SYSTEMATIC REVIEW

Adjuvant 17-hydroxyprogesterone caproate in women with history-indicated cerclage: A systematic review and meta-analysis

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Abstract

Introduction: The purpose of this study was to evaluate whether there are additional benefits of 17-hydroxyprogesterone caproate (17-OHPC) supplementation in preventing recurrent spontaneous preterm birth in women with a prophylactic cerclage.

Material and methods: Electronic databases (MEDLINE, Scopus, ClinicalTrials.gov, PROSPERO, EMBASE, Scielo and the Cochrane Central Register of Controlled Trials) were searched for studies published before June 2018. Keywords included "preterm birth", "prophylactic cerclage", "history-indicated cerclage", "pregnancy" and "17-hydroxyprogesterone caproate". Studies comparing history-indicated cerclage alone with cerclage+17-OHPC were included. The primary outcome measure was preterm birth at <24 weeks of gestation. Secondary outcome measures include preterm birth at <28 weeks, <32 weeks and <37 weeks of gestation, respiratory distress syndrome, necrotizing enterocolitis, fetal birthweight, neonatal intensive care unit stay, mean gestational age at delivery, fetal/neonatal death, neurological morbidity (intraventricular hemorrhage plus periventricular leukomalacia), neonatal sepsis and a composite of severe neonatal morbidity. Severe neonatal morbidity was defined as a composite measure of periventricular leukomalacia, intraventricular hemorrhage (grades III and IV), necrotizing enterocolitis or respiratory distress syndrome. Meta-analysis was performed using the random-effects model of DerSimonian and Laird. Risk of bias and quality assessment were performed using the ROBINS-I and GRADE tools, respectively. PROSPERO Registration Number: CRD42018094559.

Results: Five studies met the inclusion criteria and were included in the final analysis. Of the 546 women, 357 (75%) received history-indicated cerclage alone and 189 (35%) received adjuvant 17-OHPC. The composite endpoint, severe neonatal morbidity, was present in 84 of 1515 neonates. Though there was a trend toward a reduced risk of preterm birth, the summary estimate of effect was not statistically significant when comparing cerclage alone with cerclage+17-OHPC at <24 weeks (relative risk [RR] .86, 95% confidence interval [CI] .45-1.65). Similarly, we found no differences in preterm birth at <37 weeks (RR .90, 95% CI .70-1.17) and <28 weeks (RR .85, 95% CI .54-1.32) when comparing cerclage alone with cerclage+17-OHPC.

Abbreviations: 17-OHPC, 17-hydroxyprogesterone caproate; CI, confidence interval; RR, relative risk.
There were no differences in fetal birthweight, respiratory distress syndrome or necrotizing enterocolitis comparing cerclage alone with cerclage+17-OHPC.

**Conclusions:** Intramuscular 17-OHPC in combination with prophylactic cerclage in women with prior preterm birth had no synergistic effect in reducing spontaneous recurrent preterm birth or improving perinatal outcomes.

**KEYWORDS**
17-hydroxyprogesterone caproate, cerclage, preterm birth, recurrent spontaneous preterm birth

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1 | **INTRODUCTION**

Every year, many women with a history of spontaneous preterm birth and second trimester pregnancy loss are able to get a prophylactic (history-indicated) cerclage. Anatomical, biochemical and clinical evidence from retrospective cohort studies and randomized clinical trials consistently support 12-14 weeks of gestation as the optimal time to place a prophylactic cerclage in at-risk women.

However, despite the effectiveness of history-indicated cerclage in reducing the risk of spontaneous preterm birth, about one-third of women that receive prophylactic cerclage still deliver preterm. This makes adjunctive therapies appealing options in maximizing the effectiveness of prophylactic cervical cerclage in prolonging pregnancy.

The use of 17-alpha hydroxyprogesterone caproate (17-OHPC) has been associated with a greater than 30% decrease in recurrence of preterm birth in women with prior spontaneous preterm birth between 20 and 36 weeks. At 16 weeks of gestation, some obstetricians begin 17-OHPC in women with history-indicated cerclage and continue it until 36 completed weeks of gestation. When 17-OHPC is used in combination with prophylactic cerclage, it is thought to prevent preterm birth due to the synergistic effect of both therapies. The rationale for this is that 17-OHPC is thought to act as an anti-inflammatory agent and a potent inhibitor of the formation of gap-junctions between myometrial cells, thereby preventing preterm labor onset and increasing the duration of pregnancy.

However, the routine use of 17-OHPC is controversial, in part because no adequately powered prospective studies or randomized clinical trials have directly evaluated the efficacy of combination therapy (prophylactic cerclage + 17-OHPC) in this patient population. In addition, health insurance companies continually refused to issue prior authorizations to commence 17-OHPC as adjunctive therapy in women with a history-indicated cerclage, asserting that it remains investigational in this setting and is not supported by available data. One recent retrospective cohort study reported that combination therapy (cerclage+17-OHPC) was more effective than cerclage alone for preventing spontaneous preterm birth at less than 24 weeks, but not at less than 28 or 37 weeks of gestation. However, the small number of spontaneous preterm births <24 weeks in this study precludes a clear conclusion about the efficacy of combined therapy. In addition, other studies that used combination therapy did not show differences in the rates of spontaneous preterm birth comparing history-indicated cerclage+17-OHPC with cerclage alone. Thus, use of combination therapy (both prophylactic cerclage and 17-OHPC) is neither well supported nor refuted by currently available data.

Therefore, the aim of this systematic review and meta-analysis was to synthesize comprehensively the literature on the efficacy of combination therapy (prophylactic cerclage+17-OHPC) compared with prophylactic cerclage alone in women considered to be at increased risk of spontaneous recurrent preterm birth.

2 | **MATERIAL AND METHODS**

2.1 | **Data sources**

The methodology of this systematic review and meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched ClinicalTrials.gov, MEDLINE, EMBASE, Scopus, Web of Science and the Cochrane Library for studies that met our inclusion and exclusion criteria using a search strategy designed in collaboration with an experienced Librarian at the Johns Hopkins University School of Public Health. Our PubMed search incorporated both controlled MEDLINE vocabulary (ie MeSH terms) and free text keywords. Our search included controlled vocabulary terms (MeSH and free text keywords) for 17-hydroxyprogesterone or history-indicated...
cervical cerclage (study intervention), preterm birth (study outcome), pregnancy (study population) and cohort/randomized controlled trial (study design). The search strategy included Boolean operators “OR” (for related term) and “AND” (combination of different concepts). Our ClinicalTrials.gov search strategy incorporated similar search strategy, without incorporating the “cohort” and “randomized controlled trial” terms. Relevant synonyms and alternative spellings were identified via the EMBASE controlled vocabulary Emtree.

2.2 | Main outcome measures

The primary outcome of interest of this systematic review is the proportion of preterm birth at less than 24 weeks of gestation, because 24 weeks or greater is considered a viable gestational age for neonatal intervention in most centers. We assessed for the following secondary outcomes: preterm birth at <37 weeks of gestation, preterm birth at <28 weeks, respiratory distress syndrome, necrotizing enterocolitis, fetal birthweight, neonatal intensive care unit (NICU) stay, mean gestational age at delivery, fetal and neonatal death, neurological morbidity (intraventricular hemorrhage and periventricular leukomalacia), neonatal sepsis and a composite of severe neonatal morbidity. Severe neonatal morbidity was defined as a composite measure of periventricular leukomalacia, intraventricular hemorrhage (grades III and IV), surgical necrotizing enterocolitis (requiring surgical treatment or peritoneal drainage) or respiratory distress syndrome. All primary and secondary outcomes were assessed as risk ratios, except fetal birthweight, which was compared as a difference of means.

2.3 | Eligibility criteria

The protocol for this review was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42018094559) before data extraction following the PRISMA guidelines for protocols (PRISMA-P). We searched for retrospective cohort, prospective cohort studies and randomized controlled trials regarding history-indicated cerclage, either alone or in combination with 17-OHPC. We included studies of pregnant women of any age, in any country, of any gestation or parity, in any trimester of pregnancy, with one or more histories of prior spontaneous preterm birth.

Using COVIDENCE software (Veritas Health Innovation Ltd, Melbourne, Australia), two reviewers (A.E. and J.S.) independently screened titles and abstracts for full-text reviews. Duplicate entries were removed by COVIDENCE software based on matching titles, authors and journals, and then manually confirmed. A 3rd adjudicator (E.G.), whose decision was final, resolved discrepancies between reviewers. Studies were categorized by titles and abstracts as “include” or “exclude” based on relevance to the study question and adherence to the systematic review’s eligibility criteria. Titles and abstracts marked “include” were reviewed in full text. Two reviewers (A.E. and E.G.) independently read each full-text article to assess eligibility based on the pre-defined eligibility criteria described previously in this protocol. A third adjudicator (J.S.), whose decision was final, resolved discrepancies between reviewers. Full-text articles were categorized as “include” or “exclude”. Studies marked as “include” based on full-text review were included in the systematic review.

Quality assessment of the included studies was performed using the risk of bias in non-randomized studies of interventions (ROBINS-I) assessment tool for cohort studies. This tool includes three domains: pre-intervention, at-intervention and post-intervention. In the pre-intervention domain, bias due to confounding and participant selection was evaluated. Possible confounding factors for this review include maternal age, parity, race/ethnicity, body mass index, tobacco use, history of large loop excision of the transformation zone, history of failed cerclage, use of antenatal corticosteroids, mode of delivery (cesarean/vaginal), type of suture material, type of cervical cerclage (Shirodkar/McDonald), number of prior preterm births, gestational age at cerclage placement and gestational age during 17-OHPC injections. Bias due to misclassification of the intervention status (cerclage alone vs cerclage+17-OHPC) was assessed in the at-intervention domain. The post-intervention domain included bias due to departures from the intended interventions.
TABLE 2  GRADE Working Group grades of evidence for included studies

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt;23.2 wk of gestation (follow up: mean 24 wk)</td>
<td>4 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Preterm birth &lt;28 wk of gestation (follow up: mean 26.5 wk)</td>
<td>4 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Preterm birth &lt;32 wk of gestation (follow up: mean 30.2 wk)</td>
<td>2 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Preterm birth &lt;37 wk of gestation (follow up: mean 36.2 wk)</td>
<td>5 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>4 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>3 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Birthweight</td>
<td>5 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Neonatal intensive care unit (NICU) stay (follow up: mean 5.3 wk)</td>
<td>3 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Gestational age at delivery (follow up: mean 35.4 wk)</td>
<td>4 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Fetal and neonatal loss</td>
<td>3 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Neurological morbidity (intraventricular hemorrhage plus periventricular leukomalacia)</td>
<td>3 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>2 Observational studies</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>None</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence

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: We are very uncertain about the estimate.

Effects of interventions (history‐indicated cerclage alone vs history‐indicated cerclage plus adjuvant 17‐OHPC (Relative and Absolute effects) (in bold).
CI, confidence interval; MD, mean difference; RR, relative risk.
The overall GRADE evidence of this review is low‐moderate.

missing data, methods of outcome measurements and selective reporting outcomes. In particular, co‐administration of vaginal progesterone after cerclage placement or after commencing 17‐OHPC can contribute to bias during the post‐intervention domain. Each non‐randomized study was rated as having a low, moderate, serious, critical or unclear risk of bias21 (Table 1). The
The overall GRADE evidence of this review is low‐moderate.

CI, confidence interval; MD, mean difference; RR, relative risk.

Effects of interventions (history‐indicated cerclage alone vs history‐indicated cerclage plus adjuvant 17‐OHPC

Relative and Absolute effects:

<table>
<thead>
<tr>
<th>Study design</th>
<th>No. of studies</th>
<th>Risk of bias</th>
<th>Certainty assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies</td>
<td>2</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>Observational studies</td>
<td>3</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
<tr>
<td>Observational studies</td>
<td>4</td>
<td>Not serious</td>
<td>Not serious</td>
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<tr>
<td>Observational studies</td>
<td>3</td>
<td>Not serious</td>
<td>Not serious</td>
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<tr>
<td>Observational studies</td>
<td>5</td>
<td>Not serious</td>
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<tr>
<td>Observational studies</td>
<td>4</td>
<td>Not serious</td>
<td>Not serious</td>
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<td>Observational studies</td>
<td>2</td>
<td>Not serious</td>
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<tr>
<td>Observational studies</td>
<td>3</td>
<td>Not serious</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

We are very uncertain about the estimate.

Very low quality

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

High quality

GRADE Working Group grades of evidence

TABLE 2
GRADE Working Group grades of evidence for included studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
<th>Quality of evidence (GRADE)</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal sepsis</td>
<td></td>
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<td></td>
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<tr>
<td>Neurological morbidity (intraventricular hemorrhage plus periventricular leukomalacia)</td>
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<tr>
<td>Fetal and neonatal loss</td>
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<tr>
<td>Gestational age at delivery (follow up: mean 35.4 wk)</td>
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<tr>
<td>Neonatal intensive care unit (NICU) stay (follow up: mean 5.3 wk)</td>
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<tr>
<td>Birthweight</td>
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<tr>
<td>Necrotizing enterocolitis</td>
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<tr>
<td>Respiratory distress syndrome</td>
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<tr>
<td>Preterm birth &lt;37 wk of gestation (follow up: mean 36.2 wk)</td>
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<tr>
<td>Preterm birth &lt;32 wk of gestation (follow up: mean 30.2 wk)</td>
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<td></td>
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<tr>
<td>Preterm birth &lt;28 wk of gestation (follow up: mean 26.5 wk)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth &lt;23.2 wk of gestation (follow up: mean 24 wk)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>368</td>
<td>198</td>
<td>-</td>
<td>MD 51.47 lower (244.04 lower to 141.11 higher)</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>68/237 (28.7%)</td>
<td>38/136 (27.9%)</td>
<td>RR .99 (.71-1.38)</td>
<td>3 fewer per 1000 (from 81 fewer to 106 more)</td>
<td>LOW IMPORTANT</td>
</tr>
<tr>
<td>234</td>
<td>129</td>
<td>-</td>
<td>MD .48 higher (.51 lower to 1.47 higher)</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>6/154 (3.9%)</td>
<td>5/114 (4.4%)</td>
<td>RR .78 (.23-2.57)</td>
<td>10 fewer per 1000 (from 34 fewer to 69 more)</td>
<td>LOW IMPORTANT</td>
</tr>
<tr>
<td>5/215 (2.3%)</td>
<td>4/158 (2.5%)</td>
<td>RR .94 (.26-3.42)</td>
<td>2 fewer per 1000 (from 19 fewer to 61 more)</td>
<td>LOW CRITICAL</td>
</tr>
<tr>
<td>4/73 (5.5%)</td>
<td>4/48 (8.3%)</td>
<td>RR .57 (.14-2.20)</td>
<td>36 fewer per 1000 (from 72 fewer to 100 more)</td>
<td>LOW IMPORTANT</td>
</tr>
</tbody>
</table>

The quality of evidence was assessed using the Grading quality of evidence and strength of recommendations (GRADE) guidelines. The GRADE guideline covers risk of bias, inconsistency, indirectness, imprecision and publication bias. The overall quality of evidence was reported for each outcome measure as high, moderate, low or very low.
2.4 | Data collection and analysis

We obtained missing information and other relevant data via email requests to the contact authors of the included studies and the Johns Hopkins University Welch library. For the purpose of this review, we allowed a period of 1 week for the author’s response. We determined whether to perform a meta-analysis based on a qualitative assessment of whether study populations and interventions were reasonably comparable. We assumed that if studies met our inclusion criteria, the outcome of recurrent spontaneous preterm birth would be comparable across studies. We also assessed clinical, methodological and statistical evidence of heterogeneity in the studies and considered this heterogeneity in our assessment to do a meta-analysis. We then performed a pairwise meta-analysis comparing cerclage+17-OHPC vs cerclage alone. We used a random-effects model, as we expected a great deal of heterogeneity in these studies given that the studies were likely to incorporate different patient populations and use varying methodologies.

In making a decision whether to present summary relative risk estimates, we considered clinical and methodological sources of heterogeneity across studies. We investigated statistical heterogeneity by calculating the Q, the $I^2$ and the $\tau^2$ statistic. For the Q statistic, which tests the hypothesis of a common effect, we used a critical value of <.1 as the cutoff for statistical significance. For the $I^2$ statistic, which shows the inter-study heterogeneity as a proportion of the total heterogeneity, we considered $I^2$ values of 25%-50%, 51%-75%, and 76%-100% to be of low, moderate and high heterogeneity, respectively.\textsuperscript{23} We also examined the confidence intervals of the risk estimates in the Forest plots for overlap. We reported $\tau^2$, which reflects the amount of true heterogeneity. For $\tau^2$, we used a critical value of <1.0 as the cutoff for statistical significance. We performed sensitivity analyses to assess the impact of excluding studies with higher risk of bias. In the case of statistically significant heterogeneity ($P$-value of the Cochrane Q statistic <.1), the random-effects model of Der-Siman and Laird was used to obtain the pooled relative risk (RR) estimate. For studies which reported both unadjusted and adjusted risk for confounders statistically proven, we performed an aggregate data meta-analysis using the generic inverse variance method to obtain the adjusted RR for the primary outcome and for the secondary outcomes in the main analysis.\textsuperscript{24,25} Statistical analyses were conducted with Review Manager (REVMAN) 5.3.\textsuperscript{26}

3 | RESULTS

3.1 | General characteristics of the studies

The search identified 732 bibliographic references, 664 through the PubMed database, and 68 through Clinicaltrials.gov (Figure 1). After 18 duplicate papers were removed, 714 records in title and abstract form were available for further screening. We excluded 691 clearly irrelevant references through reading of the abstracts.
<table>
<thead>
<tr>
<th>Authors, year (ref., country)</th>
<th>Type of study</th>
<th>Inclusion criteria</th>
<th>Allocation procedure</th>
<th>Groups and sample size</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stetson et al, 2016 (8, USA)</td>
<td>Retrospective cohort study</td>
<td>History of previous spontaneous PTB between 20 and 36 wk of gestation</td>
<td>All women received a history-indicated cerclage from 2002 to 2012 in Chicago, IL. 17-Hydroxyprogesterone caproate therapy was started after cerclage placement between 16 and 18 wk of gestation</td>
<td>Progesterone (17-OHPC) and cerclage: 60 Cerclage only: 123</td>
<td>Multiple cerclage in the same pregnancy; multiple gestation, delivery at outside institution, abdominal cerclage, major fetal anomalies</td>
</tr>
<tr>
<td>Sinkey et al, 2018 (19, USA)</td>
<td>Retrospective cohort study</td>
<td>History of 1 or 2 previous spontaneous PTB between 20 and 36 wk of gestation in singleton gestations</td>
<td>All women received a history-indicated cerclage at (12 and 14 wk of gestation) from 2011 to 2015. 17-hydroxyprogesterone caproate therapy was started after cerclage placement between 16 and 18 wk of gestation</td>
<td>Progesterone (17-OHPC) and cerclage: 33 Cerclage only: 55</td>
<td>Multiple gestation, abdominal cerclage, cerclage placed outside of ACOG guidelines, patients simultaneously on 17-OHPC and vaginal progesterone, and patients lost to follow-up</td>
</tr>
<tr>
<td>Samson et al, 2018 (10, USA)</td>
<td>Retrospective cohort study</td>
<td>History of 3 or more prior spontaneous preterm births (singleton gestations). Women with ultrasound indicated and examination-induced cerclages were excluded from the analysis</td>
<td>All women had prophylactic cerclage placement from January 1, 2006 to December 31, 2014. Women with cerclage placed included in the study were divided into: (a) a cohort with weekly supplemental injectable 17OHP-C (cerclage-17OHP-C group) and (b) controls without supplemental injectable 17OHP-C (cerclage alone group)</td>
<td>Progesterone (17-OHPC) and cerclage: 43 Cerclage only: 59</td>
<td>Iatrogenic or indicated PTB, incomplete delivery information, delivery at a different hospital, multiple gestation, use of vaginal progesterone, abdominal cerclage, stillbirth, lethal fetal anomaly, receiving fewer than four 17OHP-C injections, therapeutic cerclage</td>
</tr>
<tr>
<td>Mackeen et al, 2013 (9, USA)</td>
<td>Retrospective cohort study</td>
<td>History of 1 or 2 prior spontaneous PTB between 20 and 36 wk (without an ultrasound-indicated cerclage) (singleton only)</td>
<td>All women received a history-indicated cerclage (at 12 and 14 wk of gestation) from 1995 to 2009. In addition, most women received progesterone (17-OHPC; starting between 16 and 20 wk of gestation). Cerclages were removed at 36-37 wk of gestation</td>
<td>Progesterone (17-OHPC) and cerclage: 14 Cerclage only: 80</td>
<td>Multiple gestation, physical exam or ultrasound-indicated cerclages, multiple cerclages placed within the current pregnancy, intrauterine fetal demise, and lethal fetal anomalies</td>
</tr>
<tr>
<td>Yemini et al, 1985 (45, Israel)</td>
<td>Randomized trial</td>
<td>History of 2 miscarriages, 2 PTB, or 1 PTB and 1 miscarriage (singleton only)</td>
<td>All women received cerclage (as soon as the fetal heart tone was audible). In addition, participants randomly received progesterone (17-OHPC; mean gestational age at start was 12 wk) or placebo</td>
<td>Progesterone (17-OHPC) and cerclage: 39 Cerclage only (and placebo): 40</td>
<td>Multiple gestation, diabetes mellitus, chronic renal disease, and chronic hypertension</td>
</tr>
</tbody>
</table>

17-OHPC, 17-hydroxyprogesterone caproate; ACOG, The American College of Obstetricians and Gynecologists; PTB, preterm birth.
Thus, we assessed 23 references for eligibility in the systematic review. After careful scrutiny, we further excluded 18 of these references as they did not fulfill the inclusion criteria (seven studies had no information on history-indicated cerclage) as these were studies including only 17-OHPC[27-33]; five studies had no information on 17-OHPC (studies including only history-indicated cerclage)[34-38]; one publication was a letter to the editor regarding another study[39]; 4 studies compared rates of preterm birth in women with singleton pregnancies and a prior spontaneous preterm birth who had transvaginal ultrasound-measured cervical length <25 mm before 24 weeks of gestation and received 17-OHPC, ultrasound-indicated cerclage, both or neither,[40-43] and 1 paper did not specifically describe the perinatal outcomes in women with prophylactic cerclage+17-OHPC in their analysis[44] (Figure 1). Subsequently, five references describing five trials met the inclusion criteria for this systematic review. The PRISMA diagram is shown in Figure 1.

Table 3 shows the summary of the participants. The studies included a total of 546 women, with 189 women receiving 17-OHPC in addition to history-indicated cerclage, and 357 receiving history-indicated cerclage alone. Four of the studies were retrospective cohort studies[8-10,19] and one was a randomized trial.[45] Four of the studies were carried out in the USA[8-10,19] and one was done in Israel.[45] Two of the studies were published in 2018,[10,19] in 2016,[8] in 2014,[9] and one in 1985.[43] All the studies included women with singleton pregnancies and a history of prior spontaneous preterm birth. Exclusion criteria were quite uniform across all the studies at baseline. These included a history of multiple gestations and of therapeutic cerclage (history or ultrasound-indicated cerclage). Other exclusion criteria related to specific studies include delivery at an outside institution,[8,10] abdominal cerclage,[8,10,19] multiple cerclages in the same women,[8,9,19] concomitant use of vaginal progesterone,[10,19] stillbirth,[9,10] lethal fetal anomalies,[8-10] women who delivered less than four 17-OHPC injections,[10] incomplete delivery information, patients lost to follow up,[10,19] diabetes mellitus, chronic renal disease and chronic hypertension.[45]

All the studies compared prophylactic cerclage with history-indicated cerclage+17-OHPC. 17-OHPC was started in the second trimester (mostly at the 16th week of gestation) and continued till the 36th week of gestation, and cerclages were removed between 36 and 37 weeks of gestation; however, the timing varied slightly between the studies.

The pooled mean gestational age at cerclage placement and at commencement of 17-OHPC administration was comparable in both groups (14.4 ± 1.6 weeks in the cerclage-only group vs 14.2 ± 1.3 weeks in the adjuvant 17-OHPC group for cerclage placement, and 16.2 ± 5.6 weeks in the cerclage-only group vs 16.4 ± 4.6 weeks in the adjuvant 17-OHPC group for 17-OHPC commencement). The primary outcome in the individual studies was spontaneous preterm birth at <24 weeks of gestation,[8] <34 weeks of gestation,[10] <35 weeks of gestation[9,19] or <37 weeks of gestation.[44] Secondary outcomes included preterm birth at <32 weeks of gestation,[9,10] preterm birth at <28 weeks of gestation,[8,10,19] respiratory distress syndrome,[8,10,19,45] necrotizing enterocolitis,[8,10,19] neonatal intensive care unit stay[8,10,19] and neonatal birthweight.[8,10,19,45] All five studies were powered for their primary outcomes and some of the common secondary outcomes.

Quality assessment of the included studies performed using the ROBINS-I tool for cohort studies is shown in Table 1. Most of the included studies showed an overall good rate with regard to bias due to selection of participants and measurement of interventions, and in the selection of the reported results of the study groups. The main weaknesses of these studies were their retrospective designs, small sample size and the lack of information on the duration of follow up. For the most part, the participants in these studies were clinically heterogeneous, with women having one, two, three or more prior preterm births. Also, all the studies ideally excluded women with risk factors that predispose to preterm birth at baseline and contraindications to cerclage placement such as multiple gestations, more than one cerclage in index pregnancy, lethal congenital fetal anomalies and stillbirth. The studies also had methodological heterogeneity, including differences with respect to number of participants in the study arms and paucity of information about study follow up.

3.2 | Synthesis of the results
We investigated statistical heterogeneity mainly using the Q statistic, I² and the τ². A priori, we specified a Q statistic of <.1 as statistically significant, and an I² statistic of 25%-50%, 51%-75% and 76%-100% as low, moderate and high heterogeneity, respectively. We also visually examined the confidence intervals of the summary estimates in the Forest plots for overlap. With respect to our primary and secondary outcomes, an I² statistic of <25%, a Q statistic of P <.01, and a τ² of <1 in the primary outcome suggest low heterogeneity. In deciding whether to proceed with a meta-analysis; with reasonable clinical and methodological heterogeneity in the studies, and considering low I² values, appreciable overlap of the confidence intervals and a τ² that wasn't substantial, it was reasonable to proceed with a meta-analysis (with subgroup analyses) to evaluate the effect of history-indicated cerclage and 17-OHPC on preterm birth.

The meta-analysis showed a 14% reduction in the risk of preterm birth at <24 weeks of gestation in women treated with prophylactic cerclage compared with history-indicated cerclage+17-OHPC. This risk reduction was not statistically significant at the 95% level (RR .86, 95% confidence interval [CI] .45-1.65) (Figure 2). Preterm birth at <28 weeks was evaluated in 4 studies.[8-10,19] Meta-analysis of these studies demonstrated a 15% reduction in the risk of preterm birth at <28 weeks in women treated with prophylactic cerclage compared with history-indicated cerclage+17-OHPC. However, this risk reduction was not shown to be statistically significant at the 95% level (RR .85, 95% CI .54-1.32) (Figure 3). Two studies evaluated preterm birth at <32 weeks as a secondary outcome.[9,10] The meta-analysis of these studies demonstrated a 26% reduction in the risk of preterm birth in women treated with history-indicated cerclage alone compared with history-indicated cerclage+17-OHPC. This risk reduction was
Preterm birth at <37 weeks was evaluated in five studies.\textsuperscript{8,10,19,45} Meta-analysis of these studies demonstrated a 10% reduction in the risk of preterm birth in women treated with prophylactic cerclage compared with history-induced cerclage+17-OHPC. However, this risk reduction was not shown to be statistically significant at the 95% level (RR 0.74, 95% CI 0.40–1.38) (Figure 4). Four studies\textsuperscript{8,10,19,45} reported respiratory distress syndrome as a secondary outcome. The meta-analysis of these trials demonstrated a 19% decrease in the risk of respiratory distress syndrome in women treated with prophylactic cerclage compared with history-induced cerclage+17-OHPC. However, this risk decrease was not shown to be statistically significant (RR 0.90, 95% CI 0.70–1.17) (Figure 5). Three studies\textsuperscript{8,10,19} reported necrotizing enterocolitis as a secondary outcome. The meta-analysis of these trials demonstrated a 40% decrease in the risk of necrotizing enterocolitis in women treated with prophylactic cerclage compared with history-induced cerclage+17-OHPC. This risk decrease was not shown to be statistically significant (RR 0.60, 95% CI 0.16–2.34) (Figure 7). There were no differences in fetal birthweight between women treated with history-induced cerclage alone and those treated with history-induced cerclage+17-OHPC (mean difference −51.47, 95% CI −244.04 to 141.11) (Figure 8).

Length of neonatal intensive care unit (NICU) stay, mean gestational age at delivery, fetal/neonatal death, neurological morbidity, neonatal sepsis and a composite of severe neonatal morbidity were assessed in the included studies (Figures 9–14). There were no statistically significant differences in outcomes comparing cerclage alone with cerclage+17-OHPC groups. Subgroup analysis was done to evaluate the outcome of preterm birth with respect to the number of prior spontaneous preterm births in the studies—1 or 2 histories of prior spontaneous preterm births (4 studies)\textsuperscript{8,9,19,45} vs 3 or more prior spontaneous preterm births (1 study)\textsuperscript{15}. The results were similar to the main analysis (Figure 15).

Publication bias was assessed using funnel plots (Figures 16–18). The funnel plots are scatterplots of the estimated effect size (relative risk estimates) of maternal and fetal outcome measures plotted on the horizontal axis against the reciprocal of standard error of the estimated effect on the vertical axis for the studies identified. Formal publication bias assessment was also done using Egger’s test. Egger’s test results were \(P = 0.02\) for preterm birth at <24 weeks, \(P = 0.04\) for preterm birth at <28 weeks, \(P = 0.01\) for preterm birth at <32 weeks, and \(P = 0.03\) for preterm birth at <37 weeks of gestation, suggesting asymmetry.

### DISCUSSION

This systematic review and meta-analysis demonstrated no differences in spontaneous preterm birth reduction in women with prophylactic cerclage alone compared with women who received cerclage and adjuvant intramuscular 17-OHPC supplementation. Even with subgroup analysis, the non-significant effect of prophylactic cerclage+17-OHPC on preterm birth remained. Though there was a trend toward a reduced risk of spontaneous preterm birth at <24, <28, <32 and <37 weeks of gestation in women who received history-induced cerclage alone compared with those who received both therapies, the summary estimates of effect did not reach statistical significance. There was a trend towards a reduced risk of respiratory distress syndrome and necrotizing enterocolitis, but the summary with history-induced cerclage+17-OHPC.
FIGURE 4  Forest plot for the risk of preterm birth at <32 wk. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 5  Forest plot for the risk of preterm birth at <37 wk. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 6  Forest plot for the risk of respiratory distress syndrome. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 7  Forest plot for the risk of necrotizing enterocolitis. [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 8  Forest plot for fetal birthweight. [Color figure can be viewed at wileyonlinelibrary.com]
The American College of Obstetricians and Gynecology and the Society for Maternal Fetal Medicine guidelines recommend that women with a prior spontaneous preterm birth are treated with either intramuscular 17-OHPC or cervical cerclage (if there is cervical insufficiency). However, the diagnosis of cervical insufficiency can be challenging due to lack of objective findings and clear diagnostic criteria, as cervical insufficiency may be accompanied by subclinical uterine contractions and cervical
shortening, both features suggestive of preterm labor. In addition, it can sometimes be difficult to ascertain whether ruptured membranes occurred before or after the onset of uterine contractions in women with a history of mid-trimester pregnancy loss. In part, the lack of clarity that surrounds prophylactic cerclage in this setting is fostered by uncertainty in identifying those women who will genuinely benefit from its use (i.e., those with genuine cervical insufficiency or truly increased risk of early preterm delivery), hence the rationale for some practitioners in clinical practice to begin weekly 17-OHPC at 16 weeks of gestation and continue this until 36 weeks as adjuvant therapy to prophylactic cerclage placement, as some women with prior spontaneous preterm deliveries would be eligible for a history-indicated cerclage and/or 17-OHPC. However, the routine use of hydroxyprogesterone caproate in women who have received history-indicated cerclage remains controversial, in part because no adequately powered prospective studies or randomized trials have directly evaluated the efficacy of combination therapy (both history-indicated cerclage and 17-OHPC) in this patient population.
We did not find any meta-analysis on the synergistic effect of 17-OHPC plus history-indicated cerclage compared with prophylactic cerclage alone. Our finding that the efficacy of combined therapy (17-OHPC and prophylactic cerclage) did not differ from cerclage alone was consistent with findings from 3 of the included studies in this meta-analysis. The 2016 publication by Stetson et al and the 1985 publication by Yemini et al demonstrated a possible synergistic effect of 17-OHPC in women who received prophylactic cerclage. The study by Stetson et al demonstrated that women who received prophylactic cerclage plus intramuscular 17-OHPC experienced a significant reduction (69%) in the rate of spontaneous preterm birth at <24 weeks compared with women who were treated with cerclage alone. However, secondary analyses excluding history-indicated cerclages revealed that the effect of 17-OHPC was seen preferentially in women with exam and ultrasound-indicated cerclages, suggesting that there is little or no additive benefit of 17-OHPC in women with prophylactic cerclage. In addition, the small number (n = 33) of spontaneous preterm births at less than 24 weeks precludes a clear conclusion about the efficacy of combined therapy.

Another concern is the notion that the synergistic effect of 17-OHPC on prophylactic cerclage may be directly related to the number of prior spontaneous preterm births. To address this question, we performed a subgroup analysis of the included studies based on the number of prior spontaneous preterm births (1 or 2) compared with studies with ≥3 prior spontaneous preterm births. Even with subgroup analysis and adjusting for potential confounders, the non-significant effect of prophylactic cerclage+17-OHPC compared with history-indicated cerclage on preterm birth and adverse neonatal outcomes remained. These results have important implications for how providers should interpret and use 17-OHPC plus cerclage in the management of women with prior preterm birth. The finding suggests that irrespective of the number of prior spontaneous preterm births, adjuvant 17-OHPC is unlikely to have a synergistic effect with prophylactic cerclage.

Our study has several strengths. The most important strength of our work rests on the fact that our systematic review and meta-analysis focused only on studies comparing 17-OHPC plus history-indicated cerclage with prophylactic cerclage alone (excluding examination and ultrasound-indicated cerclages). We contacted the authors of the included studies to extract their data on outcomes of prophylactic cerclage alone vs 17-OHPC plus prophylactic cerclage. Secondly, we adjusted for potential confounding factors in our analysis. A generic inverse variance method was used to obtain the adjusted risk estimates for studies that adjusted for statistically proven confounders. Thirdly, most of the included studies had a low risk of bias (as suggested by the Q statistic, the I^2 and the τ^2 of the Forest plots in this meta-analysis). We further performed subgroup analyses to check heterogeneity within the studies. Fourthly, all the studies used the McDonald technique of cervical cerclage placement, ensuring uniformity and reducing provider variability of the technique across all the included studies.

The small number of included studies, their retrospective non-randomized design, different periods of follow up, lack of information on exact gestational age of prior spontaneous preterm births and gestational age at cerclage placement, variations in gestational age at initiation of 17-OHPC, dissimilarity in the populations (due to different numbers of prior spontaneous preterm births) and differences in the type of suture materials used for cerclage (prolene, mersilene tape, ethibond) were limitations of this meta-analysis. The asymmetric nature of the funnel plots and the results of Egger’s test (for gestational ages <24, <28, <32 and <37 weeks of gestation) would suggest a possible publication bias. However, assessment of publication bias in this review is particularly difficult given that the number of studies were small (5 studies); funnel plots are thought to be unreliable methods of investigating potential bias if the number of studies is <10. Different provider experience in cerclage placement and number of cervical cerclage stitches placed (1 vs 2 or more reinforcement cerclages) may also have affected our results. The overall quality of evidence, as assessed by GRADE, was low or moderate for most of the observed outcomes. For example, the GRADE evidence was low for preterm birth at <28 and 32 weeks of gestation, respiratory distress syndrome and necrotizing enterocolitis; there was moderate GRADE evidence for preterm birth at <37 weeks of gestation and fetal birthweight.

Finally, this study was planned as a meta-analysis of all available studies comparing prophylactic cerclage+17-OHPC with cerclage alone, and the lack of statistically significant differences in outcomes may be related to being underpowered outcomes. The ideal method to compare the effectiveness and safety of 17-OHPC and prophylactic cerclage and prophylactic cerclage alone in women with a history of prior spontaneous preterm is by performing a direct comparison with a randomized controlled clinical trial. However, it is uncertain whether there will be such a randomized trial in the near future. We conducted a sample size calculation to determine the number of participants required to conduct such a trial. Assuming a 15% reduction in the frequency of preterm birth at <24 weeks of gestation from the prophylactic cerclage-alone group to the 17-OHPC plus prophylactic cerclage group, 1400 patients (700
randomized to each group) would be required for this study to have 80% power and a type 1 error rate of 5%. In the absence of such a trial, the findings of this systematic review and meta-analysis provide some evidence to counsel patients and inform physician providers of the efficacy of adjuvant 17-OHPC in women with prophylactic cerclage.

5 | CONCLUSION

Adjuvant therapy with weekly intramuscular 17-OHPC did not result in either a further reduction in the risk for preterm birth at <24, <28, <32 and <37 weeks of gestation or improvement of adverse neonatal outcomes related to prematurity when compared with prophylactic cerclage placement alone. Adequately powered prospective and randomized trials are recommended to provide strong recommendations on adjuvant use of intramuscular 17-OHPC in the setting of history-indicated cerclage. Such trials should be powered to investigate differences in cervical cerclage types (Shirodkar vs McDonald), number of cerclage stitches (1 vs 2 or more reinforcement cerclages), type of cervical cerclage suture (prolene, mersilene-tape, ethibond), and timing of 17-OHPC administration by gestational age after prophylactic cerclage placement. Until such studies are available, adjuvant use of 17-OHPC after placement of a prophylactic cerclage is not supported by current evidence.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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