OBSTETRICS

# Vaginal progesterone for maintenance tocolysis: a systematic review and metaanalysis of randomized trials

Anju Suhag, MD; Gabriele Saccone, MD; Vincenzo Berghella, MD

**OBJECTIVE:** We sought to evaluate the efficacy of maintenance tocolysis with vaginal progesterone compared to control (placebo or no treatment) in singleton gestations with arrested preterm labor (PTL) in a metaanalysis of randomized controlled trials.

**STUDY DESIGN:** 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," and "preterm labor" from 1966 through November 2014. We included all randomized trials of singleton gestations that had arrested PTL and then were randomized to maintenance tocolysis treatment with either vaginal progesterone or control (either placebo or no treatment). All published randomized studies on progesterone tocolysis were carefully reviewed. Exclusion criteria included maintenance tocolysis in women with preterm premature rupture of membrane, maintenance tocolysis with 17-alpha-hydroxyprogesterone caproate, and maintenance tocolysis with oral progesterone. The summary measures were reported as relative risks (RRs) with 95% confidence interval (CI). The primary outcome was preterm birth (PTB) <37 weeks.

**RESULTS:** Five randomized trials, including 441 singleton gestations, were analyzed. Women who received vaginal progesterone maintenance tocolysis for arrested PTL had a significantly lower rate of PTB <37 weeks (42% vs 58%; RR, 0.71; 95% CI, 0.57—0.90; 3 trials, 298 women). Women who received vaginal progesterone had significantly longer latency (mean difference 13.80 days; 95% CI, 3.97—23.63; 4 trials, 368 women), later gestational age at delivery (mean difference 1.29 weeks; 95% CI, 0.43—2.15; 4 trials, 368 women), lower rate of recurrent PTL (24% vs 46%; RR, 0.51; 95% CI, 0.31—0.84; 2 trials, 122 women), and lower rate of neonatal sepsis (2% vs 7%; RR, 0.34; 95% CI, 0.12—0.98; 4 trials, 368 women).

**CONCLUSION:** Maintenance tocolysis with vaginal progesterone is associated with prevention of PTB, significant prolongation of pregnancy, and lower neonatal sepsis. However, given the frequent lack of blinding and the generally poor quality of the trials, we do not currently suggest a change in clinical care of women with arrested PTL. We suggest instead well-designed placebo-controlled randomized trials to confirm the findings of our metaanalysis.

**Key words:** preterm birth, preterm labor, progesterone, tocolysis

Preterm birth (PTB), defined as birth between 20 and 36 6/7 weeks, is responsible for the majority of the 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 50% of all PTB. Tocolytic agents are drugs that can slow or stop labor contractions in the attempt to delay births preceded by PTL. Primary tocolysis is defined as tocolysis given on initial presentation of women with PTL. In most of these women, PTL stops, but as their risk of PTB remains high, 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.[1] Recently, progesterone has been used successfully for prevention of PTB, in particular in asymptomatic singleton gestations with either short cervical length[6,7] or with prior spontaneous PTB.[8] The efficacy of vaginal progesterone in preventing PTB in women with arrested PTL is not clear.

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Received Dec. 20, 2014; revised March 5, 2015; accepted March 17, 2015.

The authors report no conflict of interest.

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0002-9378/$36.00

http://dx.doi.org/10.1016/j.ajog.2015.03.031

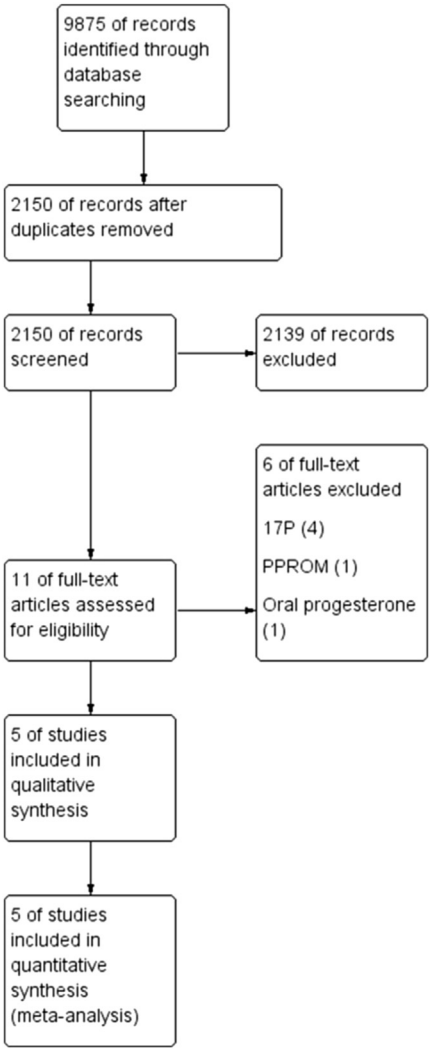
The aim of this study was to evaluate the efficacy of maintenance tocolysis with vaginal progesterone compared to control (placebo or no treatment) in singleton gestations with arrested PTL in a metaanalysis of randomized trials.

## Materials and methods

### Study design

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 key words and text words "progesterone," "tocolysis," and "preterm labor" from 1966 through November 2014. To locate additional publications, we reviewed proceedings of international society

FIGURE 1
**Flow diagram of studies identified in systematic review**




*PPROM*, preterm premature rupture of membrane; *17P*, 17-alpha-hydroxyprogesterone caproate.

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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 vaginal progesterone or control (either placebo or no treatment). All published randomized studies on progesterone tocolysis were carefully reviewed. Exclusion criteria included quasirandomized trials (ie, trials in which allocation was done on the basis of a pseudorandom sequence, eg, odd/even hospital number or date of birth, alternation), maintenance tocolysis in women with preterm premature rupture of membrane (PPROM), maintenance tocolysis with 17-alpha-hydroxyprogesterone caproate (17P), and maintenance tocolysis with oral progesterone.

Before data extraction, the protocol was registered with PROSPERO (registration number: CRD42014013706; http://www.crd.york.ac.uk/PROSPERO/).[9] The metaanalysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement.[10]

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. All authors 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.[11] 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 risk, high risk, or unclear risk of bias.[11] Risk of bias was assessed by 2 investigators (A.S., G.S.). Disagreements were resolved by consensus with a third reviewer (V.B.).

The primary outcome was PTB <37 weeks. Secondary outcomes included PTB <34 weeks, gestational age at delivery, latency, birthweight, neonatal death, admission to neonatal intensive care unit, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal sepsis. We performed a subgroup analysis by examining only those trials that included a placebo, and examined the trials by the dose of progesterone.

### Data analysis

The data analysis was completed independently by authors (G.S., A.S., V.B.) using Review Manager 5.3 (The Nordic Cochrane Center, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved with review of the entire data and independent analysis. Statistical heterogeneity between studies was assessed using the Cochrane Q statistic and $I^2$ statistics of Higgins et al.[11] 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 risks (RRs) estimate, otherwise a fixed effect models was planned.[11] The summary measures were reported as RRs, with 95% confidence interval (CI).[11] $P$ value $< .05$ was considered statistically significant.

## Results

### Study selection and study characteristics

Figure 1 shows the flow diagram of information through the different phases of the review. In all, 21 trials on progesterone as tocolytic were identified.[8,12-31] Eleven trials were identified that evaluated the effect of progesterone for maintenance tocolysis after PTL.[21-31] Six of them were excluded: 4 were excluded because 17P was evaluated[28-31]; 1 was excluded because women with PPROM were evaluated[22]; and 1 was excluded because oral progesterone was evaluated.[21] Five trials that met inclusion criteria for this metaanalysis were analyzed.[23-27]

Descriptive data for each trial are presented in Table 1. A total of 441 singleton gestations with arrested PTL were included. Most studies used 200 mg of vaginal progesterone daily. Three of 5 used no treatment as control.[23,25,27] Three studies defined PTL as the presence of at least 6 contractions in 30 minutes accompanied by cervical changes[23-25]; 1 defined it as the presence of at least 4 contractions per 20 minutes,

TABLE 1
**Descriptive data for each trial**

| Variable | Borna and Sahabi,[23] 2008 | Sharami et al,[24] 2010 | Arikan et al,[25] 2011 | Lotfalizadeh et al,[27] 2013 | Areia et al,[26] 2013 | Total |
|---|---|---|---|---|---|---|
| Study location | Iran | Iran | Turkey | Iran | Portugal | — |
| No. of patients —progesterone vs control | 70 (37 vs 33) | 163 (80 vs 83) | 83 (43 vs 40) | 73 (37 vs 36) | 52 (26 vs 26) | 441 (223 vs 218) |
| Daily dose, mg | 400 | 200 | 200 | 400 | 200 | — |
| Control | No treatment | Placebo | No treatment | No treatment | Placebo | — |
| Primary tocolytic agent | Magnesium sulfate | Magnesium sulfate | Ritodrine | Magnesium sulfate or nifedipine | Atosiban | — |
| GA at randomization, wk[a] | $24^0$—$34^6$ | $28^0$—$36^6$ | $24^0$—$34^6$ | $26^0$—$36^6$ | $24^0$—$34^6$ | — |
| Mean GA at randomization, wk | 31/32 | 33/34 | 32/32 | 34/33 | 28/29 | Mean difference −0.37 d (95% CI, −1.17 to 0.44) |
| Definition of PTL | At least 6 contractions in 30 min accompanied by cervical changes | At least 6 contractions in 30 min accompanied by cervical changes | At least 6 contractions in 30 min accompanied by cervical changes | At least 4 contractions per 20 min accompanied by 2-cm dilatation | At least 4 contractions per 20 min accompanied by cervical length <25 mm | |
| Prior PTB —progesterone vs control, n/N (%) | 5/37 (13.5%) vs 4/33 (12.1%) | 1/80 (1.3%) vs 3/83 (3.6%) | 4/43 (9.3%) vs 3/40 (7.5%) | N/R | 9/26 (34.6%) vs 9/26 (34.6%) | 28/186 (15.0%) vs 19/182 (10.4%) $P = .19$ |
| Study primary outcomes | Latency period, recurrent PTL | Latency period, PTB <37 wk, PTB <34 wk | Latency period, GA at delivery, PTB <37 wk | Rate of recurrent PTL | Latency period | — |

*CI*, confidence interval; *GA*, gestational age; *N/R*, not reported; *PTB*, preterm birth; *PTL*, preterm labor.

[a] Data presented in range.

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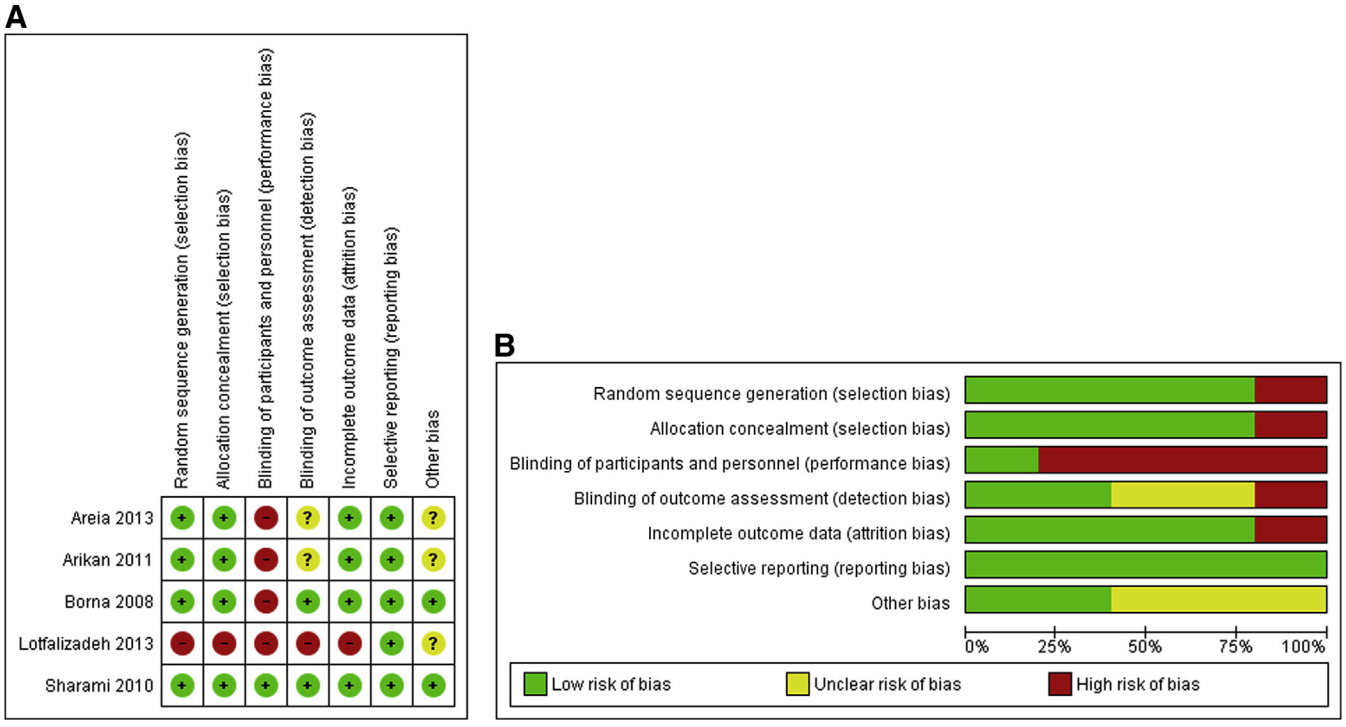
FIGURE 2
**Assessment of risk of bias**




**A**, Summary of low (+), high (−), and unclear (?) risk of bias for each trial. **B**, Risk of bias graph presented as percentages across all included studies.
Areia 2013[26]; Arikan 2011[25]; Borna 2008[23]; Lotfalizadeh 2013[27]; Sharami 2010.[24]
*Suhag. Vaginal progesterone for maintenance tocolysis. Am J Obstet Gynecol 2015.*

accompanied by 2-cm dilatation[27]; and 1 defined it as uterine contractions at least 4 per 20 minutes accompanied by cervical length <25 mm.[26]

The quality of randomized controlled trials (RCTs) included in our meta-analysis was assessed by the Cochrane Collaboration's tool[11] (Figure 2). All studies but one[27] had adequate random sequence generation and allocation concealment. One study was double blind.[24] Figure 3 shows the funnel plot for assessing publication bias for PTB <37 weeks. Potential publication bias was assessed by visual inspection of the funnel plot, and the symmetric plot suggested no publication bias.

Of the 441 singleton gestations included in the 5 trials,[23-27] 223 (50.5%) were randomized to vaginal progesterone, and 218 (49.5%) to control. Regarding important baseline characteristics of the populations in the original trials, 4 RCTs reported data about prior PTB (Table 1),[23-26] and 1 about cervical length.[26] No differences in baseline characteristics were found between the progesterone and control groups in any study. The statistical heterogeneity between the studies was very low, with no inconsistency in the RR estimates ($I^2 = 0\%$). However, given the clinical heterogeneity (eg, dose of progesterone, inclusion criteria), a random effect model was used to assessed the primary outcome.

### Synthesis of results

Women with a singleton gestation who received vaginal progesterone maintenance tocolysis for arrested PTL had a significantly lower rate of PTB <37 weeks (42% vs 58%; RR, 0.71; 95% CI, 0.57−0.90; 3 trials, 298 women) (Figure 4).

Women who received vaginal progesterone also had significantly longer latency (mean difference 13.80 days; 95% CI, 3.97−23.63; 4 trials, 368 women) (Figure 5), later gestational age at delivery (mean difference 1.29 weeks; 95% CI, 0.43−2.15; 4 trials, 368 women) (Figure 6), and lower rate of recurrent PTL (24% vs 46%; RR, 0.51; 95% CI, 0.31−0.84; 2 trials, 122 women). Regarding neonatal outcome we found no differences between progesterone and control group except for the rate of neonatal sepsis, which was lower in the progesterone group compared to control (2% vs 7%; RR, 0.34; 95% CI, 0.12−0.98; 4 trials, 368 women) (Table 2). No data about bronchopulmonary dysplasia were reported in any of the trials.

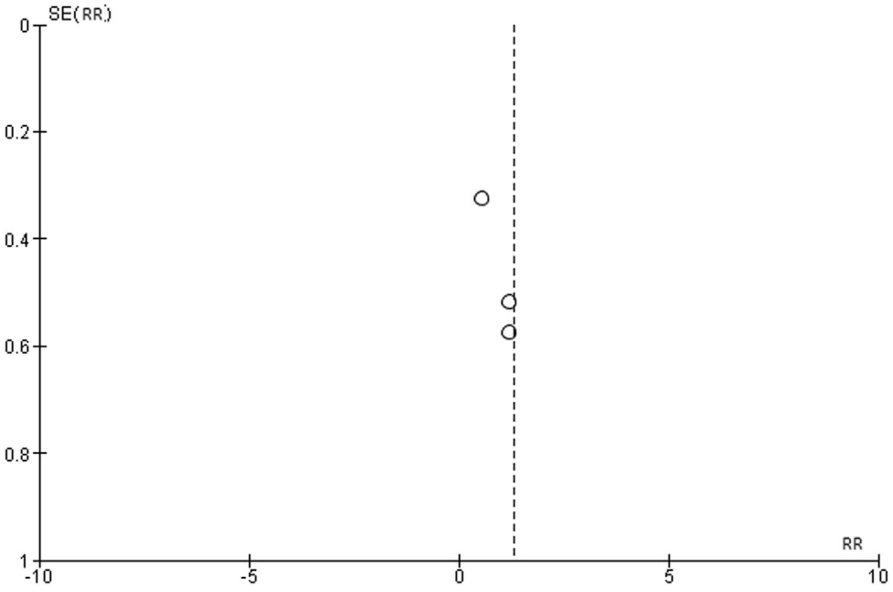
In the subgroup analysis of those trials that included placebo as control, we found that vaginal progesterone was associated with a significantly lower risk of PTB <37 weeks compared to control (39.6% vs 53.2%; RR, 0.58; 95% CI, 0.34−0.99). Due to limited data, analysis of the primary outcome in the subgroup analysis examining by dose of progesterone was not feasible.

## Comment

### Main findings

This metaanalysis of pooled data of 5 RCTs evaluating vaginal progesterone treatment for maintenance tocolysis after arrested PTL shows that maintenance tocolysis with vaginal progesterone is associated with prevention of PTB compared to controls (either placebo or no treatment). Women who received vaginal progesterone delivered >1 week later and had a longer latency from randomization to delivery. Furthermore, the incidence of recurrent PTL was noted to be significantly lower in women randomized to vaginal progesterone as compared to control group, and the rate of neonatal sepsis was lower.

FIGURE 3
**Funnel plot for assessing publication bias**




*RR*, relative risk.

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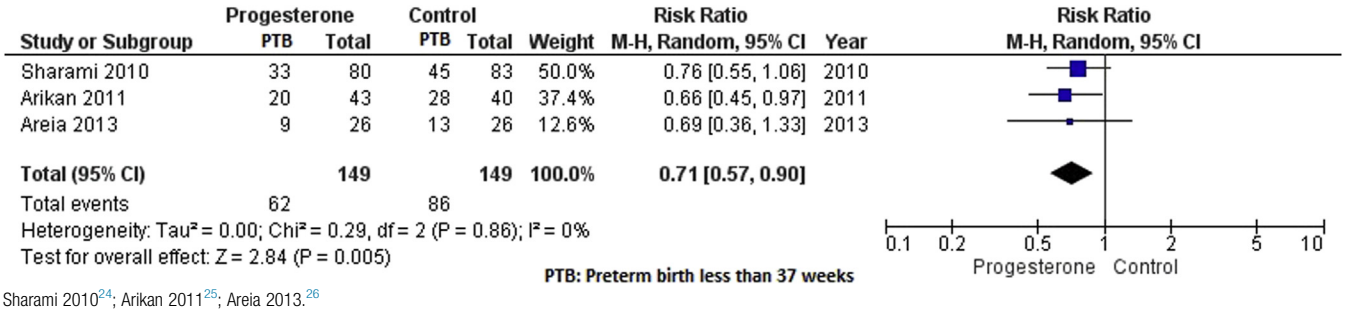
### Discussion and comparison with existing literature

PTL commonly precedes PTB. Tocolytics are often used for short-term prolongation of pregnancy, to allow the obstetrician to administer antenatal corticosteroids, and magnesium sulfate for neuroprotection, and to permit transport of patients to centers with appropriate level neonatal intensive care units.[1] After successful primary tocolysis, several maintenance tocolysis agents have been studied, but none so far have been associated with benefits.[1] Compared to placebo, maintenance tocolysis with oral betamimetics,[32] terbutaline pump,[33] calcium channel blockers,[34-36] cyclooxygenase-2 inhibitors,[37-39] magnesium sulfate,[40] oxytocin receptor antagonist[41] (atosiban), or 17P[42] have not been associated with prevention of PTB or improvement in neonatal outcomes. Maintenance tocolysis with progesterone has been studied in randomized trials, but so far no clinically useful metaanalysis of these data has been published, guidelines have not commented on its use,[1] and this intervention is not routinely discussed or used in clinical practice.

Only one 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. Moreover, their analysis combined 3 formulations of progesterone (17P, natural or vaginal progesterone, and oral progesterone) together. Including PTL and PPROM together, as well as different formulations of progesterone, makes clinical use of these data limited.

FIGURE 4
**Forest plot for preterm birth <37 weeks**




Sharami 2010[24]; Arikan 2011[25]; Areia 2013.[26]

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

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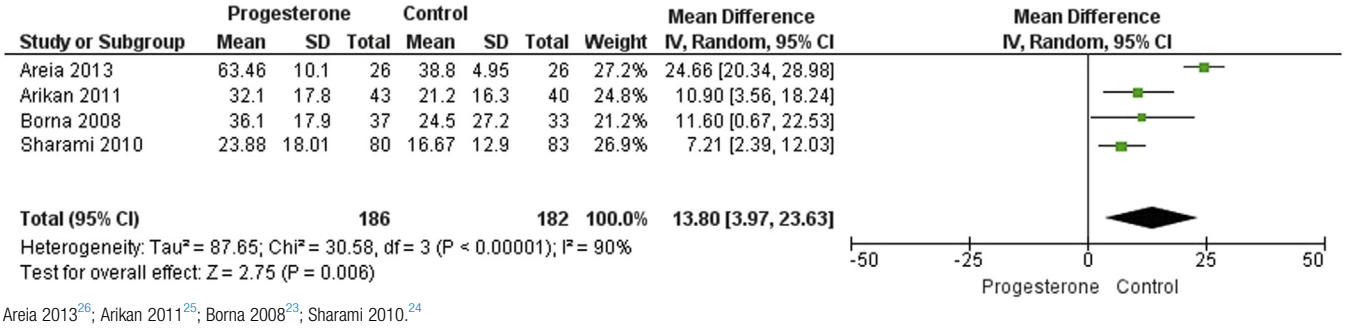
FIGURE 5
**Forest plot for latency**




Areia 2013[26]; Arikan 2011[25]; Borna 2008[23]; Sharami 2010.[24]

*CI*, confidence interval; *df*, degree of freedom; *IV*, independent variable; *SD*, standard error.

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**Strengths and limitations**

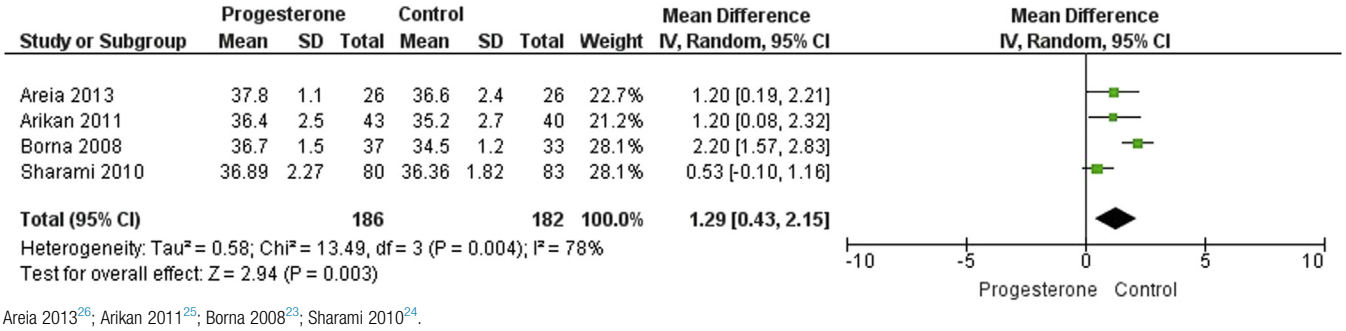
One of the strengths of our study is the inclusion of only randomized trials on vaginal progesterone maintenance tocolysis in women with arrested PTL in the only reported metaanalysis specific to this topic. Included trials uniformly defined PTL as preterm contractions with cervical change. The pooled data represent a relatively large group of patients treated with vaginal progesterone maintenance tocolysis, compared to no treatment, or placebo. Most studies had low risk of bias by Cochrane Collaboration's tool.[10] Most trials assessed latency and some neonatal outcomes. Although the risk for PTB might have been different in the trials, 4 of 5 trials (except Lotfalizadeh et al[27]) did report if study subjects had prior PTB or had other risk factors for PTB.[23-26]

Limitations of our study are those inherent to any other metaanalysis. Primary tocolysis regimen was somewhat different in the included trials. The dosage of administration of vaginal progesterone was different in various trials (200 mg in 3 trials, 400 mg in 2 trials). Only 2 of the 5 trials included the sample size calculation[23,26]; both of these studies were underpowered, however the authors were able to show longer latency in the vaginal progesterone group.[23,26] Other shortcomings of our meta-analysis are that only 2 trials of 5 had as primary outcome PTB <37 weeks,[24,25] and the limited information about neonatal outcome. No long-term outcomes were reported in any of the trials. Given the lack of blinding in some trials, there is a significant potential for bias especially for some of the secondary outcomes. Moreover, none of these trials were from the United States and so applicability to the US population may be limited. One trial reported very limited data on obstetric and perinatal outcomes.[27] While all authors were contacted for missing data, we received additional data only from 1 author.[26]

**Conclusions and implications**

In this metaanalysis of the pertinent randomized trials, maintenance tocolysis with vaginal progesterone after arrested PTL in singleton gestations was associated with significant 29% prevention of PTB <37 weeks, significant prolongation of pregnancy by >8 days, significant 49% lower rate of recurrent PTL, and significant 66% decrease in neonatal sepsis. However, given the lack of blinding in some trials and the

FIGURE 6
**Forest plot preterm birth for gestational age at delivery**




Areia 2013[26]; Arikan 2011[25]; Borna 2008[23]; Sharami 2010[24].

*CI*, confidence interval; *df*, degree of freedom; *IV*, independent variable; *SD*, standard error.

*Suhag. Vaginal progesterone for maintenance tocolysis. Am J Obstet Gynecol 2015.*

TABLE 2
**Primary and secondary outcomes**

| Variable | Borna and Sahabi,[23] 2008 | Sharami et al,[24] 2010 | Arikan et al,[25] 2011 | Lotfalizadeh et al,[27] 2013 | Areia et al,[26] 2013 | Total | RR (95% CI) |
|---|---|---|---|---|---|---|---|
| No. of patients | 70 (37 vs 33) | 163 (80 vs 83) | 83 (43 vs 40) | 73 (37 vs 36) | 52 (26 vs 26) | 441 (223/218) | — |
| PTB <37 wk[a] | N/A | 33/80 (41%) vs 45/83 (54%) | 20/43 (47%) vs 28/40 (70%) | N/A | 9/26 (35%) vs 13/26 (50%) | 62/149 (42%) vs 86/149 (58%) | 0.71 (0.57–0.90)[b] |
| PTB <34 wk[a] | N/A | 8/80 (10%) vs 9/83 (11%) | N/A | N/A | 3/26 (12%) vs 6/26 (23%) | 11/106 (10%) vs 15/109 (14%) | 0.75 (0.36–1.57) |
| Recurrent PTL[a] | 13/37 (35%) vs 19/33 (58%) | N/A | N/A | N/A | 2/26 (8%) vs 8/26 (31%) | 15/63 (24%) vs 27/59 (46%) | 0.51 (0.31–0.84)[b] |
| Mean GA delivery, wk | 37 vs 35 | 37 vs 36 | 36 vs 35 | N/A | 38 vs 37 | — | Mean difference 1.29 wk (0.43–2.15)[b] |
| Mean latency, d | 36 vs 24 | 24 vs 17 | 32 vs 21 | N/A | 63 vs 39 | — | Mean difference 13.80 d (3.97–23.63)[b] |
| Mean birthweight, g | 3101 vs 2609 | 2997 vs 3025 | 2983 vs 2585 | N/A | 2547 vs 2628 | — | Mean difference 194 g (−100.01 to 488.32) |
| Neonatal death[a] | N/A | 1/80 (1%) vs 6/83 (7%) | 0/43 vs 1/40 (3%) | N/A | 2/26 (8%) vs 2/26 (8%) | 3/149 (2%) vs 9/149 (6%) | 0.43 (0.12–1.54) |
| Admission in NICU[a] | 9/37 (24%) vs 13/33 (39%) | 3/80 (4%) vs 2/83 (2%) | 3/43 (7%) vs 3/40 (8%) | 10/37 (27%) vs 14/36 (39%) | 5/26 (19%) vs 7/26 (27%) | 30/223 (13%) vs 39/218 (18%) | 0.72 (0.47–1.08) |
| RDS[a] | 4/37 (11%) vs 12/33 (36%) | 7/80 (9%) vs 10/83 (12%) | 1/43 (2%) vs 1/40 (3%) | N/A | 2/26 (8%) vs 2/26 (8%) | 14/186 (8%) vs 25/182 (14%) | 0.54 (0.30–1.00) |
| IVH[a] | 0/37 vs 0/33 | N/A | 0/43 vs 0/40 | N/A | 0/26 vs 0/26 | 0/106 (0%) vs 0/99 (0%) | N/E |
| NEC[a] | 0/37 vs 0/33 | N/A | 0/43 vs 0/40 | N/A | 0/26 vs 0/26 | 0/106 (0%) vs 0/99 (0%) | N/E |
| Sepsis[a] | 2/37 (5%) vs 6/33 (18%) | 0/80 vs 3/83 (4%) | 2/43 (5%) vs 2/40 (5%) | N/A | 0/26 vs 1/26 (4%) | 4/186 (2%) vs 11/156 (7%) | 0.34 (0.12–0.98)[b] |

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

[a] Data are presented progesterone, n, vs control, n (percentage); [b] Statistically significant.

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generally poor quality of the trials, we do not suggest a change in clinical care of women with arrested PTL. We suggest well-designed placebo-controlled randomized trials to confirm the findings of our metaanalysis. We observed that with $\alpha$ of 0.05 and 80% power, a sample size of 250 women in each group is required to detect a 29% decrease in PTB. ■


## ACKNOWLEDGMENT

We thank Dr Areia et al[26] for providing additional data from their trial.


## REFERENCES


1. American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics. Management of preterm labor. ACOG Practice bulletin no. 127. Obstet Gynecol 2012;119:1308-17.
2. Martin J, Hamilton BE, Sutton PD, et al. Births: final data for 2005. Natl Vital Stat Rep 2007;56:1-103.
3. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. N Engl J Med 1985;312:82-90.
4. Lewit EM, Baker LS, Corman H, Shiono PH. The direct cost of low birth weight. Future Child 1995;5:32-6.
5. Lawn JE, Cousens S, Zupan J; for the Neonatal Survival Steering Team. Four million neonatal deaths: When? Where? Why? Lancet 2005;365:891-900.
6. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.
7. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011;38:18-31.
8. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379-85.
9. PROSPERO: International prospective register of systematic reviews, 2014: CRD42014013706. Available at: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID= CRD42014013706. Accessed Nov. 15, 2014.
10. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-12.
11. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (update March 2011). The Cochrane Collaboration. 2011. Available at: www.cochrane-handbook.org. Accessed Nov. 15, 2014.
12. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419-24.
13. Majihi P, Bagga R, Kalra J, Sharma M. Intravaginal use of natural micronized progesterone to prevent pre-term birth: a randomized trial in India. J Obstet Gynaecol 2009;29:493-8.
14. Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomized, double-blind, placebo-controlled study and meta-analysis. Lancet 2009;373:2034-40.
15. Lim AC, Schuit E, Bloemenkamp K, et al. 17-alpha-Hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial. Obstet Gynecol 2011;118:513-20.
16. Tan PC, King AS, Vallikkannu N, et al. Single dose 17 alpha hydroxyprogesterone caproate in preterm labor: a randomized trial. Arch Gynecol Obstet 2012;285:585-90.
17. Grobman WA, Thom EA, Spong CY, et al. 17 alpha Hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. Am J Obstet Gynecol 2012;207:390.
18. Senat MV, Porcher R, Winer N, et al. Prevention of preterm delivery by 17 alpha hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol 2013;208:194.
19. Aflatoonian A, Amouzegar H. Dehghani Firouzabadi R. Efficacy of 17alpha-hydroxyprogesterone on decreasing preterm labor in ART pregnancies: a randomized clinical trial. Iran J Reprod Med 2013;11:785-90.
20. Briery CM, Veillon EW, Klauser CK, et al. Progesterone does not prevent preterm births in women with twins. South Med J 2009;102:900-4.
21. Choudhary M, Suneja A, Vaid NB, Guleria K, Faridi MM. Maintenance tocolysis with oral micronized progesterone for prevention of preterm birth after arrested preterm labor. Int J Gynaecol Obstet 2014;126:60-3.
22. Combs CA, Garite TJ, Maurel K, et al. 17-Hydroxyprogesterone caproate to prolong pregnancy after preterm rupture of the membranes: early termination of a double-blind, randomized clinical trial. BMC Res Notes 2011;4:568.
23. Borna S, Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labor: a randomized controlled trial. Aust N Z J Obstet Gynaecol 2008;48:58-63.
24. Sharami SH, Zahiri Z, Shakiba M, Milani F. Maintenance therapy by vaginal progesterone after threatened idiopathic preterm labor: a randomized placebo-controlled double blind trial. Int J Fertil Steril 2010;4:45-50.
25. Arikan I, Barut A, Harma M, Harma IM. Effect of progesterone as a tocolytic and in maintenance therapy during preterm labor. Gynecol Obstet Invest 2011;72:269-73.
26. Areia A, Fonseca E, Moura P. Progesterone use after successful treatment of threatened preterm delivery. J Obstet Gynaecol 2013;33:678-81.
27. Lotfalizadeh M, Ghomian N, Reyhani A. The effects of progesterone therapy on the gestation length and reduction of neonatal complications in patients who had received tocolytic therapy for acute phase of preterm labor. Iran Red Crescent Med J 2013;15:e7947.
28. Facchinetti F, Paganelli S, Comitini G, Dante G, Volpe A. Cervical length changes during preterm cervical ripening: effects of 17-hydroxyprogesterone caproate. Am J Obstet Gynecol 2007;196:453.e1-4.
29. Rozenberg P, Chauveaud A, Deruelle P, et al. Prevention of preterm delivery after successful tocolysis in preterm labor by 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Am J Obstet Gynecol 2012;206:206.e1-9.
30. Regmi MC, Rijal P, Agrawal A, Uprety D. Progesterone for prevention of recurrent preterm labor after arrested preterm labor—a randomized controlled trial. Gynecol Obstet 2012;2:125.
31. Briery CM, Klauser CK, Martin RW, Magann EF, Chauhan SP, Morrison JC. The use of 17-hydroxy progesterone in women with arrested preterm labor: a randomized clinical trial. J Matern Fetal Neonatal Med 2014;27:1892-6.
32. Dodd JM, Crowther CA, Dare MR, Middleton P. Oral betamimetics for maintenance therapy after threatened preterm labor. Cochrane Database Syst Rev 2006;1:CD003927.
33. Nanda K, Cook LA, Gallo MF, et al. Terbutaline pump maintenance therapy after threatened preterm labor for preventing preterm birth. Cochrane Database Syst Rev 2002;4:CD003933.
34. Carr DB, Clark AL, Kernek K, et al. Maintenance oral nifedipine for preterm labor: a randomized clinical trial. Am J Obstet Gynecol 1999;181:822-7.
35. Lyell DJ, Pullen KM, Mannan J, et al. Maintenance nifedipine tocolysis compared with placebo—a randomized controlled trial. Obstet Gynecol 2008;112:1221-6.
36. Roos C, Spaanderman ME, Schuit E, et al. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial. JAMA 2013;309:41-7.
37. Carlan SJ, O'Brien WF, Jones MH, et al. Outpatient oral sulindac to prevent recurrence of preterm labor. Obstet Gynecol 1995;85:769-74.
38. Humprey RG, Bartfield MC, Carlan SJ, et al. Sulindac to prevent recurrent preterm labor: a randomized controlled trial. Obstet Gynecol 2001;98:555-62.
39. Bivins HA, Newman RB, Fyfe DA, et al. Randomized trial of oral indomethacin and

terbutaline for the long-term suppression of preterm labor. Am J Obstet Gynecol 1993;169:1065-70.
**40.** Han S, Crowther CA, Moore V. Magnesium maintenance therapy for preventing preterm birth after threatened preterm labor. Cochrane Database Syst Rev 2010;7:CD000940.
**41.** Valenzuela GJ, Sanchez-Ramos L, Romero R, et al. Maintenance treatment of preterm labor with the oxytocin antagonist atosiban. Am J Obstet Gynecol 2000;182:1184-90.
**42.** Saccone G, Suhag A, Berghella V. 17-alpha-Hydroxyprogesterone caproate for maintenance tocolysis: a systematic review and meta-analysis of randomized trials. Am J Obstet Gynecol 2015 [Epub ahead of print].
**43.** Su LL, Samuel M, Chong YS. Progestational agents for treating threatened or established preterm labor. Cochrane Database Syst Rev 2014;1:CD006700.