Progestogens in singleton gestations with preterm prelabor rupture of membranes: a systematic review and metaanalysis of randomized controlled trials

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OBJECTIVE DATA: Preterm prelabor rupture of membranes occurs in 3% of all pregnancies. Neonatal benefit is seen in uninfected women who do not deliver immediately after preterm prelabor rupture of membranes. The purpose of this study was to evaluate whether the administration of progestogens in singleton pregnancies prolongs pregnancy after preterm prelabor rupture of membranes.

STUDY: Searches were performed in MEDLINE, OVID, Scopus, EMBASE, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords and text words related to "progesterone," "progestogen," "prematurity," and "preterm premature rupture of membranes" from the inception of the databases until January 2018. We included all randomized controlled trials of singleton gestations after preterm prelabor rupture of membranes that were randomized to either progestogens or control (either placebo or no treatment). Exclusion criteria were trials that included women who had contraindications to expectant management after preterm prelabor rupture of membranes (ie, chorioamnionitis, severe preeclampsia, and nonreassuring fetal status) and trials on multiple gestations. We planned to include all progestogens, including but not limited to 17-α hydroxyprogesterone caproate, and natural progesterone.

STUDY APPRAISAL AND SYNTHESIS METHODS: The primary outcome was latency from randomization to delivery. Metaanalysis was performed with the use of the random effects model of DerSimonian and Laird to produce relative risk with 95% confidence interval. Analysis was performed for each mode of progestogen administration separately.

RESULTS: Six randomized controlled trials (n=545 participants) were included. Four of the included trials assessed the efficacy of 17-α hydroxyprogesterone caproate; 1 trial assessed rectal progestogen, and 1 trial had 3 arms that compared 17-α hydroxyprogesterone caproate, rectal progestogen, and placebo. The mean gestational age at time randomization was 26.9 weeks in the 17-α hydroxyprogesterone caproate group and 27.3 weeks in the control group. 17-α Hydroxyprogesterone caproate administration was not found to prolong the latency period between randomization and delivery (mean difference, 0.11 days; 95% confidence interval, −3.30 to 3.53). There were no differences in mean gestational age at delivery, mode of delivery, or maternal or neonatal outcomes between the 2 groups. Similarly, there was no difference in latency for those women who received rectal progesterone (mean difference, 4.00 days; 95% confidence interval, −0.72 to 8.72).

CONCLUSION: Progestogen administration does not prolong pregnancy in singleton gestations with preterm prelabor rupture of membranes.

Key words: 17-α hydroxyprogesterone caproate, latency, preterm prelabor rupture of membranes, progesterone, progestogens, PROM

Preterm prelabor rupture of membranes (PROM), defined as <37 weeks gestational age, occurs in approximately 3% of pregnancies and contributes to 40% of preterm births.[1] Neonatal outcomes may be improved with expectant management[2] in the absence of infection to facilitate delivery at a later gestational age. Yet, many women with preterm PROM often deliver within 1 week.[3] Antibiotics safely extend latency and decrease the risks of maternal and neonatal infection after preterm PROM.[4–6]

Progestogen administration has been studied in different populations[7–12] and has been shown to prolong a pregnancy in specific populations that are at risk of prematurity, including women with a previous spontaneous preterm birth[9,12] and those with a short cervical length.[8,11] These therapies generally are initiated in the second trimester when risk of preterm birth is identified by history or on ultrasound examination.

The underlying mechanisms of how progesterone prolongs pregnancy, although not completely understood, are thought to have to do with reduction in uterine contractility,[13] antimicrobial protein up-regulation,[14] immunosuppression, and inflammatory inhibition.[15] Specific to preterm PROM,

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AJOG at a Glance

Why was this study conducted?
The purpose of this study was to investigate whether progestogen administration after preterm prelabor rupture of membranes (PROM) increases latency of pregnancy.

Key findings
Progestogen administration did not prolong pregnancy in singleton gestations with preterm PROM.

What does this add to what is known?
This study clarifies the evidence that progestogen administration should not be commenced once a patient has experienced preterm PROM.

progesterone has been shown to inhibit the tumor necrosis factor and thrombin-induced mechanisms of membrane weakening.[16] Women with preterm PROM also have been shown to have lower levels of progesterone receptor membrane component 1, which is a protein that is mediated by progesterone to stabilize the membrane.[17] Although progestogens generally are initiated between 16 and 20 weeks gestation, initiation of progestogens up to 27 weeks[18] is associated with a decrease in the risk of preterm birth. Given this benefit in the late second trimester and the mechanisms of pregnancy prolongation in women with a risk of preterm birth, it is reasonable to suspect that the administration of progestogens would result in prolonging pregnancy after preterm PROM.

The aim of this systematic review and metaanalysis of randomized controlled trials was to evaluate the therapeutic benefit in prolonging pregnancy by the administration of progesterone therapy in singleton gestations after preterm PROM.

Materials and methods

Search strategy
The research protocol was designed a priori, defining methods for searching the literature, including and examining articles, and extracting and analyzing data. Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords and text words related to "progesterone," "prematurity," "progestogens," "membrane rupture," "17 hydroxyprogesterone," "vaginal progesterone," "tocolysis," and "preterm premature rupture or membranes" from inception of each database until March 2018 (Supplement 1). To locate additional publications, we reviewed bibliographies of identified studies and reviews articles. No restrictions for language or geographic location were applied.

Study selection
We included all randomized controlled trials of singleton gestations after preterm PROM that were randomized to progestogen vs control (either placebo or no treatment). All published randomized controlled trials on any type of progestogens after the diagnosis of preterm PROM at <37 weeks gestation were reviewed carefully. Exclusion criteria included women with short cervix, quasi-randomized trials (ie, trials in which allocation was done on the basis of a pseudo-random sequence [eg, odd/even hospital number or date of birth, alternation]) and trials that included women who had contraindications to expectant management after preterm PROM (ie, chorioamnionitis, severe preeclampsia, nonreassuring fetal status). Trials in women with multiple gestations were also excluded. We planned to include trials that evaluated any type of progestogens, including synthetic progestogens (eg, 17-α hydroxyprogesterone caproate [17-OHPC]), as well as natural progesterone. Any route of administration (eg, oral, intramuscular, rectal, vaginal) was included.

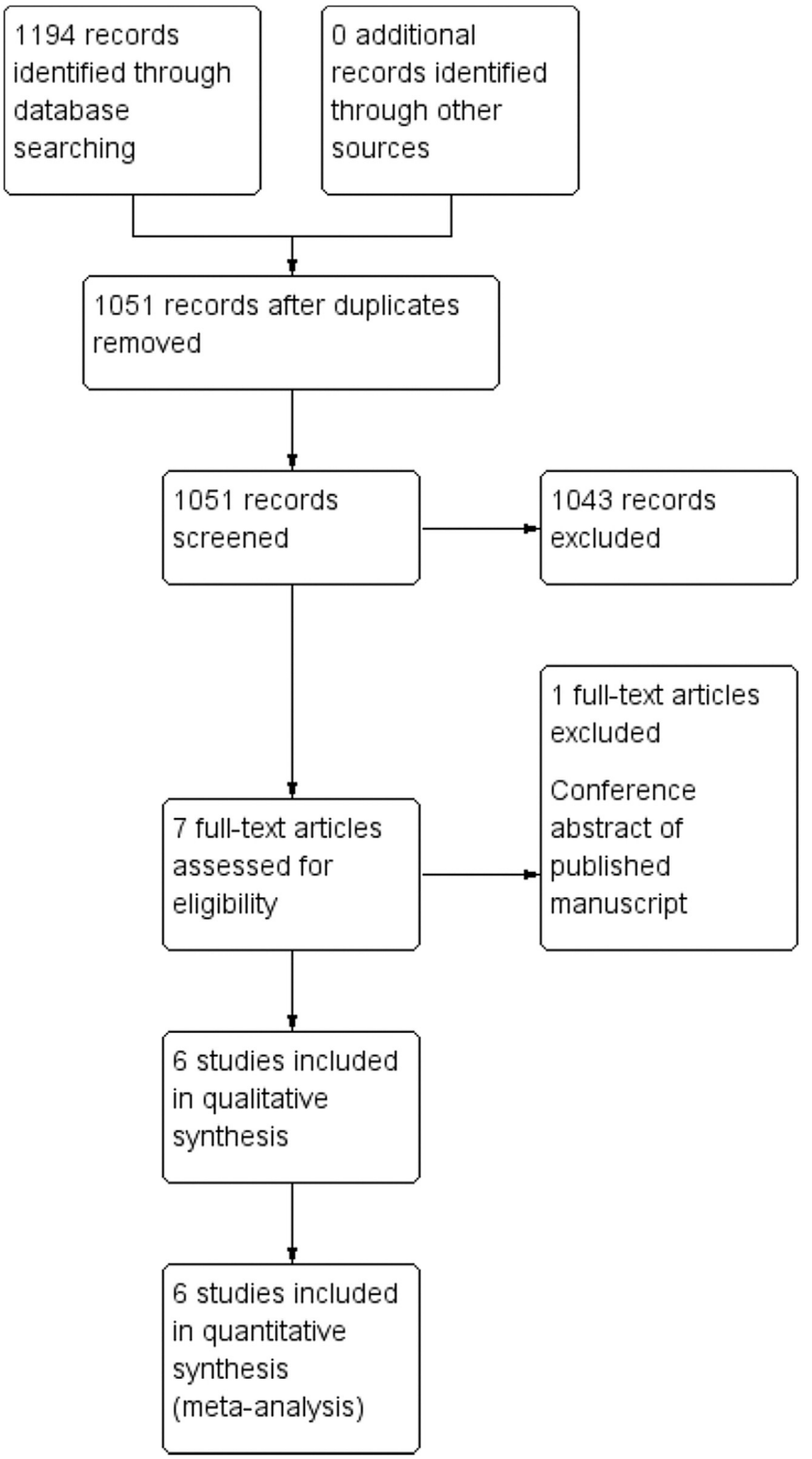
Before data extraction, the protocol was registered with PROSPERO (Registration number: CRD42017068717). The metaanalysis was reported according to the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[19]

Risk of bias
The risk of bias in each included study was assessed by 2 authors (J.Q-N. and P.P.) who used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[20] Seven domains related to risk of bias were assessed in each included trial because there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.[19]

Outcomes
Data abstraction was completed by 2 independent investigators (J.Q-N., G.S.). Each investigator independently abstracted data from each study and analyzed data separately.

The primary outcome was time from randomization until delivery (ie, latency). This outcome was chosen because neonatal outcomes after preterm PROM are correlated with gestational age at delivery.[21] Additionally, increased latency in a patient with preterm PROM improves survival[22] without increasing incidence of adverse neonatal outcomes.[2,23] The secondary outcomes were preterm birth at <37, <34, <32, and <28 weeks gestation, mean gestational age at delivery, mode of delivery, endometritis, chorioamnionitis, and neonatal outcomes that included birthweight, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, admission to neonatal intensive

FIGURE 1
PRISMA flow chart: Summary of evidence search and selection



Flow diagram of studies identified in the systematic review (Preferred Reporting Item for Systematic Reviews and Meta-analyses template).

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TABLE 1
Characteristics of the included trials

Variable	Study						
	United States: Briery et al, 2011[26]	United States: Combs et al, 2011[28]	United States: Combs et al, 2015[24]	Iran: Mirzaei and Moradi, 2015[27]	Iran: Abdali et al, 2017[29]	United States: Langen et al, 2018[25]	Total
Patients, n (n/N)	69 (33/36)	12 (4/8)	152 (74/78)	171 (57, 17-OHPC; 57, rectal progesterone; 57 control)	120 (60/60)	21 (10/11)	545 (178, 17-OPHC; 117, rectal; 250, control)
Progestogen treatment	17-OHPC	17-OHPC	17-OHPC	17-OHPC or rectal progesterone	Rectal progesterone suppositories	17-OHPC	—
Dose, route, frequency	250 mg intramuscularly, each week	250 mg intramuscularly, each week	250 mg intramuscularly, each week	17-OHPC: 250 mg intramuscularly, each week; rectal progesterone: 400 mg daily	Rectal: 400 mg progesterone suppository daily[a]	Not specified	
Control	Placebo (castor oil)	Placebo (castor oil)	Placebo (castor oil)	No treatment	Placebo (castor oil suppositories)	Vehicle without progestin component	—
Included range gestational age at randomization, wk[d]	20^0–30^0	23^0–31^6	23^0–30^6	24^0–34^0	26^0 – 32^0	24^0–32^0	—
Inclusion criteria	Singleton, vertex, diagnosis of preterm PROM	Singleton, >18 years old, diagnosis of preterm PROM	Singleton, mother ≥18 years, spontaneous preterm PROM	Singleton, live, healthy fetus, preterm PROM	Singleton, preterm PROM, desire of mother to participate in trial	Singleton, ≥18 years, confirmed preterm PROM	
Exclusion criteria	Intrauterine growth restriction <5 percentile, suspected placental abruption, confirmed placenta previa (if already taking 17-OHPC), chorioamnionitis, NRFHT, severe medical or obstetric disease (SCD with crisis, IDDM, severe preeclampsia)	Active preterm labor, suspected intraamniotic infection, NRFHT, cervical dilation ≥4 cm, fetal death, preeclampsia, active uterine bleeding, documented fetal lung maturity, known fetal abnormalities (major congenital malformation, viral infection, hydrops), allergy to 17-OHPC or castor oil, medical conditions that might adversely interact with 17-OHPC, [b]medical conditions treated with systemic steroid, cervical cerclage present at the time of PROM	Active preterm labor, suspected intraamniotic infection of inflammation, NRFHT, intrauterine fetal death, preeclampsia, active uterine bleeding, documented fetal lung maturity, other conditions that required delivery, fetal malformations of vital organs likely to require surgical repair, fetal viral infection, hydrops, cerclage present at time of preterm PROM, medical conditions treated with systemic steroids, contraindications to 17-OHPC[c]	Fetal anomaly, multiple gestations, chorioamnionitis, NRFHT, placenta abruption, placenta previa, intrauterine growth restriction, gestational diabetes mellitus, preeclampsia, severe preeclampsia	Fetal anomalies,[d] multiple gestation, preeclampsia, chronic hypertension, diabetes mellitus, gestational diabetes mellitus, abruption, cord prolapse, active labor, chorioamnionitis, patients presenting >36 hours after preterm PROM	Active infection, placental abruption, intrauterine fetal death, major congenital malformation, allergy to progestogen, those using progesterone at time of preterm PROM	

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(continued)

TABLE 1
Characteristics of the included trials *(continued)*

Variable	Study						Total
	United States: Briery et al, 2011[26]	United States: Combs et al, 2011[28]	United States: Combs et al, 2015[24]	Iran: Mirzaei and Moradi, 2015[27]	Iran: Abdali et al, 2017[29]	United States: Langen et al, 2018[25]	
Included patients already on vaginal progesterone or 17-OHPC at time of preterm PROM	No	NR	Yes[e]	NR	NR	No	
Type of latency antibiotics administered	48 hr: Ampicillin intravenously, erythromycin intravenously; 5 days: amoxicillin orally, erythromycin orally[f]	Varied by hospital site[g]	Varied by hospital site[g]	48 hr: Ampicillin intravenously; 5 days: amoxicillin orally, erythromycin orally[h]	48 hr: ampicillin IV 5 days: amoxicillin orally[i]	NR	—
Tocolysis	Not used	Permitted for first 48 hours at discretion of attending physician	Permitted for first 48 hr at discretion of attending physician	NR	Not used	Permitted for first 48 hours at discretion of attending physician	
Steroid administered	Betamethasone	Betamethasone or dexamethasone	Betamethasone	Betamethasone	Betamethasone	Betamethasone	
Magnesium sulfate for neuroprotection	NR	NR	Used per each hospital protocol	NR	Not given[i]	Administered if delivery was believed to be imminent, at discretion of treating physician	
Primary outcomes	Time from randomization to delivery	Continuation of pregnancy until 34^0 weeks or until documented fetal lung maturity from 32^0–33^6	Continuation of pregnancy until 34^0 weeks or until documented fetal lung maturity from 32^0–33^6	NR	NR	Achievement of 34 weeks gestation	—

Data are presented as total number (progesterone/control) as number (percentage) or as mean ± standard deviation.

17-OHPC, 17-α hydroxyprogesterone caproate; *IDDM*, insulin-dependant diabetes mellitus; *NR*, not reported; *NRFHT*, non-reassuring fetal heart tracing; *PROM*, prelabor rupture of membranes; *SCD*, sickle cell disease IDDM = insulin-dependant diabetes mellitus.

[a] Cyclogest 400 mg (L.D. Collins and Co, LTD, Middlesex, UK); [b] includes asthma on medications, renal insufficiency, seizure disorder, ischemic heart disease, cholecystitis, impaired liver function, or history of venous thromboembolism, breast cancer, or depression that requires hospitalization; [c] Includes allergy to drug or vehicle, current or past hormone-sensitive cancer, undiagnosed vaginal bleeding, cholestatic jaundice of pregnancy, active liver disease, uncontrolled hypertension; [d] Fetal anomalies include genetic testing, structural abnormalities discovered with sonography or trisomy screening test; [e] Study patients on vaginal progesterone before PROM were recommended to have it discontinued; a patient receiving 17-OHPC was eligible, if willing, to stop previous treatment and be assigned randomly for the trial; [f] Study followed *Eunice Kennedy Shriver* National Institute of Child Health and Human Development protocol; [g] All hospital sites had a "usual" antibiotic regimen similar to that of Mercer et al[5]; [h] Doses of antibiotics: 48 hours of intravenous ampicillin, 5 days of both amoxicillin 500 mg orally every 8 hours, erythromycin 400 mg orally every 6 hours; [i] Information obtained in communication with principle investigator.

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TABLE 2
Demographics at time of randomization for 17-α hydroxyprogesterone caproate vs control group

Demographic	Study					Total[a]
	Briery et al, 2011[26]	Combs et al, 2011[28]	Combs et al, 2015[24]	Mirzaei and Moradi, 2015[27]	Langen et al, 2018[25]	
Maternal age, y	24.0±6.4 vs 24.0±5.3	28±3 vs 33±6	29.3±5.8 vs 29.5±5.7	NR	31.7±6.3 vs 31.7±6.3[b]	28.3 vs 29.6
Maternal prepregnancy weight, lb	NR	157±35 vs 162±37	164±50 vs 162 ±45	NR	NR	160.5 vs 162
Mean gestational age at membrane rupture, wk	NR	25±7 vs 26±4	25.9± 3.0 vs 26.6±2.9	30.0±2.19 vs 30.2±2.47	NR	27.0 vs 27.6
Mean gestational age at randomization, wk	26.0 ± 6.5 vs 27.8 ±2.7	28±3 vs 27±3	26.7± 2.5 vs 27.1±2.4	NR	NR	26.9 vs 27.3
Nulliparous, n	16/33 (48.5%) vs 14/36 (38.9%)	3/4 (75.0%) vs 5/8 (62.5%)	29/74 (39.1%) vs 27/78 (34.6%)	NR	NR	48/111 (43.2) vs 46/122 (37.7)
Previous preterm birth, n/N (%)	NR	0/4 (0%) vs 0/8 (0%)	13/74 (17.6%) vs 18/78 (23.1%)	NR	3/10 (33.3%) vs 0/11 (0%)	16/88 (18.2) vs 18/97 (18.6)
Participants on progesterone at time of preterm PROM, n/N (%)	0/33 (0%) vs 0/36 (0%)	NR	3/74 (4.1%) vs 5/78 (6.4%)	NR	0/10 (0%) vs 0/11 (0%)	3/117 (2.6) vs 5/125 (4.0)

Data are presented number in the 17-α hydroxyprogesterone caproate group vs control or as mean ± standard deviation.

NR, not reported.

[a] All demographic total were not significantly different between experimental and control groups; [b] Mean maternal age is reported with standard error of the mean.

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care unit, neonatal sepsis, and neonatal death, which was defined as death of a liveborn baby within the first 28 days of life. Outcomes were assessed separately by type of progestogen and route of administration.

Statistical analysis

The data analysis was completed independently by authors (J.Q-N., G.S.) with the use of Review Manager (version 5.3; The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved with discussion and involvement of a third party (V.B.).

Data from each eligible study were extracted without modification of original data. A 2×2 table was assessed for the relative risk; for continuous outcomes, means±standard deviation were extracted and imported into Review Manager.

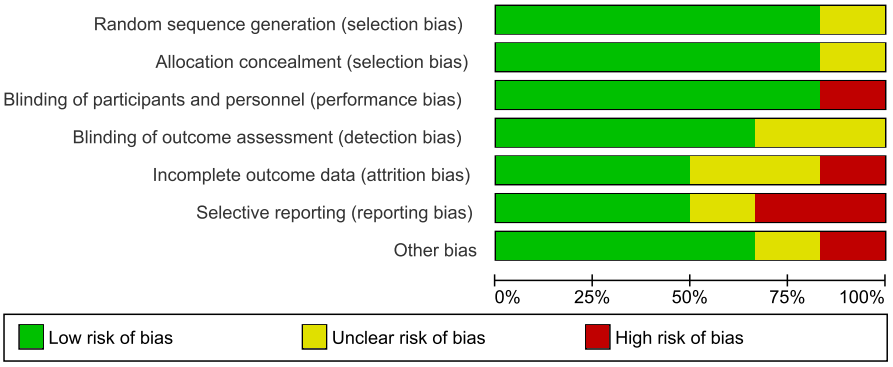
Metaanalysis was performed with the use of the random effects model of DerSimonian and Laird to produce summary treatment effects in terms of relative risk or mean difference (MD) with 95% confidence interval (CI). Heterogeneity was measured using I-squared (Higgins I^2). Potential publication biases were assessed statistically with Begg's and Egger's tests. A probability value $<.05$ was considered statistically significant.

Results

Study selection and study characteristics

Figure 1 shows the flow diagram of study retrieval in the systematic review. No trials were excluded for quasi-randomization or other methodologic exclusions. Six trials were included in this metaanalysis with a total of 525 participants (Table 1).[24-28] Patients were assigned randomly between 20+0 and 34+0 weeks. In 4 trials,[24-26,28] the intervention was 17-OHPC administered weekly. In 1 trial,[27] the patients received 17-OHPC rectal progesterone daily. One additional trial[29] assigned patients randomly to rectal progestogen daily compared with placebo.

FIGURE 2
Assessment of risk of bias



Risk of bias graph about each risk of bias item presented as percentages across all included studies.

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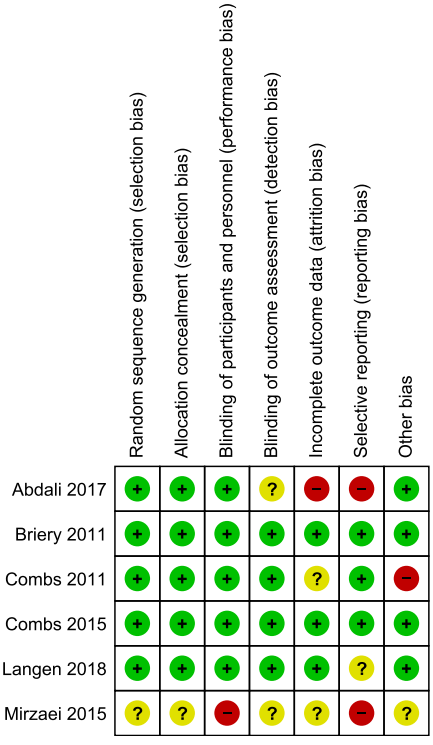
In 5 trials,[24-26,28,29] the patients received placebo as control. One trial included women who were already receiving progesterone therapy before preterm PROM, but the proportion of patients already on progesterone was small (Table 2). The experimental and control groups were similar in terms of maternal demographics (Table 2).

FIGURE 3
Assessment of risk of bias



Summary of the risk of bias for each trial: the plus sign indicates low risk of bias; the minus sign indicates high risk of bias; the question mark indicates unclear risk of bias.

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All trials administered steroids for fetal maturity, and 5 of the studies noted latency antibiotic use,[24-26,28,29] although not all studies detailed their antibiotic regimen (Table 1). The mean gestational age at time randomization was 26.9 weeks in the 17-OHPC group and 27.3 weeks in the control group. The risk of bias of the included trials that examined 17-OHPC was judged to be low overall. The risk of bias for the 2 trials that examined rectal progesterone was judged as high.[27,29] Four of the 6 trials had low risk of bias in random sequence generation and allocation concealment (Figures 2 and 3). Statistical heterogeneity within the studies was moderate with I^2=36% for the primary outcome.

Synthesis of results

There was no difference in the primary outcome (Table 3; Figure 4), which was latency from the time from randomization to delivery for those patients who received 17-OHPC (MD, 0.11 days; 95% CI, −3.30 to 3.53). The primary outcome was not significantly altered in sensitivity analysis that included only high-quality trials (MD, −1.60 days; 95% CI, −4.66 to 1.46).[24-26,28] There were no significant differences seen in secondary outcomes in the 17-OHPC analysis, which included gestational age at delivery, mode of delivery, chorioamnionitis, endometritis, or neonatal outcomes that included birthweight or adverse neonatal outcomes. The trials did not report on the incidences of preterm birth at the prespecified intervals of <37, <34, <32, and <28 weeks gestation. For the rectal progesterone analysis (Supplemental Tables 1 and 2), there was no difference in the primary outcome (MD, 4.00 days; 95% CI, −0.72 to 8.72). The neonatal intensive care unit length of stay was shorter in the rectal progesterone group (MD, −3.70 days; 95% CI, −4.25 to −3.15), and the birthweight was higher (MD, 121.27 grams; 95% CI, 96.28−146.25).

Comment

Main findings

When compared with placebo or no treatment, progestogens (17-OHPC and rectal progestin) did not alter the latency period from randomization to delivery in singleton gestations with preterm PROM. Additionally, there was no difference seen in gestational age at delivery or in mode of delivery between groups. No significant differences were noted in maternal or neonatal outcomes. The differences seen in the rectal progesterone analysis are to be interpreted with caution because these trials were judged to be high risk of bias. The quality of included trials that examined 17-OHPC was generally high.

Strengths and limitations

This is the first metaanalysis, to our knowledge, to examine progestogen administration after preterm PROM. It follows the Preferred Reporting Item for Systematic Reviews and Metaanalyses guidelines and includes trials without restriction to publication date or language. The limitations are inherent to those limitations of a metaanalysis and the included trials. Two trials had a high or unclear risk of bias in all areas of assessment, and 1 author[27] did not respond to our inquiries regarding their trials. No trials that evaluated the efficacy of vaginal progesterone in women with preterm PROM were found in our

TABLE 3
Primary and secondary outcomes for 17-α hydroxyprogesterone caproate and control groups

Outcome	Study					Total	I^2, %	Relative risk or mean difference (95% confidence interval)
	Briery et al, 2011[26]	Combs et al, 2011[28]	Combs et al, 2015[24]	Mirzaei and Moradi, 2015[27]	Langen et al, 2018[25]			
Latency from randomization to delivery, d	11.2±7.3 vs 14.5±10.0	11.3±7.2 vs 9.1±11.0[a]	17.1±16.1 vs 17.0±15.8	15.2±16.0 vs 11.5±10.1[b]	NR	13.7 vs 13.0	36	0.11 (−3.30− 3.53)
Gestational age at delivery, wk	27.3±6.9 vs 29.5±2.5	30±4 vs 28±3	29.2±2.7 vs 29.5±2.7	32.2±2.7 vs 30.9 ±5.2	NR	29.7 vs 29.5	57	0.02 (−1.40− 1.44)
Spontaneous vaginal delivery, n/N (%)	24/33 (72.7) vs 24/36 (66.7)	1/4 (25) vs 3/8 (37.5)	29/73 (39.7) vs 43/77 (55.8)	35/57 (61.4) vs 32/57 (56.1)	NR	89/167 (53.3) vs 102/178 (57.3)	34	0.95 (0.75−1.22)
Cesarean delivery, n/N (%)	9/33 (27.3) vs 12/36 (33.3)	3/4 (75) vs 5/8 (62.5)	44/73 (60.3) vs 34/77 (44.2)	22/57 (38.6) vs 25/57 (43.9)	NR	78/167 (46.7) vs 76/178 (42.7)	14	1.12 (0.86−1.45)
Chorioamnionitis, n/N (%)	4/33 (12.1) vs 8/36 (22.2)	1/4 (25) vs 1/8 (12.5)	12/73 (16.4) vs 17/77 (22.1)	15/57 (26.3) vs 13/57 (22.5)	6/10 (60) vs 2/11 (18.2)	38/177 (21.5) vs 41/189 (21.7)	26	1.02 (0.61− 1.69)
Endometritis, n/N (%)	NR	NR	4/73 (5.5) vs 3/77 (3.9)	NR	3/10 (30) vs 2/11 (18.2)	7/83 (8.4) vs 5/88 (5.7)	0	1.51 (0.52−4.42)
Birthweight, g	1216±512 vs 1396±446	1328±547 vs 1288±525	1352±501 vs 1405±470	1985±75.8 vs 1793±73.9	NR	1470.2 vs 1470.5	83	9.12 (−207.89− 226.13)
Respiratory distress syndrome, n/N (%)	22/33 (66.7) vs 28/36 (77.8)	3/4 (75) vs 7/8 (87.5)	44/73 (60.3) vs 46/77 (59.7)	NR	7/10 (70) vs 10/11 (90.9)	76/120 (63.3) vs 91/132 (68.9)	0	0.91 (0.76− 1.08)
Intraventricular hemorrhage (grade 3 or 4), n/N (%)	NR	2/4 (50) vs 0/8 (0)	1/73 (1.4) vs 1/77 (1.3)	NR	1/10 (10) vs 2/11 (18.2)	4/87 (4.6) vs 3/96 (3.1)	17	1.48 (0.29− 7.55)
Periventricular leukomalacia, n/N (%)	NR	0/4 (0) vs 0/8 (0)	1/73 (1.4) vs 2/77 (2.6)	NR	NR	1/77 (1.3) vs 2/85 (2.4)	NA	0.53 (0.05− 5.69)
Neonatal sepsis, n/N (%)	6/33 (18.2) vs 6/36 (16.7)	0/4 (0) vs 0/8 (0)	3/73 (4.1) vs 1/77 (1.3)	14/57 (24.6) vs 15/57 (26.3)	4/10 (40.0) vs 1/11 (9.1)	27/177 (15.3) vs 23/189 (12.2)	0	1.14 (0.69− 1.88)
Necrotizing enterocolitis, n/N (%)	2/33 (6.1) vs 1/36 (2.8)	1/4 (25) vs 0/8 (0)	3/73 (4.1) vs 2/77 (2.6)	NR	2/10 (20) vs 1/11 (9.1)	8/120 (6.7) vs 4/132 (3.0)	0	2.18 (0.72− 6.60)
Neonatal intensive care unit stay, d	36.4 ±31.3 vs 37.0±30.3	42±23 vs 56±48	NR	NR	NR	39.2 vs 46.5	0	−2.16 (−15.84−11.53)
Intrauterine fetal death, n/N (%)	1/33 (3.0) vs 1/36 (2.8)	0/4 (0) vs 0/8 (0)	0/73 (0) vs 0/77 (0)	0/57 (0) vs 3/57 (5.3)	0/10 (0) vs 0/11 (0)	1/177 (0.6) vs 4/189 (2.1)	3	0.42 (0.06− 3.23)
Neonatal death, n/N (%)	3/33 (9.1) vs 2/36 (5.6)	1/4 (25) vs 1/8 (12.5)	3/73 (4.1) vs 2/77 (2.6)	7/57 (12.3) vs 5/57 (8.8)	1/10 (10) vs 0/11 (0)	15/177 (8.5) vs 10/189 (5.3)	0	1.60 (0.76− 3.40)

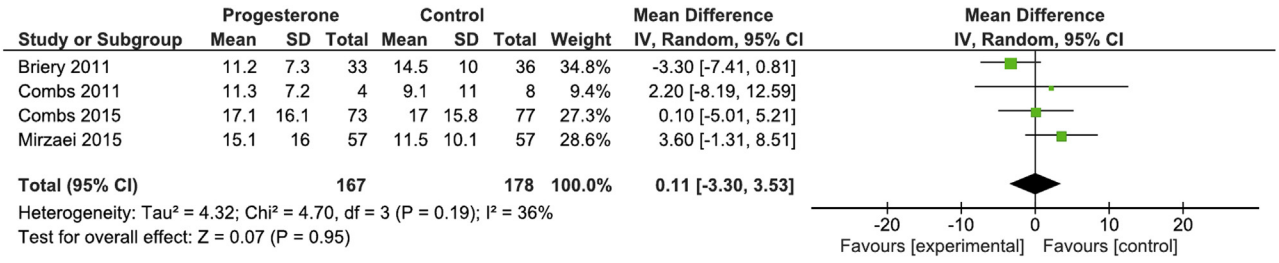
Data are presented as number of 17-α hydroxyprogesterone caproate/control (percent) as number (percentage) or as mean ± standard deviation.

NA, not applicable; *NR*, not reported.

[a] Latency originally reported in weeks; data was recalculated from published data; [b] Variable not specified if time was from rupture until delivery or time from randomization to delivery.

Quist-Nelson. Progestogens after preterm prelabor rupture of membranes. Am J Obstet Gynecol 2018.

FIGURE 4
Forest plot for primary outcome



Latency from randomization to delivery after preterm prelabor rupture of membranes.

Quist-Nelson. Progestogens after preterm prelabor rupture of membranes. Am J Obstet Gynecol 2018.

systematic review. Additionally, the details of magnesium administration, which could contribute to confounding for secondary outcomes, were not reported in all trials.

Because antibiotics previously have demonstrated benefit to prolonging latency after preterm PROM,[4,5] the varying antibiotic regimens could contribute to confounding from the effect of the progestogens. For example, 1 trial that showed an improved latency with progestogen administration did not comment on antibiotic use. Notably, the trials that were judged of high quality all used clinically comparable antibiotic regimens (Table 1); when an analysis was performed with the use of only these trials, the primary outcome remained nonsignificant.

Comparison with existing literature and implication

Our results reflect the results of each of the included individual studies that was judged to be of low risk of bias, because they did not find a difference in pregnancy latency after preterm PROM when 17-OHPC was administered. Our metaanalysis reflects the results of these trials for both our primary and secondary outcomes. Two trials did note a longer latency for patients who received progestogens. Both these trials were judged to be high risk of bias. One trial obtained these results by combining 17-OHPC and rectal progestin groups compared with control group. Our metaanalysis, however, analyzed 17-OHPC separately from rectal progesterone, and showed no significant benefit in the latency period.

Preterm PROM is a frequently encountered obstetric diagnosis, with improved neonatal outcomes when an uninfected mother is able to continue her pregnancy for a longer duration to reach a more advanced gestational age.[2,21,22] Thus, data regarding how to safely prolong pregnancy is pertinent for appropriate treatment of this population. The results of our metaanalysis suggest that progestogen administration does not alter the course of a patient once she has experienced preterm PROM. These results should encourage continued research into other interventions that could benefit this population. Our data also suggest that progestogens have different efficacy in different populations.[7–11]

In summary, the use of progestogens after preterm PROM does not prolong pregnancy compared with placebo or no treatment. ■

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Supplement 1

Search strategy used with PubMed

(PPROM OR (preterm premature rupture of membranes) OR PROM OR (premature rupture of membranes) OR (premature rupture of membrane) OR (membrane rupture) OR (prematurity)) AND (progesterone OR (17-hydroxyprogesterone caproate) OR (progestogen)) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]))

SUPPLEMENTAL TABLE 1

Demographics at time of randomization for rectal progesterone compared with control subjects

Demographic	Study	
	Mirzaei F, Moradi P, 2015[27] (n = 171)	Abdali et al, 2017[29] (n = 120)
Maternal age, y	NR	29.56±5.66 vs 29.88±5.57
Maternal weight, lb	NR	NR
Mean gestational age at membrane rupture, wk	29.75±2.79 vs 30.24±2.47	203.05±13.22 vs 203.32±15.48[a]
Mean gestational age at randomization, wk	NR	1/60 vs 0/60
Nulliparous participants	NR	NR
Previous preterm birth	NR	NR
Participants on progesterone at time of preterm PROM	NR	NR

Data are given as the mean ±standard deviation in the rectal progesterone vs the control group or as data presented as the numbers in the rectal progesterone group/control group.

NR, not reported; *PROM*, prelabor rupture of membranes.

[a] Gestational age reported in days.

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SUPPLEMENTAL TABLE 2

Primary and secondary outcomes for rectal progesterone compared with control

Variable	Study		I^2, %	Relative risk or mean difference (95% confidence interval)
	Mirzaei F, Moradi P, 2015[27] (n=171)	Abdali et al, 2017[29] (n=120)		
Latency from randomization to delivery, d	15.5±15.1 vs 11.5±10.1[a]	NR[b]	—	4.00 (−0.72−8.72)
Gestational age at delivery, wk	32.1±2.3 vs 30.9 ±5.2	212.10±12.29 vs 209.67±11.96[c]	—	1.20 (−0.28−2.68)[d]
Spontaneous vaginal delivery, n/N (%)	33/57 (57.9) vs 32/57 (56.1)	34/60 (56.7) vs 25/60 (41.7)	19	1.16 (0.89−1.53)
Cesarean delivery, n/N (%)	24/57 (42.1) vs 25/57 (43.9)	NR	—	1.08 (0.72−1.61)
Chorioamnionitis, n/N (%)	14/57 (24.6) vs 13/57 (22.5)	0/60 (0) vs 0/60 (0)	—	1.10 (0.46− 2.61)
Endometritis	NR	NR	—	
Birthweight, g	1913±64.2 vs 1793±73.9	1609.9±417.3 vs 1452.0±342.4	0	121.27 (96.28−146.25)
Respiratory distress syndrome, n/N (%)	NR	53/60 (88.3) vs 48/60 (80.0)	—	1.89 (0.69−5.20)
Intraventricular hemorrhage (grade 3 or 4)	NR	NR	—	
Periventricular leukomalacia	NR	NR	—	
Neonatal sepsis, n/N (%)	15/57 (26.3) vs 15/57 (26.3)	0/60 (0) vs 1/60 (1.75)	0	0.96 (0.53−1.76)
Necrotizing enterocolitis, n/N (%)	NR	0/60 (0) vs 0/60 (0)	—	
Neonatal intensive care unit stay, d	NR	10.53±1.10 vs 14.23±1.89	—	−3.70 (−4.25− −3.15)
Intrauterine fetal death, n/N (%)	2/57 (3.5) vs 3/57 (5.3)	NR	—	0.67 (0.12−3.84)
Neonatal death (within 28 days), n/N (%)	4/57 (5.0) vs 5/57 (8.8)	NR	—	0.80 (0.23−2.83)

Data are presented as number in rectal progesterone/control groups (percent) as number (percentage) or as mean ± standard deviation.

NR, not reported.

[a] Variable not specified whether date are time from rupture until delivery or time from randomization to delivery; [b] Latency reported as mean without standard deviation; [c] Reported in days, data per report in communication with principle investigator; [d] Calculated from Mirzaei and Moradi only because the gestational age for Abdali et al was provided in days.

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