Archives of Gynecology and Obstetrics (2019) 299:1215–1231
https://doi.org/10.1007/s00404-019-05096-x

REVIEW

Effectiveness of the cervical pessary for the prevention of preterm birth in singleton pregnancies with a short cervix: a meta-analysis of randomized trials

Faustino R. Pérez-López[1,2] · Peter Chedraui[3,4] · Gonzalo R. Pérez-Roncero[1] · Samuel J. Martínez-Domínguez[1] · The Health Outcomes and Systematic Analyses (HOUSSAY) Project

Received: 7 May 2018 / Accepted: 7 February 2019 / Published online: 19 February 2019

Abstract

Objective To assess the efficacy of cervical pessary application for the prevention of spontaneous preterm birth (SPB) in singleton pregnancies with a sonographically measured short cervix.

Methods Searches were conducted in PubMed-Medline, Embase, Scopus, Web of Science, and Cochrane Library, and clinical trial registries for randomized controlled trials (RCTs) published in all languages from inception through 28 July 2018. Inclusion criteria were registered RCTs of singleton pregnants with a short cervix (≤ 25 mm) measured at 22–24 weeks comparing the use of a cervical pessary versus controls over the risk of SPB. Risk of bias was evaluated with the Cochrane tool. Risk ratios (RRs) and mean differences and 95% confidence intervals (CIs) were calculated.

Results We identified three RCTs meeting defined inclusion criteria, including a total of 1612 pregnancies (805 used a cervical pessary). SPB risk at < 37 was lower for participants using the pessary (RR 0.46; 95% CI 0.28–0.77). Pessary application was associated with a higher risk of presenting vaginal discharge (RR 2.05; 95% CI 1.82–2.31). There were no significant differences between pessary users and controls in terms of SPB at < 28 and < 34 weeks, and for any type of preterm birth < 34 weeks; mean gestational age and infant weight at delivery; and the risks of chorioamnionitis, cesarean delivery, and perinatal or neonatal outcomes. Sub-analysis by risk of bias showed that there was a lower risk of SPB < 34 weeks (RR 0.33; 95% CI 0.16–0.66) in two RCTs with low risk of bias.

Conclusion Cervical pessary application was associated with a reduced risk of SPB at < 37 weeks and a higher risk of vaginal discharge.

Keywords Cervical pessary · Preterm birth · Preterm delivery · Short cervix · Perinatal morbidity · Neonatal morbidity · Ultrasound · Vaginal discharge

Introduction

Preterm birth (PB) is the termination of pregnancy before 37 weeks of gestation and is the principal cause of overall perinatal mortality. PB rates vary worldwide but seem to range across 184 countries from 5% to up to nearly 18%, with two thirds being spontaneous [1–3]. It disproportionately affects low and middle income countries that have low quality healthcare. Despite this, PB rates seem to vary in relation to several factors including ethnics, maternal age, plurality, health care system, geographical region, economic/educational level, stress life events, racism and other social factors [2–5]. The introduction of assisted reproduction technology has contributed to an increase in the number of multiple births and thus, an overall increase in PB rates [6,

✉ Faustino R. Pérez-López
faustino.perez@unizar.es

1 Red de Investigación en Ginecología, Obstetricia y Reproducción, Instituto Aragonés de Ciencias de la Salud (IACS), Zaragoza, Spain

2 Departament of Obstetrics and Gynecology, Hospital Clínico Lozano-Blesa, Faculty of Medicine, University of Zaragoza, Domingo Miral s/n, 50009 Zaragoza, Spain

3 Instituto de Investigación e Innovación en Salud Integral, Facultad de Ciencias Médicas, Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador

4 Facultad de Ciencias de la Salud, Universidad Católica Nuestra Señora de la Asunción, Asunción, Paraguay

7]. PB is associated with severe obstetrical risks, neonatal complications and permanent sequelae, including long-term consequences leading to immune alterations and intellectual and development disabilities [1, 8, 9]. Therefore, preventive measures that aid at gaining more weeks will have clinical benefits for the newborn, the family and the economy of the society.

Three phenotypes of PB are currently being considered: idiopathic or spontaneous preterm birth (SPB), those due to preterm premature rupture of membranes (PPROM), and medically indicated PBs [10, 11]. The demonstration of a sonographically short cervix is a useful predictor of SPB risk and both perinatal and neonatal complications [12, 13]. Different interventions have been proposed to manage a shorter cervix and prevent SPB, including cervical stitch (cerclage), the application of a cervical pessary, and progesterone therapy [14–16].

Observational studies and randomized controlled trials (RCTs) have both reported controversial results regarding the effects of the cervical pessary placement in the prevention of SPB [17–21]. Two meta-analyses with three RCTs each, including one underpowered study, have rendered controversial results, and globally meta-analyzed data found no impact of the cervical pessary on SPB rates or perinatal outcomes [22, 23]. Hence, there has been concern about some RCTs and meta-analyses that are biased due to underpowered samples or the selective choice of outcomes, which have produced the so-call "P-hacking" effect [24]. In the present systematic review and meta-analysis, we assessed registered RCTs with predefined outcomes to determine the effect of the cervical pessary placement over SPB risk (< 34 weeks) in singleton gestations with a second trimester short cervix (≤ 25 mm) as measured by transvaginal ultrasonography (TUS).

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [25], and the National Institute of Health Quality Assessment of Controlled Intervention Studies [26] and the Cochrane recommendations [27]. In addition, the study also followed the recommendations provided by Prior et al [24] to prevent bias in meta-analyses. Formal institutional review board approval was not required due to the fact that this analysis consisted of pooled data of published studies.

Search methods

The search was conducted in PubMed-Medline, Embase, Cochrane Library, Web of Science and Scopus, from database inception through August 28, 2018, without language restriction (GRPR). The following terms were used for the search of articles containing the specific content, but not limited to: "pessary", "preterm birth", and "randomized controlled trial". The reference lists of systematic reviews and identified RCTs were hand searched to locate other trials. The US Clinical Trials [28] and the UK Clinical Trials Gateway [29] databases were also searched for related RCTs (PC).

Selection criteria

Original registered RCTs with a predefined power analysis published in any language were reviewed according to the following inclusion criteria: (i) girls aged > 16 years and women with a singleton pregnancy; (ii) cervical length ≤ 25 mm, measured by TUS during the second trimester of gestation (18–24 weeks); (iii) intervention group included the placement of a cervical pessary approved for the prevention of preterm birth; and (iv) controls defined as gravids with similar cervix conditions who did not use a cervical pessary.

Studies were excluded for the following reasons: (i) non-RCTs; (ii) ultrasound cervical length measurement > 25 mm during the second trimester of pregnancy; (iii) ruptured membranes or any obstetric pathology; (iv) lack of a control group (no pessary use); (v) the simultaneous use of a cervical cerclage; (vi) narrative reviews and abstracts or communications presented at congresses, and (vii) non-registered RCTs that did not follow a pre-defined power analysis or using a non-approved pessary for the prevention of preterm birth.

Pre-specified outcomes

The primary outcome of interest was SPB before 34 weeks of gestation. Secondary outcomes were SPB < 37 and < 28 weeks, any type of preterm delivery before 34 weeks, chorioamnionitis, PPROM < 34 weeks, corticosteroid treatment for fetal lung maturation, and risks of intrauterine fetal demise and vaginal discharge. In addition, mean difference (MD) of gestational age at delivery (weeks) and birth weights (grams) as well as the rate of cesarean delivery and low birth weight (< 2500 and < 1500 g) were assessed as perinatal outcomes.

Perinatal and neonatal outcomes included neonatal sepsis, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy, respiratory distress syndrome, admission to neonatal intensive care unit (NICU), and neonatal mortality, defined as death of a live-born baby within the first 28 days of life.

Study selection and data extraction

After removal of duplicates and articles that had no available abstract, manuscripts were screened for eligibility on the basis of their title and abstract. The list of retrieved articles was screened independently by two authors to choose potentially relevant full papers (FRPL, PC). Relevant data (baseline characteristics and outcome variables) were extracted, from each full-text included article, into a previously designed data sheet (GRPR, SJMD). Discrepancies found regarding the extracted data were discussed by both authors in order to reach a consensus.

Due to the fact that some results were reported as medians and interquartile ranges or means and 95%confidence intervals (CIs) (Table 1) , appropriate calculations were performed to obtain means and standard deviations that served for the meta-analysis [30, 31].

Assessment of risk of bias

Independent assessment of the methodological quality of the selected RCTs was performed by two authors (SJMD, FRPL) using the Cochrane Risk of Bias Tool [32, 33]. This instrument evaluates seven aspects: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and research staff (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias) and any other biases. Each item was assessed and described for each RCT and reported as having either a low risk of bias, a high risk of bias, or an unclear risk of bias. RCTs presenting bias for items of randomization or blinding were automatically considered as having an overall high risk of bias.

Data synthesis and statistical analysis

Primary outcome reported in at least two RCTs were meta-analyzed (SJMD, FRPL). Meta-analysis was performed using the fixed-effects model and the Mantel–Haenszel method for outcomes owing to an anticipated scarcity of events (< 10% of the total number of individuals in an arm) [34]. Meta-analysis was performed using the random effects model [35] when fixed effect was not appropriate or when the heterogeneity of studies was moderate to high. Summary effects are reported as risk ratios (RRs) for dichotomous outcomes or a mean difference (MD) for continuous variables, both with 95% CIs.

Statistical heterogeneity was evaluated using the Cochran chi-square (Xi^2), the I^2 statistic, and the between-study variance using the tau-square (Tau^2) [30, 32]. I^2 values from 0–30% represented a low level of heterogeneity, and from 30 to 60% as moderate heterogeneity. A P value < 0.1 for the Chi-square defined the presence of heterogeneity, and a $Tau^2 > 1$ defined the presence of substantial statistical heterogeneity.

Potential publication biases were statistically assessed by means of the Begg's and Egger's tests [36]. A P value < 0.1 was considered as statistically significant.

Statistical analyses were performed with the Review Manager software (RevMan 5.3; Cochrane Collaboration, Oxford, UK) [37].

Results

Study selection and study characteristics

The flow diagram of study retrieval for the systematic review is shown in Fig. 1. Three RCTs were included in this meta-analysis [17, 19, 38], with a total of 1,612 participants (aged 16 or more), including nulliparous and multiparous gravids (Table 1). One RCT was carried out in a single Italian center [38], another in several hospitals from Spain [17], and the third in seven European countries, Chile and Australia [19]. The dates and duration of the studies, gestational age at randomization, the assessment of vaginal infections (as defined by the authors) and other clinical details are specified in Table 1. Patients were excluded if they had major obstetrical syndromes, fetal structural anomalies, vaginal bleeding, chorioamnionitis, uterine contractions, cervical dilatation, cervical cerclage, placenta previa and/or accreta (Table 1).

In one study, patients were excluded when there were preexisting vaginal infections [19]. In the two remaining studies [17, 38], the prevalence of vaginal infections or bacterial vaginosis was around 25% in both the intervention and control groups (Table 1). In the Nicolaides et al.'s study [19], a higher proportion of girls/women in the pessary group received antibiotics at randomization or at follow-up visits, as compared to the control group (20.4% vs 14.8% and 20.6% vs. 13.7%, respectively).

One study included adolescents > 16 years and adult gravids [19], and for the remaining RCTs age ranged from 18 to 50 years [17, 38]. Studied populations ranged from 300 to 932 participants [19, 38]. Inclusion criteria for all studies were to have a cervical length ≤ 25 mm, as measured by TUS between 18–22 [17] and 22^6 weeks [19].

Gestational age at randomization ranged from 22.2 ± 0.9 weeks [17] and 23.4 weeks (interquartile range 22.6 and 24.3, respectively) [19]. The cervical pessary used in all three studies was the Arabin model [39]. Pessary removal was planned at 37 weeks of pregnancy or due to some specific medical indications or by patients' election. In some studies, pessary was replaced or repositioned if expelled before the proposed time of removal (Table 1).

Table 1 Baseline characteristics, exclusion criteria and reported outcomes of the three randomized controlled trials related to the effect of cervical pessary application in girls and women with a short second trimester cervix measured with transvaginal ultrasound measurement, as reported by authors

First author, year (reference)	Study location and duration	Mean ±SD or median [IQR] age and obstetrical history	Studied population and gestational age at randomization	TVU cervix length cut-off before randomization	Exclusion criteria	Control	Intervention (type of used pessary)	Reported outcomes
Goya, 2012 [17]	Five hospitals, Spain June 2007 to June 2010	18–43 years (range) Pessary: 30.3 ± 5.1 No pessary: 29.6 ± 5.4 Nulliparous $n = 190$; parous + no previous PB $n = 149$; parous + at least 1 PB $n = 41$ Bacterial vaginosis at the time of randomization: pessary 24.0%; control 25.0%	Pessary $n = 190$; GARW 22.2 ± 0.9 Controls $n = 190$; GARW 22.4 ± 0.9	≤ 25 mm, at 18–22 weeks.	Major fetal abnormalities, painful regular uterine contractions, active vaginal bleeding, PPROM, placenta previa, or history of cone biopsy or in situ cervical cerclage	Expectant management	Arabin pessary Pessary removal at 37 weeks. Indications for pessary removal before 37 weeks included active vaginal bleeding, risk of preterm labor with persistent contractions despite tocolysis, or severe patient discomfort	Pregnancy outcomes**:** SPB < 28 weeks, SPB < 37 weeks, any delivery < 34 weeks, gestational age at delivery (weeks), tocolytic treatment, corticosteroid treatment for fetal lung maturation, chorioamnionitis, pregnancy bleeding, PROM Side effects: vaginal discharge, pessary repositioning without removal, pessary withdrawal Adverse perinatal outcomes: fetal death, neonatal death, birth weight < 1500 g, birth weight < 2500 g Neonatal outcomes: necrotizing enterocolitis, intraventricular hemorrhage, respiratory distress syndrome, retinopathy, treatment for sepsis, composite adverse outcomes

Table 1 (continued)

First author, year (reference)	Study location and duration	Mean ±SD or median [IQR] age and obstetrical history	Studied population and gestational age at randomization	TVU cervix length cut-off before randomization	Exclusion criteria	Control	Intervention (type of used pessary)	Reported outcomes
Nicolaides, 2016 [19]	Multicenter in 9 countries (England, Slovenia, Portugal, Chile, Australia, Italy, Albania, Germany, and Belgium) September 2008 to January 2013	≥ 16 years Pessary: 30.1 [26.0, 34.2] Controls: 29.5 [25.4, 34.1] Nulliparous: pessary: 53.3% Controls: 55.0% Cases with pre-existing vaginal infection: were excluded There were no significant differences between groups and the frequency of use of additional therapies	Pessary n = 465; GARW=23.4 [22.6, 24.3] Controls n = 467; GARW 23.6 [22.7, 24.4] If after 26 weeks the CL was < 10 mm, glucocorticoids were administered for fetal lung maturation	≤ 25 mm, at 20–24^{6} weeks Participants in either group who had a cervical length ≤ 15 mm, at randomization or at subsequent visits, received treatment with 200 mg/day vaginal progesterone	Maternal age <16 years, fetal death, major fetal defect, in situ cervical cerclage, painful regular uterine contractions, and ruptured membranes diagnosed before randomization	Expectant management + vaginal progesterone 200 mg/day (if TVU cervix length ≤ 15mm)	Arabin pessary + vaginal progesterone 200 mg/day (if TVU CL ≤ 15 mm) Pessary removal at 37 weeks of gestation in asymptomatic participants. Earlier removal if there was a medical indication for induction of labor or elective cesarean section, preterm labor, PROM, active vaginal bleeding, or at the request of the patient	Secondary outcome measures were birth weight (mean, <2.5 kg and <1.5 kg), perinatal (fetal or neonatal) death, a composite of major adverse events in the neonate before discharge from the hospital (any grade of intraventricular hemorrhage, the respiratory distress syndrome, any retinopathy of prematurity, or necrotizing enterocolitis), a composite of indicators of neonatal special care (admission to the NICU, mechanical ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion), and major maternal complications attributable to the pessary (maternal death, serious cervical or vaginal trauma, or chorioamnionitis)

Table 1 (continued)

First author, year (reference)	Study location and duration	Mean ±SD or median [IQR] age and obstetrical history	Studied population and gestational age at randomization	TVU cervix length cut-off before randomization	Exclusion criteria	Control	Intervention (type of used pessary)	Reported outcomes
Saccone, 2017 [38]	A single center at Naples, Italy March 2016 to May 2017	Age 18–50 years Pessary: 28.5 ± 6.2 Controls: 28.9 ± 6.5 Nulliparous: pessary: 69.3%; Controls: 70.0% No prior preterm birth Preexisting vaginal infection: pessary 24.0%; control 27.3%	Pessary $n = 150$; GARW 22.3 ± 1.4 Controls $n = 150$; GARW 22.4 ± 1.1 No previous SPBs	≤ 25 mm, at 18–23^6 weeks No prior preterm births	PPROM, lethal fetal structural abnormality, in situ cerclage, vaginal bleeding at the time of randomization, chorioamnionitis, placenta previa or accreta, ballooning of membranes outside the cervix into the vagina, cervical length of 0 mm, painful and regularuterine contractions, or history of SPB between 16^0 and 36^6 weeks gestation	Expectant management + vaginal progesterone 200 mg/day (if TVU CL ≤20 mm). 88.3% received progesterone No bed rest or activity restriction was recommended	Arabin pessary + vaginal progesterone 200 mg/day (if TVU CL ≤2 0 mm). 88.7% received progesterone No bed rest or activity restriction was recommended Pessary removal at 37 weeks of gestation or earlier if clinically indicated. Reason for earlier removal included active vaginal bleeding, preterm labor with persistent contractions and advanced cervical dilation despite tocolysis, severe discomfort, or at the request of the participant	Pregnancy outcomes: SPB < 37, 32, and 28 weeks, gestational age at delivery, latency period (time from randomization to delivery), PROM < 34 weeks of gestation, mode of delivery, maternal adverse events (vaginal discharge and pelvic discomfort), chorioamnionitis (by histopathological assessment) Neonatal outcomes: birth weight, admission to a NICU, neonatal death (within the first 28 days of life) and perinatal death (either fetal death, defined as intrauterine fetal death after 20 weeks of gestation, or neonatal death), and a composite of adverse perinatal outcomes, defined as at least 1 of the following: necrotizing enterocolitis, intraventricular hemorrhage grade 3 or 4, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity requiring therapy, blood culture–proven sepsis, and neonatal death

BMI body mass index, *CL* cervical length, *GARW* gestational age at randomization (weeks), *GW* gestational weeks, *IQR* interquartile range, mean ± standard deviation, median [interquartile range], *NICU* Neonatal Intensive Care Unit, *PB* preterm birth, *SD* standard deviation, *PPROM* preterm premature rupture of membranes, *SPB* spontaneous preterm birth, *TVU CL* transvaginal ultrasound cervix length

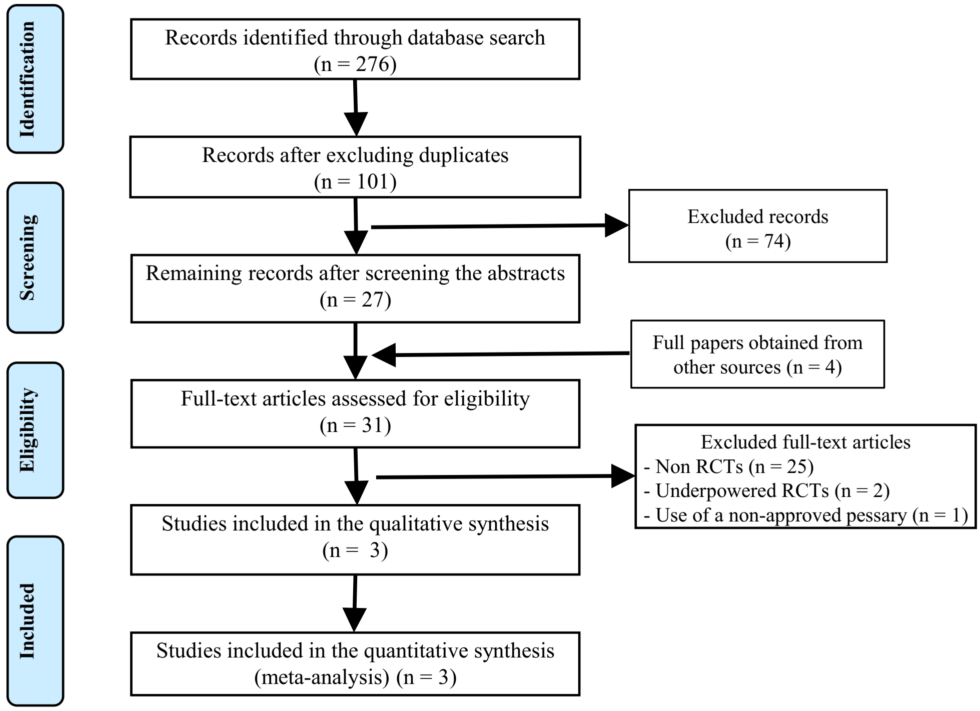

Fig. 1 Flow diagram of included and excluded studies

The primary outcome was SPB at < 34 weeks for all three studied RCTs. In one study, the control group was managed expectantly [17]. In two studies, in both the control and pessary groups, vaginal progesterone (200 mg/day) was indicated upon periodical clinical reviews and in those with a cervical length of ≤ 15 mm [19] or 20 mm [38]. Exclusion criteria and both pregnancy and neonatal outcomes varied and are detailed in Table 1.

Bias assessment

Assessment of risk of bias was performed with the Cochrane tool (Fig. 2). The three RCTs rendered a low risk of bias for random sequence generation, allocation concealment, and blinding of participants and personnel. Since in some RCTs, interventions cannot blinded to participants and/or personnel (as occurs in the present meta-analysis), it is not reasonable to consider a trial of low quality because of the lack of blinding [33]; hence, blinding bias (performance bias) was considered low in all three RCTs.

It is important to mention that one of the analyzed studies [19] had a high number of participating centers, with heterogeneous clinical settings which may have influenced clinical handling. In addition, this multi-continental RCT had a high rate of antibiotic use in the pessary group and was not audited [19]; thus, this RCT could have had a high risk of performance bias and/or other unknown bias.

Assessment of publication bias with the Begg's and Egger's tests was not possible, since only three studies were analyzed.

Data synthesis and statistical analysis

Meta-analyses of outcomes

As assessed with I^2, the various assessed outcomes (maternal, neonatal and perinatal) showed high heterogeneity. Therefore, estimation of the random-effects model [35] was used for meta-analyses as indicated in the forest plots (Figs. 3–6). The analysis of the three RCTs showed that the use of cervical pessary had no significant effect on the risk of SPB at < 34 weeks (RR 0.51; 95% CI 0.19–1.38; $I^2=90\%$) (Fig. 3, top forest plot). The risk of SPB at < 37 weeks was significantly reduced by the use of cervical pessary (RR 0.46; 95% CI 0.28–0.77; $I^2=77\%$) (Fig. 3, second forest plot). Contrary to this, in two RCTs, the risk of SPB at < 28 weeks was not affected by the use of cervical pessary (RR 0.42; 95% CI 0.16–1.09; $I^2=42\%$) (Fig. 3, third forest plot). In addition, the meta-analysis of two studies reported that the use of cervical pessary did not have any significant influence on PB of any type at < 34 weeks (RR 0.56; 95% CI 0.13–2.35; $I^2=95\%$) (Fig. 3, fourth forest plot). Pessary use was associated with a significant risk of vaginal discharge

Fig. 2 Assessment of risk of bias in the three randomized controlled trials

(RR 2.05; 95% CI 1.82–2.31; $I^2=28\%$) (Fig. 3, bottom forest plot).

Figure 4 displays (from the top to the bottom) meta-analyses of mean gestational age at delivery (weeks) and birth weight (grams) as well as the risk of chorioamnionitis, cesarean delivery, birth weight < 2500 g and neonatal sepsis. The mean difference of gestational age at delivery (MD 1.42; 95% CI − 0.41 to 3.25; $I^2=97\%$) and of birth weight (MD 86.05; 95% CI − 202.97 to 375.07; $I^2=89\%$) did not differ among the studied groups. In addition, no differences were found in the risk of chorioamnionitis (RR 0.77; 95% CI 0.34–1.73; $I^2=0\%$), cesarean delivery (RR 0.89; 95% CI 0.69–1.13; $I^2=5\%$), low birth weight (< 2500 g) (RR 0.59; 95% CI 0.16–2.16; $I^2=95\%$) or neonatal sepsis (RR 0.64; 95% CI 0.12–3.41; $I^2=83\%$).

The meta-analyses of the risk for different neonatal complications are shown in Fig. 5 (from the top to the bottom), none which were significant and included: intraventricular hemorrhage (RR 1.11; 95% CI 0.08–14.91; $I^2=62\%$), necrotizing enterocolitis (RR 0.95; 95% CI 0.11–8.18;

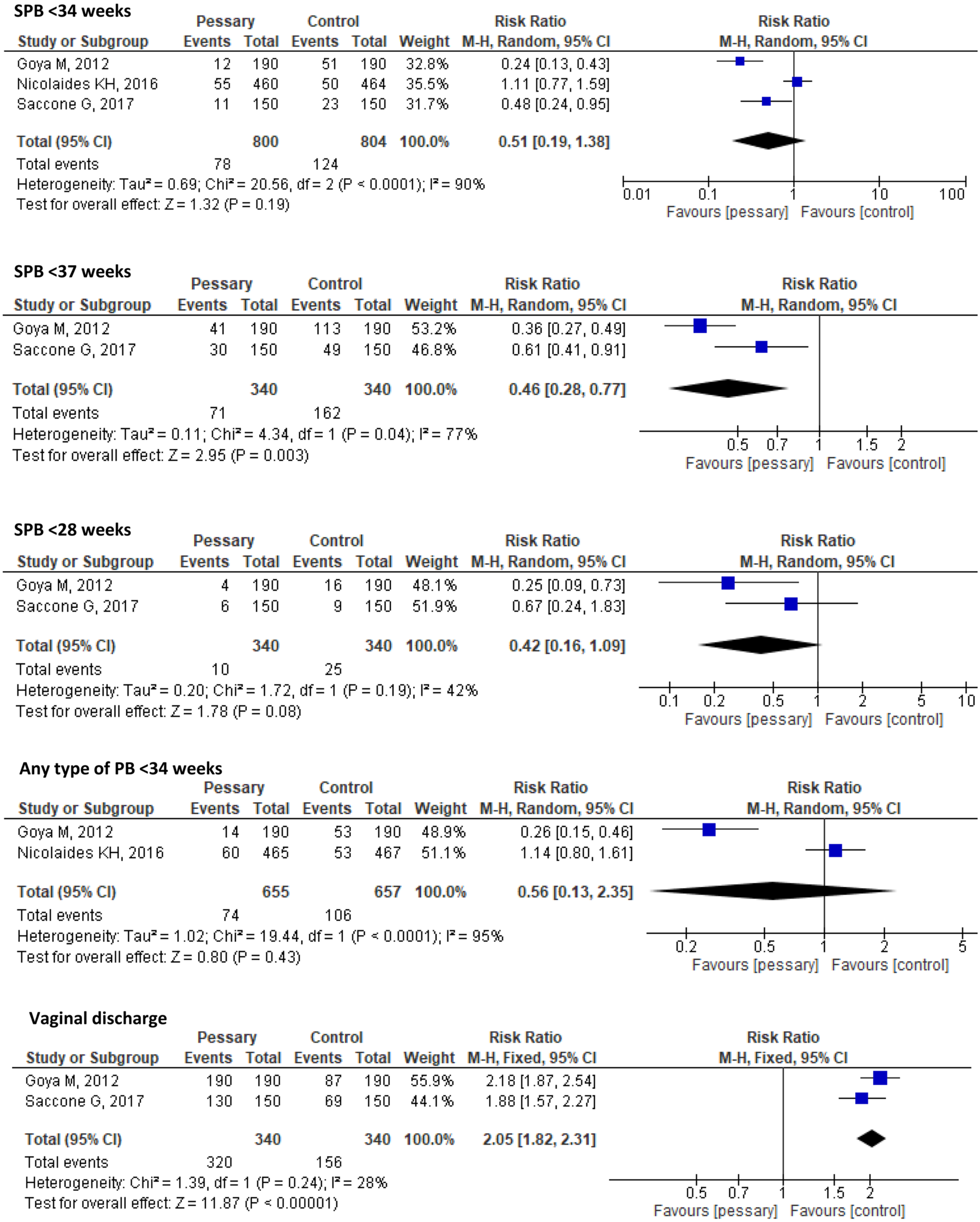

Fig. 3 Forest plot showing (from the top to the bottom) risk ratio (RR) and 95% confidence interval (CI) regarding spontaneous preterm birth < 34 weeks, < 37 weeks, < 28 weeks, and any type of preterm birth < 34 weeks. *M-H* Mantel–Haenszel

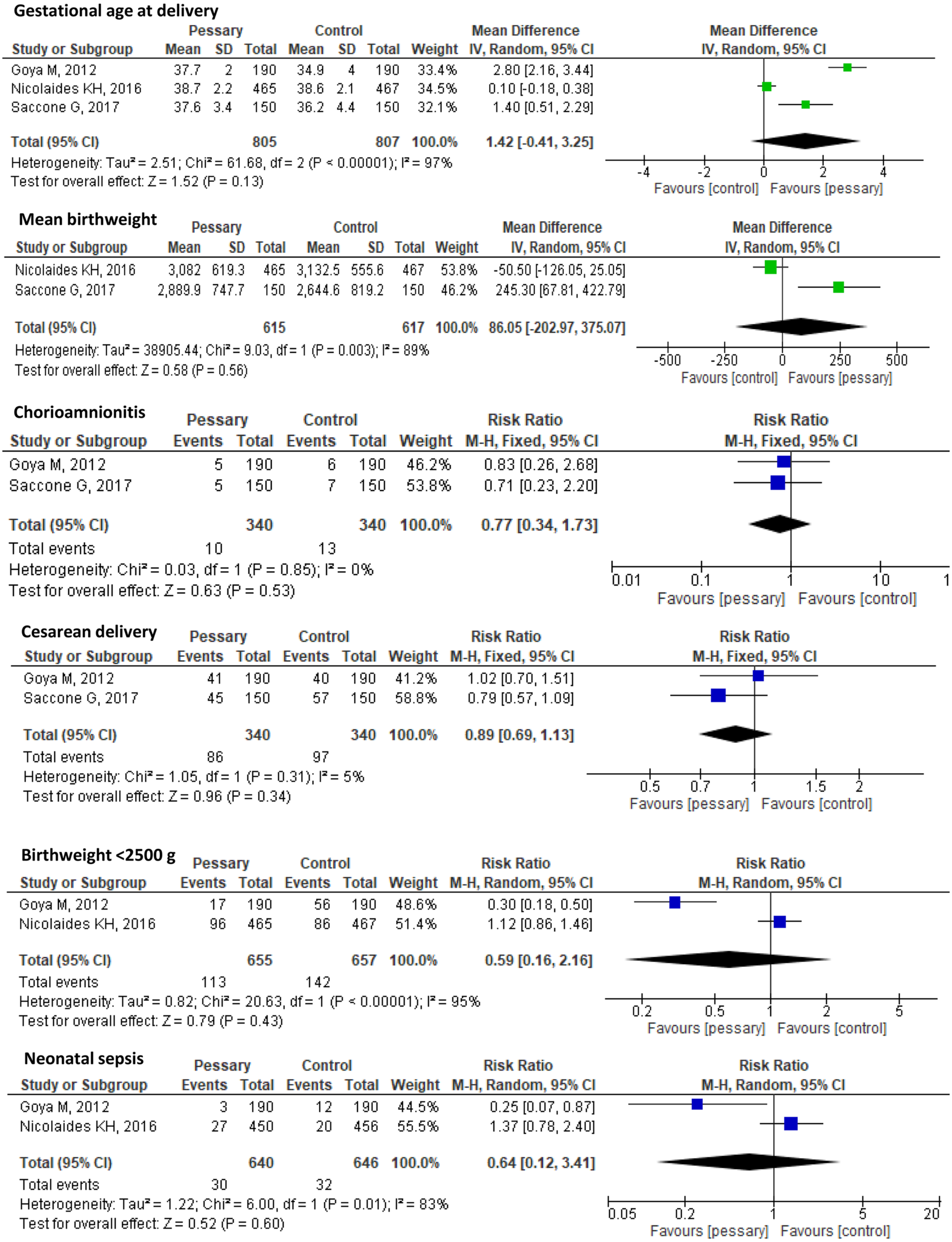

Fig. 4 Forest plot showing (from the top to the bottom) mean difference or risk ratio (RR) and 95% confidence interval (CI) regarding gestational age at delivery (weeks), mean birth weight (grams), chorioamnionitis, cesarean delivery, birth weight < 2500 g, and neonatal sepsis. *IV* inverse variance, *M-H* Mantel–Haenszel

Intraventricular haemorrhage

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Goya M, 2012	0	190	2	190	37.1%	0.20 [0.01, 4.14]
Nicolaides KH, 2016	9	450	3	456	62.9%	3.04 [0.83, 11.16]
Total (95% CI)		**640**		**646**	**100.0%**	**1.11 [0.08, 14.91]**
Total events	9		5			

Heterogeneity: Tau² = 2.35; Chi² = 2.66, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 0.08 (P = 0.94)

Necrotizing enterocolitis

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Goya M, 2012	0	190	2	190	32.7%	0.20 [0.01, 4.14]
Nicolaides KH, 2016	6	450	3	456	67.3%	2.03 [0.51, 8.05]
Total (95% CI)		**640**		**646**	**100.0%**	**0.95 [0.11, 8.18]**
Total events	6		5			

Heterogeneity: Tau² = 1.30; Chi² = 1.90, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 0.05 (P = 0.96)

Retinopathy

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Goya M, 2012	0	190	2	190	44.3%	0.20 [0.01, 4.14]
Nicolaides KH, 2016	5	450	1	456	55.7%	5.07 [0.59, 43.20]
Total (95% CI)		**640**		**646**	**100.0%**	**1.21 [0.05, 28.29]**
Total events	5		3			

Heterogeneity: Tau² = 3.45; Chi² = 2.92, df = 1 (P = 0.09); I² = 66%
Test for overall effect: Z = 0.12 (P = 0.91)

Respiratory distress syndrome

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Goya M, 2012	5	190	23	190	47.1%	0.22 [0.08, 0.56]
Nicolaides KH, 2016	28	450	25	456	52.9%	1.13 [0.67, 1.92]
Total (95% CI)		**640**		**646**	**100.0%**	**0.52 [0.10, 2.67]**
Total events	33		48			

Heterogeneity: Tau² = 1.24; Chi² = 9.18, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 0.78 (P = 0.43)

NICU admission

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Nicolaides KH, 2016	40	450	34	456	53.1%	1.19 [0.77, 1.85]
Saccone G, 2017	15	150	28	150	46.9%	0.54 [0.30, 0.96]
Total (95% CI)		**600**		**606**	**100.0%**	**0.82 [0.37, 1.79]**
Total events	55		62			

Heterogeneity: Tau² = 0.25; Chi² = 4.60, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.50 (P = 0.62)

Neonatal death

Study or Subgroup	Pessary Events	Pessary Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Goya M, 2012	0	190	1	190	15.8%	0.33 [0.01, 8.13]
Nicolaides KH, 2016	7	465	5	467	52.6%	1.41 [0.45, 4.40]
Saccone G, 2017	1	150	3	150	31.6%	0.33 [0.04, 3.17]
Total (95% CI)		**805**		**807**	**100.0%**	**0.90 [0.36, 2.25]**
Total events	8		9			

Heterogeneity: Chi² = 1.71, df = 2 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

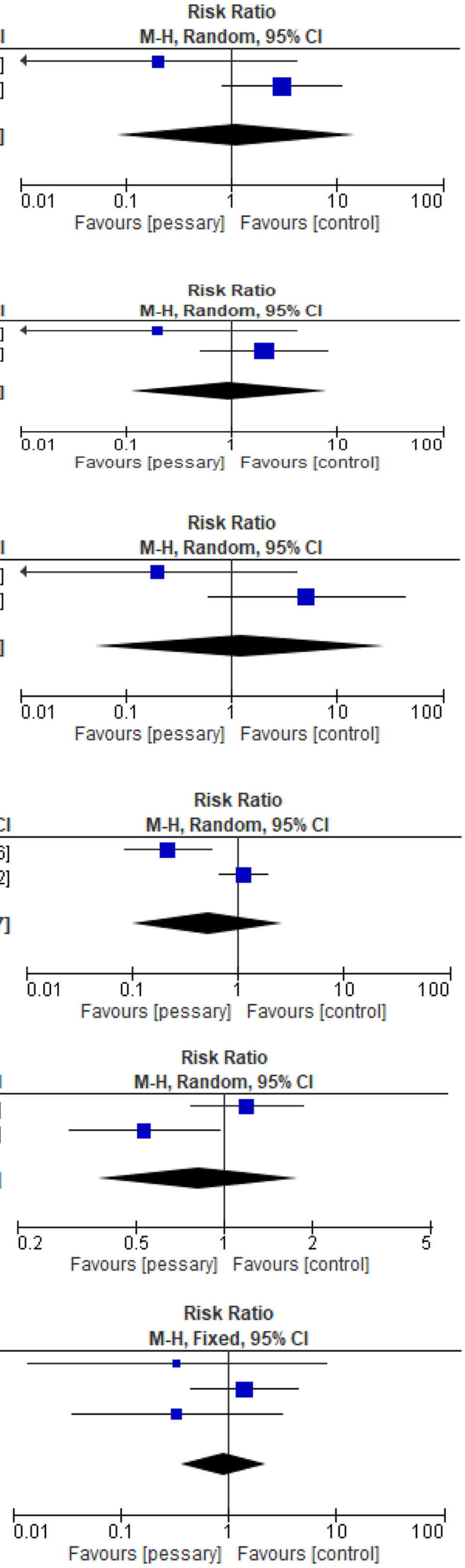

Fig. 5 Forest plot showing (from the top to the bottom) risk ratio (RR) and 95% confidence interval (CI) regarding intraventricular hemorrhage, necrotizing enterocolitis, retinopathy, respiratory distress syndrome, Neonatal Intensive Care Unit (NICU) admission, and neonatal death. *M-H* Mantel–Haenszel

$I^2 = 47\%$), retinopathy (RR 1.21; 95% CI 0.05–28.29; $I^2 = 66\%$), respiratory distress syndrome (RR 0.52; 95% CI 0.10–2.67; $I^2 = 89\%$), NICU admission (RR 0.82; 95% CI 0.37–1.79; $I^2 = 78\%$), and neonatal death (RR 0.90; 95% CI 0.36–2.25; $I^2 = 0\%$).

Sub-group analyses

A sub-group analysis evaluating the risk of SPB < 34 weeks was performed comparing two RCTs with low risk of bias [17, 38] with the multi-continental RCT with risk of bias [19] (Fig. 6). This sub-analysis showed a significant reduction of the risk of SPB < 34 weeks for RCTs with low risk of bias (RR 0.33; 95% CI 0.16–0.66; $I^2 = 58\%$). No other sub-group analyses were possible in terms of parity (nulliparous versus multiparous), history of a previous PB in parous women, or by ethnicity due to the lack of reported individualized data for all these variables.

Comment

Summary of evidence

The present systematic review and meta-analysis found that the Arabin pessary placement did not reduce the risk of SPB at < 34 weeks. However, pessary use did significantly reduce risk of SPB at < 37 weeks while increasing vaginal discharge risk. The sub-analysis of two RCTs with low risk of bias carried out in two different European countries [17, 38] also showed a significant reduction of SPB < 34 weeks as compared to the multi-continental RCT of Nicolaides et al. [19]. Risks of SPB at < 28 weeks and for any type of PB < 28 weeks were both similar among studied groups. For this gestational age cutoff (< 28 weeks), a greater sample would be required to demonstrate any possible effect. As expected, the frequency of vaginal discharge was significantly higher, as a side effect, among pessary users. In addition, no significant differences were found between pessary users and controls in terms of mean gestational age and infant weight at delivery as well as the rates of chorioamnionitis, cesarean delivery, low birth weight (< 2500 g), adverse perinatal and neonatal outcomes, NICU admission or neonatal death.

Interpretation

PB is a complex syndrome that involves epigenetic/genetic and inflammatory factors as well as several obstetric risk precursors, including genital infections, spontaneous preterm labor with intact membranes, PPROMs with subsequent preterm labor, and indicated or iatrogenic preterm delivery [39–42]. Transvaginal sonography cervical length measurement has shown to be a good predictive test for SPB risk in singleton pregnancies [41]. Previous reports have suggested an increased risk of PB due to a lower amount of collagen and changes in the microstructural of collagen alignment that may reflect differences in the mechanical loading forces [42, 43]. Cervical heterogeneity has also been documented by TUS [44].

Changes in the cervico-vaginal microbioma and mucosal immunity are frequent during pregnancy, and abnormal colonization decreases as the third trimester progresses. Abnormal vaginal microbioma during the second trimester is associated with PB risk before 34 weeks although no specific microbial community predicts SPB [45, 46]. Nonetheless, *Klebsiella pneumoniae* has been the most frequently demonstrated microorganism [47]. Evidence regarding the role of bacterial vaginosis and the risk of SPB is controversial [48–50]. Future studies should, therefore, define "infections" in a more precise manner.

Pessary guidelines state not to treat vaginal discharge with antibiotics; however, nearly 40% of participants in the pessary group were treated with antibiotics [19]. This could have affected the cervico-vaginal microbioma or the local immunity and produce genital inflammatory changes [51]. Infection and inflammation are usually associated with an increased risk of PB and neurological morbidity [52]. Therefore, it cannot be ruled out that mother and children were exposed to unnecessary increased risks, since current evidence recommends not to give antibiotics routinely in women with preterm labor and intact membranes in the absence of overt evidence of infection [53].

Vaginal progesterone was used in two of the included RCTs, both in the intervention and control groups, or was added when the cervix was below a critical certain length [19, 38]. Despite this, the rate of progesterone use was similar in all analyzed studies (combined interventions [pessary + progesterone] and controls); hence, it seems unlikely that progesterone treatment might have influenced the final results/trends for PB risks. To support this fact, a cohort study reported that cervical pessary placement plus vaginal progesterone did not reduce the risk of PB at different gestational ages (< 28, < 34, < 37 weeks) as compared to the use of the pessary alone [54].

RCTs with low risk of bias [17, 38] had probably a more homogeneous and personalized clinical assistance, hence showing the beneficial effect of the pessary use in decreasing SPB risk in comparison to the multi-continental RCT that was not audited [19]. The positive results of the Spanish and Italian RCTs could have been related not only to personalized involvement in clinical and ultrasound experience and follow-up, but also to the quality of engagement between patients and health care providers, and detailed/exhaustive information received by studied women about the risk of PB and the convenience of maintaining the pessary placed until 37 weeks [55, 56]. Future studies should assess not only clinical technology, control of the pessary placement, and the periodic assessment of the cervix length and eventual adverse effects, but also the flow of programmed information and communication from a highly trained team, empathic towards patients and their social circumstances, from the beginning of the intervention until the end of pregnancy.

Strengths and limitations

Strengths

Our study presents several strengths: (1) it is a meta-analysis of three registered RCTs; (2) it used common inclusion criteria based on ultrasound cervical length measurement which was performed at 22–24 weeks and defined SPB risk; and (3) standardized definitions for maternal, perinatal and neonatal outcomes were used for the data to be meta-analyzed. Our analysis selected registered RCTs with sufficient number of participants using a common pessary model approved for usage in women at risk of PB. In addition, our meta-analysis also provides data on perinatal and neonatal outcomes.

Our sub-analysis of the Spanish [17] and Italian [38] RCTs with low risk of bias demonstrated that pessary use and an optimal clinical or protocolized assistance may reduce the risk of SPB before 37 weeks, and even < 34 weeks. However, future studies should probably need to include more information about local changes at the cervico-vaginal site but also the general condition of the pregnant women. It seems that further studies are needed to define the interaction between genital microbiota, cervical length, lifestyle factors (e.g., stress, smoking) and specific health care for women at risk of PB [57].

Clinical limitations and future directions

The clinical limitations of the meta-analysis are inherent to the studied RCTs. For clinical trials, the training of physicians and health care providers is a prerequisite [58] for all procedures associated with the placement of the pessary, as well as follow-up and removal. It has been claimed that auditing is necessary when many centers are involved in a RCT. Pessary removal due to low compliance or its maintenance until 37 weeks may explain some differences in procedures and outcomes observed in one of the studied RCTs [19] as compared to the other two trials [17, 38].

The heterogeneity detected in meta-analyses could be related to the clinical characteristics of the studied populations, design of the analyzed studies and their corresponding clinical scenarios. Thus, there are some peculiarities: (i) one study reported on both adolescents and adult women [19]; (ii) other studies added vaginal progesterone in very short cervices (e.g., < 20 mm [38] or < 15 mm [19]) in both the control and intervention groups; (iii) one study reported a high rate of smoking [17]; (iv) in one study [19], there were a high number of women who extracted or had the pessary extracted, due to discomfort, before the proposed period of use; and (v) a recent RCT

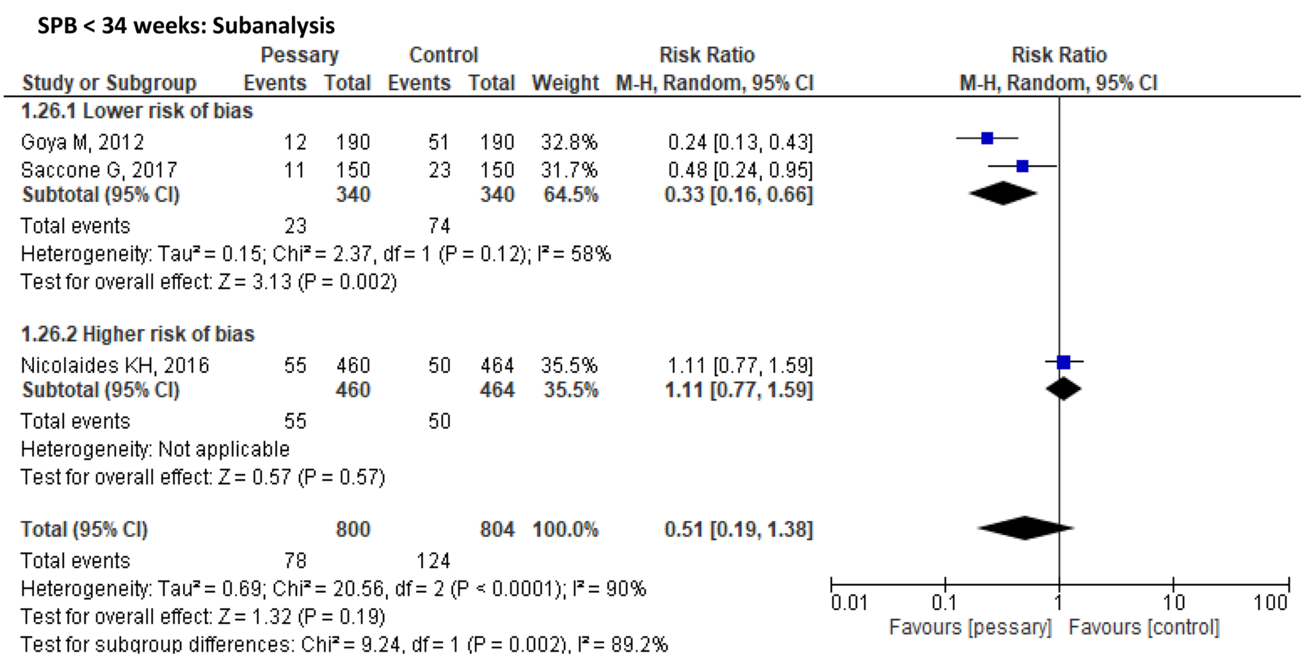

Fig. 6 Forest plot showing sub-analyses of risk of SPB < 34 comparing RCTs with low risk of bias versus the multi-continental RCT. *M-H* Mantel–Haenszel

was probably based on more detailed protocols [38]. On the other hand, recognition or identification of some of these and other RCT limitations and various confounding factors may contribute to improve standards for future research designs. Finally, some RCTs reported a proportion of pregnant women with preexisting bacterial vaginosis [17] or genital infection [38] in both the intervention and the control groups. This raises the issue that future studies should assess the effect of the pessary application exclusively in gravids without genital infection before comparing specific interventions to prevent SPB and to control changes in the vaginal microbioma.

Detailed ultrasound assessment of the utero-cervical angle (UCA) could discriminate women that would really benefit from the pessary application. In this sense, the retrospective study of Dziadosz et al. [59] reported that a UCA of $\geq 95°$ during the second trimester of pregnancy was associated with a higher rate of SPB < 37 weeks; equally, a UCA of $\geq 105°$ predicted SPB at < 34 weeks with a high sensitivity. Ultrasound examination during the mid-trimester of gestation may also study the tissue texture and consistency of the cervix, to detect structural alterations in women at risk for SPB, even after adjustment for confounders such as a previous SPB, conization, Müllerian anomalies or a short cervical length [60, 61]. Magnetic resonance imaging (MRI) may also be useful to assess the anatomic characteristics of the cervix and monitor pessary placement and follow-up in singleton pregnant women with a short cervix at risk of SPB by controlling the UCA. In addition, MRI may also allow the evaluation of SPB risk of the current pregnancy (at mid-gestation) by measuring the length and volume of the cervix in women with a previous cervical surgery or prior preterm births [62, 63].

Future studies of women at risk of SPB may be improved by including biochemical risk markers and genital microbiome assessment, in addition to the anatomic cervical evaluations performed at mid-gestation. Another future development for early SPB risk detection could be studying vaginal inflammatory response [51, 64, 65] and stress markers [66, 67]. Multiplex technology allows the testing of many biochemical risk markers in maternal blood before anatomical shortening of the cervix occurs. This technology seems useful to early identify women at very high risk of SPB [68].

Statistical limitations

The heterogeneity detected in meta-analyses, as measured with I^2, could be related to the clinical characteristics of the studied populations, design of the analyzed studies and their corresponding clinical scenarios. Limited number of studies, statistical analyses and the choice of either fixed or random models may also influence the results of the meta-analysis [34, 36, 69]. In addition, fixed-effect models are based on available evidence and do not allow generalizations, while random-effect models allow generalization beyond analyzed data including similar studies with variable characteristics [69]. We used the fixed-effect model if global assessment of an outcome showed low statistical heterogeneity and the number of events were $< 10\%$, and the random-effect model if any of the two conditions were not fulfilled. Therefore, our conclusions could be considered as robust.

The assessment of publication bias was not possible due to the fact that only three RCTs were analyzed which do not allow calculation [70]. Methodological aspects of available trials have been detailed in the risk of bias section.

Conclusion

Despite the cited limitations, basically due to the available RCTs, our meta-analysis may conclude that the use of the cervical pessary in singleton pregnancies with short mid-trimester cervices reduced the rate of SPB at < 37 weeks, without negatively affecting maternal, perinatal or neonatal outcomes. In addition, the sub-analysis of two RCTs with low risk of bias also showed that pessary use reduced the risk of SPB at < 34 weeks, contrary to the multi-continental RCT with risk of bias. Future studies should consider using technological advances, more detailed or sophisticated cervico-vaginal status evaluation, the assessment of the microbiome and other markers (serum or vaginal). We think that the details presented here will be useful for clinical practice and for the designing of future studies that will improve quality of evidence to finally establish the population that may benefit from pessary use and in which conditions these benefits are feasible.

Author contributions FRPL conceived, designed, supervised, and drafted the article. PC searched clinical trial registries and interpreted the results. GRPR conceived and designed the study, carried out the search strategy, and interpreted the results. SJMD extracted data, assessed the risk of bias, performed the meta-analyses, and interpreted the results. All authors approved the final manuscript.

Funding This research received no specific grant from any funding agency of the public, commercial, or non-profit sector. The authors received no financial support for the research, authorship, and/or publication of this article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standards This systematic review and meta-analysis were performed following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement for meta-analyses. Formal institutional review board approval was not required due to the fact that this analysis consisted of the pooling of published studies.

References

1. Stout MJ, Demaree D, Merfeld E, Tuuli MG, Wambach JA, Cole FS, Cahill AG (2018) Neonatal outcomes differ after spontaneous and indicated preterm birth. Am J Perinatol 35:494–502
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, Lawn JE (2012) National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 379:2162–2172
3. World Health Organization (2018) Preterm birth. https://www.who.int/news-room/fact-sheets/detail/preterm-birth. Accessed 25 May 2018
4. Muglia LJ, Katz M (2010) The enigma of spontaneous preterm birth. N Engl J Med 362:529–535
5. MacDorman MF (2011) Race and ethnic disparities in fetal mortality, preterm birth, and infant mortality in the United States: an overview. Semin Perinatol 35:200–208
6. Sunderam S, Kissin DM, Crawford SB, Folger SG, Jamieson DJ, Barfield WD; Centers for Disease Control and Prevention (CDC) (2014) Assisted reproductive technology surveillance--United States, 2011. MMWR Surveill Summ 63:1–28
7. Luke B (2017) Pregnancy and birth outcomes in couples with infertility with and without assisted reproductive technology: with an emphasis on US population-based studies. Am J Obstet Gynecol 217:270–281
8. Brévaut-Malaty V, Busuttil M, Einaudi MA, Monnier AS, D'Ercole C, Gire C (2010) Longitudinal follow-up of a cohort of 350 singleton infants born at less than 32 weeks of amenorrhea: neurocognitive screening, academic outcome, and perinatal factors. Eur J Obstet Gynecol Reprod Biol 150:13–18
9. Johnson S, Gilmore C, Gallimore I, Jaekel J, Wolke D (2015) The long-term consequences of preterm birth: what do teachers know? Dev Med Child Neurol 57:571–577
10. Gimenez LG, Krupitzki HB, Momany AM, Gili JA, Poletta FA, Campaña H, Cosentino VR, Saleme C, Pawluk M, Murray JC, Castilla EE, Gadow EC, Lopez-Camelo JS (2016) Maternal and neonatal epidemiological features in clinical subtypes of preterm birth. J Matern Fetal Neonatal Med 29:3153–3161
11. Henderson JJ, McWilliam OA, Newnham JP, Pennell CE (2012) Preterm birth aetiology 2004–2008. Maternal factors associated with three phenotypes: spontaneous preterm labour, preterm prelabour rupture of membranes and medically indicated preterm birth. J Matern Fetal Neonatal Med 25:642–647
12. Oncel MY, Arayici S, Celen S, Kadioglu Simsek G, Oskovi A, Uras N, Oguz SS, Erdeve O, Danisman N, Dilmen U (2013) The association of a cervical length of %3c 25 mm in high-risk pregnancies on neonatal morbidity and mortality in preterm infants. Arch Gynecol Obstet 287:893–899
13. Martell B, Di Benedetti DB, Weiss H, Zhou X, Reynolds M, Berghella V, Hassan SS (2018) Screening and treatment for short cervical length in pregnancy: a physician survey in the United States. Arch Gynecol Obstet 297:601–611
14. Alfirevic Z, Owen J, Carreras Moratonas E, Sharp AN, Szychowski JM, Goya M (2013) Vaginal progesterone, cerclage or cervical pessary for preventing preterm birth in asymptomatic singleton pregnant women with a history of preterm birth and a sonographic short cervix. Ultrasound Obstet Gynecol 41:146–151
15. Conde-Agudelo A, Romero R, Nicolaides K, Chaiworapongsa T, O'Brien JM, Cetingoz E, da Fonseca E, Creasy G, Soma-Pillay P, Fusey S, Cam C, Alfirevic Z, Hassan SS (2013) Vaginal progesterone vs. cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis. Am J Obstet Gynecol 208:42.e1–42.e18
16. Robinson JN, Norwitz ER (2018) Preterm birth: Risk factors, interventions for risk reduction, and maternal prognosis. Up to date https://www.uptodate.com/contents/preterm-birth-risk-factors-interventions-for-risk-reduction-and-maternal-prognosis. Accessed 25 May 2018
17. Goya M, Pratcorona L, Merced C, Rodó C, Valle L, Romero A, Juan M, Rodríguez A, Muñoz B, Santacruz B, Bello-Muñoz JC, Llurba E, Higueras T, Cabero L, Carreras E; Pesario Cervical para Evitar Prematuridad (PECEP) Trial Group (2012) Cervical pessary in pregnant women with a short cervix (PECEP): an open-label randomised controlled trial. Lancet 379:1800–1806 **(erratum in: Lancet 379:1790, 2012)**
18. Hui SY, Chor CM, Lau TK, Lao TT, Leung TY (2013) Cerclage pessary for preventing preterm birth in women with a singleton pregnancy and a short cervix at 20 to 24 weeks: a randomized controlled trial. Am J Perinatol 30:283–288
19. Nicolaides KH, Syngelaki A, Poon LC, Picciarelli G, Tul N, Zamprakou A, Skyfta E, Parra-Cordero M, Palma-Dias R, Rodriguez Calvo J (2016) A randomized trial of a cervical pessary to prevent preterm singleton birth. N Engl J Med 374:1044–1052
20. Karis Allen L, Schulz J, Flood C, Ross S, Naud K (2017) Retrospective cohort study of cervical pessary use in women with short cervix at risk of preterm delivery. J Obstet Gynaecol Can 39:1137–1142
21. Daskalakis G, Zacharakis D, Theodora M, Antsaklis P, Papantoniou N, Loutradis D, Antsaklis A (2018) Safety and efficacy of the cervical pessary combined with vaginal progesterone for the prevention of spontaneous preterm birth. J Perinat Med. 46:531–537
22. Jin XH, Li D, Huang LL (2017) Cervical pessary for prevention of preterm birth: a meta-analysis. Sci Rep 7:42560
23. Saccone G, Ciardulli A, Xodo S, Dugoff L, Ludmir J, Pagani G, Visentin S, Gizzo S, Volpe N, Maruotti GM, Rizzo G, Martinelli P, Berghella V (2017) Cervical pessary for preventing preterm birth in singleton pregnancies with short cervical length: a systematic review and meta-analysis. J Ultrasound Med 36:1535–1543
24. Prior M, Hibberd R, Asemota N, Thornton JG (2017) Inadvertent P-hacking among trials and systematic reviews of the effect of progestogens in pregnancy? A systematic review and meta-analysis. BJOG 124:1008–1015
25. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group (2010) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 8:336–341
26. NIH quality assessment of controlled intervention studies for randomized controlled trials (2018). https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed 12 May 2018
27. Higgins JPT, Green S (2018) Cochrane handbook for systematc reviews of interventions. https://handbook-5-1.cochrane.org/. Accessed 12 May 2018
28. US Clinical Trials (2018) https://clinicaltrials.gov. Accessed 30 March 2018
29. UK Clinical Trials Gateway (2018) https://www.ukctg.nihr.ac.uk/. Accessed 30 Mar 2018
30. Deeks JJ, Higgins JPT, On behalf of the Statistical Methods Group of The Cochrane Collaboration Statistical Algorithms in Review Manager 5 (2010) https://training.cochrane.org/handbook/statistical-methods-revman5
31. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13
32. Higgins J, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327:557–560
33. Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias

Methods Group; Cochrane Statistical Methods Group (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
34. Mantel N, Haenszel W (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 22:719–748
35. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
36. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315:629–634
37. Review Manager (RevMan) (computer program) (2014) version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen
38. Saccone G, Maruotti GM, Giudicepietro A, Martinelli P; Italian Preterm Birth Prevention (IPP) Working Group (2017) Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length: a randomized clinical trial. JAMA 318:2317–2324
39. Kyvernitakis I, Arabin B (2017) Re: Prevention of preterm birth with pessary in twins (PoPPT): a randomized controlled trial. Ultrasound Obstet Gynecol 50:408–409
40. Zhang G, Feenstra B, Bacelis J, Liu X, Muglia LM, Juodakis J, Miller DE, Litterman N, Jiang PP, Russell L, Hinds DA, Hu Y, Weirauch MT, Chen X, Chavan AR, Wagner GP, Pavličev M, Nnamani MC, Maziarz J, Karjalainen MK, Rämet M, Sengpiel V, Geller F, Boyd HA, Palotie A, Momany A, Bedell B, Ryckman KK, Huusko JM, Forney CR, Kottyan LC, Hallman M, Teramo K, Nohr EA, Davey Smith G, Melbye M, Jacobsson B, Muglia LJ (2017) Genetic associations with gestational duration and spontaneous preterm birth. N Engl J Med 377:1156–1167
41. Berghella V, Palacio M, Ness A, Alfirevic Z, Nicolaides KH, Saccone G (2017) Cervical length screening for prevention of preterm birth in singleton pregnancy with threatened preterm labor: systematic review and meta-analysis of randomized controlled trials using individual patient-level data. Ultrasound Obstet Gynecol 49:322–329
42. Sundtoft I, Langhoff-Roos J, Sandager P, Sommer S, Uldbjerg N (2017) Cervical collagen is reduced in non-pregnant women with a history of cervical insufficiency and a short cervix. Acta Obstet Gynecol Scand 96:984–990
43. Hao J, Yao W, Harris WR, Vink JY, Myers K, Donnelly E (2018) Characterization of collagen microstructural organization of human cervical tissue. Reproduction 156:71–79
44. Pachtman SL, Ghorayeb SR, Blitz MJ, Harris K, Vohra N, Sison CP, Rochelson BL (2018) Ultrasonic assessment of cervical heterogeneity for prediction of spontaneous preterm birth: a feasibility study. Am J Perinatol 35:292–297
45. Stout MJ, Zhou Y, Wylie KM, Tarr PI, Macones GA, Tuuli MG (2017) Early pregnancyvaginal microbiome trends and preterm birth. Am J Obstet Gynecol 217(3):356.e1–356.e18
46. Freitas AC, Bocking A, Hill JE, Money DM; VOGUE Research Group (2018) Increased richness and diversity of the vaginal microbiota and spontaneous preterm birth. Microbiome 6:117
47. Son KA, Kim M, Kim YM, Kim SH, Choi SJ, Oh SY et al (2018) Prevalence of vaginal microorganisms among pregnant women according to trimester and association with preterm birth. Obstet Gynecol Sci 61:38–47
48. Brabant G (2016) Bacterial vaginosis and spontaneous preterm birth. J Gynecol Obstet Biol Reprod (Paris) 45:1247–1260
49. Haahr T, Ersbøll AS, Karlsen MA, Svare J, Sneider K, Hee L, Weile LK, Ziobrowska-Bech A, Østergaard C, Jensen JS, Helmig RB, Uldbjerg N (2016) Treatment of bacterial vaginosis in pregnancy in order to reduce the risk of spontaneous preterm delivery—a clinical recommendation. Acta Obstet Gynecol Scand 95:850–860
50. Subtil D, Brabant G, Tilloy E, Devos P, Canis F, Fruchart A, BissingerC Dugimont JC, Nolf C, Hacot C, Gautier S, Chantrel J, Jousse M, DesseauveD Plennevaux JL, Delaeter C, Deghilage S, Personne A, Joyez E, Guinard E, KipnisE Faure K, Grandbastien B, Ancel PY, Goffinet F, Dessein R (2018) Early clindamycin for bacterial vaginosis in pregnancy (PREMEVA): a multicentre, double-blind, randomised controlled trial. Lancet 392:2171–2179
51. Herrera-Muñoz A, Fernández-Alonso AM, Fischer-Suárez N, Chedraui P, Pérez-López FR (2017) Maternal serum cytokine levels in pregnancies complicated with threatened preterm labour. Gynecol Endocrinol 33:408–412
52. RCOG Preterm labour, antibiotics, and cerebral palsy. Scientific impact paper no. 33 (2013) https://www.rcog.org.uk/en/guidelines-research-services/guidelines/sip33/ . Accessed 2 Dec 2018
53. Flenady V, Hawley G, Stock OM, Kenyon S, Badawi N (2013) Prophylactic antibiotics for inhibiting preterm labour with intact membranes. Cochrane Database Syst Rev 5:CD000246
54. Stricker N, Timmesfeld N, Kyvernitakis I, Goerges J, Arabin B (2016) Vaginal progesterone combined with cervical pessary: a chance for pregnancies at risk for preterm birth? Am J ObstetGynecol 214:739.e1–739.e10
55. Goya M, Cabero L, Carreras (2016) Cervical pessary and preterm singleton birth. N Engl J Med 375:e10
56. Martinelli P, Saccone G (2018) Cervical pessary and spontaneous preterm birth—reply. JAMA 319:1821–1822
57. Kindinger LM, Bennett PR, Lee YS, Marchesi JR, Smith A, Cacciatore S, Holmes E, Nicholson JK, Teoh TG, MacIntyre DA (2017) The interaction between vaginal microbiota, cervical length, and vaginal progesterone treatment for preterm birth risk. Microbiome 19(5):6
58. Willan AR (2016) Accounting for treatment by center interaction in sample size determinations and the use of surrogate outcomes in the pessary for the prevention of preterm birth trial: a simulation study. Trials 17:310
59. Dziadosz M, Bennett TA, Dolin C, West Honart A, Pham A, Lee SS, Pivo S, Roman AS (2016) Uterocervical angle: a novel ultrasound screening tool to predict spontaneous preterm birth. Am J ObstetGynecol 215:376.e1–7
60. Baños N, Murillo-Bravo C, Julià C, Migliorelli F, Perez-Moreno A, Ríos J, Gratacós E, Valentin L, Palacio M (2018) Mid-trimester sonographic cervical consistency index to predict spontaneous preterm birth in a low-risk population. Ultrasound Obstet Gynecol 51:629–636
61. Baños N, Perez-Moreno A, Julià C, Murillo-Bravo C, Coronado D, Gratacós E, Deprest J, Palacio M (2018) Quantitative analysis of cervical texture by ultrasound in mid-pregnancy and association with spontaneous preterm birth. Ultrasound Obstet Gynecol 51:637–643
62. de Tejada BM, Faltin DL, Kinkel K, Guittier MJ, Boulvain M, Irion O (2011) Magnetic resonance imaging of the cervix in women at high risk for preterm delivery. J Matern Fetal Neonatal Med 24:1392–1397
63. Cannie MM, Dobrescu O, Gucciardo L, Strizek B, Ziane S, Sakkas E, Schoonjans F, Divano L, Jani JC (2013) Arabin cervical pessary in women at high risk of preterm birth: a magnetic resonance imaging observational follow-up study. Ultrasound Obstet Gynecol 42:426–433
64. Callahan BJ, DiGiulio DB, Goltsman DSA, Sun CL, Costello EK, Jeganathan P, Biggio JR, Wong RJ, Druzin ML, Shaw GM, Stevenson DK, Holmes SP, Relman DA (2017) Replication and refinement of a vaginal microbial signature of preterm birth in two racially distinct cohorts of US women. Proc Natl Acad Sci USA 114:9966–9971
65. Stout MJ, Zhou Y, Wylie KM, Tarr PI, Macones GA, Tuuli MG (2017) Early pregnancy vaginal microbiome trends and preterm birth. Am J Obstet Gynecol 217:356.e1–356.e18

66. Ashford K, Chavan NR, Wiggins AT, Sayre MM, McCubbin A, CritchfieldAS O'Brien J (2018) Comparison of serum and cervical cytokine levels throughout pregnancy between preterm and term births. AJP Rep 8:e113–e120
67. García-Blanco A, Diago V, Serrano De La Cruz V, Hervás D, Cháfer-Pericás C, Vento M (2017) Can stress biomarkers predict preterm birth in women with threatened preterm labor? Psychoneuroendocrinology 83:19–24
68. Jelliffe-Pawlowski LL, Rand L, Bedell B, Baer RJ, Oltman SP, Norton ME, Shaw GM, Stevenson DK, Murray JC, Ryckman KK (2018) Prediction of preterm birth with and without preeclampsia using mid-pregnancy immune and growth-related molecular factors and maternal characteristics. J Perinatol 38:963–972
69. Guolo A, Varin C (2017) Random-effects meta-analysis: the number of studies matters. Stat Methods Med Res 26:1500–1518
70. Borenstein M (2011) Chapter 11: Software for publication bias. In: Borenstein M, Rothstein H (eds) Comprehensive metaanalysis: a computer program for research synthesis, pp193–220. https://www.meta-analysis.com. Accessibility verified 2 Dec 2018