p=0.20	Standard care 35/467 (7.5%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Singletons 22/431 (5.1%) RR 0.61 (95% CI 0.36-1.02) p= 0.05 Multifetal 5/43 (11.6%) RR 0.36 (95% CI 0.14-0.97) p= 0.08	Vaginal progesterone Singletons 36/430 (8.4%) Multifetal 9/28 (32.1%)	Not PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 11/150 (7.3%) RR 0.73 (95% CI 0.35-1.54) p=0.54	Standard care 15/150 (10%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8% Previous PTB 8.8 vs 14.3%	1180 I: 590 C: 590	Pessary (Arabin) 52/588 (8.8%) RR 0.983 (95% CI 0.682-1.416) No p-value	Standard care 53/589 (9%)	Not PO	+	?	+
Liem 2013a The Netherlands ProTWIN	Twins Triplets (2%)	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24% Previous PTB 7 vs 6%	813 I: 403 C: 410	Pessary (Arabin) 41/401 (10%) RR 0.86 (95% CI 0.65-1.15) No p-value	Standard care 49/407 (12%)	Not PO I: 5 cerclage C: 0 cerclage	+	?	?

Project: Prevention of preterm birth
Appendix 4.3.3.a. Intervention pessary
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				
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) 35/250 (14.0%) OR 0.83 (95% CI 0.42-1.63) p=0.47	Standard care 41/253 (16.2%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.3.b. Intervention pessary
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				
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone 15/461 (3.3%) RR 0.52 (95% CI 0.28-0.96)	Vaginal progesterone 28/435 (6.4%)	PO	?	?	?
Saccone 2017c Italy	Singletons	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 10/150 (6.7%) RR 0.71 (95% CI 0.33-1.56) p=0.52	Standard care 14/150 (9.3%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) 26/250 (10.4%) OR 0.79 (95% CI 0.37-1.68) p=0.43	Standard care 32/253 (12.6%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, Cx; cervix, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.4.a. Intervention pessary
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	Number of randomised patients n=	Results		Comments	Directness	Study limitations	Precision *
				Intervention	Control				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 12/60 (20.0%) RR 0.83 (95% CI 0.42-1.64) p=0.66	No pessary 14/58 (24.1%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Hui 2013 China	Singleton	TVS CL <25 mm Previous PTB 5.7 vs 10.9%	108 I: 53 C: 55	Pessary (Arabin) 2/53 (3.8%) RR 0.98 (95% CI 0.90-1.07) p=1.00	Digital examination at entry to simulate pessary insertion 3/55 (5.5%)	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 25/465 (5.4%) OR 1.71 (95% CI 0.89-3.29) p=0.11	Standard care 15/467 (3.2%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Singletons 8/431 (1.9%) RR 0.44 (95% CI 0.19-1.01) p= 0.04 Multifetal 2/43 (4.7%) RR 0.19 (95% CI 0.04-0.83) p= 0.15	Vaginal progesterone Singletons 18/430 (4.2%) Multifetal 7/28 (25.0%)	Not PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 7/150 (4.7%) RR 0.78 (95% CI 0.3-2.03) p=0.8	Standard care 9/150 (6.0%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm DCDA 78% MCDA 22% Previous PTB 0 vs 13%	46 I: 23 C: 23	Pessary (Bioteque cup) 4/23 (17%) RR 1.00 (95% CI 0.28-3.52) p=1.00	No pessary 4/23 (17%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.3.4.a. Intervention pessary
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	Number of randomised patients n=	Results		Comments	Directness	Study limitations	Precision *
				Intervention	Control				
Liem 2013a The Netherlands ProTWIN	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24% Previous PTB 7 vs 6%	813 I: 403 C: 410	Pessary (Arabin) 16/401 (4%) RR 0.79 (95% CI 0.50-1.27) No p-value	Standard care 21/407 (5%)	Not PO I: 5 cerclage C: 0 cerclage	+	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8% Previous PTB 8.8 vs 14.3%	1180 I: 590 C: 590	Pessary (Arabin) 19/588 (3.2%) RR 1.269 (95% CI 0.651-2.473) No p-value	Standard care 15/589 (2.5%)	Not PO	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) 17/250 (6.8%) OR 0.67 (95% CI 0.27-1.64) p=0.25	Standard care 24/253 (9.5%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, Cx; cervix, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.4.b. Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 11/60 (18.3%) RR 0.89 (95% CI 0.43-1.85) p=0.82	No pessary 12/58 (20.7%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 4/190 (2%) OR 0.23 (95% CI 0.06-0.74) p=0.0058	Standard care 16/190 (8%)	Not PO	?	?	+
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I:475 C:461	Pesary (Ingamed)+vaginal progesterone 4/461 (0.9%) RR 0.21 (95% CI 0.07-0.63) No p-value	Vaginal progesterone 18/435 (4.1%)	PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 6/150 (4.0%) RR 0.67 (95% CI 0.24-1.83) p=0.6	Standard care 9/150 (6.0%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm DCDA 78% MCDA 22% Previous PTB 0 vs 13%	46 I: 23 C: 23	Pessary (Bioteque cup) 4/23 (17%) RR 1.00 (95% CI 0.28-3.52) p=1.00	No pessary 4/23 (17%)	Not PO	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 4/68 (5.9%) RR 0.43 (95% CI 0.14-1.33) No p-value	Standard care 9/66 (13.6%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.4.b. Intervention pessary
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				
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) 13/250 (5.2%) OR 0.64 (95% CI 0.23-1.77) p=0.26	Standard care 19/253 (7.5%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochorionic diamniotic, OR; odds ratio, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.5 Intervention pessary
Outcome variable: Gesational age at delivery (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 Pessary	Control No pessary/Standard care Mean (SD)				
Dugoff 2018 USA PoPPS	Singletons	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) Median (IQR) 37.2 (30.0-39.1) p=0.99	No pessary Median (IQR) 38.1 (27.8-39.4)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singletons	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) Mean (SD) 37.7 (2.0) p<0001	Standard care Mean (SD) 34.9 (4.0)	Not PO	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) Mean (SD) 38.1 (3.4) p=0.68	Digital examination at entry to simulate pessary insertion Mean (SD) 37.8 (3.9)	Not PO	+	?	-
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary (Arabin) + vaginal progesterone Mean (SD) 37 ± 3.6 No p-value	Vaginal progesterone Mean (SD) 37.1 ± 4	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) Median (IQR) 38.9 (37.0-40.0) p=0.4	Standard care Median (IQR) 38.7 (37.1-39.9)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Mean (SD) 37.4 (3.2)	Vaginal progesterone Mean (SD) 36.9 (4.0)	Not PO	?	?	?
Saccone 2017c Italy	Singletons	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) Mean 37.6 (3.44) p=0.001	Standard care Mean (SD) 36.2 (4.37)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%) SD calculated from data	?	?	?

Project: Prevention of preterm birth
Appendix 4.3.5 Intervention pessary
Outcome variable: Gesational age at delivery (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 Pessary	Control No pessary/Standard care Mean (SD)				
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Median (IQR) 35.9 (28.9-36.9) p=0.83	No pessary Median (IQR) 35.0 (33.0-36.7)	Not PO	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 35.3 (2.9 range) p=0.01	Standard care 33.1 (3.9 range)	Not PO Unclear if median	+	?	+
Liem 2013a The Netherlands ProTWIN	Twins Triplets (2%)	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Median (IQR) 36.7 (34.7-37.4) HR 0.91 (95% CI 0.76-1.09) No p-value	Standard care Median (IQR) 36.4 (34.3-37.6)	Not PO	+	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Median (IQR) 36.6 (34.9-37.9) No p-value	Standard care Median (IQR) 36.7 (35.0-37.9)	Not PO	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Mean (SD) 34.8 (3.7) Mean difference 0.2 (-0.6-1.1) p=0.5	Standard care Mean (SD) 34.5 (4.0)	Not PO	+	?	?

C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, DCDA; dichorionic diamniotic, HR; hazard ratio, I; intervention, IQR; interquartile range, MC; monochorionic, MCDA; monochorionic diamniotic, PO; primary outcome, PTB; preterm birth, SD; standard deviation, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.6 Intervention pessary
Outcome variable: Low birth weight (<2500g)

* + 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 Pessary	Control Standard care				
Goya 2012 Spain PECEP	Singletons	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 17/190 (9%) OR 0.23 (95% CI 0.12-0.43) p=<0.0001	Standard care 56/190 (29%)	Not PO	?	?	+
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary+vaginal progesterone 17/71 (23.9%) p=0.36	Vaginal progesterone 13/73 (17.8%)	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 96/465 (20.6%) OR 1.15 (95% CI 0.83-1.59) p=0.39	Standard care 86/467 (18.4%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 28/150 (18.7%) RR 0.62 (95% CI 0.41-0.94) p=0.03	Standard care 45/150 (30.0%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 47/136 (34.6%) RR 0.72 (95% CI 0.54-0.97) p=0.01	Standard care 62/130 (47.7%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.6 Intervention pessary
Outcome variable: Low birth weight (<2500g)

* + 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 Pessary	Control Standard care				
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 395/588 (67.2%) RR 0.972 (95% CI 0.899-1.051) No p-value Neonatal level 664/1176 (56.5%) RR 0.993 (95% CI 0.925-1.065) No p-value	Standard care Pregnancy level 407/589 (69.1%) Neonatal level 670/1178 (56.9%)	Not PO	+	?	+
Liem 2013a The Netherlands ProTWIN	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnacy level 271/401 (68%) RR 0.99 (95%CI 0.9-1.09) No p-value Neonatal level 442/811 (55%) RR 0.96 (95% CI 0.86-1.06) No p-value	Standard care Pregnancy level 275/407 (68%) Neonatal level 466/823 (57%)	Not PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, I; intervention, MC; monochoriotic, OR; odds ratio, PO; primary outcome, RR; relative risk, PTB; preterm birth, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.7 Intervention pessary
Outcome variable: Very low birth weight (<1500g)

* + 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 Pessary	Control Standard care				
Goya 2012 Spain PECEP	Singletons	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 9/190 (5%) OR 0.31 (95% CI 0.13-0.72) p=0.004	Standard care 26/190 (14%)	Not PO	?	?	+
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 39/465 (8.4%) OR 1.44 (95% CI 0.87-2.37) p=0.16	Standard care 28/467 (6.0%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 10/150 (6.7%) RR 0.67 (95% CI 0.31-1.44) p=0.40	Standard care 15/150 (10.0%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 13/136 (9.5%) RR 0.73 (95% CI 0.37-1.44) No p-value	Standard care 17/130 (13.1%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.7 Intervention pessary
Outcome variable: Very low birth weight (<1500g)

* + 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 Pessary	Control Standard care				
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 60/588 (10.2%) RR 0.925 (95% CI 0.664-1.288) No p-value Fetal level 100/1176 (8.5%) RR 1.043 (95% CI 0.798-1.364) No p-value	Standard care Pregnancy level 65/589 (11.0%) Fetal level 96/1178 (8.1%)	Not PO	+	?	+
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnacy level 49/401 (12%) RR 0.93 (95% CI 0.65-1.35) No p-value Fetal level 82/811 (10%) RR 0.95 (95% CI 0.65-1.41) No p-value	Standard care Pregnancy level 53/407 (13%) Fetal level 86/823 (10%)	Not PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, I; intervention, MC; monochoriotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; relative risk, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.8 Intervention pessary
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 *
				Interventio Pessary	Control Standard care				
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary+vaginal progesterone 2/71 (2.8%)	Vaginal progesterone 2/73 (2.7%)	Not PO PNM includes NNM (not defined) + IUFD (not defined) + stillbirth	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 15/465 (3.2%) OR 1.38 (95% CI 0.63-3.04) p=0.42	Standard care 11/467 (2.4%)	Not PO PNM includes NNM (not defined) + IUFD (not defined) + termination of pregnancy (I=0 C=1) If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Fetal level 15/509 (2.9%)	Vaginal progesterone Fetal level 31/468 (6.6%)	Not PO PNM includes NNM (not defined) + stillbirth (not defined)	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 2/150 (1.3%) RR 0.50 (95% CI 0.09-2.69) p=0.68	Standard care 4/150 (2.7%)	Not PO PNM is defined as IUFD after 20 w or NNM (<28d) If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Maternal level 20/588 (3.4%) RR 0.911 (95% CI 0.502-1.651) No p-value Neonatal level 29/1176 (2.5%) RR 0.908 (95% CI 0.553-1.491) No p-value	Standard care Maternal level 22/589 (3.7%) Neonatal level 32/1178 (2.7%)	Not PO PNM includes NNM (not defined)+ IUFD (not defined)	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.8 Intervention pessary
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 *
				Interventio Pessary	Control Standard care				
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Fetal level 4/500 (0.8%) OR 0.49 (95% CI 0.07-3.25) p=0.33	Standard care Fetal level 8/506 (1.6%)	Not PO Fetal och neonatal death within 28d	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, IUFD; intrauterine fetal demise, MC; monochoriotic, MCDA; monochoriotic diamniotic, NNM; neonatal mortality, OR; odds ratio, PNM; perinatal mortality, PO; primary outcome, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.9 Intervention pessary
Outcome variable: Neonatal mortality <28d

* + 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 Pessary	Control No pessary/Standard care				
Dugoff 2018 USA PoPPS	Singletons	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 3/60 (5%) RR 0.48 (95% CI 0.13-1.84) p=0.31	No pessary 6/58 (10.3%)	Not PO <28d If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singletons	TVS CL <25 mm 11% in both groups had previous PTB	385 I:192 C: 193	Pessary (Arabin) 0/190 (0%) No p-value	Standard care 1/190 (<1%)	Not PO NNM not defined	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C:55	Pessary (Arabin) 1/53 (1.9%) RR 1.02 (95% CI 0.98-1.06) p=0.49	Digital examination at entry to simulate pessary insertion 0/55 (0%)	Not PO NNM not defined	+	?	-
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I:73 C:73	Pessary+vaginal progesterone 1/71 (1.4%) p=1	Vaginal progesterone 1/73 (1.3%)	Not PO NNM not defined	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 7/465 (1.5%) OR 1.41 (95% CI 0.45-4.48) p=0.56	Standard care 5/467 (1.1%)	Not PO NNM not defined If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I:475 C:461	Pesary (Ingamed)+vaginal progesterone Fetal level 11/499 (2.2%) RR 0.52 (95% CI 023-1.17)	Vaginal progesterone Fetal level 19/450 (4.2%)	NNM not defined Not PO	?	?	?
Saccone 2017c Italy	Singletons	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 1/150 (0.7%) RR 0.33 (95% CI 0.04-3.17) p=0.61	Standard care 3/150 (2.0%)	Not PO <28d If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?

Project: Prevention of preterm birth
Appendix 4.3.9 Intervention pessary
Outcome variable: Neonatal mortality <28d

* + 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 Pessary	Control No pessary/Standard care				
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Neonatal level 4/46 (9%) RR 1.33 (95% CI 0.32-5.63) p=1.0	No pessary Neonatal level 3/46 (7%)	Not PO <28d	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) Neonatal level 0/136 No p-value	Standard care Neonatal level 0/130	Not PO NNM not defined	+	?	+
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Maternal level 13/588 (2.2%) RR 1.447 (95% CI 0.623-3.359) No p-value Neonatal level 17/1176 (1.4%) RR 1.216 (95% CI 0.602-2.456) No p-value	Standard care Maternal level 9/589 (1.5%) Neonatal level 14/1178 (1.2%)	Not PO NNM not defined	+	?	+
Liem 2013a The Netherlands ProTWIN	Twins Triplets (2%)	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Maternal level 16/401 (4%) RR 0.90 (95% CI 0.46-1.77) No p-value Neonatal level 23/811 (3%) RR 0.83 (95% CI 0.41-1.68) No p-value	Standard care Maternal level 18/407 (4%) Neonatal level 28/823 (3%)	Not PO NNM defined as death before discharge	+	?	?

C; control, CI; confidence interval, CL; cervical length, DA; diamniotic, I; intervention, MC; monochoriotic, NNM; neonatal mortality, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.10 Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 12/60 (20%) RR 1.16 (95% CI 0.54-2.47) p=0.67	No pessary 10/58 (17.2%)	Not PO NEC, IVH (grade 3 or 4), RDS, BPD, ROP, blood culture-proven sepsis or NNM. If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 5/190 (3%) OR 0.14 (95% CI 0.04-0.39) p<0.0001	Standard care 30/190 (16%)	Not PO NEC, IVH, RDS, ROP, treatment for sepsis	?	?	+
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 30/450 (6.7%) OR 1.18 (95% CI 0.69-2.03) p=0.55	Standard care 26/456 (5.7%)	Not PO IVH, RDS, NEC or ROP If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Fetal level 98/503 (19.4%) RR 0.9 (95% CI 0.69-1.17)	Vaginal progesterone Fetal level 100/461 (21.7%)	PO Periventricular leukomalacia, severe RDS, BPD, periventricular haemorrhage grade II or higher, NEC, sepsis, stillbirth, neonatal death.	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 22/150 (14.7%) RR 0.46 (95% CI 0.29-0.72) p=0.01	Standard care 48/150 (32%)	Not PO NEC, IVH (grade 3 or 4), RDS, BPD, ROP recuiring therapy, blood culture-proven sepsis or NNM If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Fetal level 21/46 (46%) RR 1.62 (95% CI 0.92-2.82) p=0.13	No pessary Fetal level 13/46 (28%)	Not PO NEC, IVH (grade 3 or 4), RDS, BPD, ROP, blood culture-proven sepsis or NNM	+	?	-

Project: Prevention of preterm birth
Appendix 4.3.10 Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) Fetal level 8/136 (5.9%) RR 0.64 (95% CI 0.27-1.5) No p-value	Standard care Fetal level 12/130 (9.1%)	Not PO NEC, IVH, RDS, BPD, ROP recuiring therapy, proven or suspected sepsis	+	?	+
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnancy level 53/401 (13%) RR 0.98 (95% CI 0.69-1.39) No p-value Fetal level 81/811 (10%) RR 0.95 (95% CI 0.65-1.38) No p-value	Standard care Pregnancy level 55/407 (14%) Fetal level 87/823 (11%)	PO IUFD, periventricular leukomalacia of grade 2 or worse, severe RDS of grade 2 or worse, BPD, IVH of grade 2b or worse, NEC, proven sepsis, NNM within 6 w after expected term date.	+	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 88/579 (15.2%) RR 1.28 (95% CI 0.95-1.71) No p-value Fetal level 115/1147 (10%) RR 1.09 (95% CI 0.85-1.41) No p-value	Standard care Pregnancy level 69/579 (11.9%) Fetal level 105/1146 (9.2%)	IVH, RDS, ROP or NEC Not PO	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Fetal level 67/500 (13.4%) RR 0.88 (95% CI 0.6-1.31) p=0.52	Standard care Fetal level 76/506 (15%)	PO Stillbirth or neonatal death, periventricular leukomalacia, early respiratory morbidity, IVH, NEC, sepsis.	+	?	?

BPD; bronchopulmonary dysplasia, C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, IUFD; intrauterine foster death, IVH; intraventricular haemorrhage, MC; monochoriotic, MCDA; monochoriotic diamniotic, NEC; necrotizing enterocolitis, NNM; neonathal mortality, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RDS; respiratory distress syndrome, ROP; retinopathy of prematurity, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.11 Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 10/60 (16.7%) RR 1.01 (95% CI 0.45-2.31) p=1.0	No pessary 9/58 (15.5%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 5/190 (3%) OR 0.20 (95% CI 0.06-0.55) p=0.0003	Standard care 23/190 (12%)	Not PO	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) 5/53 (9.4%) RR 1.06 (95% CI 0.96-1.18) p=0.44	Digital examination at entry to simulate pessary insertion 2/55 (3.8%)	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 28/450 (6.2%) OR 1.14 (95% CI 0.66-1.99) p= 0.64	Standard care 25/456 (5.5%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Fetal level 91/499 (18.2%) RR 0.95 (95% CI 0.72-1.27)	Vaginal progesterone Fetal level 86/450 (19.1%)	PO Severe RDS	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 14/150 (9.3%) RR 0.45 (95% CI 0.25-0.81) p=0.01	Standard care 31/150 (20.7%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Fetal level 11/46 (24%) RR 1.38 (95% CI 0.61-3.10) p= 0.61	No pessary Fetal level 8/46 (17%)	Not PO	+	?	-

Project: Prevention of preterm birth
Appendix 4.3.11 Intervention pessary
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				
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) Fetal level 8/136 (5.9%) RR 0.96 (95% CI 0.37-2.47) No p-value	Standard care Fetal level 8/130 (6.1%)	Not PO	+	?	+
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 84/579 (14.5%) RR 1.25 (95% CI 0.93-1.69) No p-value Fetal level 109/1147 (9,5%) RR 1.09 (95% CI 0.84-1.41) No p-value	Standard care Pregnancy level 67/579 (11.6%) Fetal level 100/1146 (8.7%)	Not PO	+	?	+
Liem 2013a The Netherlands ProTWIN	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnancy level 27/401 (7%) RR 1.52 (95% CI 0.85-2.72) No p-value Fetal level 36/811 (4%) RR 1.26 (95% CI 0.67-2.35) No p-value	Standard care Pregnancy level 18/407 (4%) Fetal level 29/823 (4%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, I; intervention, MC; monochoriotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.12 Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 5/60 (8.3%) RR 0.87 (95% CI 0.27-2.83) p=1	No pessary 5/58 (8.6%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Fetal level 8/497 (1.6%) RR 0.72 (95% CI 0.25-2.08)	Vaginal progesterone Fetal level 10/450 (2.2%)	PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 8/150 (5.3%) RR 0.67 (95% CI 0.28-1.58) p=0.49	Standard care 12/150 (8.0%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) 4/46 (9%) RR 0.80 (95% CI 0.23-2.79) p=1.0	No pessary 5/46 (11%)	Not PO	+	?	-
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnancy level 2/401 (<1%) RR 0.34 (95% CI 0.07-1.67) Not p-value Fetal level 2/811 (<1%) RR 0.23 (95% CI 0.04-1.17) No p value	Standard care Pregnancy level 6/407 (1%) Fetal level 9/823 (1%)	PO	+	?	?
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Fetal level 6/500 (1.2%) OR 2.0 (95% CI 0.24-16.58) p=0.4	Standard care 3/506 (0.6%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.13 Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 4/60 (6.7%) RR 1.83 (95% CI 0.35-9.60) p=0.68	No pessary 2/58 (3.4%)	Not PO Grade 3 or 4 If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 0/190 (0%) p=0.5	Standard care 2/190 (1%)	Not PO Grade 2 or more	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) 0/53 (0%) RR 0.98 (95% CI 0.95-1.02) p=1.0	Digital examination at entry to simulate pessary insertion 1/55 (1.9%)	Not PO Not defined	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 9/450 (2%) OR 3.08 (95% CI 0.83-11.46) p=0.09	Standard care 3/456 (0.7%)	Not PO Any grade of IVH If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 4/150 (2.7%) RR 0.67 (95% CI 0.19-2.31) p=0.75	Standard care 6/150 (4.0%)	Not PO Grade 3 or 4 If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Fetal level 2/46 (4%) RR 2.0 (95% CI 0.19-21.3) p=1	No pessary Fetal level 1/46 (2%)	Not PO Grade 3 or 4	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) Fetal level 0/136 (0%) No p-value	Standard care Fetal level 4/130 (3%)	Not PO Grade 2 or more	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.13 Intervention pessary
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				
Liem 2013a The Netherlands ProTWIN	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnancy level 6/401 (1%) RR 1.22 (95% CI 0.37-3.98) No p-value Fetal level 8/811 (1%) RR 1.16 (95% CI 0.33-4.07) No p-value	Standard care Pregnancy level 5/407 (1%) Fetal level 7/823 (1%)	PO Grade 2B or more	+	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 16/579 (2.8%) RR 1.33 (95% CI 0.64-2.79) No p-value Fetal level 18/1147 (1.6%) RR 1.2 (95% CI 0.61-2.37) No p-value	Standard care Pregnancy level 12/579 (2.1%) Fetal level 15/1146 (1.3%)	Not PO Not defined	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Fetal level 9/500 (1.8%)	Standard care Fetal level 6/506 (1.2%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DCDA; dichorionic diamniotic, I; intervention, IVH; intraventricular haemorrhage, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.14 Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 2/60 (3.3%) RR 1.83 (95% CI 0.17-19.6) p=1	No pessary 1/58 (1.7%)	Not PO Not defined If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 0/190 (0%) p=0.5	Standard care 2/190 (1%)	Not PO Not defined	?	?	+
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 6/450 (1.3%) OR 2.04 (95% CI 0.51-8.21) p=0.32	Standard care 3/456 (0.7%)	Not PO Not defined If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Fetal level 3/497 (0.6%) RR 0.68 (95% CI 0.15-3.01) No p-value	Vaginal progesterone Fetal level 4/450 (0.9%)	PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 3/150 (2.0%) RR 0.75 (95% CI 0.17-3.29) p=0.99	Standard care 4/150 (2.7%)	Not PO Not defined If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Child level 1/46 (2%) p=1.0	No pessary Child level 0/46 (0%)	Not PO Not defined	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) Child level 0/136 (0%) No p-value	Standard care Child level 2/130 (1.5%)	Not PO Not defined	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.14 Intervention pessary
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				
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnancy level 8/401 (2%) RR 1.35 (95% CI 0.47-3.88) No p value Fetal level 8/811 (1%) RR 1.16 (95% CI 0.39-3.43) No p-value	Standard care Pregnancy level 6/407 (1%) Fetal level 7/823 (1%)	PO Not defined	+	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 6/579 (1%) RR 1.0 (95% CI 0.32-3.08) No p value Fetal level 8/1147 (0.7%) RR 1.33 (95% CI 0.46-3.83) No p-value	Standard care Pregnancy level 6/579 (1.0%) Fetal level 6/1146 (0.5%)	Not PO Not defined	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Fetal level 2/500 (0.4%) OR 0.20 (95% CI 0.03-1.50) p=0.04	Standard care Fetal level 10/506 (2.0%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.15 Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 7/60 (11.6%) RR 1.08 (95% CI 0.39-3.03) p=1.0	No pessary 6/58 (10.3%)	Not PO Proven sepsis If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 3/190 (2%) OR 0.24 (95% CI 0.04-0.90) p=0.03	Standard care 12/190 (6%)	Not PO Number of treatment for sepsis	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) 3/53 (5.7%) RR 0.96 (95% CI 0.86-1.07) p=0.72	Digital examination at entry to simulate pessary insertion 5/55 (9.4%)	Not PO Clinical sepsis	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 27/450 (6%) OR 1.39 (95% CI 0.77-2.52) p=0.28	Standard care 20/456 (4.4%)	Not PO Number of treatment for sepsis If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Fetal level 9/497 (1.8%) RR 1.36 (95% CI 0.44-4.16) No p-value	Vaginal progesterone Fetal level 6/450 (1.3%)	PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 9/150 (6.0%) RR 0.69 (95% CI 0.31-1.57) p=0.50	Standard care 13/150 (8.7%)	Not PO Blood-culture proven sepsis If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Fetal level 5/46 (11%) RR 2.5 (95% CI 0.51-12.2) p=0.43	No pessary Fetal level 2/46 (4%)	Not PO Proven sepsis.	+	?	-

Project: Prevention of preterm birth
Appendix 4.3.15 Intervention pessary
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				
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) Fetal level 4/136 (2.9%) No p-value	Standard care Fetal level 6/130 (4.6%)	Not PO Number of treatment for sepsis.	+	?	+
Liem 2013a The Netherlands ProTWIN	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnancy level 16/401 (4%) RR 0.89 (95% CI 0.45-1.77) No p-value Fetal level 19/811 (2%) RR 0.77 (95% CI 0.38-1.55) No p-value	Standard care Pregnancy level 18/407 (4%) Fetal level 25/823 (3%)	PO	+	?	?
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 41/579 (7.1%) RR 0.91 (95% CI 0.61-1.37) No p-value Fetal level 66/1147 (5.8%) RR 1.0 (95% CI 0.72-1.39) No p-value	Standard care Pregnancy level 45/579 (7.8%) Fetal level 66/1146 (5.8%)	Not PO Number of treatment for sepsis.	+	?	+
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Fetal level 9/500 (1.8%) No p-value	Standard care Fetal level 4/506 (0.8%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.16 Intervention pessary
Outcome variable: Retinopathy of prematurity (ROP)

* + 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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 2/60 (3.3%) RR 0.47 (95% CI 0.09-2.48) p=0.43	No pessary 4/58 (6.9%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 0/190 (0%) p=0.50	Standard care 2/190 (1%)	Not PO	?	?	+
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 5/450 (1.1%) OR 5.11 (95% CI 0.59-43.93) p=0.14	Standard care 1/456 (0.2%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 1/150 (0.7%) RR 0.11 (95% CI 0.01 -0.87) p=0.02	Standard care 9/150 (6.0%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Fetal level 1/46 (2%) p=1.0	No pessary Fetal level 0/46 (0%)	Not PO	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) Fetal level 0/136 (0%) No p-value	Standard care Fetal level 0/130 (0%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.16 Intervention pessary
Outcome variable: Retinopathy of prematurity (ROP)

* + 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				
Nicolaides 2016a 12 countries	Twins	MC twins: I: 18.8% C: 18.8%	1180 I: 590 C: 590	Pessary (Arabin) Pregnancy level 8/579 (1.4%) RR 2.67 (95% CI 0.71-10.0) No p-value Fetal level 12/1147 (1%) RR 4.0 (95% CI 1.13-14.13) No p-value	Standard care Pregnancy level 3/579 (0.5%) Fetal level 3/1146 (0.3%)	Not PO	+	?	+

C; control, CI; confidence interval, CL; cervical lengh, I; intervention, MC; monochoriotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.17 Intervention pessary
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				
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) 21/53 (39.6%) RR 1.13 (95% CI 0.85-1.50) p=0.54	Digital examination at entry to simulate pessary insertion 17/55 (32.1%)	Not PO	+	?	-
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary (Arabin)+vaginal progesterone 5/71 (7%) p=0.49	Vaginal progesterone 3/73 (4.1%)	Not PO	+	?	-
Nicolaides 2016b 9 countries	Singletons	TVS CL <25 mm	935 I: 466 C: 469	Pessary (Arabin) 40/450 (8.9%) OR 1.21 (95% CI 0.75-1.95) p=0.43	Standard care 34/456 (7.5%)	Not PO If CL <15 mm progesterone, I: 204 (43.9%) C: 219 (46.9%)	+	?	?
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Fetal level 104/506 (20.6%) RR 1.08 (95% CI 0.82-1.44)	Vaginal progesterone Fetal level 88/464 (19.0%)	PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 15/150 (10%) RR 0.54 (95% CI 0.30-0.96) p=0.04	Standard care 28/150 (18.7%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Pregnancy level 60/401 (15%) RR 0.8 (95% CI 0.57-1.13) No p-value Fetal level 102/811 (13%) RR 0.83 (95% CI 0.60-1.15) No p-value	Standard care Preganancy level 76/407 (19%) Fetal level 124/823 (15%)	PO	+	?	?

Project: Prevention of preterm birth
Appendix 4.3.17 Intervention pessary
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 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) Fetal level 72/500 (14.4%) OR 1.00 (95% CI 0.54-1.82) p=0.98	Standard care Fetal level 72/506 (14.2%)	PO	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.18 Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Simons 2019 The Netherlands	Twins Triplets	MC 24.4% Triplets 2.7%	I: 140 C: 118	Pessary ASQ, delayed 41/277 (14.8%) OR 1.54 (95% CI 0.83-2.85) No p-value SDQ, abnormal 19/279 (6.8%) OR 1.37 (95% CI 0.66-2.82) No p-value Physical problem 12/277 (4.3%) OR 1.28 (95% CI 0.57-2.91) No p-value Abnormal child outcome 64/281 (22.9%) OR 1.58 (95% CI 0.94-2.65) No p-value	No pessary ASQ, delayed 23/229 (10%) SDQ, abnormal 10/229 (4.4%) Physical problem 6/229 (2.6%) Abnormal child outcome 37/233 (15.9%)	4 year follow-up of the ProTWIN trial. In ProTWIN 813 women participated. ASQ delayed - based on the mean scores, 1 SD in two or more domains or 2 SD in one domain below Dutch referens group. SDQ abnormal – scores validated in Dutch population (normal, borderline, abnormal) Physical problem – 3 or more hospital admissons or 3 or more surgeries in the past 4 years. Abnormal child outcome – atleast one of defined above.	+	?	?

Project: Prevention of preterm birth
Appendix 4.3.18 Intervention pessary
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	Directness *	Study limitations *	Precision *
				Intervention	Control				
Van´t Hooft 2018 Netherlands	Twins Triplets	MC 27% Triplets 1.1%	I: 58 C: 31	Pessary Bayley-III (mean score ± SD) Cognitive n=113 101.1 ± 8.3 Mean difference -3.17 (95% CI -6.1 to -0.2) Adjusted mean difference -3.06 (95% CI -6.2-0.13) No p-value Language n=107 104.9 ± 7.9 Mean difference -0.05 (95% CI -3.7-3.6) Adjusted mean difference -0.94 (95% CI -4.7-2.9) No p-value Motor n=112 105.8 ± 8.5 Mean difference 0.6 (95% CI -2.9-4.1) Adjusted mean difference 0.35 (95% CI -3.4-4.1) No p-value	No pessary Bayley-III (mean score ± SD) Cognitive n=59 104.3 ± 7.1 Language n=55 105.0 ± 9.0 Motor n=59 105.2 ± 9.4	3 year follow-up of the ProTWIN trial. In ProTWIN 808 women participated. In adjusted analyses, adjusted for Multilevel analysis adjusting for dependence of twins or triplets and potential baseline confounders. Also adjusted for parental education (high, middle, low), smoking, ethnic origin, children being eldest in family, use of daycare, bilingual and breastfed >6 months. n/n, number of children in pessary/control group with known Bayley-III (subscale) measurement.	+	?	?

ASQ: Age and Stages Questionnaire, Bayley-III; Bayley Scales of Infant and Toddler Development-third edition, C; control, CI; confidence interval, I; intervention, MC; monochoriotic, OR; odds ratio, SD; standard deviation, SDQ: Strength and Difficulties Questionnaire

Project: Prevention of preterm birth
Appendix 4.3.19 Intervention pessary
Outcome variable: Maternal mortality <28d

* + 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 Pessary	Control Standard care				
Liem 2013a The Netherlands ProTWIN	Twins Triplets (2%)	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) 1/401 (<1%) No p-value	Standard care 0/407	Not PO	+	?	?

C; control, I; intervention, MC; monochoriotic, PO; primary outcome

Project: Prevention of preterm birth
Appendix 4.3.20 Intervention pessary
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	Control				
Liem 2013a The Netherlands ProTWIN	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Hypertensive disorder 65/401 (16%) RR 1.22 (95% CI 0.88-1.72) No p-value Eclampsia or HELLP syndrome 8/401 (2%) RR 1.2 (95% CI 0.41-3.54) No p-value	Standard care Hypertensive disorder 53/407 (13%) Eclampsia or HELLP syndrome 7/407 (2%)	Not PO No definition of hypertension. eclampsia or HELLP	+	?	?

C; control, CI; confidence interval, I; intervention, HELLP; hemolysis, elevated liver enzymes, low platelet counts, MC; monochoriotic, PO; primary outcome, RR; risk ratio

Project: Prevention of preterm birth
Appendix 4.3.21 Intervention pessary
Outcome variable: Maternal morbidity, chorionamnionits.

* + 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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) CA 7/60 (11.6%) RR 1.63 (95% CI 0.5-5.28) p=0.53	No pessary CA 4/58 (6.9%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) CA 5/190 (3%) OR 0.82 (95% CI 0.2-3.32) p=0.6	Standard care CA 6/190 (3%)	Not PO	?	?	+
Karbasian 2016 Iran	Singletons	TVS CL <25 mm	146 I: 73 C: 73	Pessary+vaginal progesterone 1/71 (1.4%) p=0.49	Vaginal progesterone 0/73 (0%)	Not PO	+	?	-
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) CA 5/150 (3.3%) RR 0.71 (95% CI 0.23-2.2) p= 0.77	Standard care CA 7/150 (4.7%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) CA 3/24 (12.5%) p= 0.23	No pessary CA 0/22 (0%)	Not PO	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) CA 2/68 (3%) RR 0.97 (95% CI 0.14-6.7) No p-value	Standard care CA 2/66 (2.9%)	Not PO	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.21 Intervention pessary
Outcome variable: Maternal morbidity, chorionamnionits.

* + 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				
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) CA 13/401 (3%) RR 0.93 (95% CI 0.43-2.01) No p-value	Standard care CA 14/407 (3%)	Not PO I: 5 cerclage C: 0 cerclage	+	?	?

C; control, CA; chorioamnionitis, CI; confidence interval, CL; cervical lengh, I; intervention, MC; monochoriotic, OR; odds ratio, PO; primary outcome, PTB; preterm birth, , RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.22 Intervention pessary
Outcome variable: Maternal morbidity, genitourinary infection

* + 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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) Any genitourinary infection 15/60 (25%) RR 1.09 (95% CI 0.58-2.06) p=0.83	No pessary Any genitourinary infection 14/58 (24.1%)	Not PO Any genitourinary infection inludes urinary tract infection, bacterial vaginosis, chlamydia, gonorrhoea, herpes simplex virus and trichomonas. If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) New vaginal infection 11/53 (20.8%) RR 1.01 (95% CI 0.83-1.22) p=0.92	Digital examination at entry to simulate pessary insertion New vaginal infection 11/58 (20%)	Not PO Candida, bacterial vaginosis, group B streptococcus, Escherichia coli	+	?	-
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone Urinary tract infection 47/475 (9.9%) p=0.5	Vaginal progesterone Urinary tract infection 52/461 (11.3%)	Not PO	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) Urinary tract infection 3/24 (12.5%)	No pessary Urinary tract infection 1/22 (4.5%)	Not PO	+	?	-
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) Urinary tract infection 4/401 (1%) No p-value	Standard care Urinary tract infection 0/407 (0%)	Not PO I: 5 cerclage C: 0 cerclage	+	?	?

C; control, CI; confidence interval, CL; cervical lengh, DA; diamniotic, I; intervention, MC; monochoriotic, PO; primary outcome, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.23 Intervention pessary
Outcome variable: Maternal morbidity, vaginal discharge

* + 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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 44/60 (73.3%) RR 1.48 (95% CI 1.15-1.89) p=0.002	No pessary 28/58 (48.3%)	Not PO If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 190/190 (100%) p=0.002	Standard care 87/190 (46%)	Not PO	?	?	+
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) 130/150 (86.7%) RR 1.88 (95% CI 1.57-2.27) p<0.001	Standard care 69/150 (46%)	Not PO If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) 19/23 (83%) RR 1.90 (95% CI 1.15-3.14) p=0.02	No pessary 10/23 (43%)	Not PO	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 68/68 (100%) p=0.01	Standard care 35/66 (53%)	Not PO	+	?	+

C; control, CI; confidence interval, CL; cervical lengh, I; intervention, MC; monochoriotic, PO; primary outcome, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography

Project: Prevention of preterm birth
Appendix 4.3.24 Intervention pessary
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				
Dugoff 2018 USA PoPPS	Singleton	TVS CL <25 mm	122 I: 61 C: 61	Pessary (Biotech cup) 19/60 (31.7%) RR 1.20 (95% CI 0.68-2.13) p=0.55	No pessary 15/58 (25.9%)	Not PO PPROM <37w If CL <20 mm progesterone, I: 84% C: 91%	?	?	-
Goya 2012 Spain PECEP	Singleton	TVS CL <25 mm 11% in both groups had previous PTB	385 I: 192 C: 193	Pessary (Arabin) 3/190 (2%) OR 0.16 (95% CI 0.03-0.58) p=0.0013	Standard care 17/190 (9%)	Not PO PPROM not defined	?	?	+
Hui 2013 China	Singletons	TVS CL <25 mm	108 I: 53 C: 55	Pessary (Arabin) 6/53 (11.3%) RR 0.96 (95% CI 0.83-1.11) p= 0.62	Digital examination at entry to simulate pessary insertion 8/55 (14.5%)	Not PO PPROM not defined	+	?	-
Pacagnella 2022 Brasil	Singletons 92.4% Twins 7.6%	All DA CL <30 mm	936 I: 475 C: 461	Pesary (Ingamed)+vaginal progesterone 26/474 (5.5%) RR 1.32 (95% CI 0.74-2.36)	Vaginal progesterone 19/458 (4.2%)	 Not PO	?	?	?
Saccone 2017c Italy	Singleton	TVS CL ≤25 mm Prior cervical surgery I: 7 (4.7%) C: 5 (3.3%)	300 I: 150 C: 150	Pessary (Arabin) <34w 2/150 (1.3%) RR 1.0 (95% CI 0.14-7.01) p>0.99	Standard care <34w 2/150 (1.3%)	Not PO PPROM <34w If CL <20 mm progesterone, I: 133 (88.7%) C: 125 (83.3%)	?	?	?
Berghella 2017a USA PoPPT	Twins	TVS CL ≤30 mm	46 I: 23 C: 23	Pessary (Bioteque cup) 4/23 (17%) RR 0.67 (95% CI 0.17-2.05) p=0.72	No pessary 6/23 (26%)	Not PO PPROM not defined	+	?	-
Goya 2016 Spain PECEP-Twins	Twins	TVS CL ≤25 mm Previous PTB I: 16.7% C: 17.6% MC twins I: 19.1% C: 17.6%	137 I: 68 C: 66	Pessary (Arabin) 1/68 (1.5%) RR 0.16 (95% CI 0.20-1.31) No p-value	Standard care 6/66 (9.1%)	Not PO PPROM <34w	+	?	+

Project: Prevention of preterm birth
Appendix 4.3.24 Intervention pessary
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				
Liem 2013a The Netherlands	Twins Triplets	Triplets I: 2% (n=9) C: 2% (n=9) MC twins I: 22% C: 24%	813 I: 403 C: 410	Pessary (Arabin) 35/401 (9%) RR 1.06 (95% CI 0.68-1.66) No p-value	Standard care 34/407 (8%)	Not PO PPROM not defined	+	?	?
Norman 2021 United Kingdom, Belgium STOPPIT-2	Twins	MCDA 20% DCDA 80% CL <35 mm	503 I: 250 C: 253	Pessary (Arabin) 12/250 (4.8%) OR 1.95 (95% CI 0.52-7.34) p=0.20	Standard care 4/253 (1.6%)	Not PO	+	?	?

C; control, CI; confidence interval CL; cervical lengh, DA; diamniotic, DCDA; dichorionic diamniotic, I; intervention, MC; monochoriotic, MCDA; monochoriotic diamniotic, OR; odds ratio, PO; primary outcome, PPROM; preterm prelabour rupture of membranes, PTB; preterm birth, RR; risk ratio, TVS; transvaginal sonography,