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17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth among singleton pregnant women with a prior history of preterm birth: a systematic review and meta-analysis of six randomized controlled trials

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To perform a systematic review and meta-analysis of all randomized controlled trials (RCTs) that investigated the clinical benefits of 17-alpha hydroxyprogesterone caproate (17OHPC) in the prevention of recurrent preterm birth (PTB) among singleton pregnant women with a previous history of PTB. We searched four major databases up till April 2021 and assessed the risk of bias in the included studies. We meta-analyzed various maternal-neonatal endpoints (n=18) and pooled them as mean difference or risk ratio (RR) with 95% confidence interval (CI) using the random-effects model. Six RCTs met the inclusion criteria, comprising 2,573 patients (17OHPC=1,617, control=956). RCTs revealed an overall low risk of bias. The rates of PTB <35 weeks (n=5 RCTs; RR, 0.77; 95% CI, 0.63-0.93; *P*=0.008), PTB <32 weeks (n=3 RCTs; RR, 0.68; 95% CI, 0.51-0.91; *P*=0.009), neonates with low birth weight (<2.5 kg) at delivery (n=3 RCTs; RR, 0.63; 95% CI, 0.5-0.79; *P*<0.001), and neonatal death (n=4 RCTs; RR, 0.41; 95% CI, 0.20-0.84; *P*=0.02) were significantly reduced in the 17OHPC group compared with the control group. Moreover, 17OHPC treatment correlated with a significantly decreased rate of retinopathy (n=2 RCTs; RR, 0.42; 95% CI, 0.18-0.97; *P*=0.004). However, there were no significant differences in the rates of neonatal intensive care unit admission, cesarean delivery, and other preterm-related complications between both the groups. Among singleton pregnant women with a prior history of PTB, 17OHPC may favorably decrease the risks of recurrent PTB and reduce the rate of neonatal death.

Keywords: 17-alpha hydroxyprogesterone caproate; Pregnancy; Preterm birth; Premature birth

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Introduction

Preterm birth (PTB) is defined as labor starting before 37 completed weeks of gestation since the last menstrual period [1]. It accounts for nearly 11% of live births worldwide [2]. Additionally, it leads to serious fetal mortality and morbidity, accounting for approximately 35% of all neonatal deaths [3].

The exact cause of preterm labor remains undetermined. However, some predisposing factors may lead to it. Examples of some maternal factors include congenital anomalies in the genital system, hormonal imbalances, and chronic medical conditions [4,5].

In women with a prior history of spontaneous PTB, all efforts are directed toward preventing the occurrence of recurrent PTB. Unfortunately, this risk seems to be unavoidable. Moreover, the available medical options have their own side effects, in addition to their doubtful efficacy [6-8]. For example, progesterone medications (either natural or synthetic) have been used to prevent the risk of PTB. However, to the best of our knowledge, there is no conclusive evidence to support their regular administration [7,9]. Recently, progesterone administration has been shown to decrease the incidence of PTBs in high-risk women [9]. As evidenced by a recent meta-analysis [9], the pooled data suggested the prophylactic use of progesterone administration to be effective in the prevention of PTB. However, these benefits may vary among women at risk, according to the underlying risk factors. Moreover, its efficacy depends on the route of administration and the dose of medication used. Nonetheless, the data were less conclusive regarding the reduction in neonatal complications [9].

Besides, the synthetic progesterone 17-alpha hydroxyprogesterone caproate (17OHPC) has been used for circumventing the recurrence of PTB in high-risk groups. Some studies have shown that 17OHPC is beneficial for decreasing the incidence of PTB [10-14]. In addition, the American College of Obstetricians and Gynecologists (ACOG) supports the use of 17OHPC for women at a risk of PTB [15]. However, recent trials have revealed that 17OHPC is not superior to placebo or no treatment in terms of the risk of PTB before 35 or 37 weeks [16,17].

Overall, the available literature reveals conflicting results about the efficacy of 17OHPC in preventing recurrent PTB. Fernandez-Macias et al. [18] conducted a meta-analysis of four randomized controlled trials (RCTs) comparing 17OHPC to placebo for the prevention of recurrent PTB. They reviewed four databases (not including EMBASE) until August 18, 2018. An updated literature search is warranted to provide contemporary evidence on the topic. We conducted a recent literature search in April 2021 and identified two more high-quality RCTs that were not previously pooled in a meta-analysis [16,17].

Therefore, we conducted a systematic review and meta-analysis of RCTs to holistically assess the efficacy of 17OHPC in the prevention of recurrent PTB among singleton pregnant women with a previous history of PTB, with an aim to provide comprehensive evidence to inform better clinical practice.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19] and adhered to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [20].

1. Eligibility criteria

Only RCTs were considered, and they were included if they met the following evidence-based PICO inclusion criteria: (i) population: pregnant women (singleton pregnancy) with a prior history of PTB; (ii) intervention: 17OHPC; (iii) comparator: any control intervention including placebo or no treatment; and (iv) outcomes: reliable extraction of any of the primary endpoints (PTB <37 weeks, PTB <35 weeks, PTB <32 weeks, neonates with low birth weight <2.5 kg at delivery, and neonatal death) or secondary endpoints (gestational age at delivery in weeks, birth weight in kg, neonatal intensive care unit [NICU] admission, bronchopulmonary dysplasia, respiratory distress syndrome, necrotizing enterocolitis, sepsis, retinopathy, intraventricular hemorrhage grade III-IV, patent ductus arteriosus, maternal corticosteroid administration, cesarean delivery, and tocolytic therapy. We excluded all secondary studies (such as meta-analyses, reviews, and conference abstracts), animal studies, pharmacokinetic studies, and studies with incomplete reported data. Moreover, we excluded patients with other risk factors of PTB such as placenta previa or a prior history of miscarriage.

2. Information sources, literature search, and study selection

We searched PubMed, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases until April 2021 for RCTs that met our inclusion criteria. We used the following search strategy: ((preterm labor) OR (preterm birth) OR (premature delivery) OR (premature labor) OR (early delivery) OR (early labor)) AND ((17-OHPC) OR (17-α-hydroxyprogesterone caproate) OR (17P) OR (hydroxyprogesterone hexanoate)).

We screened the retrieved articles in three steps. The first step involved importing the results from the electronic databases to a Microsoft Excel sheet software (Microsoft, Redmond, WA, USA) using EndNote software (Clarivate, Philadelphia, PA, USA). The second step included the title and abstract screening of the imported citations. The third step included a full-text screening of the included citations from the second step. Additionally, we manually searched the references of the included papers for possible missed RCTs. Two investigators independently completed the database search and study selection, and conflicts were resolved by consultation with a third investigator.

3. Data collection

We collected three categories of data from each included study. The first category included the baseline characteristics of the included studies and participants (such as the first author, year of publication, country, recruitment period of study participants, study groups, sample size, mean participant age, type of control treatment, and 17OHPC dose). The second category included the primary and secondary endpoints of the meta-analysis. The third category included data on the risk of bias assessment. Six investigators (in groups of two investigators per group) collected the data, and conflicts were resolved by consultation with the first investigator.

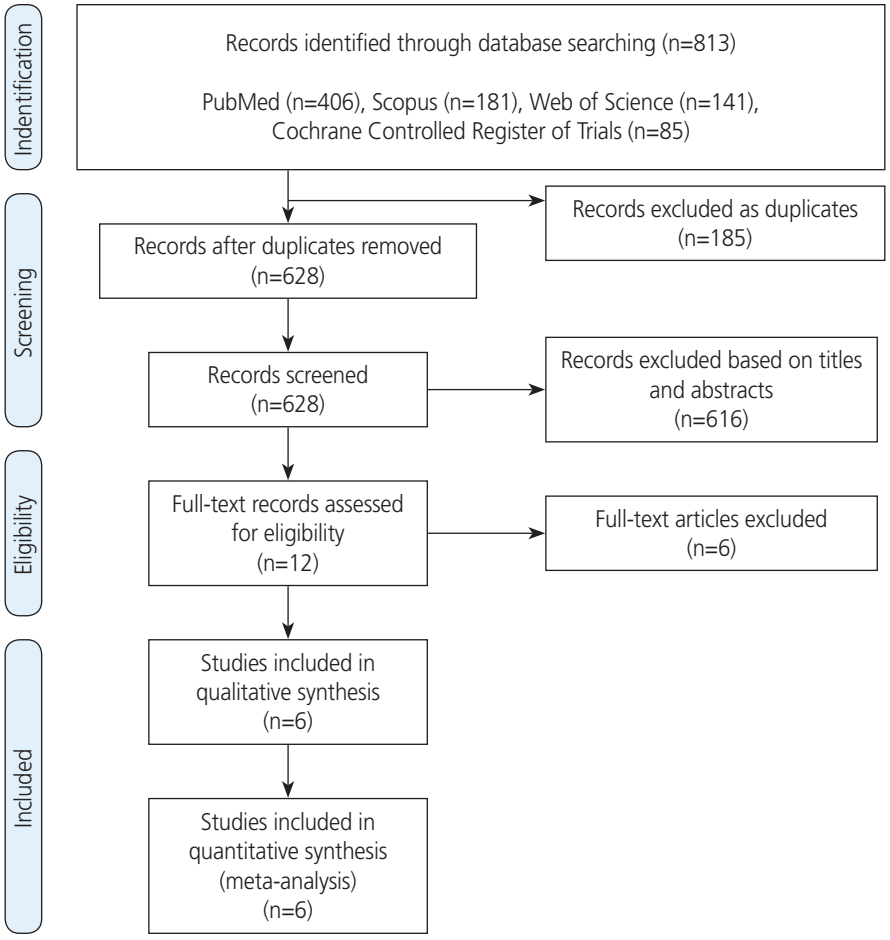

Fig. 1. The preferred reporting items for systematic reviews and meta-analyses flow diagram of the literature search.

4. Risk of bias assessment

We evaluated the risk of bias of the included studies in accordance with the Cochrane risk of bias assessment instrument [21]. This instrument assesses the following domains: (i) random sequence generation, (ii) allocation concealment, (iii) blinding of participants and personnel, (iv) blinding of outcome assessment, (v) incomplete outcome data, (vi) selective outcome reporting, and (vii) other potential sources of bias. Each domain was scored as unclear, low, or high risk. Two investigators independently executed the risk of bias assessment, and inconsistencies were rectified by consensus and consultation with a third investigator.

5. Analysis

We performed a meta-analysis of this study using the Review Manager software (Cochrane, London, UK). Our study included continuous and dichotomous outcomes. Continuous outcomes were analyzed using mean difference (MD) and 95% confidence interval (CI), whereas dichotomous outcomes were analyzed using risk ratio (RR) and 95% CI. In this meta-analysis, the different studies estimated different yet related intervention effects with assumed heterogeneity at the clinical and methodological levels. Therefore, the random-effects model was used because it is more conservative than the fixed-effects model [20]. To measure the presence of inconsistency among the studies, we used I^2 and the *P*-value of the chi-square tests [22]. Values of $P<0.1$ or $I^2>50\%$ were significant indicators of the presence of interstudy heterogeneity. We attempted to solve the inconsistency of heterogeneous outcomes using Cochrane's leave-one-out method, if applicable [20]. Subgroup analysis was performed for PTB rates of <37 weeks and <35 weeks based on cervical length at enrollment. Publication bias was assessed using funnel plots.

Results

1. Summary of included RCTs

Fig. 1 shows the PRISMA flow diagram of the literature search. Overall, six RCTs met the strict inclusion criteria, comprising a total of 2,573 patients (1,617 and 956 patients were assigned to the 17OHPC and control groups, respectively) [11-13,16,17,23]. The baseline characteristics of the included studies are summarized in Table 1.

Table 1. The baseline characteristics of patients in the included studies

Study	Country	Recruitment period (weeks)	Group	N	Age (yr)	17OHPC dose	Type of treatment in control group	Period of 17OHPC use (weeks)	Cervical length at enrollment (mm)
Blackwell et al. [16] (2020)	USA	$16^{0/7}$ to $20^{6/7}$ weeks	17OHPC	1,130	30.0±5.2	250 mg IM weekly	Placebo	16 to 36	Non-selected
			Control	578	29.2±5.2				
Ibrahim et al. [13] (2010)	Egypt	Second trimester (weeks not specified)	17OHPC	25	25.3±4.15	250 mg IM weekly	Placebo	14 to 36	Non-selected
			Control	25	25.6±3.85				
Jafarpour et al. [17] (2020)	Iran	$16^{0/7}$	17OHPC	50	25.4±2.6	250 mg IM weekly	No placebo	16 to 37	>30
			Control	50	25.0±2.38				
Meis et al. [12] (2003)	USA	16^{+0} to 20^{+6} weeks	17OHPC	310	26.0±5.6	250 mg IM weekly	Placebo	16 to 36	Non-selected
			Control	153	26.5±5.4				
Berghella et al. [23] (2010)	USA	16^{+0} to 22^{+6} weeks	17OHPC	52	26.3±4.5	250 mg IM weekly	No placebo	16 to 36	<25
			Control	100	26.8±5.3				
Saghafi et al. [11] (2011)	Iran	16 weeks	17OHPC	50	28.98±5.36	250 mg IM weekly	No placebo	16 to 37	Non-selected
			Control	50	29.32±5.69				

Values are presented as mean±standard deviation unless otherwise indicated.
17OHPC, 17-alpha hydroxyprogesterone caproate; IM, intramuscularly.

2. Risk of bias assessment

The included RCTs yielded an overall low risk of bias. Fig. 2 displays the risk of bias summary and a graph of the included RCTs. Supplementary Table 1 shows the detailed authors' judgment of the risk of bias of the included RCTs.

3. Meta-analysis of primary endpoints

1) Rates of PTB <37 weeks, <35 weeks, and <32 weeks

The pooled analysis showed no significant difference between groups regarding the rate of PTB <37 weeks (n=6 RCTs; RR, 0.79; 95% CI, 0.62-1.01; *P*=0.06). However, the

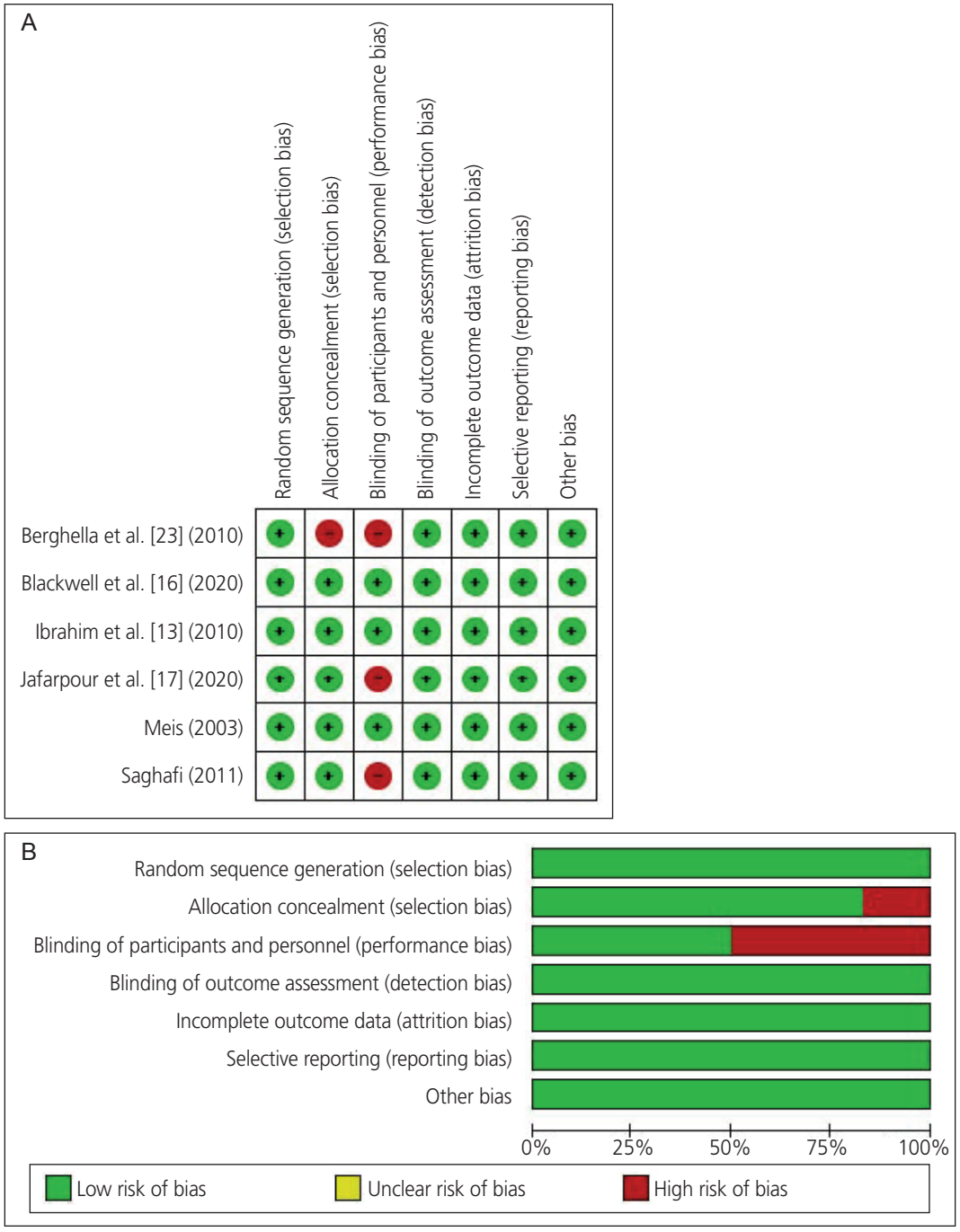

Fig. 2. The risk of bias summary (A) and graph (B) of the included studies.

rates of PTB <35 weeks (n=5 RCTs; RR, 0.77; 95% CI, 0.63-0.93; *P*=0.008) and PTB <32 weeks (n=3 RCTs; RR, 0.68; 95% CI, 0.51-0.91; *P*=0.009) were significantly lower in the 17OHPC group than in the control group. The pooled analysis was heterogeneous only for the outcome of PTB <37 weeks (*P*=0.004 and I^2=71%), and a sensitivity analysis failed to resolve the interstudy heterogeneity. On the other hand, the remaining outcomes were homogeneous (*P*=0.33 and I^2=13%, *P*=0.46 and I^2=0%, respectively) (Fig. 3). Subgroup analysis according to the cervical length at enrollment showed that patients with a non-selected cervical length achieved significantly lower rates of PTB <37 weeks (n=3 RCTs; RR, 0.64; 95% CI, 0.53-0.76; *P*<0.001) and PTB <35 weeks (n=2 RCTs; RR, 0.63; 95% CI, 0.46-0.85; *P*=0.002) than those in the other patient categories (Supplementary Fig. 1).

2) Rate of neonates with low birth weight <2.5 kg at delivery

The pooled analysis showed that the rate of neonates with a low birth weight (<2.5 kg) at delivery did not differ between both the groups (n=4 RCTs; RR, 0.79; 95% CI, 0.45-1.37; *P*=0.40). The pooled analysis was heterogeneous (*P*=0.002, I^2=79%). Between-study heterogeneity was resolved (c=0.75 and I^2=0%) after the omission of the Saghafi et al. [11] study, and the re-pooled rate of neonates with low birth weight

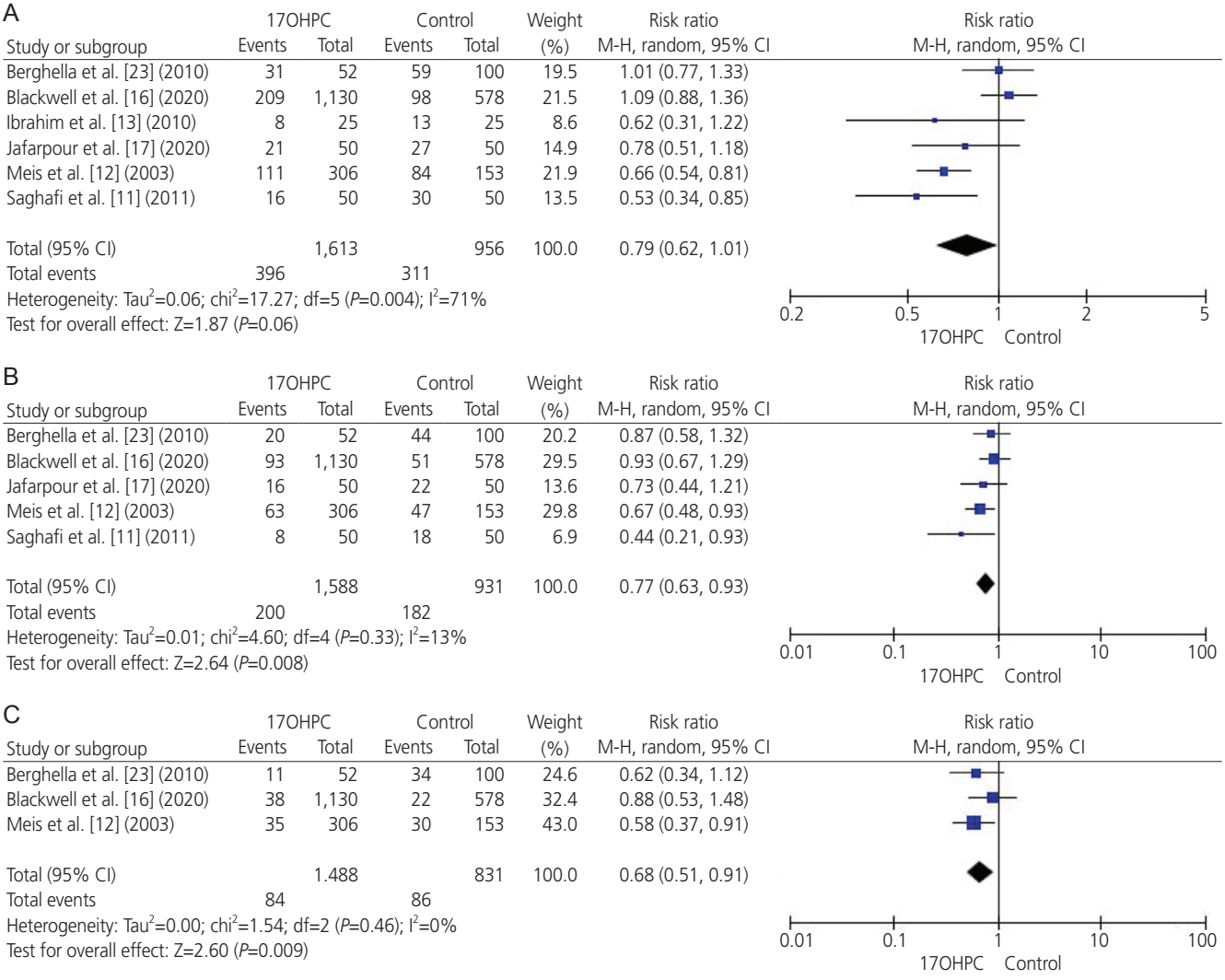

Fig. 3. Meta-analysis of the rates of preterm birth <37 weeks (A), <35 weeks (B), and <32 weeks (C). 17OHPC, 17-alpha hydroxyprogesterone caproate; M-H, Mantel-Haenszel; CI, confidence interval.

(<2.5 kg) at delivery was significantly lower in the 17OHPC group compared with the control group (n=3 RCTs; RR, 0.63; 95% CI, 0.5-0.79; *P*<0.001) (Fig. 4).

3) Rate of neonatal death

The pooled analysis showed that the rate of neonatal death was significantly lower in the 17OHPC group compared with the control group (n=4 RCTs; RR, 0.41; 95% CI, 0.20-0.84; *P*=0.02). The pooled analysis was homogeneous (*P*=0.31 and I^2=17%) (Fig. 5).

4. Meta-analysis of secondary endpoints

1) Mean gestational age at delivery

The pooled analysis showed that the mean gestational age at delivery did not differ between both the groups (n=2 RCTs; MD, 1.63 weeks; 95% CI, -0.49 to 3.76; *P*=0.13). The pooled analysis was heterogeneous (*P*<0.001 and I^2=90%) (Supplementary Fig. 2).

2) Mean birth weight at delivery

The pooled analysis showed that the mean birth weight at delivery was significantly increased in the 17OHPC group

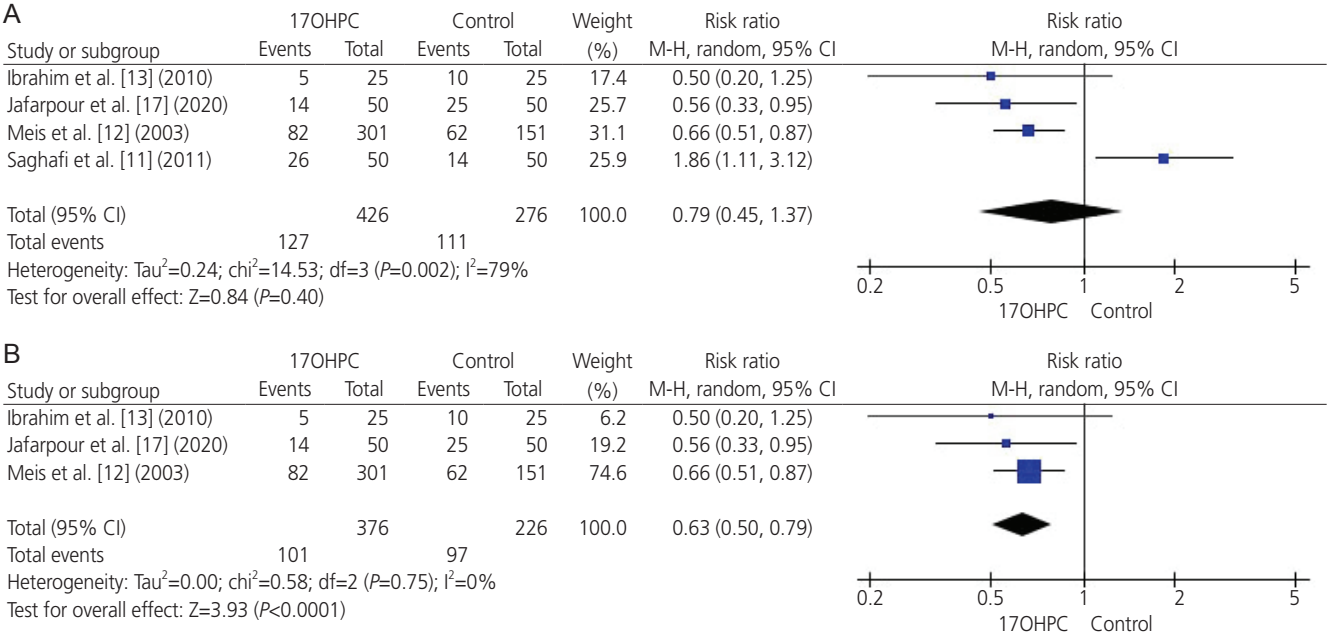

Fig. 4. Meta-analysis of the rates of a low birth weight (<2.5 kg) at delivery before (A) and after (B) sensitivity analysis using the leave-one-out method. 17OHPC, 17-alpha hydroxyprogesterone caproate; M-H, FULL NAME; CI, confidence interval.

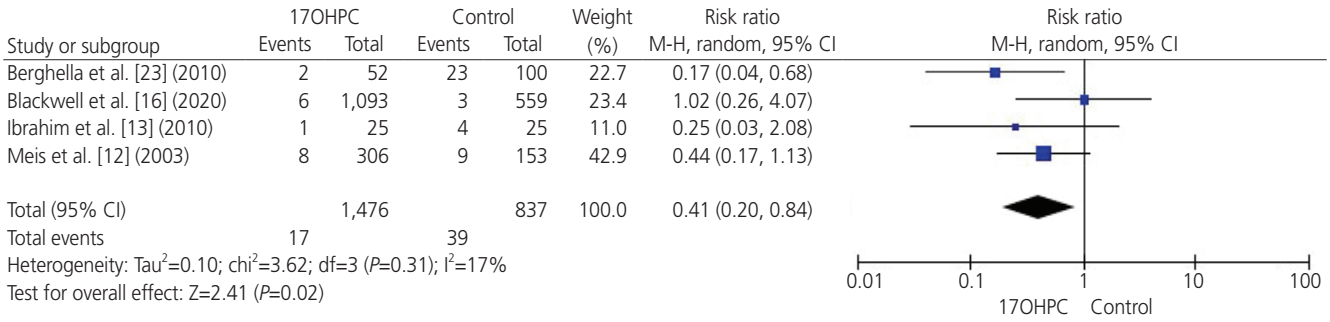

Fig. 5. Meta-analysis of the rate of neonatal death. 17OHPC, 17-alpha hydroxyprogesterone caproate; M-H, Mantel-Haenszel; CI, confidence interval.

compared with the control group (n=3 RCTs; MD, 0.12 kg; 95% CI, -0.06 to 0.30; *P*=0.19). The pooled analysis was heterogeneous (*P*=0.02 and I^2=75%). Interstudy heterogeneity was resolved (*P*=0.50 and I^2=0%) after the omission of the study of Blackwell et al. [16], and the re-pooled mean birth weight at delivery was significantly higher in the 17OHPC group than in the control group (n=2 RCTs; MD, 0.21 kg; 95% CI, 0.07-0.35; *P*=0.004) (Supplementary Fig. 3).

3) Neonatal complications: NICU admission, bronchopulmonary dysplasia, respiratory distress syndrome, necrotizing enterocolitis, sepsis, retinopathy, intraventricular hemorrhage grade III-IV, and patent ductus arteriosus

The pooled analysis showed that the rate of retinopathy (n=2 RCTs; RR, 0.42; 95% CI, 0.18-0.97; *P*=0.004) was significantly reduced in the 17OHPC group compared with the control group. Conversely, the rates of NICU admission (n=2 RCTs; RR, 0.72; 95% CI, 0.21-2.49; *P*=0.61), bronchopulmonary dysplasia (n=2 RCTs; RR, 0.93; 95% CI, 0.12-6.98; *P*=0.95), respiratory distress syndrome (n=2 RCTs; RR, 0.83; 95% CI, 0.49-1.39; *P*=0.47), sepsis (n=2 RCTs; RR, 1.01; 95% CI, 0.41-2.47; *P*=0.99), retinopathy of necrotizing enterocolitis (n=2 RCTs; RR, 0.22; 95% CI, 0.02-1.95; *P*=0.17), intraventricular hemorrhage grade III/IV (n=2 RCTs; RR, 1.44; 95% CI, 0.22-9.64; *P*=0.70), and patent ductus arteriosus (n=2 RCTs; RR, 0.46; 95% CI, 0.20-1.03; *P*=0.06) did not show significant difference between both the groups (Supplementary Fig. 4).

4) Maternal outcomes: rates of cesarean delivery, corticosteroid therapy, and tocolytic therapy

The pooled analysis showed that the rates of cesarean delivery (n=2 RCTs; RR, 1.04; 95% CI, 0.89-1.21; *P*=0.65), corticosteroid therapy (n=2 RCTs; RR, 0.88; 95% CI, 0.69-1.11; *P*=0.28), and tocolytic therapy (n=2 RCTs; RR, 1.09; 95% CI, 0.86-1.39; *P*=0.47) did not differ significantly difference between both the groups. All outcomes were homogenous (*P*>0.1 and I^2<50%) (Supplementary Fig. 5).

5. Publication bias

Supplementary Fig. 6 shows the funnel plots for outcomes with overall effect sizes derived from at least three RCTs. Visual (qualitative) inspection of funnel plots revealed asymmetry. However, since the number of included studies was small (n<10 RCTs per outcome), the results of publication bias should be interpreted with caution as they would be unreliable [22]. Therefore, quantitative analysis of publication bias was not performed using the Egger test or the Begg & Mazumada test.

Discussion

In this meta-analysis, we evaluated the efficacy of 17OHPC at preventing PTB by pooling data from six RCTs, comprising a total of 2,573 patients (1,617 and 956 patients in the 17OHPC and control groups, respectively). Overall, compared with the control group, the rates of PTB (<35 and <32 weeks), neonates with a low birth weight (<2.5 kg), neonatal death, neonatal necrotizing enterocolitis, and neonatal retinopathy were beneficially reduced in the 17OHPC group. Moreover, in contrast to the control group, 17OHPC treatment was correlated with a higher mean birth weight. Nevertheless, there were no significant difference between both the groups with respect to the rates of neonatal (NICU admission, bronchopulmonary dysplasia, respiratory distress, and intraventricular hemorrhage grade III/IV) and maternal (cesarean delivery, corticosteroid therapy, and tocolytic therapy) outcomes.

PTB represents a syndrome rather than a disease that is associated with different etiologies and pathological pathways [4,5]. Therefore, it is difficult to identify the factors that may affect the response to medical treatment. This meta-analysis showed that 17OHPC significantly decreased the rates of PTB at <35 and <32 weeks. Interestingly, only two RCTs [11,12] consistently demonstrated a statistically significant reduction in the rate of PTB. However, in the 2020 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG) study (an international multicenter RCT), Blackwell et al. [16] did not confirm the efficacy of 17OHPC at preventing recurrent PTB in singleton pregnancies. Despite the large sample size of 1,708 patients (1,130 and 578 patients in the 17OHPC and placebo groups, respectively), the authors concluded that the sample size was "underpowered," which could have negatively impacted the efficacy endpoint assessment of PTB to reveal statistically significant benefits. Moreover, the authors reported a more frequent rate of stillbirth in the 17OHPC group, although the difference was not statistically significant. Nevertheless, the authors later negated this

relationship between 17OHPC and stillbirth after a detailed clinical assessment.

Comparing 17OHPC treatment with vaginal progesterone suppositories, Pirjani et al. [24] included asymptomatic patients with short cervix as evidenced by ultrasonography (cervical length <25 mm). They found that the two interventions yielded similar effects with no significant difference in the hazard of PTB (14% and 10.4%, respectively). Moreover, they studied the majority of patients for 15 weeks assessing cervical length changes and found no significant difference between both the interventions. Moreover, Choi et al. [25] conducted recent RCT comparing vaginal micronized progesterone to intramuscular 17OHPC and concluded equal efficacy for preventing PTB before 37 weeks of gestation.

In the study by Fernandez-Macias et al. [18], a meta-analysis of the outcome of the rate of low birth weight (<2.5 kg) at delivery was based on only two RCTs (n=2). However, the meta-analysis in our study was based on a larger number of RCTs (n=4 RCTs). This could explain the intergroup difference in the observed overall effect sizes. The results of Saghafi et al. [11] are very different from those of the other studies included in this meta-analysis [12,13,16,17,23]. There are two potential reasons for this inconsistency. First, only the findings of Saghafi et al. [11] showed substantially opposite results compared with the others, and the overall effect size showed a significant interstudy heterogeneity (P=0.002, I^2=79%). When we removed the Saghafi et al. [11] using a leave-one-out sensitivity analysis, we resolved the interstudy heterogeneity and reached a homogeneous conclusion (Fig. 4B). Thus, the Saghafi et al. [11] study could have been an outlier. The second reason is that it could be a technical typo by the authors when they reported their findings (Table 1 in their manuscript [11]). This is because the authors showed that the mean newborn weight (g) was significantly increased in the 17OHPC group compared with the control group (2,695 g vs. 2,399 g, P=0.02). However, unexpectedly, the rate of low-birth weight neonates (<2,500 g) was significantly higher in the 17OHPC group than in the control group (52% vs. 28%, P<0.05). The authors could have mistakenly switched the percentages between the groups, i.e., it should have been 28% for the 17OHPC group and 52% for the control group.

Cervical length is a key determinant of PTB [26]. In our meta-analysis, the subgroup analysis revealed that the rates of PTB <37 weeks and PTB <35 weeks were significantly lower in patients who had non-selected cervical length at the time of study inclusion and randomization. These data suggest that women with short cervices are unlikely to gain obstetric benefits from 17OHPC administration. Nevertheless, because of the small number of studies included in the subgroup analyses, the data should be interpreted with caution, and additional large-sized RCTs are needed to confirm these conclusions.

All the included studies in this meta-analysis started 17OHPC as early as 14/16 weeks of gestation until 36/37 weeks of gestation to prevent the risk of PTB. However, the rates of complaints have not been consistently reported. Carter et al. [27] performed a large retrospective cohort study of roughly 3400 patients who received 17OHPC to reduce the risk of PTB. The authors revealed that the early administration of 17OHPC and better 17OHPC compliance correlated significantly with decreased frequencies of PTB. Similar findings were reported by Ning et al. [28].

According to the U.S. Food and Drug Administration [29] and a narrative review [30] of two large RCTs [12,16], 17OHPC is well tolerated and has a favorable safety profile. The most frequently reported adverse events of 17OHPC are mild injection-related side effects, such as tenderness, swelling, bruising, itching, and urticaria. Nausea and diarrhea can also occur at very low rates (less than 5% of patients). Moreover, the rate of severe adverse events culminating in 17OHPC discontinuation is very rare and does not exceed 1.5%. In addition, 17OHPC did not increase the risk of perinatal death. Moreover, maternal-related adverse events of 17OHPC are uncommon and comparable to placebo, including gestational diabetes mellitus, preeclampsia, venous thromboembolism, and cholestasis.

Fernandez-Macias et al. [18] performed a meta-analysis of four RCTs comparing 17OHPC to placebo among singleton pregnant women with a previous history of PTB. The study concluded that 17OHPC could potentially decrease the hazards of neonatal death and recurrent PTB <37, <35, and <28 weeks. Our meta-analysis is supported by some strengths. First, we included six RCTs that reported a larger sample size and far more detailed maternal and neonatal endpoints (n=18). Most importantly, our meta-analysis incorporated the high-quality PROLONG study [16] and another important study by Jafarpour et al. [17] Thus, our study presents the most contemporary and premium evidence on the effect of 17OHPC versus placebo/no treatment at preventing recurrent

PTB among patients with a previous history of PTB. Moreover, the majority of included RCTs yielded a low risk of bias in nearly all assessed domains. However, this meta-analysis is not without its limitations, including the small number of RCTs and their respective small sample sizes. Additional limitations include the heterogeneity of some pooled outcomes as well as the pooling of data from only two RCTs.

Conclusion

Among singleton pregnant women with a prior history of PTB, this systematic review and meta-analysis suggests that 17OHPC may favorably decrease the risk of recurrent PTB (<35 and <32 weeks). Moreover, 17OHPC may advantageously decrease the rates of neonatal death and retinopathy. Considering the efficacy of 17OHPC versus control, future research should include multi-centric trials examining the therapeutic efficacy and safety of 17OHPC versus active comparators or the combination of 17OHPC and an active progestogen.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

This study does not require approval of the Institutional Review Board because no patient data is contained in this article.

Patient consent

Not applicable.

Funding information

None.

Supplementary material

Supplementary Table 1, Supplementary Fig. 1-6 associated with this article can be found online at https://doi.org/10.5468/ogs.21264.

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