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Vaginal progesterone *vs* intramuscular 17α-hydroxy-progesterone caproate for prevention of recurrent spontaneous preterm birth in singleton gestations: systematic review and meta-analysis of randomized controlled trials

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KEYWORDS: prematurity; prevention; progesterone; transvaginal ultrasound; ultrasound cervical length

ABSTRACT

Objective *Randomized controlled trials (RCTs) have recently compared intramuscular 17α-hydroxy-progesterone caproate (17-OHPC) with vaginal progesterone for reducing the risk of spontaneous preterm birth (SPTB) in singleton gestations with prior SPTB. The aim of this systematic review and meta-analysis was to evaluate the efficacy of vaginal progesterone compared with 17-OHPC in prevention of SPTB in singleton gestations with prior SPTB.*

Methods *Searches of electronic databases were performed to identify all RCTs of asymptomatic singleton gestations with prior SPTB that were randomized to prophylactic treatment with either vaginal progesterone (intervention group) or intramuscular 17-OHPC (comparison group). No restrictions for language or geographic location were applied. The primary outcome was SPTB < 34 weeks. Secondary outcomes were SPTB < 37 weeks, < 32 weeks, < 28 weeks and < 24 weeks, maternal adverse drug reaction and neonatal outcomes. The summary measures were reported as relative risk (RR) with 95% CI. Risk of bias for each included study was assessed.*

Results *Three RCTs (680 women) were included. The mean gestational age at randomization was about 16 weeks. Women were given progesterone until 36 weeks or delivery. Regarding vaginal progesterone, one study used 90 mg gel daily, one used 100 mg suppository daily and one used 200 mg suppository daily. All included RCTs used 250 mg intramuscular 17-OHPC weekly in the comparison group. Women who received vaginal progesterone had significantly lower rates of SPTB < 34 weeks (17.5% vs 25.0%; RR, 0.71 (95% CI, 0.53–0.95); low quality of evidence) and < 32 weeks (8.9% vs 14.5%; RR, 0.62 (95% CI, 0.40–0.94); low quality of evidence) compared with women who received 17-OHPC. There were no significant differences in the rates of SPTB < 37 weeks, < 28 weeks and < 24 weeks. The rate of women who reported adverse drug reactions was significantly lower in the vaginal progesterone group compared with the 17-OHPC group (7.1% vs 13.2%; RR, 0.53 (95% CI, 0.31–0.91); very low quality of evidence). Regarding neonatal outcomes, vaginal progesterone was associated with a lower rate of neonatal intensive care unit admission compared with 17-OHPC (18.7% vs 23.5%; RR, 0.63 (95% CI, 0.47–0.83); low quality of evidence). For the comparison of 17-OHPC vs vaginal progesterone, the quality of evidence was downgraded for all outcomes by at least one degree due to imprecision (the optimal information size was not reached) and by at least one degree due to indirectness (different interventions).*

Conclusions *Daily vaginal progesterone (either suppository or gel) started at about 16 weeks' gestation is a reasonable, if not better, alternative to weekly 17-OHPC injection for prevention of SPTB in women with singleton gestations and prior SPTB. However, the quality level of the summary estimates was low or very low as assessed by GRADE, indicating that the true effect may be, or is likely to be, substantially different from the estimate of the effect. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.*

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INTRODUCTION

Spontaneous preterm birth (SPTB) remains the number one cause of perinatal mortality in many countries, including the USA. Prior SPTB is one of the most important risk factors for SPTB; women with prior SPTB have about an 18–54% risk of recurrent preterm birth[1,2]. In singleton gestations with prior SPTB at 20 to 36 + 6 weeks' gestation, intramuscular 17α-hydroxyprogesterone caproate (17-OHPC), preferably started at 16–20 weeks until 36 weeks, has been recommended[3,4]. This is based on trials showing that 250 mg 17-OHPC weekly is associated with significantly lower incidences of recurrent SPTB and adverse neonatal outcomes compared with placebo[5,6]. However, several randomized controlled trials (RCTs) have also shown the efficacy of vaginal progesterone in reducing the risk of SPTB in singletons with prior SPTB, compared with placebo[6].

The aim of this meta-analysis was to evaluate the efficacy of vaginal progesterone compared with 17-OHPC in prevention of SPTB in asymptomatic singleton gestations with prior SPTB.

METHODS

Eligibility criteria

This meta-analysis was performed according to a protocol recommended for systematic reviews[7]. The research protocol was designed *a priori*, defining methods for a search of the literature, including examining articles and extracting and analyzing the data. Searches were performed in MEDLINE, OVID, Scopus, ClinicalTrials.gov, the PROSPERO International Prospective Register of Systematic Reviews, Scielo, EMBASE and the Cochrane Central Register of Controlled Trials with the use of a combination of keywords and text words related to 'preterm birth', 'preterm delivery', 'singleton', 'cervical length', 'progesterone', 'progestogens', 'vaginal', '17-alpha-hydroxy-progesterone caproate' and 'intramuscular', from inception of each database to January 2016. No restrictions for language or geographic location were applied.

Study selection

We included all RCTs of asymptomatic singleton gestations with prior SPTB that were randomized to prophylactic treatment with either vaginal natural progesterone (intervention group) or intramuscular 17-OHPC (comparison group). Exclusion criteria included quasirandomized trials (i.e. trials in which allocation was done on the basis of a pseudorandom sequence, e.g. odd/even hospital number or date of birth, alternation) and trials involving women with short cervical length (CL) or with preterm labor at the time of randomization. Trials of women with multiple gestations were also excluded.

Risk of bias

The risk of bias in each included study was assessed using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[7]. 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. Studies were categorized as 'low risk', 'high risk' or 'unclear risk' of bias by the review authors[7].

For this review, the quality of the evidence was assessed using the GRADE approach in order to assess the quality of the body of evidence relating to the primary and secondary outcomes. GRADEpro Guideline Development Tool was used to import data from Review Manager 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes was produced using the GRADE approach. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. The quality of the evidence (and its interpretation) was judged as follows: high quality (further research is very unlikely to change our confidence in the estimate of effect), moderate quality (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), very low quality (there is considerable uncertainty about the estimate). The judgments about quality were justified, documented and incorporated into the reporting of results for primary and secondary outcomes[8].

Data abstraction

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. The primary outcome was incidence of SPTB < 34 weeks. Secondary outcomes were SPTB < 37 weeks, < 32 weeks, < 28 weeks and < 24 weeks, maternal adverse drug reaction (i.e. number of women who experienced adverse drug reaction) and neonatal outcomes including birth weight (in grams), admission to neonatal intensive care unit (NICU), respiratory distress syndrome (RDS) (either transient tachypnea of the newborn or severe RDS), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) (Grade 3 or 4), severe necrotizing enterocolitis (NEC) (Grade 3 or

4), neonatal sepsis (culture-proven sepsis) and perinatal death. Perinatal death was defined as either fetal mortality (i.e. fetal death after 20 weeks) or neonatal mortality (i.e. death of a live-born baby within the first 28 days). All authors of the original trials were contacted in order to obtain missing data where possible.

Data analysis

The data analysis was completed using Review Manager 5.3[7]. The completed analyses were then compared and any difference was resolved with review of the entire data and independent analysis. The summary measures were reported as summary relative risk (RR) or as summary mean difference (MD) with 95% CI, using the random-effects model of DerSimonian and Laird. I^2 (Higgins I^2) greater than 0% was used to identify heterogeneity. Potential publication biases were assessed statistically using Begg's and Egger's tests if ≥ 10 studies were available[7]. A P-value < 0.05 was considered statistically significant.

All review stages were conducted independently by two reviewers (G.S., V.B.) who assessed inclusion criteria, risk of bias, data extraction and data analysis. Disagreements were resolved by discussion with a third reviewer (A.K.).

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement[9]. Before data extraction, the review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration no.: CRD42016033361).

RESULTS

Study selection and study characteristics

Five RCTs were assessed for eligibility[10–14] and two were excluded[13,14], one because it compared vaginal progesterone with intramuscular natural progesterone, not 17-OHPC[13], and the other because it explicitly included women with preterm labor at the time of randomization[14] (Figure 1). Three RCTs, including a total of 680 women, met the inclusion criteria and were therefore included in the meta-analysis[10–12]. One study included 74% of the total sample of the meta-analysis[10]. The quality of RCTs included in our meta-analysis was assessed by the Cochrane Collaboration's tool[7]. All the included studies had low risk of bias in 'allocation concealment' and 'random sequence generation'. Blinding was considered difficult to achieve given the different route of administration (vaginal *vs* intramuscular) and none of the included RCTs was double blinded (Figure 2). Publication bias could not be assessed given the small (< 10) number of studies included. Statistical heterogeneity within the trials was low ($I^2 = 0\%$) with no inconsistency in risk estimate for the primary outcome and for all secondary outcomes.

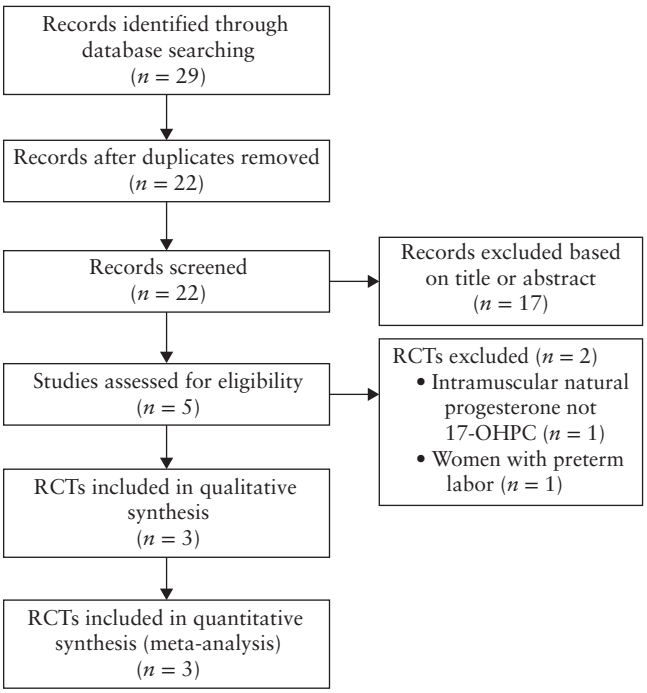

Figure 1 Flowchart of randomized controlled trials (RCTs) identified for systematic review. 17-OHPC, 17α-hydroxyprogesterone caproate.

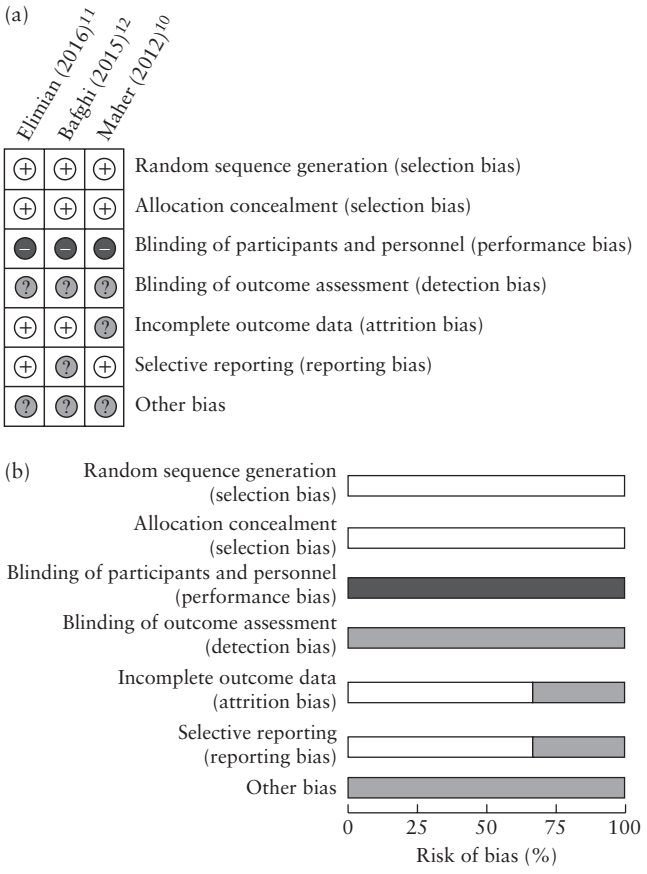

Figure 2 Risk of bias following *The Cochrane Handbook*[7] in individual randomized controlled trials (RCTs) (a) and across RCTs (b) included in meta-analysis. Only first author of each study is given. Risk of bias: □, +, low; ▒, ?, unclear; ■, −, high.

The characteristics of the included trials are summarized in Table 1. All studies included only asymptomatic singleton gestations with prior SPTB between 16 + 0 and 36 + 6 weeks. Bafghi *et al.* also included women without prior SPTB and with short CL on transvaginal ultrasound[12]. We obtained the original database of this study[12] from the authors and excluded women without prior SPTB from the analysis and those with a short CL on transvaginal ultrasound, and included only asymptomatic singleton gestations with prior SPTB between 16 + 0 and 36 + 6 weeks. Maher *et al.* explicitly excluded women with a short cervix, defined as transvaginal sonographic CL < 25 mm at the time of randomization[10], whereas in the RCT by Elimian *et al.*, participants did not undergo CL assessment[11].

One RCT enrolled women between 14 and 18 weeks' gestation[10] and two between 16 and 20 weeks[11,12]. The mean gestational age at randomization was about 16 weeks in both study groups.

All the included studies gave progesterone until 36 weeks or delivery. Of the 680 women included, 348 (51%) were randomized to vaginal progesterone (intervention group), while 332 (49%) were randomized to intramuscular 17-OHPC (comparison group).

Regarding the intervention (vaginal natural progesterone), Maher *et al.* used 90 mg gel daily[10], Elimian *et al.* used 100 mg suppository daily[11] and Bafghi *et al.* used 200 mg suppository daily[12]. All included trials used 250 mg intramuscular 17-OHPC weekly in the comparison group[10–12]. Additional unpublished data were obtained from the authors of two of the included trials[11,12] (Table 2).

Synthesis of results

Women who received vaginal progesterone had a significantly lower rate of SPTB < 34 weeks (17.5% *vs* 25.0%; RR, 0.71 (95% CI, 0.53–0.95); three trials, 680 participants; Figure 3; low quality of evidence) and < 32 weeks (8.9% *vs* 14.5%; RR, 0.62 (95% CI, 0.40–0.94); three trials, 680 participants; low quality of evidence) compared with women who received intramuscular 17-OHPC. There were no significant differences in the rate of SPTB < 37 weeks, < 28 weeks and < 24 weeks between the two groups. The proportion of women who reported adverse drug reactions was significantly lower for those receiving vaginal progesterone compared with 17-OHPC (7.1% *vs* 13.2%; RR, 0.53 (95% CI, 0.31–0.91); two trials, 535 participants; very low quality of evidence). Regarding neonatal outcomes, vaginal progesterone was associated with a lower rate of admissions to NICU compared with 17-OHPC (18.7% *vs* 23.5%; RR, 0.63 (95% CI, 0.47–0.83); three trials, 680 participants; low quality of evidence), while there were no differences for other neonatal outcomes, including birth weight, and incidences of RDS, BPD, IVH, NEC, sepsis and perinatal death (Table 2).

DISCUSSION

Main findings

This pooled meta-analysis of three RCTs, including 680 women with a singleton gestation and prior SPTB, showed that daily vaginal progesterone, started at about 16 weeks' gestation, is associated with significantly lower rates of SPTB < 34 weeks, adverse maternal side effects and admission to NICU compared with intramuscular 17-OHPC.

Strengths and limitations

One of the strengths of our study is the inclusion of RCTs in a specific population, i.e. singleton gestations with prior SPTB. Prior SPTB is one of the most important risk factors for preterm delivery[1]. Furthermore, no prior meta-analysis has compared vaginal to intramuscular progestogens. This meta-analysis included all trials

Table 1 Characteristics of randomized controlled trials comparing vaginal progesterone to intramuscular 17α-hydroxyprogesterone caproate (17-OHPC) injection for prevention of recurrent spontaneous preterm birth (SPTB) included in systematic review and meta-analysis

Characteristic	*Maher (2012)[10]*	*Bafghi (2015)[12]*	*Elimian (2016)[11]*	*Total*
Country	Saudi Arabia	Iran	USA	—
Sample size (*n*)*	502 (253 *vs* 249)	33 (16 *vs* 17)	145 (79 *vs* 66)	680 (348 *vs* 332)
Dose of vaginal progesterone	90 mg gel daily	200 mg suppository daily	100 mg suppository daily	—
Dose of 17-OHPC	250 mg weekly	250 mg weekly	250 mg weekly	250 mg weekly
Exclusions for CL at randomization	CL < 25 mm	CL < 25 mm	CL not assessed	—
GA range at randomization (weeks)	14 + 0 to 18 + 6	16 + 0 to 20 + 6	16 + 0 to 20 + 6	14 + 0 to 20 + 6
GA at randomization (weeks, mean ± SD)*	15.3 ± 1.2 *vs* 15.4 ± 1.2	16.1 ± 2.9 *vs* 16.6 ± 1.2	17.9 ± 2.1 *vs* 18.0 ± 1.8	16.5 ± 2.1 *vs* 16.6 ± 1.4 (MD = −0.1 (95% CI, −0.3 to 0.1))
Primary outcome assessed	SPTB < 34 weeks	GA at delivery	SPTB < 37 weeks	—

Only first author is given for each study. *Vaginal progesterone *vs* intramuscular 17-OHPC. CL, cervical length; GA, gestational age; MD, mean difference.

Table 2 Primary and secondary outcomes of randomized controlled trials comparing vaginal progesterone with intramuscular 17α-hydroxyprogesterone caproate (17-OHPC) injection for prevention of recurrent spontaneous preterm birth (SPTB) included in meta-analysis

Outcome	*Maher (2012)*[10] *(n = 253 vs 249)*	*Bafghi (2015)*[12] *(n = 16 vs 17)*	*Elimian (2016)*[11] *(n = 79 vs 66)*	*Total (n = 348 vs 332)*	*RR or MD‡ (95% CI)*
SPTB < 37 weeks	83 (32.8) *vs* 88 (35.3)	5 (31.3) *vs* 6 (35.3)*	30 (38.0) *vs* 29 (43.9)	118 (33.9) *vs* 123 (37.1)	0.91 (0.74–1.11)
SPTB < 34 weeks	42 (16.6) *vs* 64 (25.7)	5 (31.3) *vs* 6 (35.3)*	14 (17.7) *vs* 13 (19.7)	61 (17.5) *vs* 83 (25.0)	0.71 (0.53–0.95)†
SPTB < 32 weeks	21 (8.3) *vs* 35 (14.1)	0 (0) *vs* 4 (23.5)*	10 (12.7) *vs* 9 (13.6)*	31 (8.9) *vs* 48 (14.5)	0.62 (0.40–0.94)†
SPTB < 28 weeks	8 (3.2) *vs* 9 (3.6)	0 (0) *vs* 0 (0)*	8 (10.1) *vs* 7 (10.6)*	16 (4.6) *vs* 16 (4.8)	0.91 (0.44–1.86)
SPTB < 24 weeks	3 (1.2) *vs* 3 (1.2)	0 (0) *vs* 0 (0)*	4 (5.1) *vs* 2 (3.0)*	7 (2.0) *vs* 5 (1.5)	1.27 (0.41–3.98)
Adverse drug reaction	19 (7.5) *vs* 35 (14.1)	0 (0) *vs* 0 (0)*	NA	19/269 (7.1) *vs* 35/266 (13.2)	0.53 (0.31–0.91)†
Birth weight (g)	2637 ± 737 *vs* 2562 ± 780	2514 ± 609 *vs* 2550 ± 912*	2777 ± 1131 *vs* 2680 ± 840	—	72.32‡ (44.53–191.84)
Admission to NICU	39 (15.4) *vs* 64 (25.7)	7 (43.8) *vs* 2 (11.8)*	19 (24.1) *vs* 12 (18.2)	65 (18.7) *vs* 78 (23.5)	0.63 (0.47–0.83)†
RDS	19 (7.5) *vs* 26 (10.4)	7 (43.8) *vs* 2 (11.8)*	9 (11.4) *vs* 5 (7.6)	35 (10.1) *vs* 33 (9.9)	1.02 (0.65–1.60)
BPD	3 (1.2) *vs* 4 (1.6)	0 (0) *vs* 0 (0)*	1 (1.3) *vs* 0 (0)*	4 (1.2) *vs* 4 (1.2)	0.95 (0.26–3.51)
IVH	5 (2.0) *vs* 5 (2.0)	0 (0) *vs* 0 (0)*	1 (1.3) *vs* 4 (6.1)*	6/348 (1.7) *vs* 9/315 (2.9)	0.62 (0.23–1.71)
NEC	3 (1.2) *vs* 2 (0.8)	0 (0) *vs* 0 (0)*	1 (1.3) *vs* 2 (3.0)	4 (1.2) *vs* 4 (1.2)	0.93 (0.24–3.62)
Sepsis	5 (2.0) *vs* 4 (1.6)	0 (0) *vs* 1 (5.9)*	1 (1.3) *vs* 3 (4.5)*	6 (1.7) *vs* 8 (2.4)	0.73 (0.27–1.99)
Perinatal death	6 (2.4) *vs* 10 (4.0)	0 (0) *vs* 0 (0)*	5 (6.3) *vs* 7 (10.6)	11 (3.2) *vs* 17 (5.1)	0.59 (0.28–1.24)

Data are given as *n* (%) or mean ± SD for vaginal progesterone *vs* 17-OHPC. *Additional unpublished data obtained from authors of original trials. †Statistically significant. ‡Mean difference (MD). BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NA, not available; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; RR, relative risk.

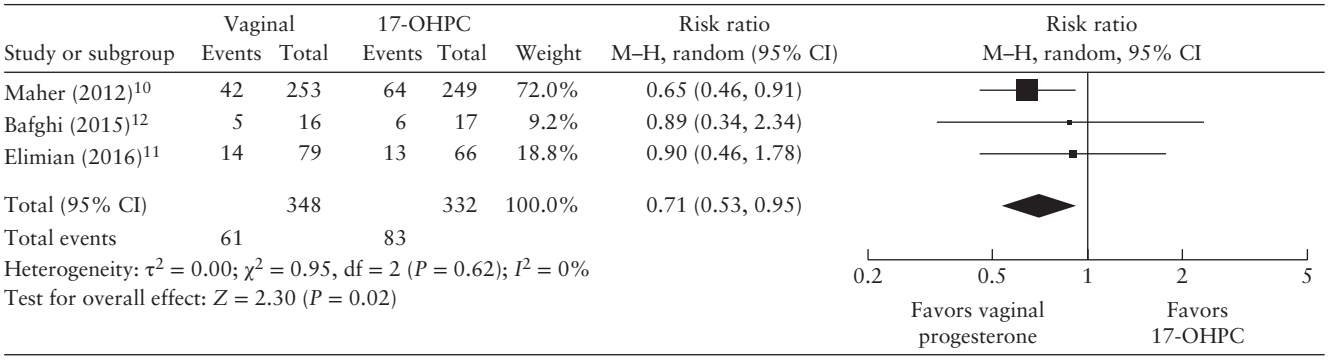

Figure 3 Forest plot for risk of recurrent spontaneous preterm birth (SPTB) < 34 weeks in women with singleton pregnancy and prior SPTB randomized to vaginal progesterone or intramuscular 17α-hydroxyprogesterone caproate (17-OHPC) injection. Only first author of each study is given. M–H, Mantel–Haenszel test.

published so far on this topic, including studies of high quality and with a low risk of bias, according to the Cochrane risk of bias tools. The statistical heterogeneity within the studies was low.

A limitation of our study is that we found only three trials that met the inclusion criteria. Furthermore, different doses of daily vaginal progesterone (90 mg gel, and 100 and 200 mg suppository) were used in each study, making it unclear which of these doses and/or formulations of vaginal progesterone should be preferred. Many outcomes were underpowered, including neonatal outcomes; however, these are indeed uncommon outcomes with an overall low incidence. None of the included trials was double blinded. Blinding could have been accomplished if a placebo had been utilized in each treatment arm. This was therefore a considerable source of bias that may have affected treatment of these women or their neonates. Given that there were only three trials and the majority of data were from only one of these studies, there was little power to discern significant heterogeneity and therefore to posit which model (fixed *vs* random effects) was the proper one. More than half of the women included in the analysis (502/680) were from one large study[10], which therefore drives the summary statistics[7]. We included the two smaller studies in order to allow for a more powerful analysis, especially for secondary outcomes.

Quality of evidence

The quality of evidence for each outcome is summarized in Table S1. For comparison of 17-OHPC *vs* vaginal progesterone, the quality of evidence was downgraded because of serious imprecision. Primary and secondary outcomes were imprecise because studies included relatively few patients with few events and thus had wide CIs around the estimate of the effect, and because the optimal information size was not reached. The quality of the evidence was also downgraded another level because of serious indirectness, owing to the different interventions used[8].

Implications

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal Fetal Medicine (SMFM) both recommend the use of 17-OHPC to prevent recurrent SPTB[3,4]. Data on the efficacy of 17-OHPC have generally been published earlier than data on the efficacy of vaginal progesterone, regarding comparison of these administration routes to placebo[2,5,6,15,16]. So far, four trials have compared weekly intramuscular injections with placebo or routine care and five have studied vaginal progesterone, as per the latest Cochrane Review in women with prior SPTB[6].

Most recently, a new large randomized study, the OPPTIMUM study, did not find significant effect of vaginal progesterone on prevention of preterm birth in 1228 women at risk of SPTB due to three major risk factors: prior SPTB; positive fetal fibronectin test; or short CL (< 25 mm) on transvaginal ultrasound[17]. It is noteworthy that the OPPTIMUM study was underpowered to detect a meaningful difference between vaginal progesterone and placebo in the subgroup of women with a short cervix, with a *post-hoc* statistical power of only 26% to detect a 23% reduction in the risk of SPTB < 34 weeks[17]. In a meta-analysis of five RCTs, including the OPPTIMUM study, Romero *et al.* showed that in women with a mid-trimester short CL, progesterone is associated with a significant reduction in the risk of preterm delivery and neonatal morbidity and mortality, without any deleterious effects on neurodevelopmental outcome[18].

As both routes have been shown to be effective against placebo in women with singleton gestation and prior SPTB[2,5,6], the next question to consider is how they compare with each other. Some studies have shown that natural progesterone, including vaginal progesterone, is preferable because of a lack of undesirable side effects, such as sleepiness, fatigue and headaches, compared with synthetic progestogens, including 17-OHPC[19]. Additionally, there is some concern that injection of 17-OHPC may increase the risk of early fetal death[19,20]. Our study showed a non-significant 29% reduction in perinatal death in women who received vaginal progesterone compared with 17-OHPC; however, our meta-analysis was not sufficiently powered for such a rare outcome.

The fact that vaginal progesterone was associated with lower rates of SPTB, fewer adverse side effects and neonatal benefits compared with intramuscular 17-OHPC needs to be correlated with cost-effectiveness. While no data on cost-effectiveness were reported in the three included trials, the cost of vaginal progesterone (about $11/day or about $77/week)[21] is much lower than that of 17-OHPC (> $500/week)[22] in the USA.

Conclusion

Compared with intramuscular 17-OHPC, vaginal progesterone in women with prior SPTB is associated with at least seven benefits: (1) reduced risk of recurrent SPTB[10–12]; (2) fewer adverse maternal side effects[10–12]; (3) fewer NICU admissions[10–12]; (4) lower cost[21,22]; (5) better compliance[10,12,23]; (6) women's preferred choice[12,21]; and (7) greater satisfaction[9,23].

In summary, we consider daily vaginal progesterone (suppository or gel) a reasonable, if not better, alternative therapy to weekly intramuscular 17-OHPC for prevention of SPTB in women with asymptomatic singleton pregnancy and prior SPTB. Given the clear and positive effect of progestogen in women with prior SPTB, we suggest offering 250 mg 17-OHPC weekly or 90–200 mg vaginal progesterone daily, starting from 16 weeks and continuing until 36 weeks or delivery, to asymptomatic women with prior SPTB. However, the quality levels of the summary estimates were low/very low, as assessed by GRADE, indicating that the true effect may be, or is likely to be, substantially different from the estimate of the effect.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Summary of findings and quality of evidence of randomized controlled trials (RCTs) included in meta-analysis

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Comparación entre la progesterona vaginal y el 17α-hidroxiprogesterona caproato intramuscular para la prevención del parto pretérmino espontáneo recurrente en embarazos con feto único: revisión sistemática y metaanálisis de ensayos controlados aleatorios

RESUMEN

Objetivo Recientemente se han realizado varios ensayos controlados aleatorios (ECA) que comparaban el caproato de 17α-hidroxiprogesterona (17-OHPC, por sus siglas en inglés) por vía intramuscular con la progesterona por vía vaginal para la reducción del riesgo de parto pretérmino espontáneo (PPTE) en embarazos con feto único de gestantes con historial de PPTE. El objetivo de esta revisión sistemática y metaanálisis fue evaluar la eficacia de la progesterona vaginal en comparación con la 17-OHPC en la prevención de embarazos con feto único de gestantes con historial de PPTE.

Métodos Se realizaron búsquedas en bases de datos electrónicas para identificar todos los ECA con embarazos de feto único asintomáticos con historial de PPTE antes de ser asignados al azar a un tratamiento profiláctico, ya fuera con progesterona vaginal (grupo de intervención) o con 17-OHPC intramuscular (grupo de control). No se aplicaron restricciones respecto al idioma o la ubicación geográfica. El resultado primario fue PPTE < 34 semanas. Los resultados secundarios fueron PPTE <37 semanas, < 32 semanas, < 28 semanas y < 24 semanas, la reacción materna adversa al fármaco y los resultados neonatales. Las medidas del resumen se reportaron como riesgo relativo (RR) con IC del 95%. Para cada estudio incluido se evaluó el riesgo de sesgo.

Resultados Se incluyeron tres ECA (680 mujeres). La media de la edad gestacional en el momento de la aleatorización fue de 16 semanas. A las mujeres se les administró progesterona hasta la semana 36 o hasta el parto. Con respecto a la progesterona vaginal, un estudio utilizó gel de 90 mg diariamente, otro utilizó un supositorio diario de 100 mg y el otro utilizó un supositorio diario de 200 mg. Todos los ECA incluidos en el grupo de comparación utilizaron 250 mg semanales de 17-OHPC por vía intramuscular. Las mujeres que recibieron progesterona vaginal tuvieron tasas significativamente más bajas de PPTE < 34 semanas (17,5% vs. 25,0%; RR 0,71 (IC 95%, 0,53–0,95); calidad de la evidencia baja) y < 32 semanas (8,9% vs. 14,5%; RR 0,62 (IC 95%, 0,40–0,94); calidad de evidencia baja), en comparación con las mujeres que recibieron 17-OHPC. No hubo diferencias significativas en las tasas de PPTE < 37 semanas, < 28 semanas y < 24 semanas. La tasa de mujeres que reportaron reacciones adversas a los medicamentos fue significativamente menor en el grupo de progesterona vaginal en comparación con el grupo de 17-OHPC (7,1% vs. 13,2%; RR 0,53 (IC 95%, 0,31–0,91); calidad de la evidencia muy baja). En cuanto a los resultados neonatales, la progesterona vaginal se asoció a una menor tasa de admisiones en la unidad neonatal de cuidados intensivos en comparación con la 17-OHPC (18,7% vs. 23,5%; RR 0,63 (IC 95%, 0,47–0,83); calidad de evidencia baja). Para la comparación del 17-OHPC con la progesterona vaginal se rebajó la calidad de las pruebas para todos los resultados en al menos un grado debido a imprecisiones (no se alcanzó el tamaño óptimo de la información) y en al menos un grado debido al carácter indirecto de los estudios (diferentes intervenciones).

Conclusiones La progesterona vaginal administrada diariamente (ya fuera como supositorio o como gel) desde la semana 16 de gestación es una alternativa razonable, si no mejor, a una inyección semanal de 17-OHPC para la prevención de PPTE en mujeres con embarazos de feto único e historial de PPTE. Sin embargo, el nivel de calidad de las estimaciones del resumen fue bajo o muy bajo según lo evaluado por GRADE, lo que indica que el verdadero efecto puede ser, o es probable que sea, sustancialmente diferente de la estimación del efecto.

单胎妊娠时黄体酮阴道给药与肌肉注射 17α-己酸羟孕酮预防复发性自发性早产：系统回顾和随机对照试验的 meta 分析

目的：最近有随机对照试验（randomized controlled trials，RCTs）对比了有自发性早产（spontaneous preterm birth，SPTB）既往史的单胎妊娠中肌肉注射 17α-己酸羟孕酮（intramuscular 17α-hydroxyprogesterone caproate，17-OHPC）与黄体酮阴道给药降低 SPTB 的风险。本篇系统回顾和 meta 分析的目的是评估在有 SPTB 既往史的单胎妊娠中黄体酮阴道给药对比 17-OHPC 预防 SPTB 的疗效。

方法：检索电子数据库，查找关于有 SPTB 既往史的无症状单胎妊娠的所有 RCTs，RCTs 中将患者随机分为接受黄体酮阴道给药（干预组）或肌肉注射 17-OHPC（对照组）。对语言或地理位置无限制。主要结局为孕 34 周前发生 SPTB。次要结局为孕 37 周前、孕 32 周前、孕 28 周前和孕 24 周前发生 SPTB，母亲不良药物反应以及新生儿结局。综合检测结果以相对危险度（relative risk，RR）和 95%CI 表示。对每项纳入研究的偏倚风险进行评估。

结果：纳入 3 项 RCTs（680 例孕妇）。随机分组时平均孕周约为 16 周。给予孕妇黄体酮，直至孕 36 周或分娩。在黄体酮阴道给药组中，一项研究采用每日 90 mg 凝胶，一项采用每日 100 mg 栓剂，另外一项研究采用每日 200 mg 栓剂。对照组中，所有纳入的 RCTs 均采用每周 250 mg 17-OHPC 肌肉注射。与 17-OHPC 组孕妇相比，黄体酮阴道给药组孕妇孕 34 周前 [17.5%和 25.0%；RR，0.71（95% CI，0.53~0.95）；低质量证据]和孕 32 周前[8.9%和 14.5%；RR，0.62（95% CI，0.40~0.94）；低质量证据]SPTB 的发生率明显较低。孕 37 周前、孕 28 周前和孕 24 周前 SPTB 的发生率无明显差异。黄体酮阴道给药组与 17-OHPC 组比较，孕妇不良药物反应的发生率明显较低[7.1%和 13.2%；RR，0.53（95% CI，0.31~0.91）；极低质量证据]。在新生儿结局方面，与 17-OHPC 组比较，黄体酮阴道给药组新生儿重症监护病房住院率较低[18.7%和 23.5%；RR，0.63（95% CI，0.47~0.83）；低质量证据]。对 17-OHPC 和黄体酮阴道给药进行比较，所有结局的证据质量由于不精确降低至少一级（未达到最佳信息量），由于间接性至少降低一级（不同干预措施）。

结论：为了预防有 SPTB 既往史的单胎妊娠孕妇发生 SPTB，在约孕 16 周时开始每日黄体酮阴道给药（栓剂或凝胶）是每周注射 17-OHPC 的一项合理的，即使不是更好的替代方案。然而，根据 GRADE，综合评估的质量水平较低或极低，表明真实的效果可能或很可能与估计的效果大不相同。