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Vaginal progesterone vs intramuscular 17-hydroxyprogesterone caproate for prevention of recurrent preterm birth: a randomized controlled trial

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Rupsa C. Boelig, MD, MS; Corina N. Schoen, MD; Heather Frey, MD; Alexis C. Gimovsky, MD; Edward Springel, MD; Sami Backley, MD; Vincenzo Berghella, MD

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Does vaginal progesterone prevent recurrent preterm birth in women with a singleton gestation and a history of spontaneous preterm birth?Evidence from a systematic review and meta-analysis

Agustin CONDE-AGUDELO, MD, MPH, PhD • Roberto ROMERO, MD, DMedSci

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Original Research

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Vaginal progesterone vs intramuscular 17-hydroxyprogesterone caproate for prevention of recurrent preterm birth: a randomized controlled trial

Rupsa C. Boelig, MD, MS; Corina N. Schoen, MD; Heather Frey, MD; Alexis C. Gimovsky, MD; Edward Springel, MD; Sami Backley, MD; Vincenzo Berghella, MD

Introduction

- Preterm birth is one of the leading causes of neonatal morbidity and mortality
- Increased risk for short- term, long-term neurodevelopmental disabilities, chronic diseases in adulthood, and mortality in early to mid-adulthood
- A history of spontaneous preterm birth is a major risk factor for recurrent preterm birth (a 2.5- to 4-fold increased)

Introduction

Progesterone

- Blocks uterine activity by binding to nuclear progesterone receptors
- **Vaginal progesterone**: bioidentical to human progesterone
  - Associated with decidual activation, inflammation, cervical remodeling, and PTB in translational models
- **17- hydroxyprogesterone caproate (17- OHPC)**: synthetic progestin
  - Does not have the same cellular and immunomodulatory effects as natural progesterone

Introduction

FDA:

- **Vaginal progesterone** is not approved
- **IM 17-OHPC** was conditionally approved for the prevention of recurrent PTB
  - a confirmatory trial (17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations [PROLONG]) did not demonstrate the efficacy
  - 3 meta-analyses, supported the efficacy of vaginal progesterone and 17-OHPC in PTB prevention in high-risk singleton pregnancies

Introduction

ACOG:

- Recommends offering **either vaginal progesterone or 17-OHPC**

SMFM:

- Only recommends offering **17-OHPC**

National Institute for Health and Care Excellence (UK):

- Only recommends offering **vaginal progesterone**

Whether vaginal progesterone is superior to intramuscular 17-OHPC in the prevention of recurrent PTB in patients with singleton pregnancies who had a previous sPTB

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Whether vaginal progesterone is superic prevention of recurrent PTB in patients v previous sPTB

Table 1. Screening and Interventions for Prevention of Preterm Birth

Cervical length ultrasound	IM 17-OHPC	Vaginal progesterone	Ultrasound-indicated cerclage	Physical examination-indicated cerclage	Cervical pessary
Singleton pregnancy, no prior preterm birth					
Cervix should be visualized at the time of the 18 0/7–22 6/7 weeks of gestation anatomy assessment	Not indicated	Recommended for cervical length less than 25 mm	Insufficient data; possibly of benefit if the cervical length is less than 10 mm	Consider	Not indicated
Singleton pregnancy, prior spontaneous preterm birth					
Serial (every 1–4 weeks) endovaginal ultrasound measurement of cervical length beginning at 16 0/7 and repeated until 24 0/7 weeks of gestation	Offer progesterone supplementation (either 17-OHPC or vaginal progesterone)	Offer progesterone supplementation (either 17-OHPC or vaginal progesterone) If not on progesterone already, consider with a cervical length less than 25 mm (versus cerclage)	Consider with a cervical length less than 25 mm (versus vaginal progesterone if not already on progesterone supplementation)	Consider	Not indicated
Multiple gestation					
Cervix should be visualized at the time of the 18 0/7–22 6/7 weeks of gestation anatomy assessment	Not indicated	Insufficient data	Insufficient data	Consider	Not indicated

Abbreviations: IM, intramuscular; 17-OHPC, 17-alpha hydroxyprogesterone caproate.

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Materials and Methods

- Prospective **open-label RCT**

Vaginal progesterone
(200 mg suppository daily)

v.s

Intramuscular 17- OHPC
(250 mg intramuscular weekly)

for prevention of recurrent sPTB in patients with a previous sPTB

- Starting at **16 0/7 to 23 6/7** weeks of gestation and continued **until 36 6/7 weeks of gestation or delivery**

Participants

- >=18 years old with an estimated gestational age (GA) of <24 weeks
- Had a previous sPTB of a singleton pregnancy between 16 0/7 and 36 6/7 weeks of gestation
- Not already initiated progesterone therapy for PTB prevention

Exclusion criteria

- history of an adverse reaction or contraindication to progesterone
- placenta previa or placenta accrete
- major fetal anomaly diagnosed on ultrasound or known chromosomal disorder
- multifetal gestation
- preterm labor, premature rupture of membranes
- clinical chorioamnionitis at the time of enrollment

- Patients were managed as standard of care, including the recommendation for cervical length screening between 16 0/7 and 23 6/7 weeks of gestation. Cerclage placement was not an exclusion.
- The participants could change progesterone allocation (crossover) or cease all progestin therapy completely (discontinuation) if they so choose. This was not an exclusion.

Outcome measures

- The primary outcome: the **incidence of PTB at <37 weeks of gestation**
- Secondary outcomes:

  PTB at <34 and <28 weeks of gestation, GA at delivery, medication adherence and satisfaction, and neonatal outcomes, including 5-minute Apgar score, ICU admission, and birthweight

Planned subgroup analyses

(1) transvaginal cervical length of <25 and >25 mm at 16 to 24 weeks of gestation

(2) presence or absence of a history- indicated cerclage

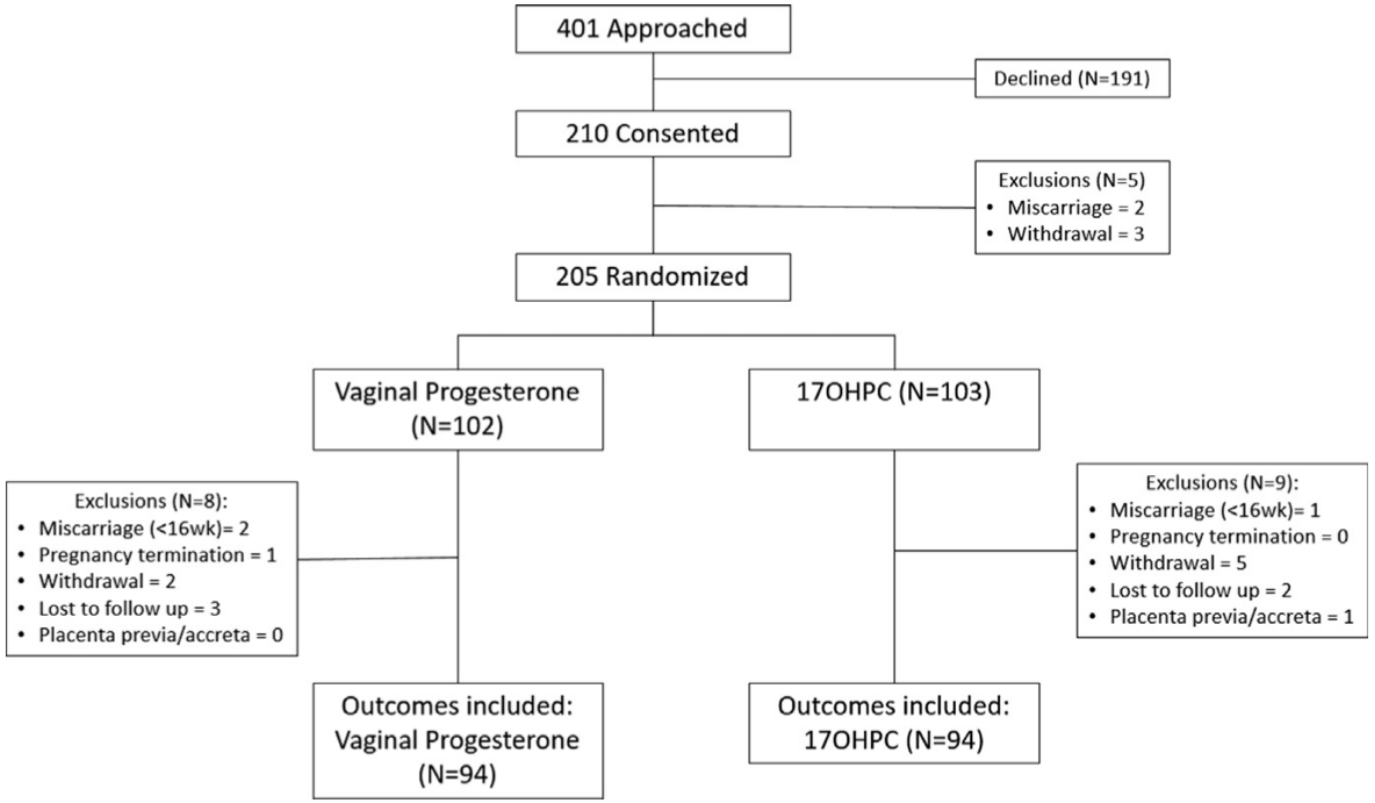
(3) progesterone initiation at 16 to 20 and 20 to 24 weeks of gestation

- The outcomes of PTB at <37, <34, and <28 weeks of gestation were assessed in the subgroup analyses

Results

- September 2016 to April 2021

FIGURE 1
Study flow diagram



17-OHPC, 17-hydroxyprogesterone caproate.

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TABLE 1
Comparison of baseline characteristics between randomization groups

Characteristic	Vaginal progesterone (n=94)	17-OHPC (n=94)
Study site		
Thomas Jefferson University	37 (39)	37 (39)
Baystate Health	32 (34)	31 (33)
Ohio State University	14 (15)	14 (15)
Virginia Commonwealth University	7 (7)	8 (5)
George Washington University	4 (4)	4 (4)
Race		
Black, non-Hispanic	42 (47)	51 (54)
White, non-Hispanic	26 (28)	19 (20)
Asian	1 (1)	0 (0)
Hispanic	21 (22)	24 (25)
Other	4 (4)	0 (0)
BMI (kg/m^2)	30.0±7.6	29.6±7.6
Number of previous sPTB	1.5±0.9	1.3±0.9
>1 previous sPTB	31 (33)	16 (17)
Earliest previous sPTB (wk)	29.4±6.5	29.2±6.1
Previous full-term delivery	45 (48)	49 (52)
Chronic hypertension	14 (15)	9 (10)
Type II diabetes mellitus	4 (4)	6 (6)
Anxiety or depression	24 (26)	25 (27)
Smoking	19 (20)	22 (23)
Opiate use disorder	8 (9)	11 (12)
GA at enrollment	14.8±3.1	14.9±3.4
History-indicated cerclage this pregnancy	7 (7.4)	8 (8.5)

Data are presented as number (percentage) or mean±standard deviation. The diagnosis of anxiety or depression was based on the documentation of these characteristics in the prenatal record as per patient self-report.

17-OHPC, 17-hydroxyprogesterone caproate; *BMI*, body mass index; *GA*, gestational age; *sPTB*, spontaneous preterm birth.

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Preterm birth outcome

TABLE 2
Comparison of preterm birth-related outcomes between the randomization groups

Variable	Vaginal progesterone (n=94)	17-OHPC (n=94)	*P* value	Relative risk ormean difference (95% CI)
PTB<37 wk	29 (30.9)	36 (38.3)	.28	0.81 (0.54–1.20)
sPTB<37 wk	21 (22.3)	26 (27.7)	.40	0.81 (0.49–1.33)
PTB<34 wk	9 (9.6)	14 (14.9)	.26	0.64 (0.29–1.41)
PTB<28 wk	1 (1.1)	4 (4.3)	.37	0.25 (0.03–2.20)
GA at delivery (wk)	37.36±2.72	36.34±4.10	.047	1.02 (0.01–2.01)
Cervical length<25 mm	17/83 (20.5)	14/88 (15.9)	.44	1.29 (0.68–2.44)
Cerclage	15/87 (17.2)	13/86 (15.1)	.70	1.14 (0.58–2.25)
Ultrasound	13 (14.9)	12 (13.9)		
Examination	2 (2.2)	1 (1.1)		

Data are presented as number (percentage), mean±standard deviation, or number/total number (percentage), unless otherwise i

17-OHPC, 17-hydroxyprogesterone caproate; *CI*, confidence interval; *GA*, gestational age; *PTB*, preterm birth; *sPTB*, spontaneous preterm birth.

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Patients in the vaginal progesterone group had a later GA of delivery compared with those in the 17-OHPC group

Other perinatal outcomes

- Similar in vaginal progesterone compared with 17-OHPC
- Higher rate of **polyhydramnios** noted in the vaginal progesterone group

TABLE 3
Comparison of neonatal outcomes between randomization groups

Variable	Vaginal progesterone (n=90)	17-OHPC(n=91)	*P* value	Relative risk or mean difference (95% CI)
Male	56 (62.2)	57 (62.6)	.95	0.99 (0.54–1.80)
Birthweight	2940±738	2793±740	.19	147.00 (−72.00 to 366.00)
5-min Apgar score<7	1/88 (1.1)	4/82 (4.9)	.20	0.23 (0.03–2.04)
NICU admission	31 (34.4)	25 (28.1)	.36	1.23 (0.79–1.90)
Perinatal mortality	0 (0)	3 (3.3)	.25	NA
Respiratory distress syndrome	8/89 (8.8)	8/88 (8.8)	.98	0.99 (0.39–2.52)
Grade III or IV IVH	0/89 (0)	0/88 (0)	NA	NA
Sepsis	0/89 (0)	0/88 (0)	NA	NA
NEC	0/89 (0)	0/88 (0)	NA	NA
Composite neonatal morbidity or mortality	8/89 (9.0)	11/89 (12.4)	.47	0.73 (0.31–1.72)

Data are presented as number (percentage), mean±standard deviation, or number/total number (percentage), unless otherwise indicated. Composite neonatal morbidity and mortality were defined as having at least one of the following: respiratory distress syndrome, grade III or IV IVH, culture-proven sepsis, NEC, or perinatal mortality up to 28 days of life.

17-OHPC, 17-hydroxyprogesterone caproate; *CI*, confidence interval; *IVH*, intraventricular hemorrhage; *NA*, not available; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit.

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TABLE 4
Comparison of perinatal outcomes between randomization groups

Variable	Vaginal progesterone (n=94)	17-OHPC (n=94)	*P* value	Relative risk (95% CI)
Preeclampsia or gestational hypertension	14 (14.9)	14 (14.9)	>.99	1.00 (0.51–1.98)
GDM	10(10.6)	10 (10.6)	>.99	1.00 (0.44–2.29)
Fetal growth restriction	6 (6.4)	3 (3.2)	.31	2.00 (0.52–7.76)
Polyhydramnios	6 (6.4)	0 (0)	.03	NA
Oligohydramnios	2 (2.1)	0 (0)	.50	NA
Sexually transmitted infection	6 (6.4)	6 (6.4)	>.99	1.00 (0.34–2.99)
Cesarean delivery	20 (21.3)	29 (30.9)	.13	0.69 (0.42–1.13)
Maternal mortality	0 (0)	0 (0)	NA	NA

Data are presented as number (percentage), unless otherwise indicated.

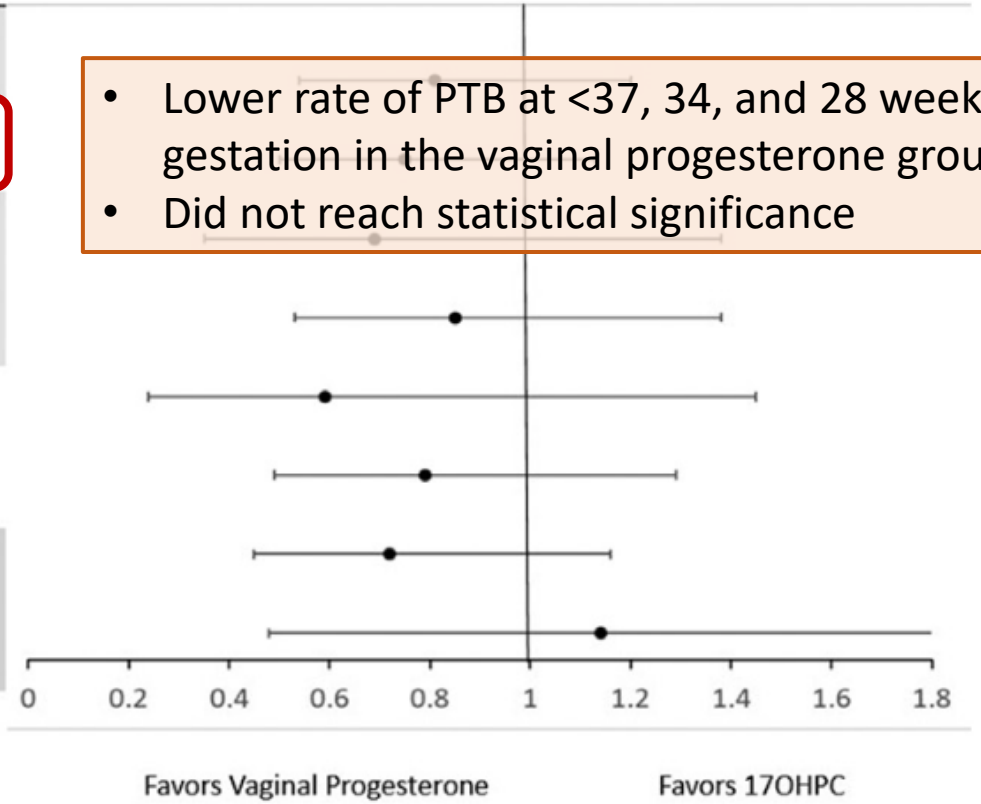
17-OHPC, 17-hydroxyprogesterone caproate; *CI*, confidence interval; *GDM*, gestational diabetes mellitus; *NA*, not available.

Boelig et al. Vaginal progesterone vs intramuscular 17-hydroxyprogesterone caproate for recurrent preterm birth prevention. Am J Obstet Gynecol 2022.

FIGURE 3
Subgroup analyses for outcome of PTB at <37 weeks

Risk Preterm Birth<37 week with Vaginal Progesterone vs 17OHPC by Subgroup

	Vaginal Progesterone	17OHPC	P-value	RR (95% CI)	P-value for interaction
Overall	29/94 (31%)	36/94 (38%)	0.28	0.81 (0.54-1.20)	N/A
Progesterone initiation 16-20wk	28/91 (31%)	31/76 (42%)	0.18	0.75 (0.50-1.13)	0.25
Cerclage	8/22 (36%)	11/21 (52%)	0.29	0.69 (0.35-1.38)	
No cerclage	21/72 (29.2%)	25/73 (34.2%)	0.51	0.85 (0.53-1.38)	0.56
Cervical length <25mm	5/17 (29%)	7/14 (50%)	0.24	0.59 (0.24-1.45)	
Cervical length ≥25mm	19/66 (28.8%)	27/74 (36.5%)	0.33	0.79 (0.49-1.29)	0.47
1 prior sPTB	18/63 (28.6%)	31/78 (39.7%)	0.17	0.71 (0.45-1.16)	
>1 prior sPTB	11/35 (35.5%)	5/16 (31.3%)	0.77	1.14 (0.48-2.71)	0.36



- Lower rate of PTB at <37, 34, and 28 weeks of gestation in the vaginal progesterone group
- Did not reach statistical significance

Comparison of PTB at <37 weeks of gestation by randomization group in selected subgroups.

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Subgroup analyses for outcome of PTB at <37 weeks

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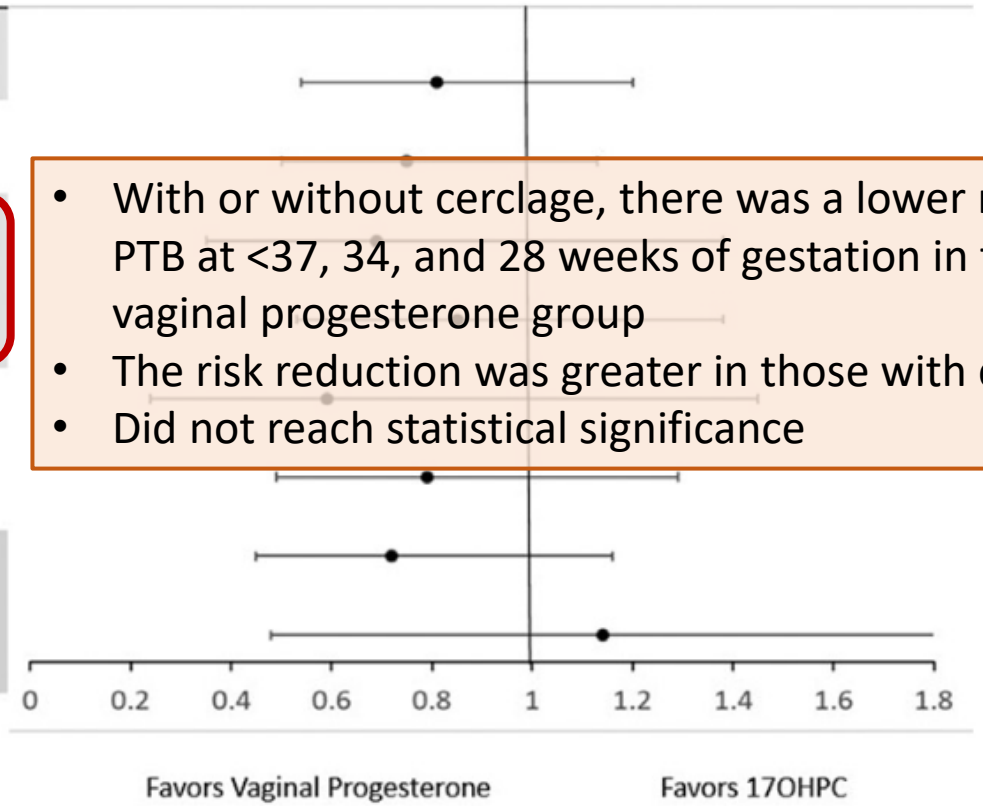

- With or without cerclage, there was a lower rate of PTB at <37, 34, and 28 weeks of gestation in the vaginal progesterone group
- The risk reduction was greater in those with cerclage
- Did not reach statistical significance

Comparison of PTB at <37 weeks of gestation by randomization group in selected subgroups.

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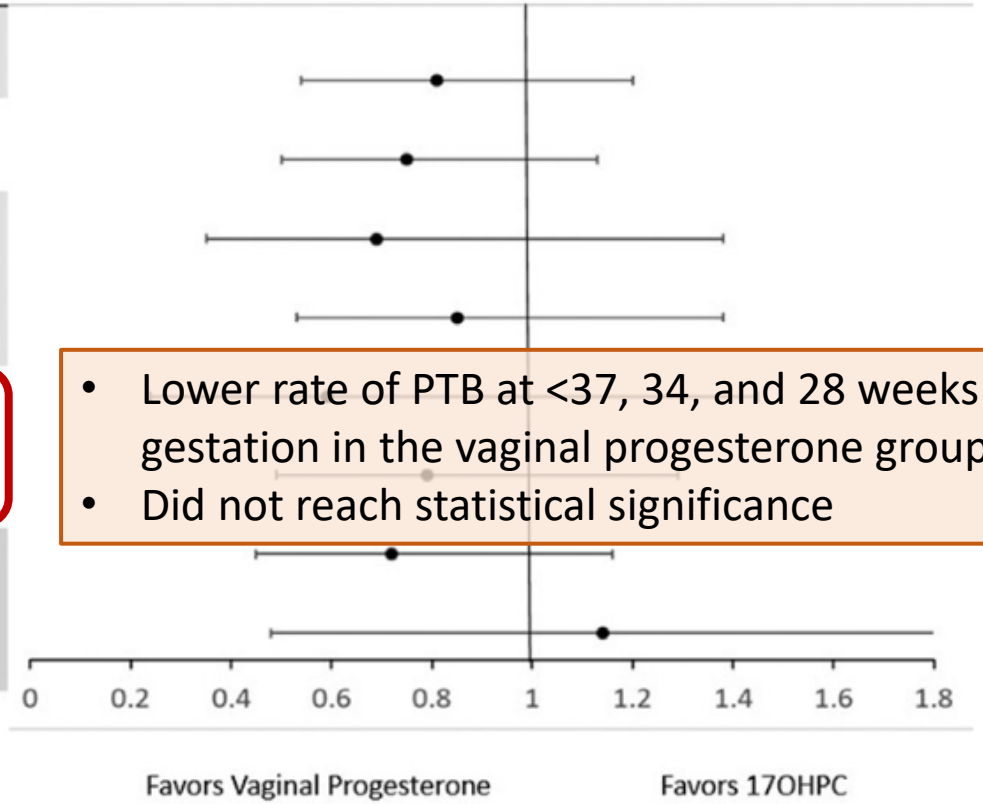

- Lower rate of PTB at <37, 34, and 28 weeks of gestation in the vaginal progesterone group
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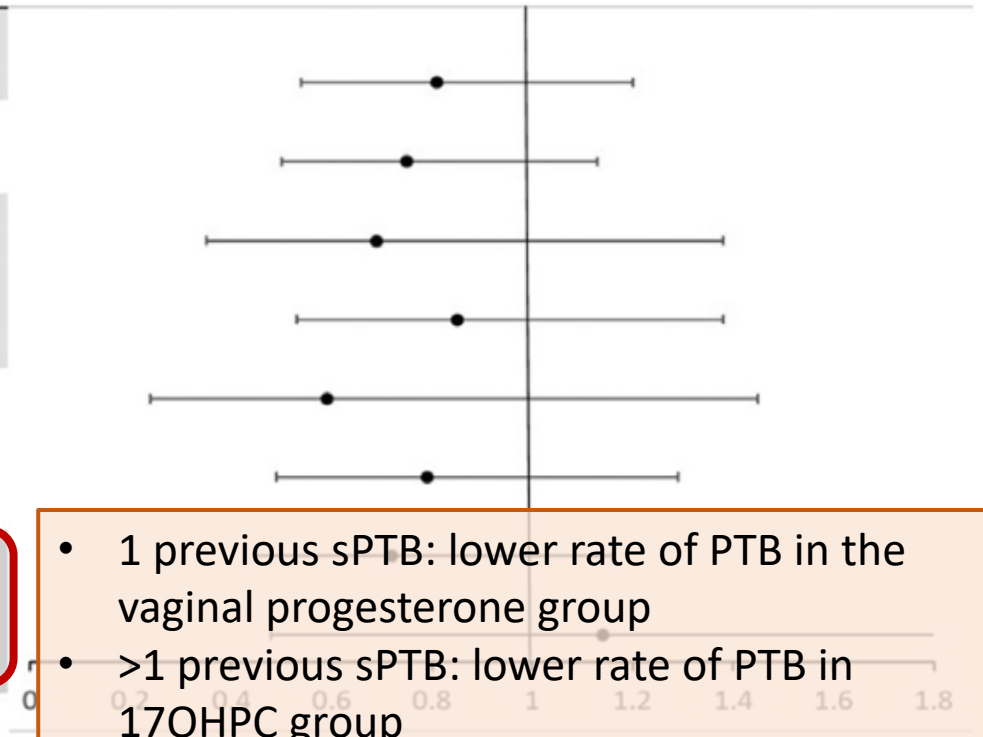
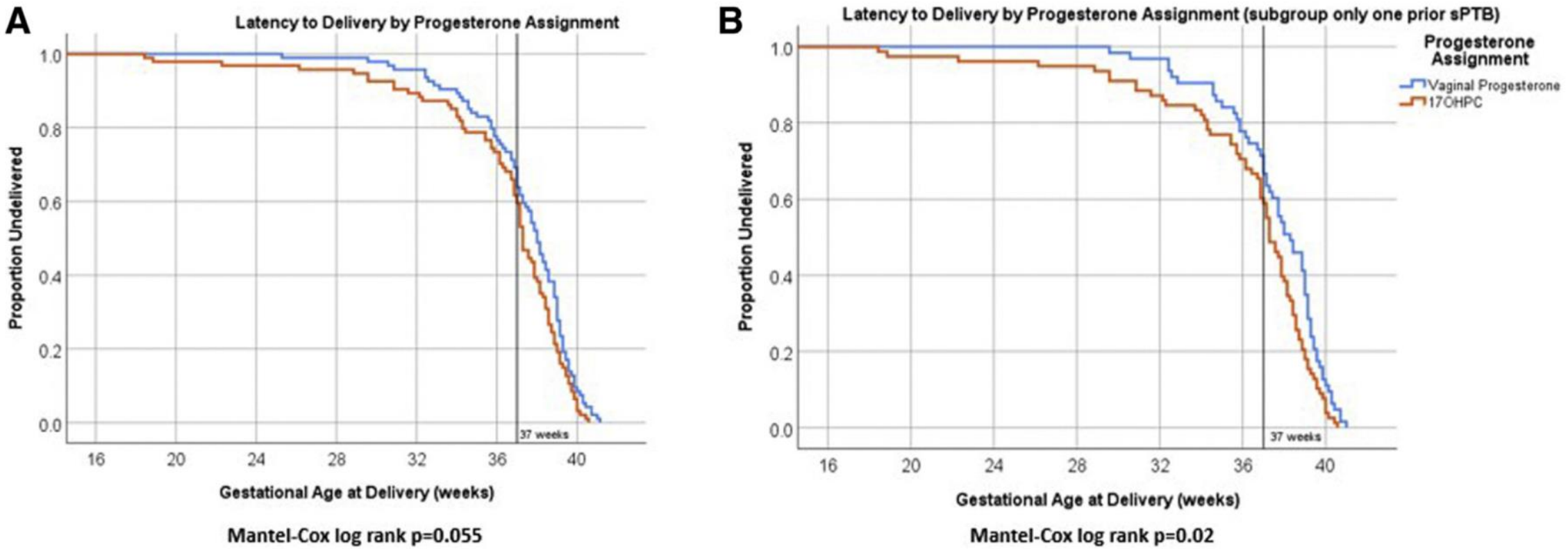


- 1 previous sPTB: lower rate of PTB in the vaginal progesterone group
- >1 previous sPTB: lower rate of PTB in 17OHPC group
- Did not reach statistical significance

Comparison of PTB at <37 weeks of gestation by randomization group in selected subgroups.

FIGURE 2
Kaplan-Meier survival curve for latency to delivery



Comparison of gestational age of delivery by progesterone assignment in (**A**) the entire study population (94 participants in the vaginal progesterone group and 94 participants in the 17-OHPC group) and (**B**) subgroup of those with only 1 previous sPTB (63 participants in the vaginal progesterone group and 78 participants in the 17-OHPC group).

Those in the vaginal progesterone group demonstrated
a significantly increased latency to delivery and later mean GA at delivery (37.6±2.5 vs 36.1±4.4 weeks)

Adherence and satisfaction

TABLE 5
Comparison of satisfaction and adherence outcomes between the randomization groups

Variable	Vaginal progesterone (n=94)	17-OHPC (n=94)	*P* value	RR orMD (95% CI)
GA at progesterone initiation (wk)	16.9±1.4[a]	17.8±2.5[b]	.001	−0.91 (−1.46 to −0.37)
Progesterone initiated at >20 wk of gestation	2 (2.2)[a]	15 (16.5)[b]	.001	0.13 (0.03–0.55)
Continued assigned medication until delivery	64/88 (72.7)	61/88 (69.3)	.62	1.05 (0.87–1.27)
Switched formulation	8/88 (9.1)	13/88 (14.8)	.25	0.62 (0.27–1.41)
Stopped all progesterone medications	16/88 (18.2)	14/88 (15.9)	.69	1.14 (0.59–2.12)
Variable	**Vaginal progesterone (n=86)**	**17-OHPC (n=78)**	***P* value**	**RR orMD (95% CI)**
Mean percentage adherence (number of doses taken/number of doses prescribed)	82±27	78±35	.41	MD: 0.04 (−0.06 to 0.14)
Mean satisfaction (1–5 scale)	3.77±1.18	4.06±1.00	.10	MD: −0.28 (−0.63 to 0.05)

Data are presented as mean±standard deviation, number (percentage), or number/total number (percentage), unless otherwise indicated.

17-OHPC, 17-hydroxyprogesterone caproate; *CI*, confidence interval; *MD*, mean difference; *RR*, relative risk.

[a] n=93; [b] n=91.

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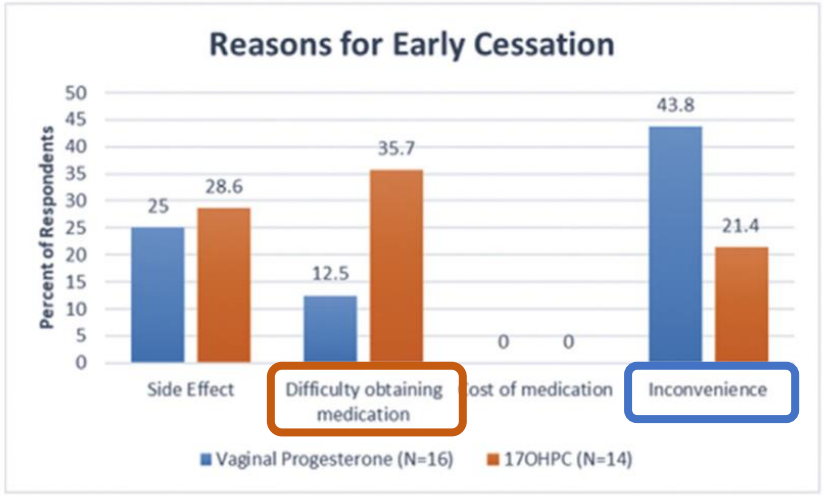
FIGURE 4
Reasons for therapy cessation or crossover

A



B

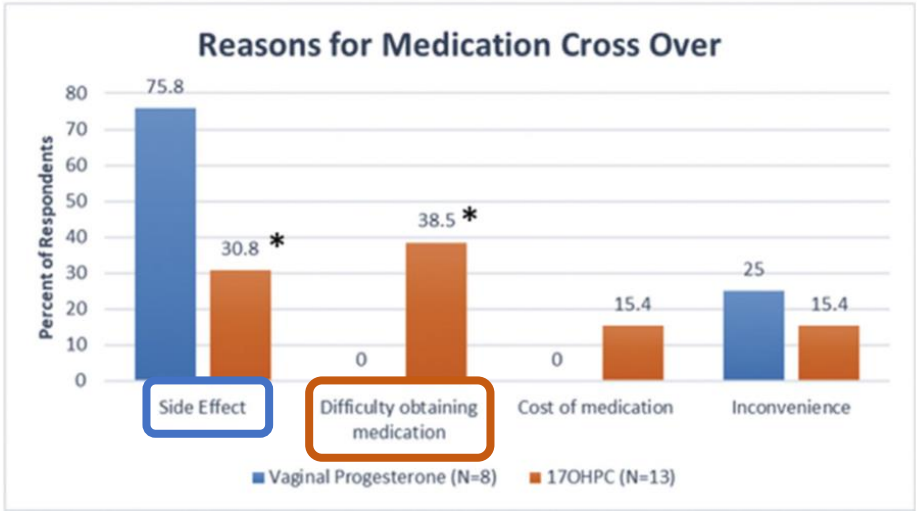
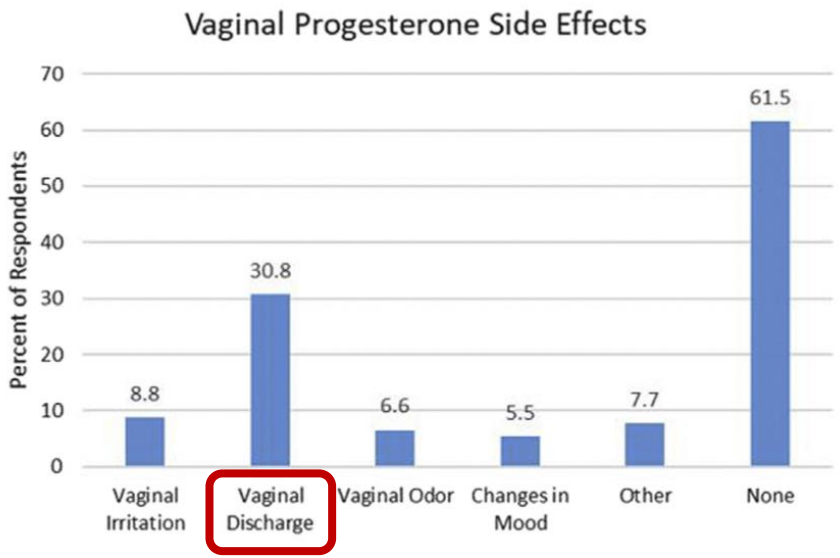
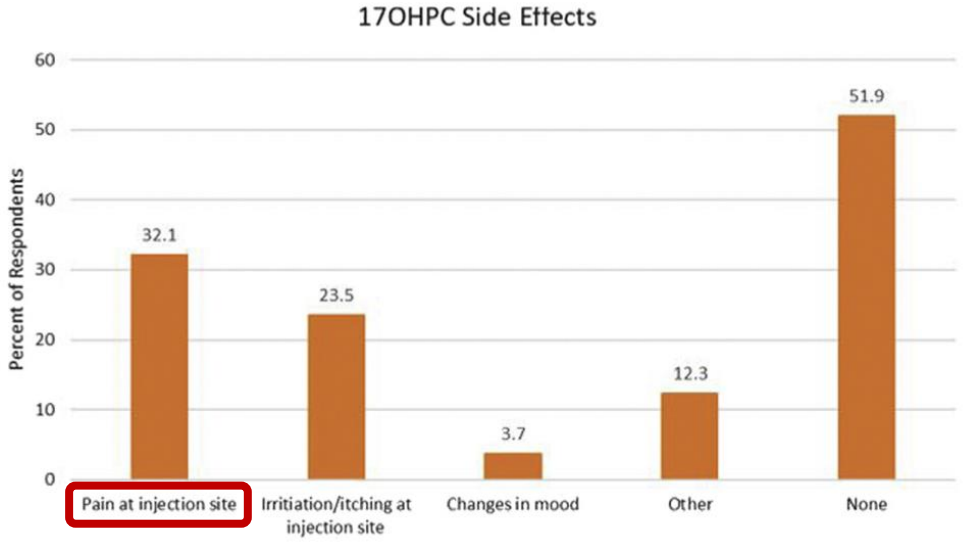


FIGURE 5
Reported side effects





Discussion

- Vaginal progesterone did not reduce PTB risk by 50% compared with 17- OHPC
- The neonates in the vaginal progesterone group did **deliver at a later GA**
- Vaginal progesterone is an acceptable alternative to 17-OHPC and access to medication to enable timely initiation of therapy is an important consideration in therapy selection

Strengths

- Large RCT comparing vaginal progesterone with 17-OHPC
- A high rate of protocol adherence
- Pragmatic trial that reflects the real-world efficacy of medication assignment
- Multicenter trial with a diverse patient population

Limitations

- Most subgroup analyses were small, limiting the ability to conclude differential efficacy within those subgroups
- Underpowered for many secondary outcomes
- As a pragmatic trial, results reflected a combination of medication efficacy and proper (or not) medication use
- Adherence to medications was by self-report
- Cerclage was offered as indicated and may impact apparent efficacy of either intervention

Conclusion

- Our results supported the current ACOG guidance, allowing for offering patients with previous PTB either formulation
- Vaginal progesterone did not reduce the risk of recurrent PTB by 50% compared with 17-OHPC among patients with singleton pregnancies who had a previous sPTB
- Vaginal progesterone lead to later GA of delivery

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Does vaginal progesterone prevent recurrent preterm birth in women with a singleton gestation and a history of spontaneous preterm birth?Evidence from a systematic review and meta-analysis

Agustin CONDE-AGUDELO, MD, MPH, PhD • Roberto ROMERO, MD, DMedSci

Published: April 20, 2022 • DOI: https://doi.org/10.1016/j.ajog.2022.04.023

Introduction

- 2003 ACOG: recommended **17-OHPC** for patients with a singleton gestation and a history of spontaneous preterm birth
- 2021 ACOG: recommended offering either **vaginal progesterone or 17- OHPC** on prevention of spontaneous preterm birth

- Evidence base: meta-analysis (31 trials of vaginal progesterone, 17-OHPC, and oral progesterone in asymptomatic women at increased risk for preterm birth)
- Did not report results separately for the subgroup

Introduction

- 2003 ACOG: recommended **17-OHPC** for patients with a singleton gestation and a history of spontaneous preterm birth
- 2021 ACOG: recommended offering either **vaginal progesterone or 17- OHPC** on prevention of spontaneous preterm birth

To **assess the efficacy and safety of vaginal progesterone** to prevent recurrent preterm birth and adverse perinatal outcomes in singleton gestations with a history of spontaneous preterm birth

Material and methods

- We included **randomized controlled trials** in which **asymptomatic women** with a **singleton gestation** and a **history of at least one spontaneous preterm birth** in any of their previous pregnancies
- Randomly allocated to receive vaginal progesterone or placebo/no treatment for the prevention of preterm birth

Material and methods

Exclusion:

- Quasi-randomized trials
- Trials assessing vaginal progesterone in women with threatened or arrested preterm labor or second-trimester bleeding
- Trials in which vaginal progesterone was administered in the first trimester to prevent miscarriage

Outcome measures

- The primary outcomes: preterm birth **<37 and <34 weeks** of gestation

Assessment of risk of bias

- Using the **Cochrane risk of bias tool 2 (RoB 2)**

(1) bias arising from the randomization process

(2) bias due to deviations from intended interventions

(3) bias due to missing outcome data

(4) bias in measurement of the outcome

(5) bias in the selection of the reported result

Statistical analysis

- Subgroup analyses:
  - sample size
  - setting
  - study center status
  - trial registration status
  - mean gestational age at treatment initiation
  - daily dose of vaginal progesterone

- We carried out **sensitivity analyses** by including only studies at overall low risk of bias

Assessment of quality of evidence

- The quality (certainty) of the body of evidence was assessed by using the 5 GRADE criteria (overall risk of bias, consistency of effect, imprecision, indirectness, and publication bias)
- 4 levels: high, moderate, low, very low

Results

- Ten studies, 2958 women with a singleton gestation and a history of spontaneous preterm birth
- Seven studies had a sample size <150 and 3 had a sample size >600
- Daily dose of vaginal progesterone: 90 mg in 1 study, 100 mg in 6 studies, 200 mg in 2 studies, and 400 mg in 1 study
- Most studies administered the treatment from **20-24 to 34-36 weeks** of gestation

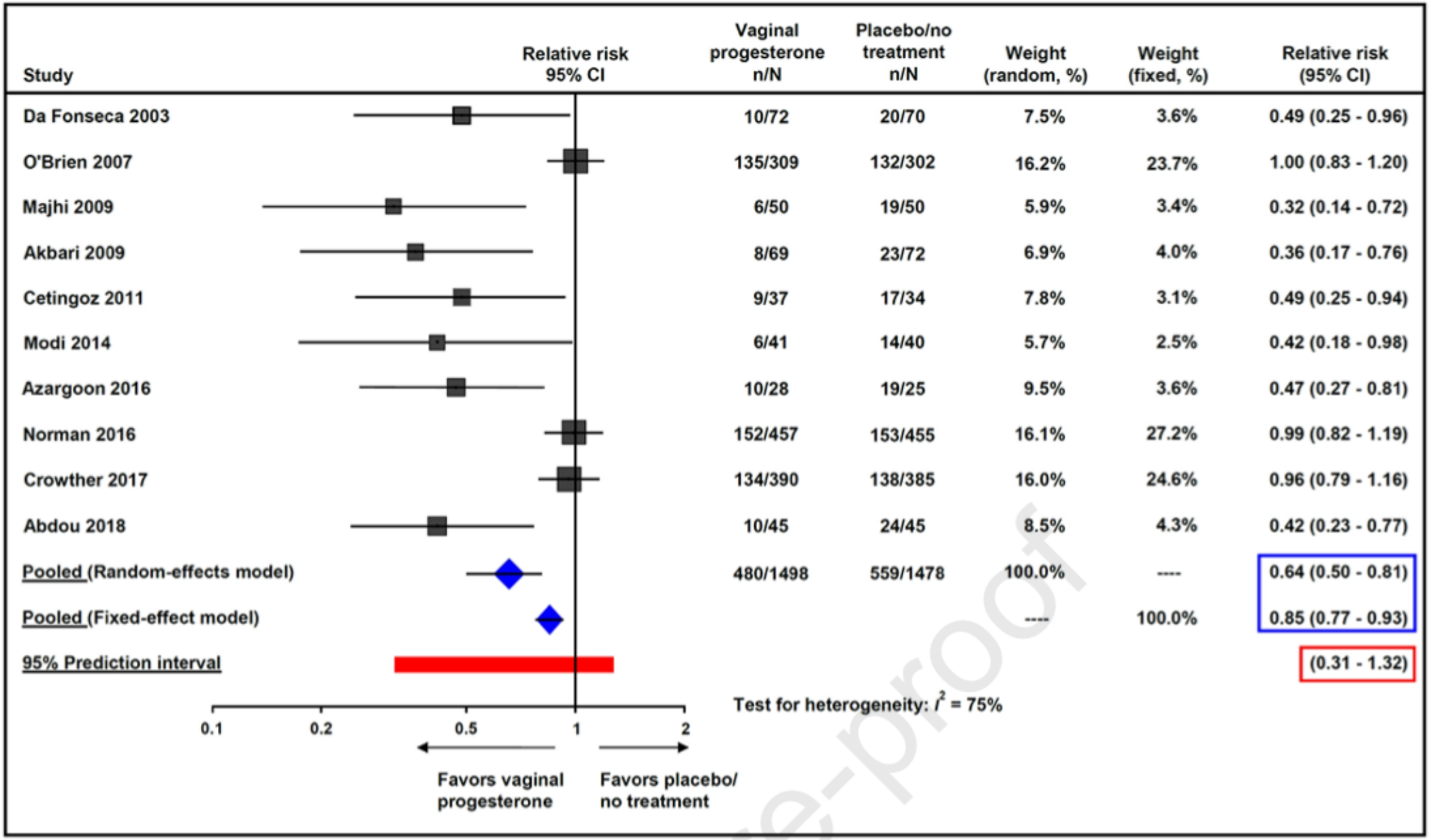
Risk of bias

Study	Bias arising from the randomization process	Bias due to deviations from the intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Da Fonseca 2003	+	−	+	+	+	−
O'Brien 2007 (Large)	+	+	+	+	+	+
Majhi 2009	+	+	+	?	+	?
Akbari 2009	?	?	+	?	?	−
Cetingoz 2011	+	+	+	+	+	+
Modi 2014	+	+	?	+	?	−
Azargoon 2016	?	+	+	+	+	?
Norman 2016 (Large)	+	+	+	+	+	+
Crowther 2017 (Large)	+	+	+	+	+	+
Abdou 2018	?	+	+	?	?	−

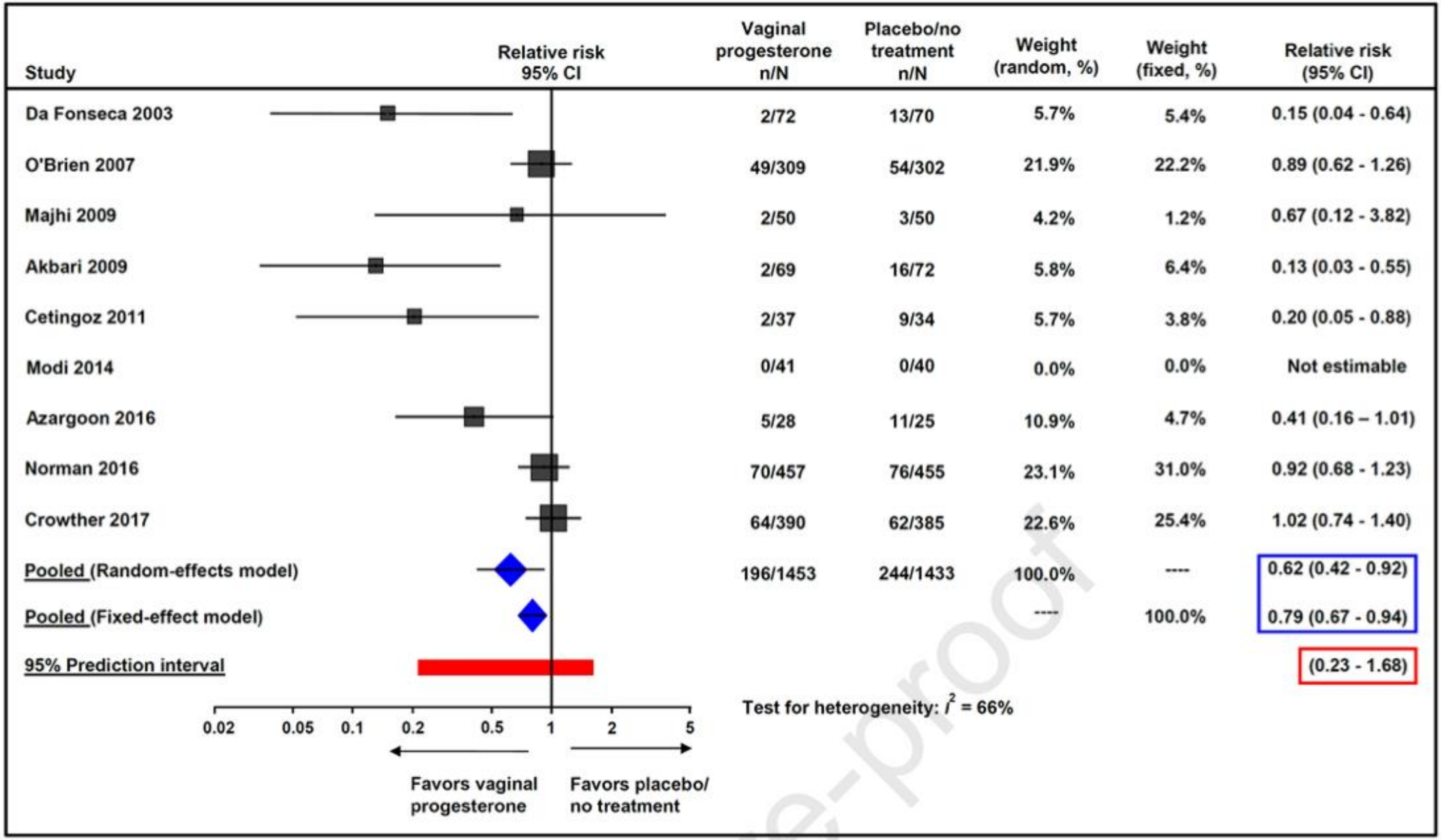
+ Low risk of bias ? Some concerns − High risk of bias

Primary outcomes

- Vaginal progesterone was associated with **a significant decrease in the risk of preterm birth** <37 weeks of gestation (32.0% vs 37.8%) and preterm birth <34 weeks of gestation (13.5% vs 17.0%)



preterm birth <37 weeks of gestation



preterm birth <34 weeks of gestation

Secondary outcomes

TABLE 2. Effect of vaginal progesterone on pregnancy, maternal, and perinatal outcomes

Outcome	No of trials	Vaginal progesterone		Placebo/no treatment		Relative risk (95% CI)	*P* value	I^2, %	95% Prediction interval for the RR
Preterm birth <28 weeks	9[72-74,76-81]	62/1429	(4.3%)	56/1406	(4.0%)	1.12 (0.70-1.78)	0.64	18	0.51-2.49
Threatened preterm labor or need for tocolysis	5[72-74,76,80]	176/866	(20.3%)	196/845	(23.2%)	0.82 (0.63-1.06)	0.12	37	0.48-1.42
Use of antenatal corticosteroids	2[73,80]	211/699	(30.2%)	213/687	(31.0)	0.98 (0.83-1.14)	0.76	0	NA
Cesarean delivery	3 [73,74,80]	215/749	(28.7%)	191/737	(25.9%)	1.11 (0.94-1.31)	0.21	0	NA
Any maternal adverse event	3[73,76,80]	385/740	(52.0%)	369/718	(51.4%)	1.01 (0.89-1.15)	0.88	41	NA
Discontinuation of treatment because of adverse events	4 [73,74,76,80]	44/790	(5.6%)	31/768	(4.0%)	1.38 (0.88-2.14)	0.16	0	NA
Preterm prelabor rupture of membranes	4[73,74,76,80]	88/794	(11.1%)	85/775	(11.0%)	1.02 (0.77-1.35)	0.87	0	NA
Preeclampsia	2[74,80]	12/440	(2.7%)	8/435	(1.8%)	1.48 (0.61-3.58)	0.38	NA	NA
Gestational hypertension	2[74,80]	6/440	(1.4%)	5/435	(1.2)	1.19 (0.37-3.85)	0.78	0	NA
Gestational diabetes mellitus	2[74,80]	45/440	(10.2%)	40/435	(9.2%)	1.12 (0.75-1.67)	0.59	0	NA
Respiratory distress syndrome	6[73-76,80,81]	84/896	(9.4%)	114/883	(12.9%)	0.62 (0.37-1.04)	0.07	57	0.18-2.13
Necrotizing enterocolitis	4[73,74,76,80]	5/782	(0.6%)	8/766	(1.0%)	0.64 (0.22-1.90)	0.42	0	NA
Intraventricular hemorrhage	4[73,75,76,80]	17/801	(2.1%)	15/788	(1.9%)	1.11 (0.56-2.22)	0.76	0	NA
Grade III/IV intraventricular hemorrhage	4[73,74,76,80]	2/782	(0.3)	2/766	(0.3)	0.98 (0.14-6.94)	0.98	0	NA
Neonatal sepsis	5[73-76,80]	15/827	(1.8%)	22/825	(2.7%)	0.69 (0.29-1.68)	0.42	26	0.14-3.32
Retinopathy of prematurity	2[76,80]	12/422	(2.8%)	9/414	(2.2%)	1.32 (0.56-3.09)	0.53	NA	NA

Secondary outcomes

Bronchopulmonary dysplasia	3[74,76,80]	10/473	(2.1%)	5/464	(1.1%)	1.97 (0.68-5.71)	0.21	NA	NA
Periventricular leukomalacia	2[76,80]	0/423	(0.0)	1/414	(0.2)	0.33 (0.01-8.03)	0.49	NA	NA
Fetal death	6[73,74,76,78-80]	16/1271	(1.3%)	15/1251	(1.2%)	1.05 (0.52-2.13)	0.89	0	0.52-2.13
Neonatal death	7[73-76,78-80]	20/1340	(1.5%)	32/1323	(2.4%)	0.65 (0.36-1.15)	0.14	0	0.36-1.15
Perinatal death	6[73,74,76,78-80]	33/1271	(2.6%)	37/1251	(3.0%)	0.90 (0.56-1.45)	0.67	0	0.56-1.45
Birthweight <1500 g	4 [73,74,76,80]	55/781	(7.0%)	42/762	(5.5%)	1.28 (0.87-1.89)	0.21	0	NA
Birthweight <2500 g	5[73-76,80]	206/850	(24.2%)	229/834	(27.5%)	0.77 (0.54-1.10)	0.15	64	0.33-1.82
Admission to NICU	6[73,74,75,76,80,81]	129/896	(14.4%)	183/883	(20.7%)	0.53 (0.33-0.85)	0.01	67	0.16-1.79
Use of mechanical ventilation	5[73-76,80]	78/825	(9.5%)	104/825	(12.6%)	0.65 (0.39-1.08)	0.10	44	0.21-2.00
Patent ductus arteriosus	3[73,74,80]	18/721	(2.5%)	15/718	(2.1%)	1.19 (0.61-2.36)	0.61	0	NA

Data are n/N.
CI, confidence interval; *NA*, not applicable; *NICU*, neonatal intensive care unit; *RR*, relative risk.

Secondary outcomes

- O’Brien et al: assess neurodevelopmental outcomes at 2 y/o (N=293)

  no significant differences in developmental delay, mean weight, length and head circumference, chronic morbid conditions, and congenital abnormalities not detected at birth

- Norman et al: Bayley-III cognitive composite score at 2 y/o (N=656)

  no significant in the risk of moderate or severe neurodevelopmental impairment, visual or hearing impairment, and disability in renal, gastrointestinal, or respiratory function

Subgroup and sensitivity analysis

	Preterm birth <37 weeks of gestation							Preterm birth <34 weeks of gestation						
Subgroup	**No. of trials**	**Vaginal progesterone**		**Placebo/no treatment**		**Relative risk (95% CI)**	**I^2, %**	**Interaction *P* value**	**No. of trials**	**Vaginal progesterone**		**Placebo/no treatment**		**Relative risk (95% CI)**	**I^2, %**	**Interaction *P* value**
Study sample size, n								<0.00001								<0.0001
<150	7[72,74-78,81]	59/342	(17.3%)	136/336	(40.5%)	0.43 (0.33-0.55)	0		6[160,161,162,163]	13/297	(4.4%)	52/291	(17.9%)	0.27 (0.15-0.49)	0	
≥150	3[73,79,80]	421/1156	(36.4%)	423/1142	(37.0%)	0.98 (0.88-1.09)	0		3[162-164]	183/1156	(15.8%)	192/1142	(16.8%)	0.94 (0.78-1.13)	0	
Study setting								<0.00001								0.0003
Low/middle-income countries	7[72,74-78,81]	59/342	(17.3%)	136/336	(40.5%)	0.43 (0.33-0.55)	0		6[162]	13/297	(4.4%)	52/291	(17.9%)	0.27 (0.15-0.49)	0	
High-income countries	2[79,80]	286/847	(33.8%)	291/840	(34.6%)	0.97 (0.85-1.11)	0		2[162]	134/847	(15.8%)	138/840	(16.4%)	0.96 (0.77-1.20)	0	
Both low/middle- and high-income countries	1[73]	135/309	(43.7%)	132/302	(43.7%)	1.00 (0.83-1.20)	NA		1[162]	49/309	(15.9%)	54/302	(17.9%)	0.89 (0.62-1.26)	NA	
Study center status								<0.00001								0.0003
Single center	7[72,74-78,81]	59/342	(17.3%)	136/336	(40.5%)	0.43 (0.33-0.55)	0		6[160,161,162,163]	13/297	(4.4%)	52/291	(17.9%)	0.27 (0.15-0.49)	0	
Multicenter	3[73,79,80]	421/1156	(36.4%)	423/1142	(37.0%)	0.98 (0.88-1.09)	0		3[162-164]	183/1156	(15.8%)	192/1142	(16.8%)	0.94 (0.78-1.13)	0	
Trial registration status								<0.0001								0.0002
Registered	5[73,77-80]	437/1225	(35.7%)	456/1207	(37.8%)	0.88 (0.72-1.07)	62		5[162]	188/1225	(15.3%)	203/1207	(16.8%)	0.90 (0.74-1.11)	15	
Not registered	5[72,74-76,81]	43/273	(15.8%)	103/271	(38.0%)	0.42 (0.31-0.57)	0		4[162]	8/228	(3.5%)	41/226	(18.1%)	0.21 (0.10-0.44)	0	
Mean gestational age at treatment initiation, weeks								0.01								<0.0001
<24	6 [73,74,78-81]	447/1279	(35.0%)	485/1262	(38.4%)	0.76 (0.60-0.98)	75		5[162]	190/1234	(15.4%)	206/1217	(16.9%)	0.91 (0.76-1.09)	0	
≥24	4[72,75-77]	33/219	(15.1%)	74/216	(34.3%)	0.44 (0.31-0.63)	0		4[162]	6/219	(2.7%)	38/216	(17.6%)	0.16 (0.07-0.36)	0	
Daily dose of vaginal progesterone, mg								0.97								0.54
90-100	7[72,73-77,80]	308/968	(31.8%)	363/953	(38.1%)	0.62 (0.45-0.85)	75		7[162]	121/968	(12.5%)	157/953	(16.5%)	0.51 (0.28-0.92)	72	
≥200	3[78,79,81]	172/530	(32.5%)	196/525	(37.3%)	0.61 (0.32-1.14)	84		2[162]	75/485	(15.5%)	87/480	(18.1%)	0.69 (0.32-1.47)	64	

Data are n/N.
CI, confidence interval; *NA*, not applicable.

Subgroup and sensitivity analysis

Subgroup	Preterm birth <37 weeks of gestation: No. of trials	Vaginal progesterone	Placebo/no treatment	Relative risk (95% CI)	I^2, %	Interaction *P* value	Preterm birth <34 weeks of gestation: No. of trials	Vaginal progesterone	Placebo/no treatment	Relative risk (95% CI)	I^2, %	Interaction *P* value
Study sample size, n						<0.00001						<0.0001
<150	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[160,161,162,163]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
≥150	3[73,79,80]	421/1156 (36.4%)	423/1142 (37.0%)	0.98 (0.88-1.09)	0		3[162-164]	183/1156 (15.8%)	192/1142 (16.8%)	0.94 (0.78-1.13)	0	
Study setting						<0.00001						0.0003
Low/middle-income countries	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[162]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
High-income countries	2[79,80]	286/847 (33.8%)	291/840 (34.6%)	0.97 (0.85-1.11)	0		2[162]	134/847 (15.8%)	138/840 (16.4%)	0.96 (0.77-1.20)	0	
Both low/middle- and high-income countries	1[73]	135/309 (43.7%)	132/302 (43.7%)	1.00 (0.83-1.20)	NA		1[162]	49/309 (15.9%)	54/302 (17.9%)	0.89 (0.62-1.26)	NA	
<24	6 [73,74,78-81]	447/1279 (35.0%)	485/1262 (38.4%)	0.76 (0.60-0.98)	75		5[162]	190/1234 (15.4%)	206/1217 (16.9%)	0.91 (0.76-1.09)	0	
≥24	4[72,75-77]	33/219 (15.1%)	74/216 (34.3%)	0.44 (0.31-0.63)	0		4[162]	6/219 (2.7%)	38/216 (17.6%)	0.16 (0.07-0.36)	0	
Daily dose of vaginal progesterone, mg						0.97						0.54
90-100	7[72,73-77,80]	308/968 (31.8%)	363/953 (38.1%)	0.62 (0.45-0.85)	75		7[162]	121/968 (12.5%)	157/953 (16.5%)	0.51 (0.28-0.92)	72	
≥200	3[78,79,81]	172/530 (32.5%)	196/525 (37.3%)	0.61 (0.32-1.14)	84		2[162]	75/485 (15.5%)	87/480 (18.1%)	0.69 (0.32-1.47)	64	

Data are n/N.
CI, confidence interval; *NA*, not applicable.

- Small studies: vaginal progesterone significantly reduced the risk of preterm birth <37 wks & <34 wks of gestation
- Large studies: little or no difference between vaginal progesterone and placebo/no treatment groups in the risk of preterm birth 37 wks & <34 wks of gestation

Subgroup and sensitivity analysis

Subgroup	Preterm birth <37 weeks of gestation: No. of trials	Vaginal progesterone	Placebo/no treatment	Relative risk (95% CI)	I^2, %	Interaction *P* value	Preterm birth <34 weeks of gestation: No. of trials	Vaginal progesterone	Placebo/no treatment	Relative risk (95% CI)	I^2, %	Interaction *P* value
Study sample size, n						<0.00001						<0.0001
<150	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[160,161,162,163]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
≥150	3[73,79,80]	421/1156 (36.4%)	423/1142 (37.0%)	0.98 (0.88-1.09)	0		3[162-164]	183/1156 (15.8%)	192/1142 (16.8%)	0.94 (0.78-1.13)	0	
Study setting						<0.00001						0.0003
Low/middle-income countries	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[162]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
High-income countries	2[79,80]	286/847 (33.8%)	291/840 (34.6%)	0.97 (0.85-1.11)	0		2[162]	134/847 (15.8%)	138/840 (16.4%)	0.96 (0.77-1.20)	0	
Both low/middle- and high-income countries	1[73]	135/309 (43.7%)	132/302 (43.7%)	1.00 (0.83-1.20)	NA		1[162]	49/309 (15.9%)	54/302 (17.9%)	0.89 (0.62-1.26)	NA	
Study center status						<0.00001						0.0003
Single center	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[160,161,162,163]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
Multicenter	3[73,79,80]	421/1156 (36.4%)	423/1142 (37.0%)	0.98 (0.88-1.09)	0		3[162-164]	183/1156 (15.8%)	192/1142 (16.8%)	0.94 (0.78-1.13)	0	
Trial registration status						<0.0001						0.0002
Registered	5[73,77-80]	437/1225 (35.7%)	456/1207 (37.8%)	0.88 (0.72-1.07)	62		5[162]	188/1225 (15.3%)	203/1207 (16.8%)	0.90 (0.74-1.11)	15	
Not registered	5[72,74-76,81]	43/273 (15.8%)	103/271 (38.0%)	0.42 (0.31-0.57)	0		4[162]	8/228 (3.5%)	41/226 (18.1%)	0.21 (0.10-0.44)	0	
Mean gestational age at treatment initiation, weeks						0.01						<0.0001
<24	6 [73,74,78-81]	447/1279 (35.0%)	485/1262 (38.4%)	0.76 (0.60-0.98)	75		5[162]	190/1234 (15.4%)	206/1217 (16.9%)	0.91 (0.76-1.09)	0	
≥24	4[72,75-77]	33/219 (15.1%)	74/216 (34.3%)	0.44 (0.31-0.63)	0		4[162]	6/219 (2.7%)	38/216 (17.6%)	0.16 (0.07-0.36)	0	
Daily dose of vaginal progesterone, mg						0.97						0.54
90-100	7[72,73-77,80]	308/968 (31.8%)	363/953 (38.1%)	0.62 (0.45-0.85)	75		7[162]	121/968 (12.5%)	157/953 (16.5%)	0.51 (0.28-0.92)	72	
≥200	3[78,79,81]	172/530 (32.5%)	196/525 (37.3%)	0.61 (0.32-1.14)	84		2[162]	75/485 (15.5%)	87/480 (18.1%)	0.69 (0.32-1.47)	64	

Data are n/N.
CI, confidence interval; *NA*, not applicable.

Subgroup and sensitivity analysis

Subgroup	Preterm birth <37 weeks of gestation: No. of trials	Vaginal progesterone	Placebo/no treatment	Relative risk (95% CI)	I^2, %	Interaction *P* value	Preterm birth <34 weeks of gestation: No. of trials	Vaginal progesterone	Placebo/no treatment	Relative risk (95% CI)	I^2, %	Interaction *P* value
Study sample size, n						<0.00001						<0.0001
<150	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[160,161,162,163]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
≥150	3[73,79,80]	421/1156 (36.4%)	423/1142 (37.0%)	0.98 (0.88-1.09)	0		3[162-164]	183/1156 (15.8%)	192/1142 (16.8%)	0.94 (0.78-1.13)	0	
Study setting						<0.00001						0.0003
Low/middle-income countries	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[162]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
High-income countries	2[79,80]	286/847 (33.8%)	291/840 (34.6%)	0.97 (0.85-1.11)	0		2[162]	134/847 (15.8%)	138/840 (16.4%)	0.96 (0.77-1.20)	0	
Both low/middle- and high-income countries	1[73]	135/309 (43.7%)	132/302 (43.7%)	1.00 (0.83-1.20)	NA		1[162]	49/309 (15.9%)	54/302 (17.9%)	0.89 (0.62-1.26)	NA	
Study center status						<0.00001						0.0003
Single center	7[72,74-78,81]	59/342 (17.3%)	136/336 (40.5%)	0.43 (0.33-0.55)	0		6[160,161,162,163]	13/297 (4.4%)	52/291 (17.9%)	0.27 (0.15-0.49)	0	
Multicenter	3[73,79,80]	421/1156 (36.4%)	423/1142 (37.0%)	0.98 (0.88-1.09)	0		3[162-164]	183/1156 (15.8%)	192/1142 (16.8%)	0.94 (0.78-1.13)	0	
Trial registration status						<0.0001						0.0002
Registered	5[73,77-80]	437/1225 (35.7%)	456/1207 (37.8%)	0.88 (0.72-1.07)	62		5[162]	188/1225 (15.3%)	203/1207 (16.8%)	0.90 (0.74-1.11)	15	
Not registered	5[72,74-76,81]	43/273 (15.8%)	103/271 (38.0%)	0.42 (0.31-0.57)	0		4[162]	8/228 (3.5%)	41/226 (18.1%)	0.21 (0.10-0.44)	0	
Mean gestatio												<0.0001
<24												
≥24	4[72,75-77]	33/219 (15.1%)	74/216 (34.3%)	0.44 (0.31-0.63)	0		4[162]	6/219 (2.7%)	38/216 (17.6%)	0.16 (0.07-0.36)	0	
Daily dose of vaginal progesterone, mg						0.97						0.54
90-100	7[72,73-77,80]	308/968 (31.8%)	363/953 (38.1%)	0.62 (0.45-0.85)	75		7[162]	121/968 (12.5%)	157/953 (16.5%)	0.51 (0.28-0.92)	72	
≥200	3[78,79,81]	172/530 (32.5%)	196/525 (37.3%)	0.61 (0.32-1.14)	84		2[162]	75/485 (15.5%)	87/480 (18.1%)	0.69 (0.32-1.47)	64	

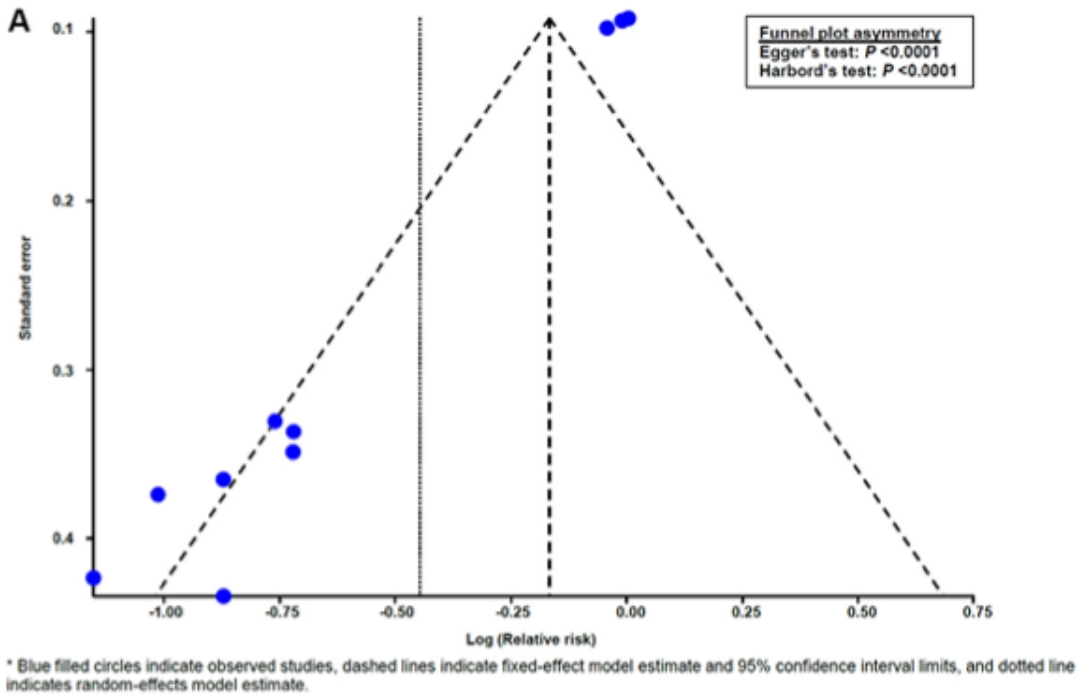
No evidence of a different effect related to daily dose of vaginal progesterone

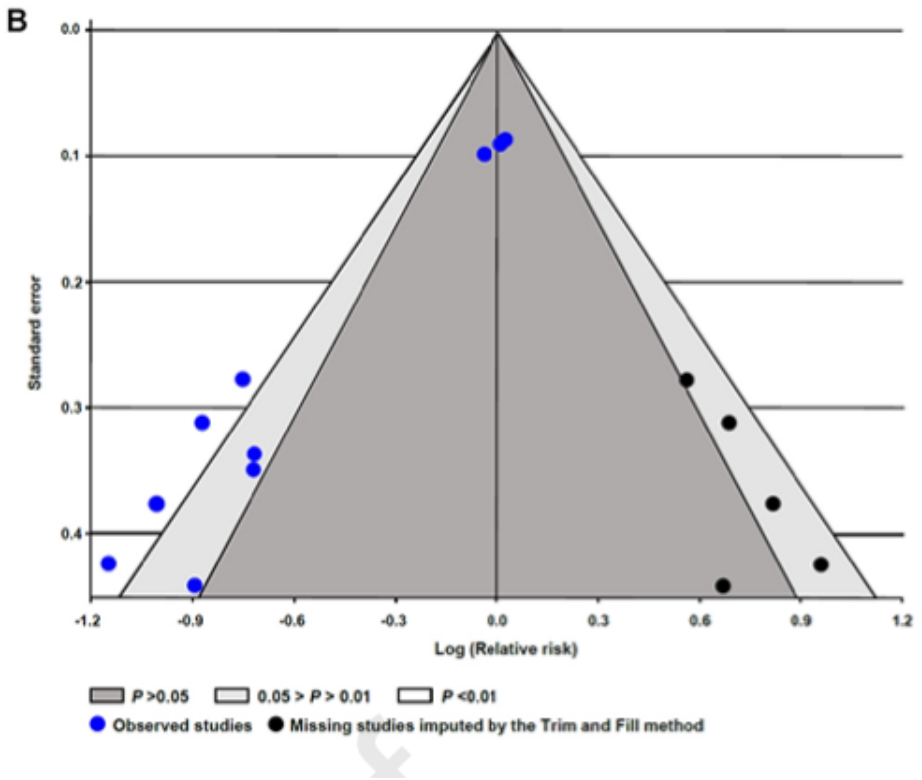
Data are n/N.
CI, confidence interval; *NA*, not applicable.

Subgroup and sensitivity analysis

- Restricted to the 4 trials at overall low risk of bias
- Did not reduce the risk of preterm birth <37 weeks of gestation (RR, 0.96; 95% CI, 0.84-1.09; $I2$ = 31%) and <34 weeks of gestation (RR, 0.90; 95% CI, 0.71-1.15; $I2$ = 34%)
- Did not significantly decrease the risk of NICU admission

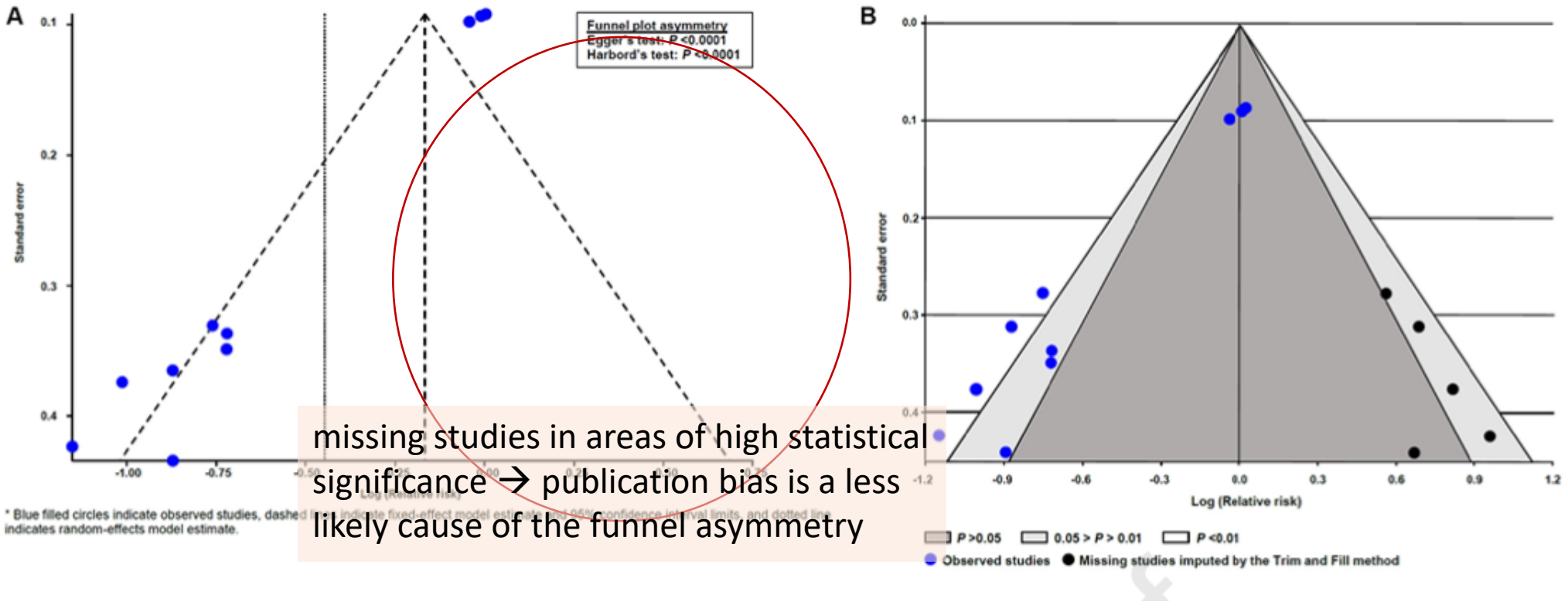
Small-study effects and publication bias





Pronounced asymmetry, which was statistically significant according to the Egger's and Harbord's tests

Small-study effects and publication bias



missing studies in areas of high statistical significance → publication bias is a less likely cause of the funnel asymmetry

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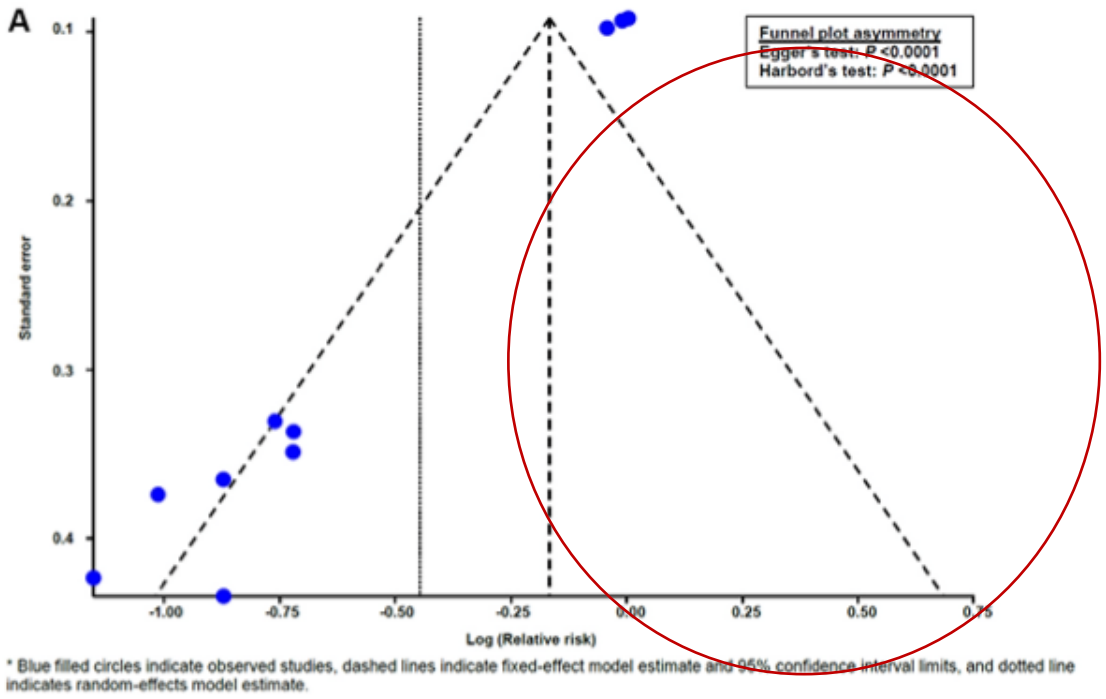
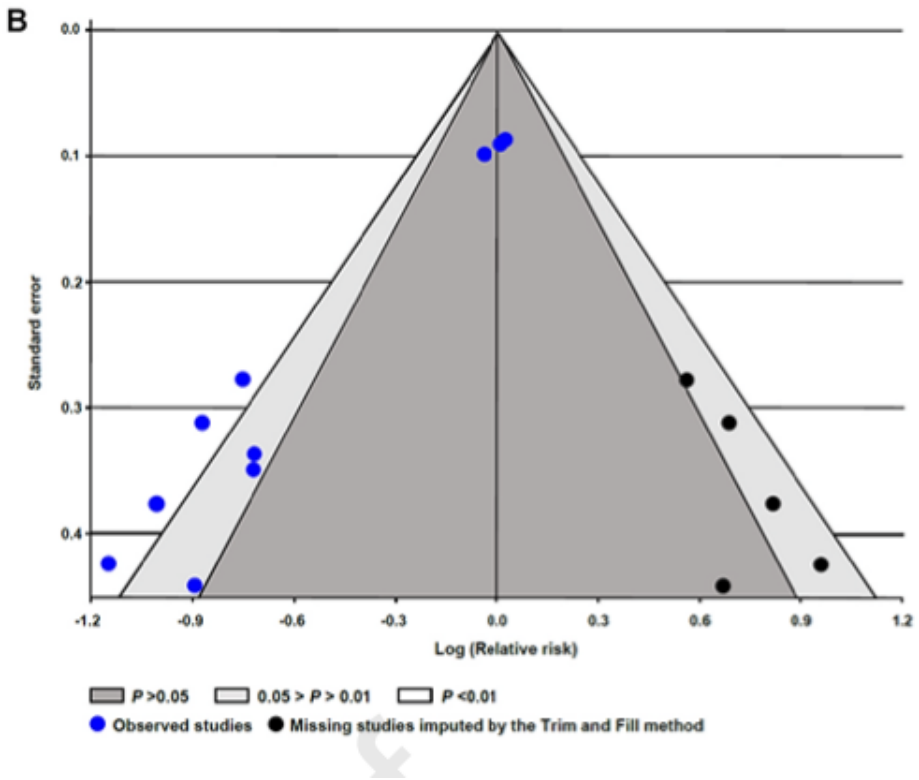




Pronounced asymmetry, which was statistically significant according to the Egger's and Harbord's tests

Trim and Fill method to adjust for small-study effects
→ turned into a non-statistically significant result

Quality of evidence based on GRADE

- Evidence was judged to be of "**very low quality**" for the primary outcomes of preterm birth <37 and <34 weeks of gestation
  - serious inconsistency because of considerable or substantial heterogeneity, probably a result of small-study effects, serious risk of bias in more than one-half of studies

- Most secondary outcomes were downgraded for serious or very serious imprecision and/or inconsistency

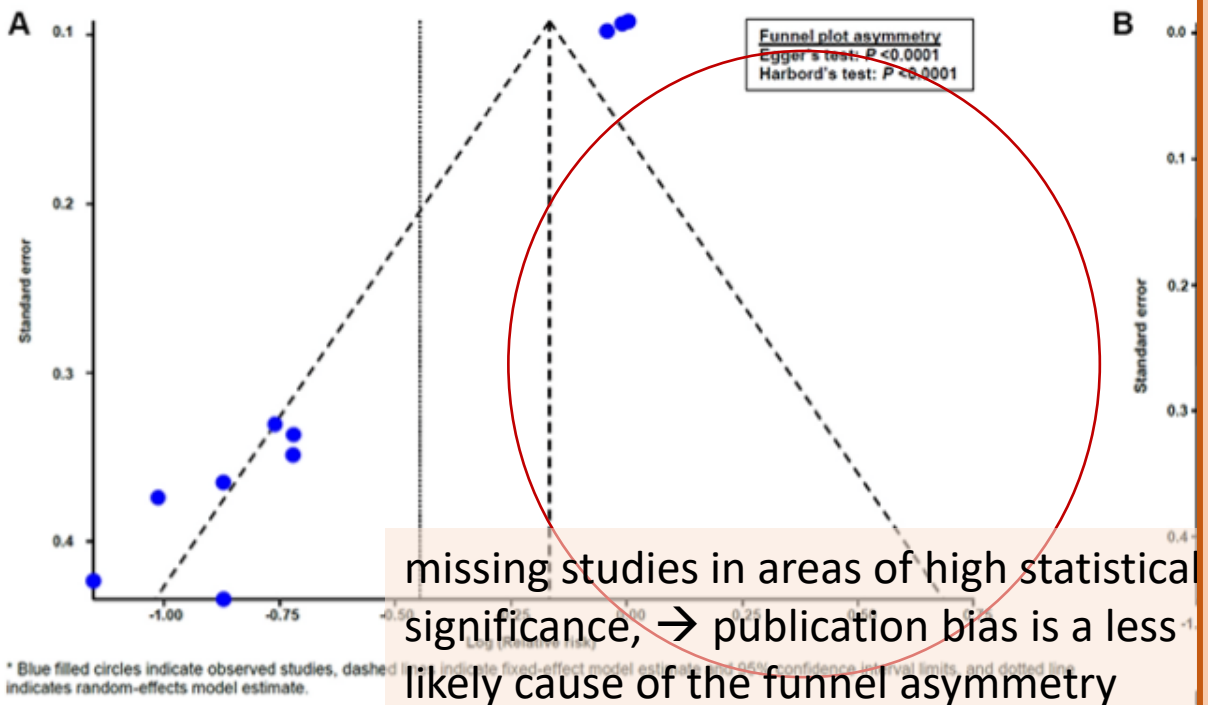
Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of evidence (GRADE)
	Risk with placebo/no treatment	Risk with vaginal progesterone			
Preterm birth <37 weeks	378 per 1000	242 per 1000 (189 to 306)	RR 0.64 (0.50 to 0.81)	2976 (10 studies)	⊕⊖⊖⊖ Very low[b,c]
Preterm birth <34 weeks	170 per 1000	106 per 1000 (72 to 57)	RR 0.62 (0.42 to 0.92)	2886 (9 studies)	⊕⊖⊖⊖ Very low[c,d]
Preterm birth <28 weeks	40 per 1000	45 per 1000 (28 to 71)	RR 1.12 (0.70 to 1.78)	2835 (9 studies)	⊕⊕⊕⊖ Moderate[e]
Respiratory distress syndrome	129 per 1000	80 per 1000 (48 to 134)	RR 0.62 (0.37 to 1.04)	1779 (6 studies)	⊕⊖⊖⊖ Very low[c,f,g]
Necrotizing enterocolitis	10 per 1000	7 per 1000 (2 to 20)	RR 0.64 (0.22 to 1.90)	1548 (4 studies)	⊕⊕⊖⊖ Low[h]
Intraventricular hemorrhage	19 per 1000	21 per 1000 (11 to 42)	RR 1.11 (0.56 to 1.22)	1589 (4 studies)	⊕⊕⊖⊖ Low[h]
Grade III/IV intraventricular hemorrhage	3 per 1000	3 per 1000 (0 to 18)	RR 0.98 (0.14 to 6.94)	1548 (4 studies)	⊕⊕⊖⊖ Low[h]
Neonatal sepsis	27 per 1000	18 per 1000 (8 to 45)	RR 0.69 (0.29 to 1.68)	1652 (5 studies)	⊕⊖⊖⊖ Very low[c,h]
Retinopathy of prematurity	22 per 1000	29 per 1000 (12 to 67)	RR 1.32 (0.56 to 3.09)	836 (2 studies)	⊕⊕⊖⊖ Low[h]
Bronchopulmonary dysplasia	11 per 1000	21 per 1000 (7 to 62)	RR 1.97 (0.68 to 5.71)	937 (3 studies)	⊕⊕⊖⊖ Low[h]
Periventricular leukomalacia	2 per 1000	1 per 1000 (0 to 19)	RR 0.33 (0.01 to 8.03)	837 (2 studies)	⊕⊕⊖⊖ Low[h]
Fetal death	12 per 1000	13 per 1000 (6 to 26)	RR 1.05 (0.52 to 2.13)	2522 (6 studies)	⊕⊕⊖⊖ Low[h]
Neonatal death	24 per 1000	16 per 1000 (9 to 28)	RR 0.65 (0.36 to 1.15)	2663 (7 studies)	⊕⊕⊖⊖ Low[i]

Perinatal death	30 per 1000	27 per 1000 (17 to 43)	RR 0.90 (0.56 to 1.45)	2522 (6 studies)	⊕⊕⊖⊖ Low[h]
Birthweight <1500 g	55 per 1000	71 per 1000 (48 to 104)	RR 1.28 (0.87 to 1.89)	1543 (4 studies)	⊕⊕⊕⊖ Moderate[i]
Birthweight <2500 g	275 per 1000	211 per 1000 (148 to 302)	RR 0.77 (0.54 to 1.10)	1684 (5 studies)	⊕⊕⊖⊖ Low[f,g]
Admission to NICU	207 per 1000	110 per 1000 (68 to 176)	RR 0.53 (0.33 to 0.85)	1779 (6 studies)	⊕⊕⊖⊖ Low[c,f]
Use of mechanical ventilation	126 per 1000	82 per 1000 (49 to 136)	RR 0.65 (0.39 to 1.08)	1650 (5 studies)	⊕⊕⊖⊖ Low[g,k]
Patent ductus arteriosus	21 per 1000	25 per 1000 (13 to 49)	RR 1.19 (0.61 to 2.36)	1439 (3 studies)	⊕⊕⊖⊖ Low[h]
Threatened preterm labor or need for tocolysis	232 per 1000	190 per 1000 (146 to 246)	RR 0.82 (0.63 to 1.06)	1711 (5 studies)	⊕⊕⊖⊖ Low[g,k]
Use of antenatal corticosteroids	310 per 1000	304 per 1000 (257 to 353)	RR 0.98 (0.83 to 1.14)	1386 (2 studies)	⊕⊕⊕⊕ High
Cesarean delivery	259 per 1000	288 per 1000 (244 to 339)	RR 1.11 (0.94 to 1.31)	1486 (3 studies)	⊕⊕⊕⊖ Moderate[i]
Any maternal adverse event	514 per 1000	519 per 1000 (457 to 591)	RR 1.01 (0.89 to 1.15)	1458 (3 studies)	⊕⊕⊕⊕ High
Discontinuation of treatment because of adverse events	40 per 1000	56 per 1000 (36 to 86)	RR 1.38 (0.88 to 2.14)	1558 (4 studies)	⊕⊕⊕⊖ Moderate[i]
Preterm prelabor rupture of membranes	110 per 1000	112 per 1000 (84 to 148)	RR 1.02 (0.77 to 1.35)	1569 (4 studies)	⊕⊕⊕⊖ Moderate[i]
Preeclampsia	18 per 1000	27 per 1000 (11 to 66)	RR 1.48 (0.61 to 3.58)	875 (2 studies)	⊕⊕⊖⊖ Low[h]
Gestational hypertension	11 per 1000	14 per 1000 (4 to 44)	RR 1.19 (0.37 to 3.85)	875 (2 studies)	⊕⊕⊖⊖ Low[h]
Gestational diabetes mellitus	92 per 1000	103 per 1000 (69 to 154)	RR 1.12 (0.75 to 1.67)	875 (2 studies)	⊕⊕⊕⊖ Moderate[i]

Discussion

- Subgroup analyses showed that the intervention effects **significantly differed between small and large studies**
- All small studies were conducted at a single center in low/middle-income countries, and most were not registered
  - All were individually associated with significantly larger treatment effect estimates of vaginal progesterone in the subgroup analyses

Discussion



missing studies in areas of high statistical significance, → publication bias is a less likely cause of the funnel asymmetry

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- ➢ Publication bias
- ➢ Clinical heterogeneity
- ➢ Low-quality studies reporting inflated effect sizes

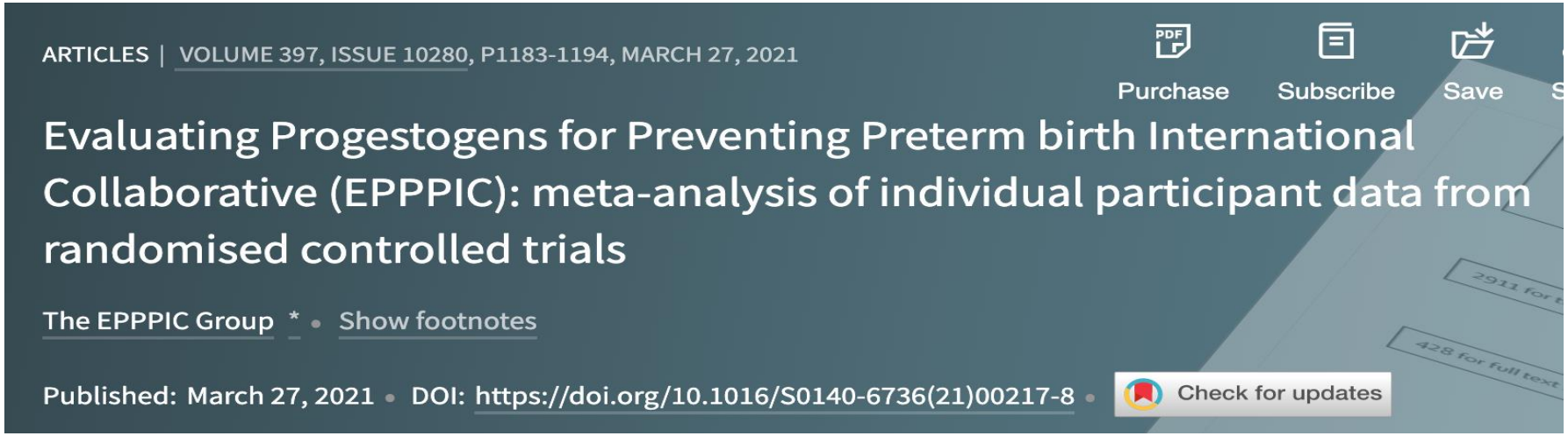
- Trials at high or unclear risk of bias significantly associated with exaggerated beneficial intervention effect

- Our systematic review: high risk of bias (N=4), some concerns of bias (N=2)

Summary

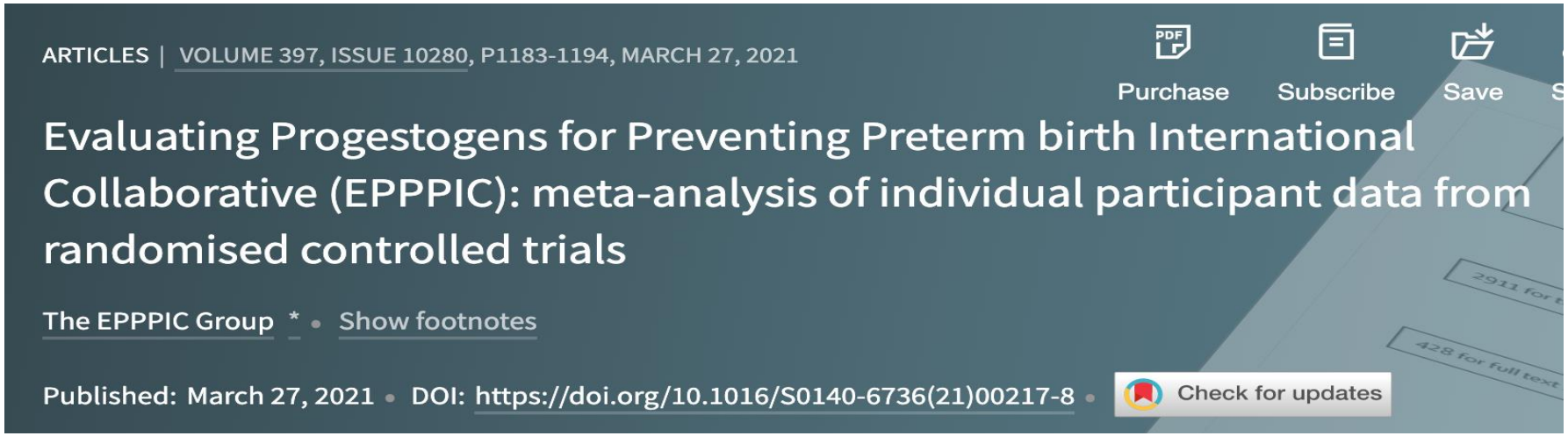
- **Small-study effects** in the meta-analyses of the effect of vaginal progesterone on preterm birth are mainly explained by the poor methodological quality of most small trials
- It has been claimed that in the presence of small-study effects restriction of analyses to high-quality, large trials might provide more valid estimates than overall analyses of trials

Comparison with existing literature



- Assess the efficacy of progestogens (vaginal progesterone, 17-OHPC and oral progesterone) to prevent preterm birth in asymptomatic high-risk women
- Vaginal progesterone was associated with a significant reduction in the risk of preterm birth <34 weeks of gestation in singleton pregnancies
- No significant differences in the risk of preterm birth <37 and <28 wks , perinatal death, serious neonatal complications, and maternal complications

Comparison with existing literature



- It grouped together women with a history of spontaneous preterm birth, short cervix, congenital uterine anomalies, uterine leiomyomas, pregnancy after assisted reproductive technologies, or a positive fetal fibronectin test combined with other clinical risk factors into a single category
- Did not address small-study effects nor did it perform sensitivity analyses

Comparison with existing literature

Research

Interventions to prevent spontaneous preterm birth in women with singleton pregnancy who are at high risk: systematic review and network meta-analysis

BMJ 2022 ; 376 doi: https://doi.org/10.1136/bmj-2021-064547 (Published 15 February 2022)
Cite this as: *BMJ* 2022;376:e064547

- Vaginal progesterone appeared to be the most effective in decreasing the risk of preterm birth
- Combined patients with several risk factors for preterm birth (history of spontaneous preterm birth, midtrimester loss, cervical insufficiency due to cervical surgery, uterine anomalies, and short cervix) into a single group
- Did not assess small-study effects

Strengths and limitations

Strengths	Limitations
• Rigorous methodology • Inclusion of a larger number • Thorough investigation of sources of heterogeneity and causes of small-study effects	• Various trials did not report results for several adverse maternal and perinatal outcomes • Unable to perform subgroup analyses according to the number of previous sPTB and the GA of previous sPTB • Only 2 trials reported data on the long-term effects of prenatal exposure to vaginal progesterone

Conclusions and implications

- There is **no convincing evidence** supporting vaginal progesterone use in women with a singleton gestation and a history of spontaneous preterm birth

- Should be offered to patients with a singleton gestation and a history of spontaneous preterm birth only if they are diagnosed with a sonographic short cervix (cervical length ≤25 mm) in the midtrimester

Thank you very much!