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Review article

Role of progesterone, cerclage and pessary in preventing preterm birth in twin pregnancies: A systematic review and network meta-analysis

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A B S T R A C T

Objective: To determine the role of progesterone, pessary and cervical cerclage in reducing the risk of (preterm birth) PTB in twin pregnancies and compare these interventions using pairwise and network meta-analysis.
Study design: Medline, Embase, CINAHL and Cochrane databases were explored. The inclusion criteria were studies in which twin pregnancies were randomized to an intervention for the prevention of PTB (any type of progesterone, cervical cerclage, cervical pessary, or any combination of these) or to a control group (e.g. placebo or treatment as usual). Interventions of interest were either progesterone [vaginal or oral natural progesterone or intramuscular 17a-hydroxyprogesterone caproate (17-OHPC)], cerclage (McDonald or Shirodkar), or cervical pessary.
The primary outcome was PTB < 34 weeks of gestation. Both primary and secondary outcomes were explored in an unselected population of twin pregnancies and in women at higher risk of PTB (defined as those with cervical length <25 mm). Random-effect head-to-head and a multiple-treatment meta-analyses were used to analyze the data and results expressed as risk ratios.
Results: 26 studies were included in the meta-analysis. When considering an unselected population of twin pregnancies, vaginal progesterone, intra-muscular17-OHPC or pessary did not reduce the risk of PTB < 34 weeks of gestation (all $p > 0.05$). When stratifying the analysis for spontaneous PTB, neither pessary, vaginal or intramuscular 17-OHPC were associated with a significant reduction in the risk of PTB compared to controls (all $p > 0.05$), while there was no study on cerclage which explored this outcome in an unselected population of twin pregnancies. When considering twin pregnancies with short cervical length ($\leq$25 mm), there was no contribution of either pessary, vaginal progesterone, intra-muscular 17-OHPC or cerclage in reducing the risk of overall PTB < 34 weeks of gestation.
Conclusions: Cervical pessary, progesterone and cerclage do not show a significant effect in reducing the rate of PTB or perinatal morbidity in twins, either when these interventions are applied to an unselected population of twins or in pregnancies with a short cervix.

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Contents

Introduction

Twin pregnancies are at increased risk of perinatal mortality and morbidity compared to singleton, mainly as a result of fetal anomalies, growth disorders or preterm birth (PTB) [1,2]. PTB is the major determinant of adverse perinatal outcome in twin pregnancies, with an estimated incidence of 59 % and 11 % before 37 and 32 weeks of gestation, respectively [1]. The large majority of PTB in twins is spontaneous, following either preterm premature rupture of membranes (PROM) or spontaneous onset of labor, although a significant proportion of these pregnancies are delivered preterm after iatrogenic obstetrical interventions for maternal-fetal indications [1].

In singleton pregnancies, prophylactic administration of progesterone in women at risk has been shown to decrease the risk of PTB, perinatal mortality and morbidity [3].

Conversely, extrapolating objective evidence on the effective prevention in twins is challenging. Small sample size, different outcome measures and the inclusion of cases at increased risk of PTB, such as pregnancies with monochorionicity-related complications hampers the ability to determine whether such interventions may reduce the incidence of PTB in twin pregnancies. More importantly, studies on PTB prevention in twin pregnancies do not compare different types of interventions. Therefore, it is difficult to conclude which intervention is likely to be more effective.

The aim of this systematic review was to determine the role of progesterone, pessary and cervical cerclage in reducing the risk of PTB in twin pregnancies and compare these interventions using pairwise and network meta-analyses.

Material and methods

Data sources

This review was performed according to an a-priori designed protocol and recommended for systematic reviews and meta-analysis [4]. MEDLINE, Embase and CINAHL were searched electronically on the March 2021 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for “twin pregnancies” and “preterm birth” (Supplementary Table 1). The search and selection criteria were restricted to English language. The reference lists of relevant articles and reviews were hand searched for additional reports. The PRISMA guidelines were followed [5]. The study was registered with the PROSPERO database (Registration number: CRD42019127901).

Eligibility criteria, main outcomes measures

Inclusion criteria were studies in which twin pregnancies were randomized to an intervention for the prevention of preterm birth (any type of progesterone, cervical cerclage, cervical pessary, or any combination of these) or to a control group (e.g. placebo or treatment as usual) Interventions of interest were either type of progesterone (natural progesterone per vagina or oral, or intramuscular 17a-hydroxyprogesterone caproate [17-OHPC]), cerclage (McDonald or Shirodkar), or pessary.

The primary outcome was PTB < 34 weeks of gestation.

The secondary outcomes were:

- PTB < 37 weeks
- PTB < 32 weeks
- PTB < 28 weeks
- PTB < 24 weeks
- Gestational age at delivery (weeks), expressed as continuous variable
- Preterm premature rupture of the membranes (PPROM), defined as the rupture of the membranes before 37 weeks of gestation
- Cesarean section (CS)
- Tocolytic therapy
- Steroid administration
- Vaginal discharge
- Vaginal infections
- Urinary tract infections
- Chorioamnionitis
- Intra-uterine death (IUD), defined as death of either twin from 22 weeks of gestations
- Neonatal death (NND), defined as the death of either newborn up to 28 days of life
- Perinatal death, defined as the sum of IUD and NND
- Apgar score <7 at 3 minutes
- Birthweight (BW) <2500 g
- BW < 1500 g
- BW expressed as continuous variable
- Respiratory distress syndrome (RDS)

- Bronchopulmonary dysplasia (BPD)
- Need for mechanical ventilation
- Intraventricular hemorrhage (IVH) (any grade)
- Periventricular leukomalacia (PVL) (any grade)
- Necrotizing enterocolitis (NEC)
- Retinopathy of prematurity
- Sepsis
- Admission to neonatal intensive care unit (NICU)
- Length of in-hospital stay

Both primary and secondary outcomes were explored in an unselected population of twin pregnancies and in that at higher risk of PTB [including only twins with a cervical length (CL) <25 mm)].

Data collection and analysis

Two reviewers (FDA, AK) independently extracted data. Inconsistencies were discussed among the reviewers until consensus was reached. For those articles in which the relevant information was not reported but the methodology was such that the information might have been recorded initially, the authors were contacted requesting the data.

Risk of bias was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [6]. According to this tool, the risk of bias of each included study is judged according to five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in selection of the reported result. Although the RoB2 tool does not provide an overall risk of bias assessment, the overall risk of bias was considered low if four or more domains were rated as low risk (not counting 'other biases'), with at least one of them being sequence generation or allocation concealment, according to what reported in previous systematic reviews of intervention. Finally, the quality of evidence and strength of recommendations were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodologyfor network meta-analyses (GRADEpro, Version 20. McMaster University, 2014) [7].

The purpose of the present meta-analysis was to integrate the available evidence in PTB management among twin pregnancies, and to help identify which, among four interventions (pessary, vaginal administration of progesterone, intramuscular administration of 17α-hydroxyprogesterone caproate – IM 17-OHPC; cerclage) plus a watchful waiting approach (expectant management), is the most effective in preventing PTB. To do this, two data synthesis approaches were used. First, we performed random-effect head-to-head meta-analyses comparing the risk of PTB and of other maternal and neonatal adverse outcomes in women treated with (a) pessary; (b) vaginal progesterone; (c) IM 17-OHPC; (d) cerclage. Only data extrapolated from prospectively registered studies were included in the pooled analysis. All head-to-head meta-analyses were performed twice: (a) considering an unselected population of twin pregnancies; (b) including only twin pregnancies with a CL < 25 mm. Overall, a total of 25 outcomes were analyzed. The main outcome was the incidence of PTB, defined as birth occurring before 34 completed weeks of gestation, and assessed twice: (a) including all PTBs; (b) considering only spontaneous PTB. Additionally, PTB was assessed at other four time points (before 37, 32, 28 and 24 weeks of gestation). Among the secondary outcomes, three were continuous (gestational age at birth; birthweight; length of in-hospital stay), the other were 21 categorical. Of the latter, eight outcomes assessed maternal morbidity (PPROM; cesarean section; need for tocolysis; steroids administration; vaginal discharge; urinary tract infection; vaginal infection; chorioamnionitis); the remaining 13 outcomes evaluated several neonatal adverse events: death (stratified as intrauterine, neonatal or perinatal); composite morbidity; Apgar score <7; low birthweight (separately assessed as <2500 g and <1500 g); RDS; BPD; need for mechanical ventilation; IVH; PVL; NEC; retinopathy; sepsis; admission to NICU. For each head-to-head meta-analysis, the results were expressed as Risk Ratios and 95 % confidence intervals (CI) [8]. The statistical heterogeneity was quantified using the I^2 metric [9].

Second, for the primary outcome, in the absence of an RCT directly comparing all interventions to prevent PTB in twin pregnancies <34 weeks, a multiple-treatment meta-analysis (MTM) provides the best evidence on the most effective approach [10]. This methodology allows indirect head-to-head comparisons of all interventions through a common comparator, and subsequent ranking of the interventions [11]. MTM has the advantage that it can incorporate the evidence from all comparisons of different treatments within a single analysis. This allows a better appreciation of the relative merits of each treatment within a common analytical framework [11]. The model was fitted in a Bayesian framework, using the network package in Stata [12], and its estimates were relative effect sizes and their credibility intervals [11]. In the MTM framework, we considered the following network nodes: (a) pessary; (b) vaginal progesterone; (c) IM 17-OHPC; (d) cerclage. We run separate MTM analyses according to the gestational risk, either considering (a) an unselected population of twin pregnancies, and (b) only women at high risk of PTB, for a total of 12 separate MTM analyses.

In order to assess the different contribution of each direct comparison to the estimation of the network summary effect, a contribution plot using the Stata command *netweight* was performed [13]. In the plot, the weight of each comparison (expressed as percentage), is a combination of the variance of the direct treatment effect and the network structure [14].

In the absence of closed loops in the network, a formal statistical assessment of inconsistency was not possible [15], and inconsistency is not assumed by definition [16]. However, this does not imply that the transitivity assumption will necessarily hold: to check the validity of the transitivity assumption,we evaluated the potential differences in the gestational age and the cervical length (CL) across all the studies included in the network meta-analysis. When data were insufficient for this assessment, we assumed that the transitivity assumption was met [17].

Finally, for the outcomes where a network meta-analysis was performed the interventions were ranked according to their Surface Under the Cumulative RAnking curve values (SUCRA), which reflect the likelihood of an intervention of being among the best [18]. Higher SUCRA values indicate higher probabilities of an intervention consistently being among the best.

The quality rating of each analysis was assessed following the GRADE Working Group approach for network meta-analyses which, among other aspects such as risk of bias of the studies, takes into consideration the network assumptions to rate the quality of the evidence, downgrading its score if there is heterogeneity, intransitivity or incoherence [18]. For most of the secondary outcomes, given the relative scarcity of the studies included in each comparison, and the missingness of data, inconsistency would be likely to occur, thus we did not perform any MTM calculation, and used only direct comparison head-to-head meta-analyses.

Small study effects (potentially caused by publication bias) were assessed using funnel plots, and formally tested through the Egger regression asymmetry test for those meta-analyses including ≥10 studies. When less than ten studies are included, the available tests are at very high risk of bias because of the lack of statistical power [6].

Table 1
General characteristics of the included studies.

Author	Year	Country	Period considered	Inclusion criteria[a]	Intervention	Description of intervention	Indication for intervention	Primary outcome	Intervention sample size	Comparison sample size
Rehal [19]	2021	United Kingdom, Italy, Spain, Bulgaria, France, Belgium	2017–2019	All twin pregnancies at 11–14 weeks	Progesterone	Vaginal progesterone (300 mg/2 daily from 11–14 to 34 weeks	Prophylactic	sPTB < 34 weeks	582	587
Merced [20]	2019	Spain	2010–2014	Twin pregnancies with CL less than 20 mm after an episode of threatened preterm labor	Arabin Pessary	Arabin Pessary	CL ≤20 mm	sPTB < 34 weeks	67	65
Dang [21]	2019	Vietnam	2016–2017	Asymptomatic twin pregnancies with CL less than 38 mm	Pessary vs Progesterone	Arabin Pessary; Vaginal progesterone (400 mg/daily) from 16–22 weeks	CL < 38 mm	PTB < 34 weeks	150	150
Berghella [22]	2017	United States	2004–2016	Asymptomatic twin pregnancies with short cervix between 18 + 0–27 + 6 weeks	Pessary	Bioteque^{TM} cup	CL ≤30 mm	PTB (overall) <34 weeks	23	23
Goya [23]	2016	Spain	2011–2014	Asymptomatic twin pregnancies with a short cervix at between 18–22 weeks	Pessary	Arabin Pessary	CL ≤ 25 mm	sPTB < 34 weeks	68	66
Nicolaides [24]	2016	United Kingdom	2008–2011	All twin pregnancies at 20–24 + 6 weeks	Pessary	Arabin Pessary	Prophylactic	sPTB < 34 weeks	590	590
Liem [25]	2013	The Netherlands	2009–2012	All twin pregnancies at 12–20 weeks	Pessary	Arabin Pessary	Prophylactic	Composite poor perinatal outcome	403	410
El-Refaie [26]	2016	Egypt	2012–2014	DC twin pregnancies with CL between 20–25 mm at 20–24 weeks	Vaginal progesterone	Progesterone suppositories (400 mg/daily from 20–24 to 37 weeks	Cl between 20–25 mm	sPTB < 34 weeks	116	108
Awwad [27]	2015	Lebanon	2006–2011	All twin pregnancies at 16–20 weeks	Intramuscular 17OHPC	Intramuscular injection of 250 mg 17 OHPC /weekly from 16–20 to 36 weeks	None (unselected population)	PTB< 37 weeks	194	94
Brizot [28]	2015	Brazil	2007–2013	All twin pregnancies between 18 and 21 + 6 weeks of gestation	Vaginal progesterone	Progesterone ovules 100 mg/daily	None (unselected population)	Difference in mean GA at birth	189	191
Senat [29]	2013	France	2006–2010	Asymptomatic twin pregnancies with CL < 25 mm at 24 + 0–31 + 6 weeks	Intramuscular 17OHPC	Intramuscular injection of 500 mg 17 OHPC /weekly from 16–20 to 36 weeks	CL < 25 mm	Time from randomization to delivery	82	83
Serra [30]	2012	Spain	2005–2008	All DC twin pregnancies from 11–13 to 20 weeks of gestation	Vaginal progesterone	Progesterone pessaries 200–400 mg/daily from 20 to 34 weeks	None (unselected population)	PTB< 37 weeks	194	96
Wood [31]	2102	Canada	2006–2010	All twin pregnancies at 16 + 0–20 + 6 weeks of gestation	Vaginal progesterone	Progesterone gel 90 mg/daily	None (unselected population)	GA at birth	42	42
Aboulghar [32]	2012	Egypt	2008–2010	All DC twin pregnancies at 15–19 weeks of gestation	Vaginal progesterone	Vaginal natural progesterone suppositories 200 mg twice daily	None (unselected population)	PTB < 37 and 34 weeks	49	42
Combs [33]	2011	United States	2004–2009	All DC twin pregnancies at 16–24 weeks of gestation	Intramuscular 17OHPC	Intramuscular injection of 250 mg 17 P/weekly from 16–24 to 34 weeks	None (unselected population)	Composite neonatal morbidity	160	78
Lim [34]	2011	The Netherlands	2006–2009	All twin pregnancies at 15–19 weeks of gestation	Intramuscular 17OHPC	Intramuscular injection of 250 mg 17 OHPC /weekly from 15–19 to 34 weeks	None (unselected population)	Adverse neonatal outcome	336	335
Rode [35]	2011	Denmark/Austria/United Kingdom	2006–2008	All diamniotic pregnancies at 18–24 weeks	Vaginal progesterone	Progesterone pessaries 200 mg/ daily from 20–23 + 6–33 + 6 weeks	None (unselected population)	PTB < 34 weeks	334	343
Klein [36]	2011	Denmark/Austria/United Kingdom	2006–2009	Twin pregnancies with CL < 30 mm at 20–24 weeks	Vaginal progesterone	Progesterone pessaries 200 mg/ daily from 20–23 + 6–33 + 6 weeks	CL < 30 mm	PTB < 34 weeks	17	30
Cetingoz [37]	2011	Turkey	2004–2007	All twin pregnancies at 24 weeks	Vaginal progesterone	Progesterone suppositories (100 mg/daily from 24 to 34 weeks	None (unselected population)	PTB< 37 weeks	28	39
Durnwald [38]	2010	United States	2004–2005	Twin pregnancies with a short C at 16–20 weeks of gestation	Intramuscular 17OHPC	Intramuscular injection of 250 mg 17 OHPC/weekly from 16–20 to 35 weeks	CL<10th or 25th percentile	Delivery or fetal death <35 weeks	20	201

Table 1 (*Continued*)

Author	Year	Country	Period considered	Inclusion criteria[a]	Intervention	Description of intervention	Indication for intervention	Primary outcome	Intervention sample size	Comparison sample size
Briery [39]	2009	United States	NS	All twin pregnancies at 20–30 weeks	Intramuscular 17OHPC	Intramuscular injection of 250 mg 17 OHPC weekly from 20–30 to 34 weeks	None (unselected population)	PTB< 35 weeks	16	14
Norman [40]	2009	United Kingdom	2004–2008	All twin pregnancies at 22 weeks of gestation	Vaginal progesterone	Progesterone gel 100 mg/daily	None (unselected population)	PTB or IUD < 34 weeks	250	250
Rouse [41]	2007	United States	2004–2006	All twin pregnancies at 16–20 weeks of gestation	Intramuscular 17OHPC	Intramuscular injection of 250 mg 17 OHPC /weekly from 16–20 to 35 weeks	None (unselected population)	Delivery or fetal death <35 weeks	325	330
Fonseca [42]	2007	United Kingdom	2003–2006	Twin pregnancies with CL < 15 mm at 20–25 weeks	Vaginal progesterone	Vaginal micronized progesterone 200 mg/daily from 24 to 33 + 6 weeks	CL < 15 mm	sPTB < 34 weeks	11	13
Berghella [43]	2004	United States	1998–2003	Asymptomatic twin pregnancies with CL < 25 mm	Cerclage	McDonald cerclage	CL < 25 mm	PTB < 35 weeks	3	1
Eskndar [44]	2007	Saudi Arabia	2004–2006	All twin pregnancies at 12–14 weeks of gestation	Cerclage	McDonald cerclage	None (unselected population)	PTB<37 weeks	76	100
Althusius [45]	2001	The Netherlands	1995–2000	Twin pregnancies with CL < 25 mm	Cerclage	McDonald cerclage	CL < 25 mm	PTB < 34 weeks	8	9
Rust [46]	2001	United States	1998–2000	Twin pregnancies with US dilatation or shortening of the cervix at 16–24 weeks of gestation	Cerclage	McDonald cerclage	CL < 25 mm	GA at birth	13	14

CL, cervical length; PTB, preterm birth; sPTB, spontaneous preterm birth; 17 P, 17-progesterone; 17-OHPC, 17a-hydroxyprogesterone caproate; GA, gestational age; IUD, intrauterine death; NS, not specified.
[a] inclusion criteria refer to the main population analyzed in each individual study, not considering the sub-group analyses.

RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and Stata, version 13.1 (Stata Corp., College Station, TX, 2013) were used to perform head-to-head meta-analyses MTMs, respectively.

Results

General characteristics of the studies

383 articles were identified, 41 were assessed with respect to their eligibility for inclusion and 28 studies were included in the systematic review (Table 1 and Fig. 1) [19–46], while 26 studies were included in the meta-analysis [19,21–25,27,20–46]. The excluded studies and the reasons for their exclusion are outlined in Supplementary Table 2.

Four studies (2473 pregnancies) explored the use of cervical pessary vs no intervention in reducing the risk of PTB in twin pregnancies; out of these, two studies included an unselected population of twins while two included those with a short CL (Table 1). Regarding the type of pessary adopted, three studies used Arabin while one used Bioteque cup.

Eighteen studies (5821 pregnancies) explored the role of progesterone compared to no intervention in reducing the risk of PTB in twins (Table 1); out of these, 14 included unselected populations of twin pregnancies, while 4 exclusively included those with a short cervical length (CL). Regarding the type of progesterone, 7 studies used intra-muscular injection of 17-OHCP, while 11 vaginal progesterone.

Four studies (224 pregnancies) explored the role of cerclage compared to no intervention in reducing the risk of PTB (Table 1); all the included studies used McDonald cerclage and all except one included twins with a short CL on mid-trimester ultrasound. There was only one study comparing two interventions (pessary vs vaginal progesterone).

The results of the quality assessment of the included studies using RoB2 tool are presented in Supplementary Table 3. Results of the direct, indirect and network estimates of all network meta-analyses comparing the risk of PTB (<34 weeks), including the quality of evidence as assessed by the GRADE score and the reasons for downgrading it are reported in Supplementary Table 4, and Figs. 2 and 3. For the main outcome, the quality of evidence for most of the performed comparisons was moderate.

Synthesis of the results

Primary outcome (PTB < 34 weeks)

Ten studies explored the role of vaginal progesterone compared to no intervention in reducing the risk of PTB in unselected populations of twin pregnancies. Overall, vaginal progesterone did not reduce the risk of PTB < 34 weeks of gestation (6 studies, 2672 pregnancies; RR: 1.04; 95 % CI: 0.84–1.30 - p = 0.7). Likewise, there was no contribution of either intra-muscular 17-OHPC (3 studies, 923 pregnancies; RR: 1.09; 95 % CI: 0.74–1.60 - p = 0.7) or pessary (1 study, 1177 pregnancies; RR: 1.07; 95 % CI: 0.82–1.38 - p = 0.6) in affecting the risk of PTB, while there was no study exploring the role of cerclage in reducing PTB in unselected population (Table 2, Fig. 4, Supplementary Figs. 1–4).

There was only one study comparing two different interventions (pessary vs vaginal progesterone) in asymptomatic twin pregnancies with CL < 38 mm at 16–22 weeks of gestation). The study reported no difference in the risk of PTB < 34 weeks of gestation between the two groups [19].

When stratifying the analysis on spontaneous PTB, neither pessary (1 study, 1177 pregnancies; RR: 1.05; 95 % CI: 0.79–1.41 - p = 0.7), vaginal (3 studies, 2134 pregnancies; RR: 1.08; 95 % CI: 0.80–1.46 - p = 0.6) or intra-muscular 17-OHPC (2 studies, 893

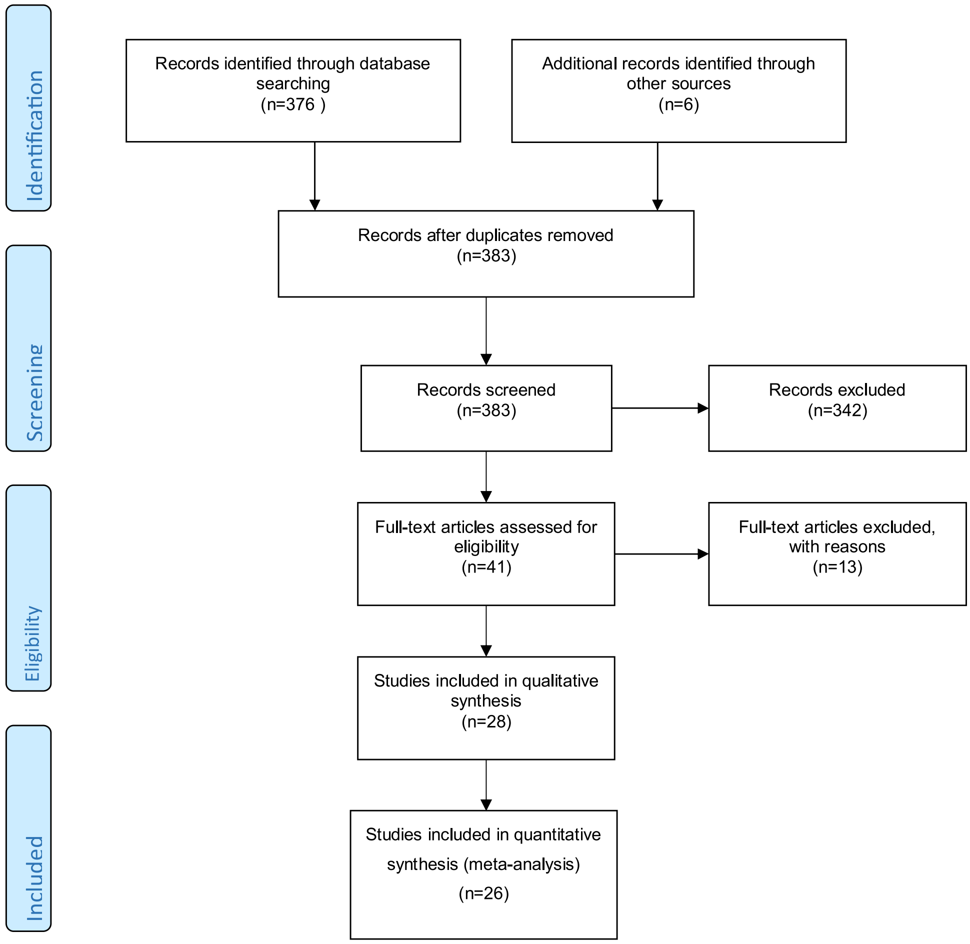

Fig. 1. Systematic review flowchart.

pregnancies; RR: 1.16; 95 % CI: 0.92–1.46 - p = 0.2) were associated with a significant reduction in the risk of PTB compared to controls, while there was no study on cerclage which explored this outcome in an unselected population of twin pregnancies (Table 2).

When a network meta-analysis was used to compare the different interventions, no difference emerged between pessary, vaginal or intra-muscular 17-OHPC in reducing the rate of PTB < 34 weeks when such interventions were applied to both an unselected population of twins (Table 3).

The cumulative probabilities of being the most efficacious treatments for pessary, vaginal progesterone, intramuscular progesterone or expectant management were: 31.6 %, 20.4 %, 43.8 % and 4.2 %, respectively, when considering an unselected population of twin pregnancies. For women with a CL ≤ 25 mm, the probabilities of being the best approach were: 4.0 % (pessary), 10.7 % (vaginal progesterone), 24.4 % (intramuscular progesterone) and 0.6 % (expectant management). For this subgroup of women, cerclage showed the highest probability of being the best approach

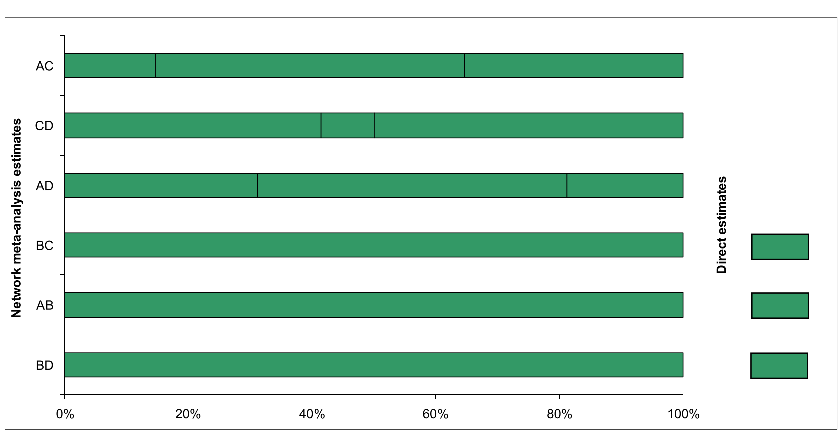

Fig. 2. All women – Study limitations for each network estimate for pairwise comparisons of different treatments, in women at risk of preterm birth (<34 weeks). Calculations are based on the contributions of direct evidence. The colours are based on the risk of bias (green: low; yellow: moderate; red: high). The initial judgements about the risk of bias in the direct estimates are shown on the right side of the figure (there is no direct evidence for AC, CD and AD). The names of the treatments are reported below. A = Pessary; B = Expectant management; C = Vaginal Progesterone; D = intramuscular 17α-hydroxyprogesterone caproate (IM 17-OHPC).

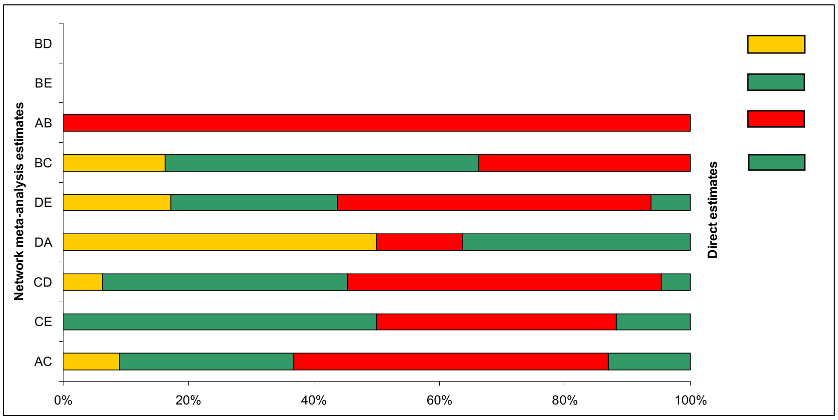

Fig. 3. Women with cervical length <25 mm - Study limitations for each network estimate for pairwise comparisons of different treatments, in women at risk of preterm birth (<34 weeks). Calculations are based on the contributions of direct evidence. The colours are based on the risk of bias (green: low; yellow: moderate; red: high). The initial judgements about the risk of bias in the direct estimates are shown on the right side of the figure (there is no direct evidence for BD and BE). The names of the treatments are reported below.
A = Pessary; B = Expectant management; C = Vaginal Progesterone; D = intramuscular 17α-hydroxyprogesterone caproate (IM 17-OHPC); E = Cerclage.

Table 2
Results of the head-to-head meta-analysis comparing the likelihood of preterm birth in twin pregnancies treated with (1) pessary; (2) vaginal progesterone; (3) intramuscular 17α-hydroxyprogesterone caproate; (4) cerclage versus untreated twin pregnancies (expectant management). For each outcome, pooled risk estimates are reported for all interventions combined and separately for each intervention. All analyses were performed twice, either considering (a) an unselected population of twin pregnancies and (b) twin pregnancies with cervical length <25 mm.

	A. Unselected population of twin pregnancies				B. Women with cervical length <25 mm			
	N. studies (sample)	Pooled RR (95 % CI)	p	I^2, %	N. studies (sample)	Pooled RR (95 % CI)	p	I^2, %
1. Preterm birth <34 weeks in treated vs untreated twin pregnancies								
Pessary vs expectant management	1 (1177) [22]	1.07 (0.82–1.38)	0.6	–	3 (371) [20–22]	0.91 (0.42–1.96)	0.8	79
Vaginal progesterone vs expectant management	6 (2672) [19,28,30,32,35,37]	1.04 (0.84–1.30)	0.7	38	1 (35) [26]	0.95 (0.64–1.40)	0.8	–
IM 17-OHPC vs expectant management	3 (923) [31,37,39]	1.09 (0.74–1.60)	0.7	39	1 (165) [27]	1.45 (0.94–2.25)	0.09	–
Cerclage vs expectant management	0	–	–	–	3 (48) [41,43,44]	2.13 (0.74–6.15)	0.16	31
2.Spontaneous preterm birth <34 weeks in treated vs untreated twin pregnancies								
Pessary vs expectant management	1 (1177) [22]	1.05 (0.79–1.41)	0.7	–	2 (348) [21,22]	0.72 (0.25–2.06)	0.5	67
Vaginal progesterone v expectant management	3 (2134) [19,28,35]	1.08 (0.80–1.46)	0.6	41	0	–	–	–
IM 17-OHPC vs expectant management	2 (893) [31,39]	1.16 (0.92–1.46)	0.2	0	0	–	–	–
Cerclage vs expectant management	0	–	–	–	2 (21) [41,43]	1.20 (0.29–4.90)	0.8	12
3. Preterm birth <37 weeks in treated vs untreated twin pregnancies								
Pessary vs expectant management	2 (1985) [22,23]	0.96 (0.89–1.02)	0.2	0	2 (157) [21,22]	0.95 (0.77–1.16)	0.6	0
Vaginal progesterone vs expectant management	8 (3250) [19,28,30–32,35,37,39]	1.03 (0.94–1.13)	0.5	33	1 (35) [26]	0.98 (0.80–1.21)	0.9	–
IM 17-OHPC vs expectant management	5 (1879) [25,31,32,37,39]	1.03 (0.95–1.12)	0.4	19	2 (178) [27,32]	0.95 (0.70–1.30)	0.8	39
Cerclage vs expectant management	1 (176) [42]	1.15 (0.70–1.91)	0.6	–	3 (48) [41,43,44]	1.20 (0.92–1.57)	0.2	0
4. Preterm birth <32 weeks in treated vs untreated twin pregnancies								
Pessary vs expectant management	2 (1985) [22,23]	0.92 (0.70–1.20)	0.5	0	1 (23) [41]	4.58 (0.66–33.4)	0.13	–
Vaginal progesterone vs expectant management	4 (2514) [19,28,30,35]	1.02 (0.82–1.26)	0.9	0	1 (35) [26]	0.72 (0.42–1.26)	0.3	–
IM 17-OHPC vs expectant management	3 (1194) [25,31,32]	1.09 (0.56–2.11)	0.8	66	2 (178) [27,32]	1.24 (0.29–5.36)	0.8	85
Cerclage vs expectant management	0	–	–	–	3 (48) [41,43,44]	1.62 (0.52–4.99)	0.4	46
5. Preterm birth <28 weeks in treated vs untreated twin pregnancies								
Pessary vs expectant management	2 (1985) 22,23	0.98 (0.60–1.59)	0.9	10	2 (157) [20,21]	0.87 (0.15–1.08)	0.9	57
Vaginal progesterone vs expectant management	4 (2514) [19,28,30,35]	0.94 (0.69–1.27)	0.7	0	1 (35) [26]	0.71 (0.27–1.87)	0.5	–
IM 17-OHPC vs expectant management	3 (1194) [25,31,32]	0.85 (0.51–1.42)	0.5	0	1 (15) [32]	0.33 (0.09–1.28)	0.1	–
Cerclage vs expectant management	0	–	–	–	3 (48) [41,43,44]	1.40 (0.48–4.08)	0.5	24
6. Preterm birth <24 weeks in treated vs untreated twin pregnancies								
Pessary vs expectant management	0	–	–	–	1 (23) [20]	1.83 (0.19–17.5)	0.6	–
Vaginal progesterone vs expectant management	1 (1169) [19]	0.58 (0.31–1.09)	0.09	–	0	–	–	–
Cerclage vs expectant management	0	–	–	–	3 (48) [41,43,44]	1.15 (0.51–2.56)	0.7	0

RR, Risk Ratio; CI, Confidence Interval; IM 17-OHPC = intramuscular 17α-hydroxyprogesterone caproate.

(60.3 %). However, these figures were bases upon a very small number of included cases, which affects the robustness of these findings.

Secondary outcomes

Prevention of PTB and maternal outcomes. Fifteen studies (6121 pregnancies) explored the role of the different interventions in preventing PTB < 37 weeks of gestation. None of these interventions, including pessary (2 studies, 1985 pregnancies; RR: 0.96; 95 % CI: 0.89–1.02 - p = 0.2), vaginal progesterone (8 studies, 3250 pregnancies; RR: 1.03; 95 % CI: 0.94–1.13 - p = 0.5), intra-muscular 17-OHPC (5 studies, 1879 pregnancies; RR: 1.03; 95 % CI: 0.95–1.12 - p = 0.4) or cerclage (1 study, 176 pregnancies; RR: 1.15; 95 % CI: 0.10–1.91 - p = 0.6), significantly reduced the risk of PTB, when compared to women with no intervention. Likewise, none of the explored interventions reduced the risk of PTB < 32 or PTB < 28 weeks compared to controls (all p > 0.05; Table 2).

Five studies (2084 pregnancies) explored the risk of PPROM in women receiving these interventions. Neither pessary (1 study, 808 pregnancies; RR: 1.04; 95 % CI: 0.67–1.64 - p = 0.9), vaginal progesterone (1 study, 290 pregnancies; RR: 0.82; 95 % CI: 0.20–3.38 - p = 0.8) nor intra-muscular 17-HPC (3 studies; 986 pregnancies; RR: 1.21; 95 % CI: 0.77–1.89 - p = 0.4) reduced the risk of PPROM compared to women not receiving these interventions (Supplementary Table 5).

Prophylactic administration of vaginal progesterone (5 studies, 1924 pregnancies; RR 0.93, 95 % CI 0.88–0.99, p = 0.02) was associated with a significantly lower rate of CS, while there was no difference in the need for CS in women receiving intra-muscular 17-OHPC compared to controls (3 studies, 1558 pregnancies; RR: 1.01; 95 % CI: 0.93–1.10, p = 0.8). Conversely, the risk of CS was significantly increased (1 study, 808 pregnancies; RR 1.18, 95 % CI 1.02–1.36, p = 0.03) in women receiving pessary, although only one study was included in this outcome (Supplementary Table 5).

When assessing the association between the explored interventions and the need for administration of steroids or tocolytics, the use of either pessary, vaginal and intramuscular 17-OHPC progesterone was not associated with a reduction in steroids administration or tocolytic therapy compared to controls (all p > 0.05) (Supplementary Table 5).

There was no difference in the rate of vaginal discharge and infections, UTI or chorioamnionitis in women treated with pessary, vaginal progesterone or intra-muscular 17-OHPC compared to controls (all p > 0.05) (Supplementary Table 5).

Furthermore, there was no significant difference in the mean gestational age at birth between women receiving pessary (2 studies, 1985 pregnancies; MD: 0.09; 95 % CI: -0.30; 0.48 - p = 0.6), vaginal progesterone (5 studies, 2023 pregnancies; MD: -0.09; 95 % CI: -0.32; 0.14 - p = 0.5) or intra-muscular 17-OHPC (5 studies, 1879 pregnancies: MD: 0.33; 95 % CI: -0.71; 1.38 - p = 0.6) compared to controls when such interventions were used in an unselected population of twin pregnancies (Supplementary Table 6).

No difference was also found when comparing pessary (1 study, 2354 pregnancies; MD: -22.0; 95 % CI: -64.0; -20.0 - p = 0.3), vaginal progesterone (4 studies, 3152 pregnancies; MD: -24.6; 95 % CI: -113.0; 63.5 - p = 0.6) or intra-muscular 17-OHPC (3 studies, 1980 pregnancies: MD: 36.5; 95 % CI: -119; 192 - p = 0.6) in terms of birthweight (Supplementary Table 6).

Finally, pessary was not associated with a reduction of length of in-hospital stay (1 study, 136 pregnancies; MD: -3.0; 95 % CI: -9.21; 3.21 - p = 0.3), while women receiving vaginal progesterone had a mean longer hospitalization compared to controls (2 studies, 801 pregnancies; MD: 3.30; 95 % CI: 1.25; 5.35 – p < 0.01). Conversely, women receiving intra-muscular 17-OHPC progesterone had a mean lower hospitalization compared to controls (2 studies, 636 pregnancies; MD: -3.93; 95 % CI: -6.87; -0.99 – p = 0.009) (Supplementary Table 6).

Secondary outcomes: fetal and neonatal outcomes

Twelve studies (2 pessary, 5 vaginal progesterone, 5 on intramuscular 17-OHPC and none cerclage; 11612 pregnancies) explored the role of each intervention in reducing the risk of perinatal mortality. Overall, neither pessary (RR: 0.69; 95 % CI: 0.40–1.19 - p = 0.2), nor vaginal progesterone (RR: 1.13; 95 % CI: 0.61–2.10 - p = 0.7) or intra-muscular 17-OHPC (RR: 0.82; 95 % CI: 0.46–1.49 - p = 0.5) were associated with a significant reduction in the risk of IUD. Likewise, none of these interventions reduced the

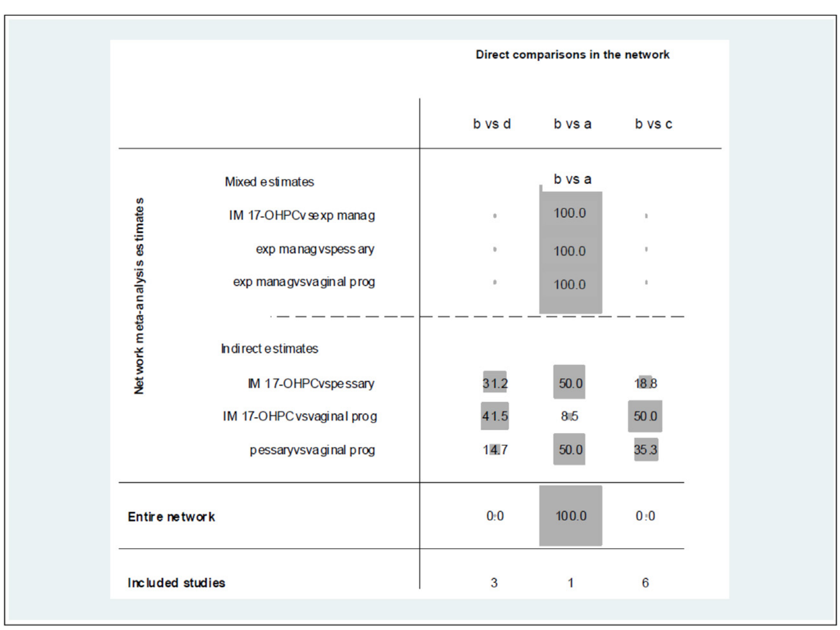

Fig. 4. All women - Contribution plot for the multiple-treatment meta-analysis of preterm birth (<34 weeks). The size of each square is proportional to the weight attached to each direct summary effect (horizontal axis) for the estimation of each network summary effect (vertical axis). The numbers express the weights as percentages. a = Pessary; b = Expectant management; c = Vaginal Progesterone; d = intramuscular 17α-hydroxyprogesterone caproate (IM 17-OHPC).

Table 3
Results of the multiple-treatment meta-analysis comparing the risk of pre-term birth (<34 weeks) in twin pregnancies treated with (1) pessary; (2) vaginal progesterone; (3) intramuscular 17α-hydroxyprogesterone caproate; (4) cerclage. All analyses were performed twice, either considering (a) an unselected population of twin pregnancies and (b) twin pregnancies with cervical length <25 mm.

	Unselected population of twin pregnancies		Twin pregnancies with cervical length <25 mm	
	RR (95 % CI)	p	RR (95 % CI)	p
1. Pessary vs Vaginal Progesterone	0.98 (0.58−1.67)	0.9	0.89 (0.08−16.7)	0.9
2. Pessary vs IM 17-OHPC	1.12 (0.60−2.07)	0.7	2.0 (0.24−16.6)	0.5
3. Vaginal Progesterone vs IM 17-OHPC	1.14 (0.70−1.85)	0.6	2.19 (0.07−65.2)	0.7
4. Pessary vs cerclage	–	–	4.73 (0.62−36.1)	0.13
5. Vaginal Progesterone vs cerclage	–	–	5.24 (0.21−129)	0.3
6. IM 17-OHPC vs cerclage	–	–	2.37 (0.20−27.7)	0.5

RR, Risk Ratio; CI, Credible Intervals; IM 17-OHPC, intramuscular 17α-hydroxyprogesterone caproate.

risk of NND or PND when applied to an unselected population of twin pregnancies with a CL ≤ 25 mm on ultrasound (all p > 0.05; Supplementary Table 7).

Neonatal and perinatal mortality was not significantly influenced by pessary, vaginal progesterone or intra-muscular 17-OHPC when compared to pregnancies not receiving these interventions. Finally, cervical pessary, vaginal progesterone or intra-muscular 17-OHPC did not modify the risk of composite morbidity, Apgar score < 7, BW < 2500 and 1500 g, RDS, BPD, need for mechanical ventilation, IVH, PVL, NEC, PVL, NEC, retinopathy, and neonatal sepsis or admission to NICU (Supplementary Table 7).

Sub-group analyses: twin pregnancies with short cervical length (≤ 25 mm)

When the analysis was restricted to the pregnancies with CL ≤ 25 mm on ultrasound, there was no contribution of either pessary (3 studies, 371 pregnancies; RR: 0.91; 95 % CI: 0.42−1.96 - p = 0.8), vaginal progesterone (1 study, 35 pregnancies; RR: 0.95; 95 % CI: 0.64−1.40 - p = 0.8), intra-muscular 17-OHPC (1 study, 165 pregnancies; RR: 1.45; 95 % CI: 0.94−2.25 - p = 0.09) or cerclage (3 studies, 48 pregnancies; RR: 2.13; 95 % CI: 0.74−6.15 - p = 0.16) in reducing the risk of overall PTB < 34 weeks of gestation (Table 2, Supplementary Figs. 5–9).

When taking into account studies reporting the risk of spontaneous PTB, both pessary (2 studies, 348 pregnancies; RR: 0.72; 95 % CI: 0.25−2.06 – p = 0.5) and cerclage (2 studies, 21 pregnancies; RR: 1.20; 95 % CI: 0.29−4.90 – p = 0.8) did not reduce the risk of spontaneous PTB in twin pregnancies with a short cervix. The cervical pessary, vaginal progesterone, intra-muscular 17-OHPC or cerclage did not reduce the risk of PTB < 37, <32, <28 or <24 weeks of gestations in women with a short cervix (Table 2).

Cervical pessary, vaginal progesterone, intra-muscular 17-OHPC or cerclage did not reduce the risk of PPROM, CS, need for tocolytics, steroids administration, chorioamnionitis or infection in women with a short cervix (Supplementary Table 5).

When assessing perinatal outcomes, none of the explored intervention was associated with a reduced risk of IUD, NND, composite morbidity, Apgar score <7, IVH, PVL, retinopathy, neonatal sepsis or admission to NICU. Conversely, IM 17-OHPC was associated with a higher risk of perinatal death (RR: 9.11, 95 % CI1.17−71.1, p = 0.04), although this outcome was assessed by only one study. Vaginal progesterone significantly reduced the risk of very low BW (RR: 0.46, 95 % CI 0.2−0.7, p = 0.002) although this outcome was assessed only by one study, while cervical cerclage was associated with a significantly higher risk of both BW < 2500 (RR: 1.36, 95 % CI 1.0–1.8, p = 0.02) and BW < 1500 (RR: 3.14, 95 % CI 1.5–6.6, p = 0.002), both are likely to be as the consequence of PTB (Supplementary Table 7).

As per unselected twin pregnancies, no difference was found between pessary, vaginal or intra-muscular 17-OHPC in reducing the rate of PTB < 34 weeks when a network meta-analysis was used to compare the different interventions also in pregnancies presenting with a CL ≤ 25 mm on ultrasound (Table 3).

Discussion

Main findings

The findings from this systematic review show that neither cervical pessary nor progesterone are associated with a significant reduction in the risk of PTB when applied to an unselected population of twin pregnancies. Likewise, none of these interventions are associated with a reduced risk of maternal and perinatal outcomes, including mortality and morbidity.

Strengths and limitations

Thorough literature search, assessment of a multitude of maternal and perinatal clinical outcome, stratification of the analysis according to cervical length and computation of multiple treatment meta-analyses represent the main strengths of the present systematic review. The relatively small sample size of some of the explored treatments was one of the major limitations of the present systematic review. Furthermore, the primary outcome of the included studies was mainly the incidence of PTB, and the large majority of these studies were not powered for the neonatal outcomes, including morbidity and mortality. In this scenario, the beneficial effect of progesterone in reducing the incidence of some aspect of neonatal morbidity may represent a spurious finding rather than an actual effect of progesterone on the perinatal outcome, highlighting the need of larger studies adequately powered on neonatal outcome in order to confirm such association. Likewise, we could not stratify the analysis according to maternal and pregnancy characteristics. More importantly, there was a large heterogeneity in the definition of short cervix among the included studies and the subgroup analysis including the pregnancies with a CL < 25 mm only was affected by small number of included studies and even smaller number of events. Moreover, computation of the effect of cerclage was affected by the lack of data on unselected population of twin pregnancies and very small sample size of the included cases in the sub-group analyses including women with a short cervix only. Finally, any network meta-analysis is based on three assumptions: absence of heterogeneity, transitivity and coherence. Although significant incoherence was not found, heterogeneity and/or intransitivity was detected in several of the networks. This is an important limitation of the results, although assessed using the GRADE approach [13]. Although this resulted in several "low" quality of evidence ratings - which should be interpreted accordingly - it also gives confidence in results evaluated as of "moderate" and "high" quality. Despite these limitations, the present study represents the most comprehensive up to date systematic review on the role of cervical pessary, progesterone and cerclage in reducing the risk of PTB in twin pregnancies.

Comparison with other systematic reviews

A recent systematic review by Jarde et al. explored the role of these interventions in reducing the risk of PTB in twins. The primary outcomes were PTB < 37 and 34 weeks of gestation and neonatal death. The authors reported that none of the explored interventions reduced the risk of the primary outcomes. However, women receiving vaginal progesterone, had a significant reduction in some secondary outcomes, including very low birthweight and need for mechanical ventilation [47]. In an individual patient data (IPD) meta-analysis including only RCTs comparing vaginal progesterone with placebo/no treatment in women with a twin gestation and a mid-trimester sonographic cervical length ≤25 mm, Romero et al. reported that vaginal progesterone, compared with placebo/no treatment, was associated with a statistically significant reduction in the risk of PTB < 35, 34, 33, 32 and 30 weeks of gestation. Furthermore, progesterone was also associated with a reduction in NND, RDS, need for mechanical ventilation, BW < 1500 g, and composite neonatal morbidity and mortality [48]. There was no significant difference in the neurodevelopmental outcome at 4–5 years of age between the vaginal progesterone and placebo groups. However, the study was affected by the small number of included women (n = 303) resulting in low statistical power for some of the explored outcomes. However, it is important to acknowledge the advantages of the IPD approach of this meta-analysis [48].

Likewise, a systematic review by Saccone et al., including three RCT on pessary vs no intervention in twins did not report any significant contribution of such intervention in reducing the risk of PTB or improving the neonatal outcome although the review was hampered by the small number of included studies and the large heterogeneity of the inclusion criteria [49].

Finally, another IPD meta-analysis by Saccone et al. explored the role of cerclage in twin pregnancies with a short cervical length reporting no difference in the rate of PTB between women undergoing cerclage and controls. Conversely, the rates of very low BW and of RDS were significantly higher in the cerclage group than in the control group [50].

Clinical and research implications

Many would argue that the prevention of PTB is the most important challenge in maternal-fetal medicine. PTB represents the main determinant of the perinatal mortality and morbidity worldwide with estimated financial cost of around $26 billion per year only in the United States [1]. The main problem when trying to apply preventative strategies is that PTB is not a unique disease but rather a syndrome characterized by multiple etiologies which acts by activating what it was defined as "the common pathway of parturition", resulting in the anatomical, biochemical, endocrinologic, and clinical events which lead to PTB mainly through three events: increased uterine contractility, cervical ripening and decidual membrane activation.

In singleton pregnancies, cervical pessary, cerclage and progesterone have been similarly shown to reduce the risk of PTB, especially when these interventions are applied to a population at risk for this condition, such as women with a past history of prior PTB or a short cervical length on mid-trimester ultrasound [3].

In the present systematic review, we did not find any beneficial effect of any of the explored intervention in reducing the primary outcome in twin pregnancies.

However, PTB is the major cause of perinatal morbidity and mortality also in twin gestations [1,2,51]. A likely explanation of the lack of association between the explored interventions and the observed outcomes might be the heterogeneous pathophysiology of PTB in twin pregnancies. Contrary to singleton pregnancies, PTB in twins is mostly the result of uterine overdistension leading to increased contractility. In this scenario, interventions directed to maintain cervical competence are less likely to be effective than in singletons. Moreover, the increased risk of PTB in twins is also related to complications related to monochorionicity and monoamnionicity [52–55]. Therefore Therefore, drawing objective evidence on the actual role of these strategies in twin pregnancies is challenging because most of the included studies considered mainly unselected populations of twins, while those focusing on the twin pregnancies at risk were limited by the very small sample size and the large heterogeneity in the definition of pregnancies at risk.

Conclusions

Cervical pessary, progesterone and cerclage do not significantly reduce the risk of PTB in twins, either when these interventions are applied to all pregnancies and to those with a short cervix. Large multicenter studies which are adequately powered for perinatal outcomes are needed in order to confirm these observations and elucidate whether the administration of progesterone in women with twin pregnancy and short cervix could improve the perinatal outcome.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2021.04.023.

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