17-alpha-hydroxyprogesterone caproate for maintenance tocolysis: a systematic review and metaanalysis of randomized trials

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We sought to evaluate the efficacy of maintenance tocolysis with 17-alpha-hydroxyprogesterone caproate (17P) compared to control (either placebo or no treatment) in singleton gestations with arrested preterm labor (PTL), in a metaanalysis of randomized trials. Electronic databases (MEDLINE, OVID, Scopus, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials) were searched from 1966 through July 2014. Key words included "progesterone," "tocolysis," "preterm labor," and "17-alpha-hydroxyprogesterone caproate." We performed a metaanalysis of randomized trials of singleton gestations with arrested PTL and treated with maintenance tocolysis with either 17P or control. Primary outcome was preterm birth (PTB) <37 weeks. This metaanalysis was performed following the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) statement. The protocol was registered with PROSPERO (registration no: CRD42014013473). Five randomized trials met inclusion criteria, including 426 women. Women with a singleton gestation who received 17P maintenance tocolysis for arrested PTL had a similar rate of PTB <37 weeks (42% vs 51%; relative risk [RR], 0.78; 95% confidence intervals [CI], 0.50—1.22) and PTB <34 weeks (25% vs 34%; RR, 0.60; 95% CI, 0.28—1.12) compared to controls. Women who received 17P had significantly later gestational age at delivery (mean difference, 2.28 weeks; 95% CI, 1.46—13.51), longer latency (mean difference, 8.36 days; 95% CI, 3.20—13.51), and higher birthweight (mean difference, 224.30 g; 95% CI, 70.81—377.74) as compared to controls. Other secondary outcomes including incidences of recurrent PTL, neonatal death, admission to neonatal intensive care unit, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal sepsis were similar in both groups. Maintenance tocolysis with 17P after arrested PTL is not associated with prevention of PTB compared to placebo or no treatment in a metaanalysis of the available randomized trials. As 17P for maintenance tocolysis is associated with a significant prolongation of pregnancy, and significantly higher birthweight, further research is suggested.

Key words: metaanalysis, preterm labor, progesterone, tocolysis

Preterm birth (PTB), defined as birth <37 weeks, is responsible for most neonatal morbidity and mortality in the United States,[1-3] and 35% of all US health care spending on infants.[4] Globally, about 28% of the 4 million annual neonatal deaths are directly attributable to PTB.[5]

Preterm labor (PTL) is the final pathway for about half of all PTB. Tocolytic agents include a wide range of drugs that can slow or stop labor contractions delaying births caused by PTL. Primary tocolysis is tocolysis given on initial presentation of women with PTL. In most of these women, PTL stops. Their risk of PTB remains high and so some have advocated use of maintenance tocolysis, ie, tocolysis after arrested PTL. So far, no maintenance tocolytic agent has been shown to be beneficial in preventing PTB. Recently, progesterone has been used successfully for prevention of PTB, in particular in asymptomatic women with either short cervical length[6,7] or prior spontaneous PTB.[8] The efficacy of progesterone in preventing PTB in symptomatic women with arrested PTL is not clear.

The objective of this metaanalysis was to evaluate the efficacy of maintenance tocolysis with 17-alpha-hydroxyprogesterone caproate (17P) compared to placebo or no treatment in singleton gestations with arrested PTL in a metaanalysis of randomized trials.

Materials and methods

Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials with the use of a combination of key words and text words related to "progesterone," "tocolysis," "preterm labor," and "17-alpha-hydroxyprogesterone caproate" from 1966 through July 2014. To locate additional publications, we reviewed proceedings of international society meetings on PTB and tocolysis and bibliographies of identified studies and reviews articles. No restrictions for language or geographic location were applied.

We included randomized trials of singleton gestations that had arrested PTL and then were randomized to maintenance tocolysis treatment with either 17P or control (either placebo or no treatment). All published randomized

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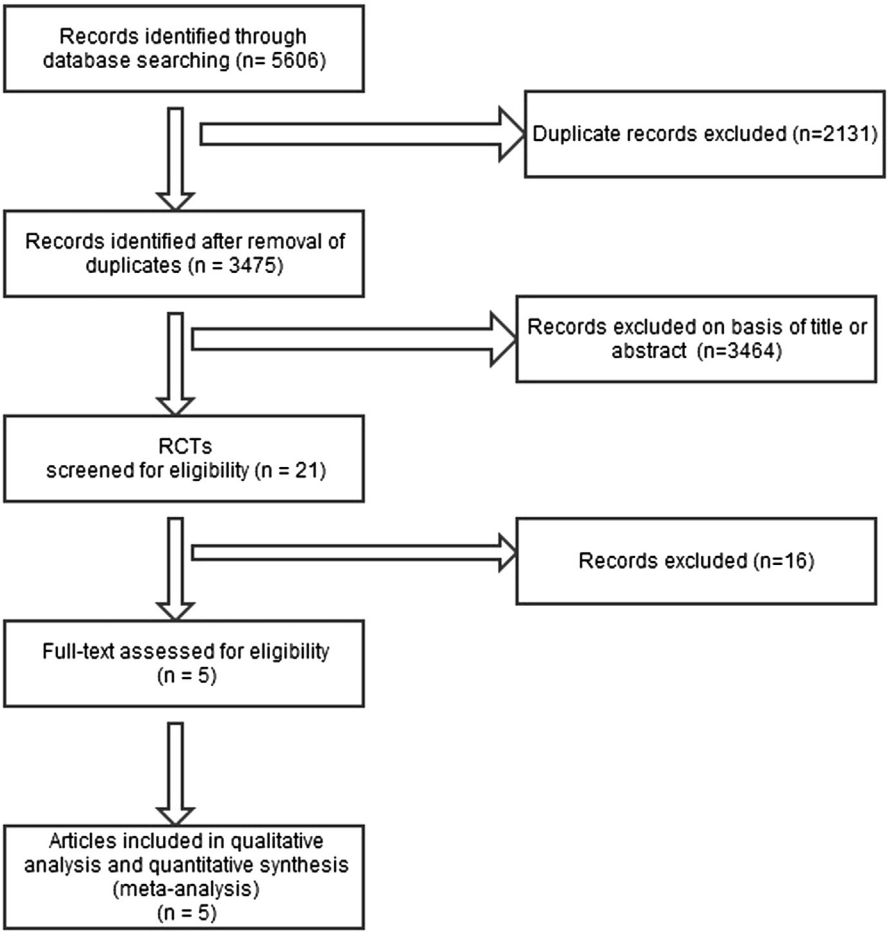
studies on progesterone tocolysis were carefully reviewed. Exclusion criteria included quasirandomized trials, maintenance tocolysis in women with preterm premature rupture of membrane (PPROM) and maintenance tocolysis with vaginal progesterone.

Data abstraction was completed by 3 independent investigators (G.S., A.S., V.B.). Each investigator independently abstracted data from each study and analyzed data separately. Differences were reviewed, and further resolved by common review of the entire data set. Data abstracted included number of study patients, number of patients in intervention and control groups, dosage of 17P, route and frequency of administration of 17P, gestational age at randomization, gestational age at delivery, interval from randomization to delivery (ie, latency), PTB <37 weeks, PTB <34 weeks, spontaneous PTB <37 weeks, spontaneous PTB <34 weeks, birthweight, neonatal death, admission to neonatal intensive care unit (NICU), neonatal respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and neonatal sepsis. For studies that did not stratify data, composite data were extracted. When possible, authors of included trials were contacted for missing data.

The risk of bias in each included study was assessed by using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[9] Seven domains related to risk of bias were assessed in each included trial since 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, high, or unclear risk of bias.[9]

The primary outcome included PTB <37 weeks. Secondary outcomes included PTB <34 weeks, gestational of delivery, latency, spontaneous PTB <37 weeks, spontaneous PTB <34 weeks, birthweight, neonatal death, NICU, RDS, BPD, IVH, NEC, and neonatal sepsis.

FIGURE 1
Flow of information through different phases of review



RCT, randomized controlled trial.

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The data analysis was completed independently by authors (G.S., A.S., V.B.) using Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved with review of the entire data set and independent analysis. Statistical heterogeneity between studies was assessed using the Cochrane Q statistic and Higgins I^2 statistics. In case of statistical significant heterogeneity (P value of the Cochrane Q statistic < .1) the random effects model of DerSimonian and Laird was used to obtain the pooled relative risk (RR) estimate, otherwise a fixed effect models was planned. The summary measures were reported as RR, with 95% confidence interval (CI). P value less than .05 was considered statistically significant.

Before data extraction, the protocol was registered with PROSPERO (registration number: CRD42014013473).[10] The metaanalysis was performed following the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) statement.[11]

This study had no funding source.

Results

Twenty-one trials on progesterone as tocolytic were identified.[8,12-31] Eleven randomized trials evaluating the effect of progesterone in maintenance therapy during PTL were identified.[21-31] Five

TABLE 1
Descriptive data for each trial

Variable	Facchinetti et al,[28] 2007	Rozenberg et al,[29] 2012	Regmi et al,[30] 2012	Lotfalizadeh et al,[27] 2013	Briery et al,[31] 2014	Total
Study location	Italy	France	Nepal	Iran	United States	—
No. of patients, n (intervention vs control)	60 (30 vs 30)	188 (94 vs 94)	60 (29 vs 31)	73 (37 vs 36)	45 (22 vs 23)	426 (212 vs 214)
Dose, mg	341	500	250	250	250	—
Frequency of 17P treatment	Twice weekly	Twice weekly	Weekly	Weekly	Weekly	—
Control	No treatment	No treatment	No treatment	No treatment	Placebo	—
Primary tocolytic agent	Atosiban	Nifedipine, nicardipine, or salbutamol	Nifedipine	Magnesium sulfate or nifedipine	Magnesium sulfate, calcium channel blockers, or antiprostaglandin drugs	—
Range GA at randomization, wk	From 25^{+0} to 33^{+6}	From 24^{+0} to 31^{+6}	From 28^{+0} to 34^{+6}	From 26^{+0} to 36^{+0}	From 20^{+0} to 30^{+6}	—
Mean GA at randomization, wk	30 vs 30	28 vs 28[a]	33 vs 33	34 vs 33	29 vs 27	Mean difference 0.50 wk (95% CI, 0.24−1.25)[a]
Study primary outcomes	CL shortening at discharge, and at day 7 and 21 of discharge	Latency period	Latency period and rate of recurrent PTL within 48 h	Rate of recurrent PTL	Preterm delivery <37 wk	—

Data are presented as 17P vs placebo.

CI, confidence interval; *CL*, cervical length; *GA*, gestational age; *PTL*, preterm labor; *17P*, 17-alpha-hydroxyprogesterone caproate.

[a] GA at randomization of Rozenberg et al[29] in 2012 was not included in analysis because SD was not reported.

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were excluded because vaginal progesterone was evaluated[21,23-26]; 1 was excluded because women with preterm rupture of the membranes were evaluated.[22] Five trials that met inclusion criteria for this metaanalysis were analyzed.[27-31] No similar systematic review was found. Figure 1 shows the flow diagram of information through the different phases of the review.

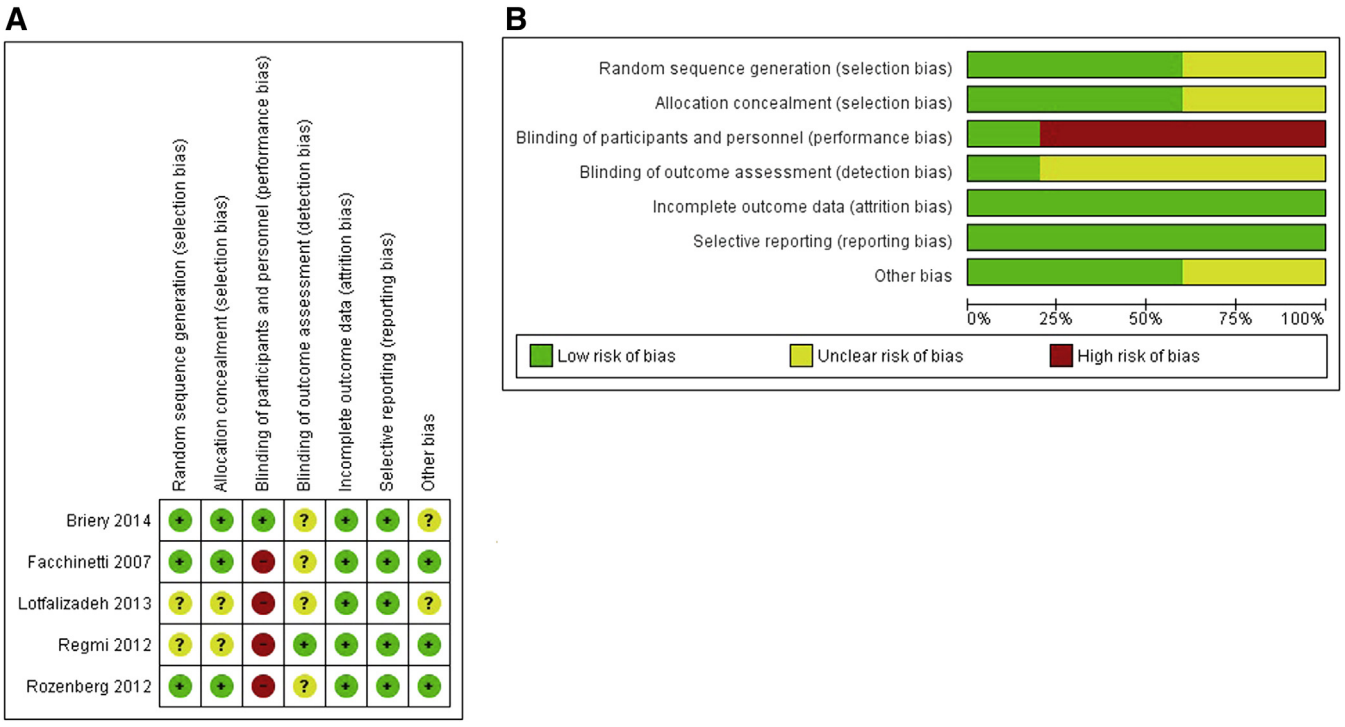
Descriptive data for each trial are presented in Table 1. A total of 426 singleton gestations with arrested PTL were included. Most studies used 17P 250 mg intramuscularly weekly. Four of 5 used no treatment as control.[31]

The quality of randomized controlled trials included in our metaanalysis was assessed by the Cochrane Collaboration's tool[9] (Figure 2). All studies had low risk of bias in incomplete outcome data and selective reporting. One study was double blind.[31] Figure 3 shows funnel plot for assessing publication bias for PTB <37 weeks; the symmetric plot suggested no publication bias (Figure 3).

Three studies defined PTL as the presence of at least 6 contractions in 30 minutes accompany to cervical changes[28,30,31]; one defined it as the presence of at least 4 contractions per minute, accompanied by 2-cm dilatation;[27] the other one defined it as painful uterine contractions at least 2 per 10 minutes accompanied by cervical length <25 mm.[29] Regarding the tocolytic regimens that were used for patients in the included studies, 1 study used magnesium sulfate or nifedipine[27]; 1 used magnesium sulfate, calcium channel blockers, or antiprostaglandin drugs[31]; 1 used atosiban[28]; whereas the other 2 used nifedipine or other calcium channel blockers[29,30] (Table 1).

Of the 426 singleton gestations included in the 5 trials,[27-31] 212 (49.8%) were randomized to 17P, while 214 (50.2%) to control. Women with a singleton gestation who received 17P maintenance tocolysis for arrested PTL had a similar rate of PTB <37 weeks (42% vs 51%; RR, 0.78; 95% CI, 0.50−1.22) (Table 2 and Figure 4) and PTB <34 weeks (25% vs 34%; RR, 0.60;

FIGURE 2
Assessment of risk of bias



A, Summary of risk of bias for each trial: low (+), high (−), or unclear (?).[9] **B**, Each risk of bias item presented as percentages across all included studies.

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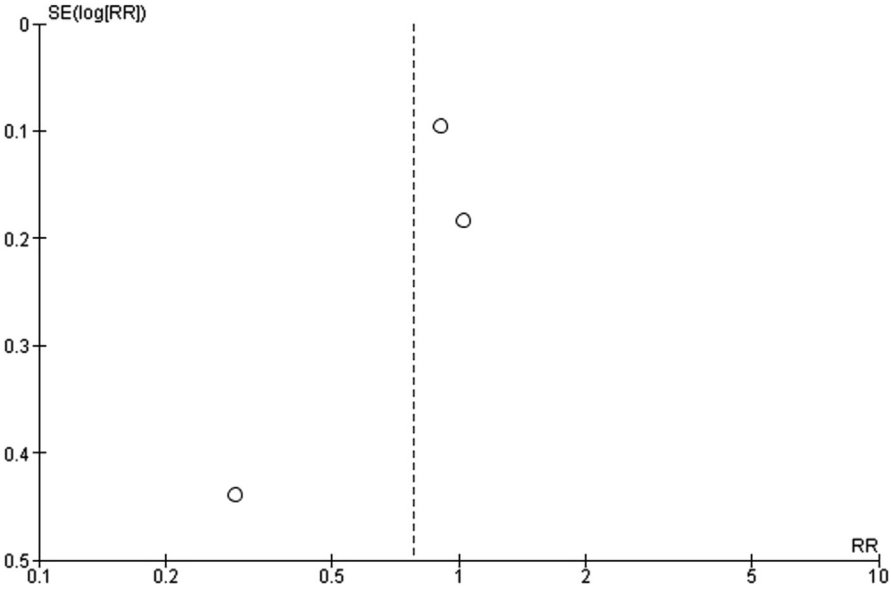
95% CI, 0.28−1.12) compared to controls. Women who received 17P had significantly later gestational age at delivery (mean difference, 2.28 weeks; 95% CI, 1.46−3.10), longer latency (mean difference, 8.36 days; 95% CI 3.20−13.51), and higher birthweight (mean difference, 224.30 g; 95% CI, 70.87−377.74) as compared to control group. Other secondary outcomes including incidences of recurrent PTL, neonatal death, NICU, RDS, BPD, IVH, NEC, and sepsis were similar in both groups (Table 2). Data about spontaneous PTB <37 weeks and spontaneous PTB <34 weeks were not available.

Comment

This metaanalysis of pooled data of 5 randomized controlled trials evaluating 17P treatment for maintenance tocolysis after arrested PTL shows that maintenance tocolysis with 17P is not associated with prevention of PTB compared to controls (placebo or no treatment). Latency from randomization to delivery

FIGURE 3
Funnel plot for assessing publication bias



RR, relative risk.

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TABLE 2
Primary and secondary outcomes

Variable	Facchinetti et al,[28] 2007	Rozenberg et al,[29] 2012	Regmi et al,[30] 2012	Lotfalizadeh et al,[27] 2013	Briery et al,[31] 2014	Total	RR (95% CI)
No. of patients	60 (30 vs 30)	188 (94 vs 94)	60 (29 vs 31)	73 (37 vs 36)	45 (22 vs 23)	426 (212 vs 214)	—
PTB <37 wk	5/30 vs 17/30	37/94 vs 36/94	N/A	N/A	19/22 vs 22/33	61/146 (42%) vs 75/147 (51%)	0.78 (0.50–1.22)
PTB <34 wk	N/A	15/94 vs 19/94	N/A	N/A	14/22 vs 21/23	29/116 (25%) vs 40/117 (34%)	0.60 (0.28–1.12)
Recurrent PTL	N/A	N/A	11/29 vs 20/31	N/A	N/A	11/29 (38%) vs 20/31 (65%)	0.59 (0.34–1.00)
Mean GA delivery, wk	N/A	38 vs 38[a]	37 vs 34	N/A	32 vs 30	—	Mean difference 2.28 wk (95% CI, 1.46–3.10)[a,b]
Mean latency, d	N/A	61 vs 63[a]	25 vs 16	N/A	23 vs 16	—	Mean difference 8.36 d (95% CI, 3.20–13.51)[a,b]
Mean birthweight, g	3103 vs 2809	2930 vs 2850[a]	2903 vs 2781	N/A	1693 vs 1536	—	Mean difference 224.30 g (70.87–377.74)[a,b]
Neonatal death	N/A	0/94 vs 0/94	N/A	N/A	0/22 vs 3/23	0/116 (0%) vs 3/117 (3%)	0.15 (0.01–2.73)
Admission in NICU	N/A	24/94 vs 16/94	3/29 vs 2/31	8/37 vs 14/36	N/A	35/160 (22%) vs 32/161 (20%)	1.09 (0.71–1.66)
RDS	N/A	14/94 vs 12/94	3/29 vs 2/31	N/A	7/22 vs 10/23	24/145 (16%) vs 24/148 (16%)	1.02 (0.62–1.69)
BPD	N/A	2/94 vs 1/94	N/A	N/A	N/A	2/94 (2%) vs 1/94 (1%)	2.02 (0.18–22.68)
IVH	N/A	N/A	N/A	N/A	0/22 vs 6/23	0/22 (0%) vs 6/23 (26%)	0.08 (0.11–1.35)
NEC	N/A	1/94 vs 1/94	N/A	N/A	0/22 vs 3/23	1/116 (1%) vs 4/117 (3%)	0.34 (0.05–2.13)
Sepsis	N/A	N/A	2/29 vs 2/31	N/A	1/22 vs 7/23	3/51 (6%) vs 9/54 (17%)	0.35 (0.10–1.25)

Data are presented as number 17-alpha-hydroxyprogesterone caproate vs number placebo.

BPD, bronchopulmonary dysplasia; *CI*, confidence interval; *GA*, gestational age; *IVH*, intraventricular hemorrhage; *N/A*, not available; *NEC*, necrotizing enterocolitis; *NICU*, neonatal intensive care unit; *PTB*, preterm birth; *PTL*, preterm labor; *RDS*, respiratory distress syndrome; *RR*, relative risk.

[a] GA at delivery, latency, and birthweight of Rozenberg et al[29] in 2012 were not included in analysis because SD was not reported; [b] Statistically significant.

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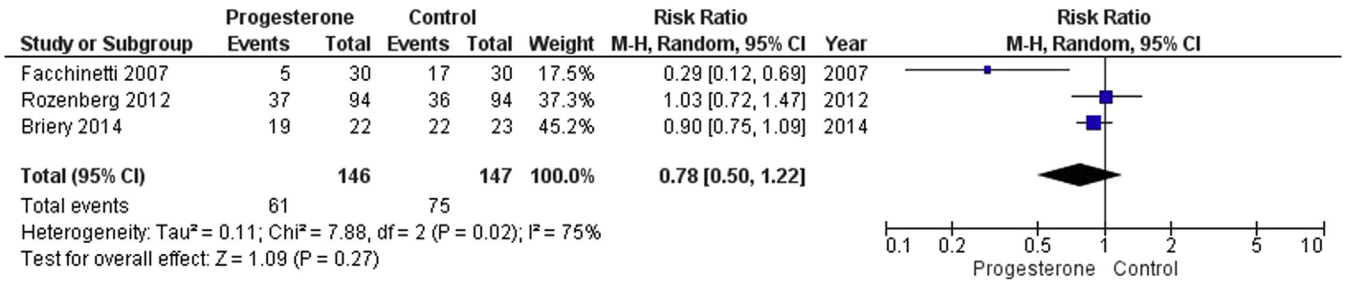
FIGURE 4
Forest plot analysis of PTB at <37 weeks of gestation for singletons with prior PTB[28,29,31]



CI, confidence interval; *M-H*, Mantel-Haenszel; *PTB*, preterm birth.

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was significantly prolonged by 8 days in the 17P group compared to controls. Women who received 17P were randomized about half a week later regarding gestational age, and delivered about 2 weeks later compared to controls. Regarding neonatal outcomes, women who received 17P had babies with a significantly higher birthweight as compared to the control group, while other neonatal outcomes were similar.

PTL commonly precedes PTB. Tocolytics are often used for short-term prolongation of the pregnancy, to allow the obstetricians to administer antenatal corticosteroids for fetal maturation, and magnesium sulfate for neuroprotection, as well as the transport of patients to tertiary care centers with level III NICUs.[32] After successful primary tocolysis for steroid benefit, maintenance tocolysis does not seems to prevent PTB and improve neonatal outcomes.[32] Compared to placebo, maintenance tocolysis with oral betamimetics,[33] terbutaline pump,[34] calcium channel blockers,[35-37] cyclooxygenase-2 inhibitors,[38-40] magnesium sulfate,[41] or oxytocin receptor antagonist[42] (atosiban) have not been associated with prevention of PTB. Maintenance tocolysis with progesterone has been studied in randomized trials, but so far guidelines have not commented on its use,[32] and this intervention is not routinely discussed or used in clinical practice.

Only 1 other metaanalysis evaluated use of progesterone for treatment of PTL.[43] The Cochrane Review on progestational agents for treating threatened or established PTL included a subgroup analysis of progesterone for maintenance tocolysis in women with both arrested PTL and PPROM together.[43] Moreover, their analysis combined 3 formulation of progesterone (17P, natural or vaginal progesterone, and oral progesterone) together and did not include all available randomized controlled trials. Including PTL and PPROM together, as well as different formulations of progesterone, makes clinical use of these data limited.

One of the strengths of our study is inclusion of only randomized trials on 17P maintenance tocolysis in women with arrested PTL. Included trials clearly defined PTL as preterm contractions with cervical change. The pooled data represent a relatively large group of patients treated with 17P maintenance tocolysis, compared mostly to no treatment, or placebo. Most studies had low risk of bias by Cochrane Collaboration's tool.[9] All trials assessed the incidence of PTB, and the majority assessed some neonatal outcomes. Another strength of our study is that it is the only reported metaanalysis of 17P for maintenance tocolysis in women with arrested PTL.

Limitations of our study are those inherent to any other metaanalysis. The risk for PTB might have been different in the trials. For example, most trials (except 1[28]) did not report if study subjects had prior PTB or had other risk factors for PTB. The primary tocolysis regimen was different in the included trials. The dosage and frequency of administration of 17P was somewhat different in various trials. Only 1 of the 5 trials included the sample size calculation; however the authors were unable to complete full enrollment of the study subjects due to relocation of one of the study authors.[31] Other limitations of our metaanalysis are that only 1 trial of 5 had as primary outcome PTB <37 weeks,[31] and the limited information about neonatal outcome. Furthermore, only 3 trials had data on the primary outcome variable of PTB <37 weeks and these 3 trials all utilized a different concentration and dosing interval for 17P. The heterogeneity between trials was high for PTB <37 weeks. Lastly, the sample sizes in the various subgroups are not of sufficient size to rule out a type II error for the outcome variables measured.

In this metaanalysis of the pertinent randomized trials, maintenance tocolysis with 17P after arrested PTL was not associated with prevention of PTB, but there was a significant 8 days' prolongation of pregnancy, and significantly higher birthweight. Given that there was also no benefit in other neonatal outcomes, 17P maintenance tocolysis cannot be currently recommended for clinical use, but further research is necessary. We observed that with an α of 0.05 and 80% power, a sample size of 480 patients in each group is required to detect a reduction in PTB <37 weeks from 51% to 42%. ■

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