Published in final edited form as:

Am J Obstet Gynecol. 2013 January ; 208(1): 42.e1–42.e18. doi:10.1016/j.ajog.2012.10.877.

VAGINAL PROGESTERONE VERSUS CERVICAL CERCLAGE FOR THE PREVENTION OF PRETERM BIRTH IN WOMEN WITH A SONOGRAPHIC SHORT CERVIX, SINGLETON GESTATION, AND PREVIOUS PRETERM BIRTH: A SYSTEMATIC REVIEW AND INDIRECT COMPARISON META-ANALYSIS

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Abstract

OBJECTIVE—No randomized controlled trial has directly compared vaginal progesterone and cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix in the midtrimester, singleton gestation, and previous spontaneous preterm birth. We performed an indirect comparison of vaginal progesterone versus cerclage, using placebo/no cerclage as the common comparator.

STUDY DESIGN—Adjusted indirect meta-analysis of randomized controlled trials.

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DISCLOSURE: The majority of the authors report no conflict of interest except as stated in this paragraph. Dr. John M. O'Brien was involved in studies of progesterone gel treatment for preterm birth prevention sponsored by Columbia Laboratories, Inc., the manufacturer of the preparation used in the PREGNANT trial and a previous trial of vaginal progesterone in women at risk for preterm delivery. Dr. O'Brien serves on Advisory Boards and is a Consultant for Watson Pharmaceuticals, a company with a financial interest in marketing vaginal progesterone gel for the prevention of preterm birth. He and others are listed in the patent on the use of all progesterone compounds to prevent preterm birth. (US Patent Number 7,884,093: Progesterone for the Treatment and Prevention of Spontaneous Preterm Birth). George Creasy is an employee of Columbia Laboratories, Inc.

RESULTS—Four studies evaluating vaginal progesterone versus placebo (158 patients) and five evaluating cerclage versus no cerclage (504 patients) were included. Both interventions were associated with a statistically significant reduction in the risk of preterm birth <32 weeks of gestation and composite perinatal morbidity and mortality compared with placebo/no cerclage. Adjusted indirect meta-analyses did not show statistically significant differences between vaginal progesterone and cerclage in reducing preterm birth or adverse perinatal outcomes.

CONCLUSION—Based on state-of-the-art methodology for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the midtrimester, singleton gestation, and previous preterm birth. The selection of the optimal treatment may depend upon adverse events, cost and patient/clinician preferences.

Keywords

prematurity; uterine cervix; transvaginal ultrasound; perinatal mortality; admission to neonatal intensive care unit; birth weight <1500 g; progesterin

INTRODUCTION

Most of the efforts to prevent preterm birth have been focused on the treatment of symptoms or signs of activation of the common pathway of parturition^{1–5} (i.e. increased uterine contractility,^{6–28} preterm cervical ripening^{29–41} and/or membrane decidual activation).^{42–56} Although the detection of increased uterine contractility^{57–66} has been the focus of clinicians and reproductive biologists for decades, emerging clinical^{67–76} and laboratory-based evidence^{77–96} suggests that focusing on the uterine cervix may yield approaches to identify the patient at risk for preterm delivery as well as interventions to prevent it.^{97–115}

A sonographic short cervix has emerged as a powerful predictor of preterm birth.^{67–74,116–122} It is unlikely that this condition is due to a single cause, and a multiple causation model of a sonographic short cervix has been proposed (e.g. a short cervix is syndromic in nature).^{75,123,124} Such model would have biological, diagnostic, prognostic and therapeutic implications.^{3,75} Indeed, patients may have a short cervix after DES exposure in utero,^{125–127} a cervical conization,^{128–145} a LEEP procedure,^{146–150} intrauterine infection/inflammation,^{151–161} a decline in progesterone action,^{162–165} and the challenging condition clinically referred to as idiopathic cervical insufficiency.^{166–173}

Three interventions have been proposed to manage patients with a sonographic short cervix: 1) vaginal progesterone administration;^{101–105} 2) a cervical cerclage for patients with a prior history of preterm birth;^{174–177} and 3) a vaginal pessary.^{97–99} Recently, a combination of vaginal progesterone and a pessary has been reported to be a successful method to reduce the rate of preterm delivery in twin gestations with a cervix of <25mm.¹⁷⁸

Two independent randomized clinical trials^{101,104} and an individual patient data meta-analysis showed that vaginal progesterone decreases the rate of preterm delivery and neonatal morbidity/mortality in women with a sonographic short cervix.¹⁷⁹ This is the case for patients with or without a prior history of preterm birth.¹⁷⁹ The placement of a cervical cerclage appears to be indicated in patients presenting with acute cervical insufficiency,^{180–187} and perhaps, in some patients, with a prior history of preterm birth and a sonographic short cervix of <25mm.^{174–177} Thus, there appear to be two interventions that may reduce the rate of preterm delivery in patients with a prior history of preterm birth and a cervix of <25mm: vaginal progesterone administration and a cervical cerclage.

Recently, two professional organizations have recommended that cerclage may be considered for the management of women with a singleton gestation, prior spontaneous preterm birth and a cervical length <25 mm before 24 weeks of gestation.^{188,189} This recommendation was mainly based on an individual patient data (IPD) meta-analysis of randomized controlled trials showing that cerclage is associated with a statistically significant reduction in the risk of preterm birth at <37, <35, <32, <28, and <24 weeks of gestation, and composite perinatal morbidity and mortality when compared with no cerclage.¹⁷⁶ However, another IPD meta-analysis demonstrated that vaginal progesterone administration to women with a sonographic short cervix (<25 mm) in the midtrimester significantly decreased the risk of preterm birth at <35, <34, <33, <30, and <28 weeks of gestation and composite neonatal morbidity and mortality when compared to placebo.¹⁷⁹ In addition, a subgroup analysis showed that vaginal progesterone was associated with a significant reduction in the risk of preterm birth at <33 weeks of gestation and composite neonatal morbidity and mortality in women with a short cervix (<25mm), singleton gestation, and previous spontaneous preterm birth.¹⁷⁹

The availability of vaginal progesterone and cerclage for the prevention of preterm birth in women with a short cervix, singleton gestation and previous spontaneous preterm birth could create a dilemma for physicians and patients alike about the optimal choice of treatment.¹⁹⁰ Thus far, there are randomized controlled trials that have directly compared vaginal progesterone and cerclage has not been performed. In the absence of this evidence, indirect meta-analysis has emerged as an accepted and valid methodology for comparing competing interventions with each other using a common comparator.^{191–194}

We performed an adjusted indirect meta-analysis to compare the treatment effects of vaginal progesterone versus cerclage in asymptomatic women with a cervical length <25 mm in the midtrimester, singleton gestation, and previous spontaneous preterm birth for the prevention of preterm birth. Initially, we conducted an IPD meta-analysis to evaluate the efficacy of vaginal progesterone versus placebo in patients with such characteristics. Then, the summary estimates and measures of uncertainty were used together with those reported in the IPD meta-analysis that evaluated cerclage versus no cerclage¹⁷⁷ to perform the adjusted indirect comparison meta-analysis.

MATERIALS AND METHODS

The study was conducted based on a prospectively prepared protocol, and is reported using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses of randomized controlled trials¹⁹⁵ and suggested guidelines for IPD¹⁹⁶ and indirect meta-analyses.¹⁹⁷

Literature search

We searched MEDLINE, EMBASE, CINAHL, and LILACS (all from inception to May 31, 2012), the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html) (1960 to May 31, 2012), ISI Web of Science (<http://www.isiknowledge.com>) (1960 to May 31, 2012), Research Registers of ongoing trials (www.clinicaltrials.gov, www.controlled-trials.com, www.centerwatch.com, www.anzctr.org.au, <http://www.nihr.ac.uk>, and www.umin.ac.jp/ctr), and Google scholar using a combination of keywords and text words related to *progesterone* (“progesterone”, “progestins”, “progestogen”, “progestagen”, “progestational agent”), *cervical cerclage* (“cerclage”, “cervical stitch”, “cervical suture”, “cervical ligation”, “shirodkar suture”, “shirodkar operation”, “shirodkar stitch”, “shirodkar procedure”, “McDonald suture”, “McDonald procedure”, “McDonald method”, “McDonald technique”), *short cervix* (“short cervical length”, “short cervix”, “cervical shortening”) and

preterm birth (“preterm”, “premature”). Congress proceedings of international society meetings of maternal-fetal and reproductive medicine and international meetings on preterm birth, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also searched. Experts in the field were contacted to identify further studies. No language restrictions were applied.

Study selection

We included randomized controlled trials in which asymptomatic women with a sonographic short cervix (cervical length <25 mm) in the midtrimester, singleton gestation, and previous spontaneous preterm birth at less than 37 weeks of gestation were randomly allocated to receive vaginal progesterone versus placebo/no treatment, or cerclage versus no cerclage for the prevention of preterm birth. Trials were included if the primary aim of the study was to prevent preterm birth in women with such characteristics, or if the primary aim was to prevent preterm birth in women with other characteristics, but outcomes were available for patients with a pre-randomization cervical length <25 mm in the midtrimester, singleton gestation, and previous preterm birth. Trials were excluded if they: 1) were quasi-randomized; 2) evaluated the interventions only in women with multiple gestations; 3) evaluated vaginal progesterone in women with actual or threatened preterm labor, second trimester bleeding or premature rupture of membranes; 4) evaluated the administration of progesterone in the first trimester only to prevent miscarriage; 5) assessed history-indicated cerclage (placed for the sole indication of poor obstetric history), physical examination-indicated cerclage (placed for second-trimester cervical dilatation), or compared different cerclage techniques or outpatient cerclage versus inpatient cerclage; 6) compared cerclage with 17 α -hydroxyprogesterone caproate; or 7) did not provide data for women with cervical length <25 mm in the midtrimester, singleton gestation, and previous preterm birth

All published studies deemed suitable were retrieved and reviewed independently by two authors (A.C-A. and R.R.) to determine inclusion. Disagreements were resolved through consensus.

Outcome measures

The prespecified primary outcome measures were preterm birth <32 weeks of gestation and composite perinatal morbidity and mortality (defined as the occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal death). Secondary outcome measures included preterm birth at <37, <35, and <28 weeks of gestation, respiratory distress syndrome, necrotizing enterocolitis, grade III/IV intraventricular hemorrhage, neonatal sepsis, bronchopulmonary dysplasia, perinatal mortality, a composite neonatal morbidity outcome (defined as the occurrence of any of the above mentioned neonatal morbidities), birth weight <1500 g and <2500 g, and admission to the neonatal intensive care unit (NICU).

Assessment of risk of bias

The risk of bias in each included study was assessed by using the criteria recently outlined in the Cochrane Handbook for Systematic Reviews of Interventions.¹⁹⁸ Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Review authors' judgments were categorized as “low risk” of bias, “high risk” of bias or “unclear risk” of bias. The assessments considered the risk of *material* bias rather than *any* bias. “Material bias” is defined as a bias of sufficient magnitude to have a notable impact on the

results or conclusions of the trial. The risk of bias in each trial included was assessed individually by two reviewers (A.C-A. and R.R.). Any differences of opinion regarding assessment of risk of bias were resolved by discussion.

Data extraction

Two authors (A.C-A. and R.R.) extracted data from each study on participants (inclusion and exclusion criteria, number of women and fetuses/infants in randomized groups, baseline characteristics, and country and date of recruitment), study characteristics (randomization procedure, concealment allocation method, blinding of clinicians, women and outcome assessors, completeness of outcome data for each outcome, including attrition and exclusions from the analysis, and intention to treat analysis), details of interventions (aim, gestational age at trial entry, daily dose of vaginal progesterone and duration of treatment, cerclage type and suture used, and cointerventions), and outcomes (number of outcome events/total number in women with a cervical length <25 mm, singleton gestation, and previous spontaneous preterm birth. Women with multiple gestations, no previous spontaneous preterm birth, or cervical length ≥ 25 mm were excluded. For studies assessing cerclage, data on proportions and relative risks (RRs) with 95% confidence intervals (CIs) for each outcome measure were extracted from the IPD meta-analysis by Berghella et al.¹⁷⁷ Disagreements in extracted data were resolved by discussion among reviewers.

Statistical analysis

Statistical analyses were based on an intent-to-treat basis and included all randomized women and their fetuses/infants. For studies assessing vaginal progesterone, IPD were combined in a two-stage approach in which outcomes were analyzed in their original trial and then summary statistics combined using standard summary data meta-analysis techniques to give an overall measure of effect (summary RR with 95% CI).¹⁹⁹ A similar approach was used in the IPD meta-analysis of trials that evaluated cerclage versus no cerclage.¹⁷⁷ Heterogeneity of the results among studies was tested with the quantity I^2 ,²⁰⁰ and Mantel-Haenszel Q statistics. I^2 values $\geq 50\%$ or $P < .10$ for Mantel-Haenszel Q statistics indicated a substantial level of heterogeneity. Fixed-effects models were used if substantial statistical heterogeneity was not present. Otherwise, random-effects models were used.

The number needed to treat (NNT) for benefit or harm with their 95% CIs were calculated for the primary outcomes for which there was a statistically significant reduction or increase in risk difference based on control event rates in the included trials.²⁰¹ Publication and related biases were assessed visually by examining the symmetry of funnel plots and statistically by using the Egger test.²⁰² A P value $< .1$ was considered to indicate significant asymmetry.

The adjusted indirect comparison meta-analysis of vaginal progesterone versus cerclage was performed according to the most widely applied indirect comparison method by Bucher et al.²⁰³ The Canadian Agency for Drugs and Technologies in Health¹⁹³ and others^{191,194,204} have identified this method as the most suitable approach for performing indirect treatment comparisons of randomized controlled trials. In this method, the randomization of each trial is maintained, and the direct comparisons A versus B and C versus B with the common comparator link B are used to yield an indirect comparison of A versus C. As vaginal progesterone and cerclage have been compared to placebo and no cerclage, respectively, indirect comparison was enabled by the “common” placebo/no cerclage arms. An extension of the Bucher approach was used to convert the summary estimates (lnRRs) and measures of uncertainty (variances) from the two meta-analyses into a RR and 95% CI representing the difference between vaginal progesterone (p) and cerclage (c) as follows:¹⁹³

$$\bullet \ln(RR_{pc \text{ Indirect}}) = \Sigma \ln(RR_{pc})$$

$$\bullet 95\% \text{ CI of } \ln(RR_{pc \text{ Indirect}}) = \Sigma \ln(RR_{pc}) \pm Z_{\alpha/2} \sqrt{\Sigma Var(\ln(RR_{pc}))}$$

where Var indicates the square of the standard error (variance) and $Z_{\alpha/2}$ is the upper 95% percentile of the standard normal distribution. All values were back transformed to give the estimate of RR_{pc} with a 95% CI.

To examine the assumption of similarity of treatment effects, we investigated the effect of patient and trial characteristics on both direct and indirect comparison results using sensitivity analyses. A predefined sensitivity analysis was conducted, by excluding patients that received progesterone in trials that evaluated cerclage versus no cerclage, and patients that received a cerclage in studies that compared vaginal progesterone with placebo, to explore the impact of these co-interventions on the effect size for preterm birth and perinatal mortality. This analysis was performed because it is unclear if the effects of progesterone and cerclage are additive in women with a short cervix, singleton gestation, and previous spontaneous preterm birth. An additional sensitivity analysis was planned to evaluate the effect of study quality on the main outcomes by excluding trials with high risk of bias.

One author (A.C-A.) conducted all statistical analyses using Review Manager (RevMan) version 5.1.6 (Nordic Cochrane Centre, Copenhagen, Denmark) for performing direct meta-analyses, and Indirect Treatment Comparison (ITC) software version 1.0 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada) to perform adjusted indirect comparison meta-analyses.

Informed consent was provided by the patients upon enrollment in the each of the original trials. In this study, the data were not used for any other purpose other than those of the original trial, and no new data were collected. Therefore, informed consent specifically for this project was not considered necessary. This study was exempted for review by the Human Investigations Committee of Wayne State University. No patient identifiers were provided by any investigator.

RESULTS

Of the 5606 relevant citations identified, the abstracts were reviewed and 32 studies were retrieved because they were considered potentially relevant to this indirect meta-analysis. Twenty-three studies were excluded^{205–227} (Figure 1). The remaining nine trials met the inclusion criteria and provided data for 662 women with a cervical length <25 mm at midtrimester, singleton gestation, and previous spontaneous preterm birth at less than 37 weeks of gestation.^{101,104,113,115,174,228–231} Four studies evaluated vaginal progesterone versus placebo (158 women)^{101,104,228,229} and five evaluated cerclage versus no cerclage (504 women).^{113,115,174,230,231}

The main characteristics of studies included in this indirect comparison meta-analysis are presented in Table 1. All four studies that evaluated vaginal progesterone were double-blind, placebo-controlled trials.^{101,104,228,229} None of the studies that assessed cerclage was double-blind. Seven trials (two that evaluated vaginal progesterone^{101,104} and all five that evaluated cerclage^{113,115,174,230,231}) examined the interventions in women with a sonographic short cervix, one evaluated the use of vaginal progesterone in women with a

history of spontaneous preterm birth,²²⁸ and the remainder evaluated the use of vaginal progesterone in women with a prior spontaneous preterm birth, uterine malformations or twin gestation.²²⁹ Only one trial was specifically designed to evaluate the use of cerclage in women with a cervical length <25 mm at midtrimester, singleton gestation, and previous spontaneous preterm birth.¹⁷⁴ The primary outcome was preterm birth <37 weeks for one trial,²²⁹ <35 weeks for 2 trials,^{113,174} <34 weeks for two trials,^{101,115} <33 weeks for two trials,^{104,231} 32 weeks for one trial,²²⁸ and gestational age at delivery for the remaining study.²³⁰

Gestational age at cervical length screening varied between 14 and 25 weeks of gestation although most studies performed screening before 25 weeks of gestation.^{104,113,115,174,228–231} Of the four trials that evaluated vaginal progesterone, two used gel (90 mg/day),^{104,228} one used capsules (200 mg/day),¹⁰¹ and the other used suppositories (100 mg/day).²²⁹ The treatment was initiated at 24 weeks of gestation in two trials,^{101,229} between 20 and 23 weeks of gestation in one trial,¹⁰⁴ and between 18 and 22 weeks of gestation in the remaining study.²²⁸ Two studies^{101,229} reported that participating women received study medication from enrollment until 34 weeks of gestation, and two^{104,228} from enrollment until 36 6/7 weeks of gestation. In the study by Hassan et al,¹⁰⁴ five women received an emergency cerclage. Among the five trials that evaluated cerclage, four used the McDonald procedure^{113,115,174,230} and one used the Shirodkar technique.²³¹ Rescue cerclage in women allocated to the no cerclage group was allowed in three studies based on physical examination¹⁷⁴ or based on ultrasonographic cervical changes.^{115,230} Prophylactic antibiotics and tocolytics were administered to most participating women in three studies,^{115,230,231} whereas bed rest was recommended to all women recruited in two trials.^{113,115} In the trial by Owen et al,¹⁷⁴ 99 women received 17 α -hydroxyprogesterone caproate and one received vaginal progesterone.²³²

All nine studies included in the meta-analysis had adequate random sequence generation and allocation concealment, were free of selective outcome reporting, and had no obvious risk of other biases. In the four trials that evaluated vaginal progesterone, there was blinding of participants, health care providers and outcome assessors. In the five trials evaluating cerclage, study participants and healthcare providers were not blinded and it was unclear if outcome assessors were masked to intervention allocations after inclusion of patients into the study. However, we judged that assessment and measurement of most outcomes included in our review are considered objective in nature and were not likely to be influenced by lack of blinding in studies that evaluated cerclage. All but one study¹⁰⁴ had adequate handling of incomplete outcome data. Overall, all nine trials were considered to be at low risk of bias.

Direct comparisons

The use of either vaginal progesterone or cerclage in patients with a cervical length <25 mm in the midtrimester, singleton gestation, and previous spontaneous preterm birth was associated with a significant reduction in the risk of preterm birth <32 weeks of gestation (RR 0.47, 95% CI 0.24–0.91 for vaginal progesterone and RR 0.66, 95% CI 0.48–0.91 for cerclage) and composite perinatal morbidity and mortality (RR 0.43, 95% CI 0.20–0.94 for vaginal progesterone and RR 0.64, 95% CI 0.45–0.91 for cerclage) when compared with placebo and no cerclage, respectively (Table 2). The number of patients who needed to be treated with vaginal progesterone rather than with placebo to prevent one case of preterm birth <32 weeks of gestation or composite perinatal morbidity/mortality was 7 (95% CI, 5–38 for preterm birth <32 weeks of gestation and 5–69 for composite perinatal morbidity/mortality). The corresponding NNTs for cerclage were 10 (95% CI, 7–38) and 11 (95% CI, 7–45), respectively.

Infants whose mothers received vaginal progesterone had a significantly lower risk of composite neonatal morbidity and admission to NICU than infants whose mothers had received placebo. Patients allocated to cerclage had a statistically significant reduction in the risk of preterm birth <37, <35, and <28 weeks of gestation, and birth weight <1500 g when compared to those allocated to no cerclage.

Indirect comparison

Adjusted indirect comparison meta-analyses showed that, compared with cerclage, treatment with vaginal progesterone was associated with a non-significant 29% reduction in the risk of preterm birth <32 weeks of gestation (RR 0.71, 95% CI 0.34–1.49) and 33% non-significant decrease in the risk of composite perinatal morbidity and mortality (RR 0.67, 95% CI 0.29–1.57). Adjusted indirect comparison between vaginal progesterone and cerclage indicated that there was no significant difference for any of the secondary outcome measures. Estimated RRs ranged from 0.28 for bronchopulmonary dysplasia to 1.79 for grade III/IV intraventricular hemorrhage, but all 95% CIs included 1. These results indicate that vaginal progesterone and cerclage are not significantly different in terms of efficacy for reducing the risk of preterm birth and adverse perinatal outcomes.

Sensitivity analysis

Vaginal progesterone and cerclage significantly decreased the risk of preterm birth at <32 and <35 weeks of gestation in a sensitivity analysis that excluded both patients who received progestogens in trials evaluating cerclage and those in whom a cerclage was placed in trials evaluating vaginal progesterone (Table 3). Cervical cerclage compared to no intervention was associated with a reduction in the rate of preterm birth at <37 weeks of gestation and perinatal mortality; however, indirect comparisons between vaginal progesterone and cerclage indicate that there were no significant differences between the two interventions. Sensitivity analyses based on trial quality were not performed because all trials were considered at low risk for biases.

There was low statistical heterogeneity in all but two meta-analyses (admission to NICU and birth weight <2500 g in comparison of cerclage versus no cerclage). Funnel plots showed no asymmetry, either visually or in terms of statistical significance.

COMMENT

Principal findings of the study

In women with a sonographic short cervix in the midtrimester, singleton gestation, and previous spontaneous preterm birth, (1) vaginal progesterone administration was associated with a significant 53% reduction in the risk of preterm birth at <32 weeks, 57% decrease in the risk of composite perinatal morbidity and mortality, and a significantly lower rate of composite neonatal morbidity and admission to NICU when compared with placebo; (2) the placement of a cervical cerclage showed a significant 34% reduction in the risk of preterm birth at <32 weeks, 36% decrease in the risk of composite perinatal morbidity and mortality, and a significantly lower rate of preterm birth at <37, <35, and <28 weeks of gestation, and birth weight <2500 g when compared with no cerclage; and (3) there were no significant differences between the efficacy of vaginal progesterone and cerclage in the prevention of preterm birth or adverse perinatal outcomes. These findings were consistent with sensitivity analyses that excluded patients who received both progestins (17 α -hydroxyprogesterone caproate or vaginal progesterone) and cerclage.

Strengths and limitations of the study

Strengths of the study include: 1) use of the most rigorous methodology for performing an indirect comparison meta-analysis of randomized controlled trials. Specifically, we applied an adequate method to undertake the indirect comparisons, assessed the assumption of similarity of treatment effects using sensitivity and subgroup analyses, evaluated statistical homogeneity, and reported the results adequately; 2) indirect comparisons were performed by using data obtained from IPD meta-analyses^{105,177} of two direct comparisons; 3) the access to data from individual patients enabled a more rigorous analysis from what is possible with published data; 4) a broad and deep literature search was performed to identify relevant studies; 5) the high methodological quality of the majority of trials included in the review; 6) all patients included in the review had a cervical length <25 mm at or before 25 weeks of gestation, singleton gestation, and previous spontaneous preterm birth at less than 37 weeks of gestation; 7) the remarkable similar rates of preterm birth and adverse perinatal outcomes found in control groups of trials that evaluated vaginal progesterone and cerclage (Table 2) making more homogeneous the common comparator placebo/no cerclage in indirect meta-analyses; 8) the evidence of clinical and statistical homogeneity for most of the outcomes evaluated; 9) the sensitivity analysis, by excluding patients who did receive both progesterone and cerclage, was consistent with (and thus supportive of) our overall findings; and 10) the symmetrical funnel plots suggesting absence of publication and related biases in our meta-analyses.

There are some potential limitations of our study. In recent years, the adjusted indirect comparison method has been used in health care decision-making to compare competing treatments in the absence of direct evidence about their relative effectiveness. The largest evaluation of the consistency between direct and indirect comparisons of trials found that there was a statistically significant inconsistency in 16 of 112 (14%) comparisons which may be more common with subjectively assessed outcomes, fewer trials included in analyses, and statistically significant results from either direct or indirect comparisons.²³³ A recent simulation study reported that indirect comparisons may be underpowered to determine treatment differences, particularly when there is moderate to large between-study heterogeneity.²³⁴ In addition, the risk of overestimation could be large when the indirect comparison of interest relies on just one trial for one of the two direct comparisons. Almost all outcome measures included in our study were objectively assessed and most direct meta-analyses had a low statistical heterogeneity. However, the comparisons cerclage versus no cerclage and vaginal progesterone versus placebo relied mainly on one¹⁷⁴ and two trials,^{101,104} respectively.

Another potential limitation of this indirect meta-analysis was that 20% of women in the control group of trials evaluating cerclage received 17 α -hydroxyprogesterone caproate compared with none in the control group of trials evaluating vaginal progesterone. This difference could potentially mean that the control groups, which were used as the common comparator, are not similar. Nevertheless, the sensitivity analysis performed by excluding these patients showed no significant differences in the results obtained with overall meta-analyses. In addition, there is no evidence that 17-alpha-hydroxyprogesterone caproate can decrease the risk of preterm birth in women with a short cervix.²³⁵

Given the apparent equivalence in efficacy between vaginal progesterone and cerclage, differences in adverse effects are key variables that clinicians and patients with a singleton pregnancy and previous spontaneous preterm birth should consider when selecting an optimal treatment for a sonographic short cervix in the midtrimester. The IPD meta-analysis by Romero et al¹⁰⁵ showed that rates of maternal adverse effects, discontinuation of treatment because of adverse effects, and congenital anomalies did not differ significantly between the vaginal progesterone and placebo groups. The IPD meta-analysis by Berghella

et al,¹⁷⁷ which evaluated cerclage versus no cerclage, did not provide data on adverse events but the trial by Owen et al,¹⁷⁴ which contributed with 60% of patients of this meta-analysis, reported that surgical and anesthetic complications associated with cerclage placement were uncommon. Nonetheless, a recently updated Cochrane review that assessed the use of cerclage in women with a singleton gestation at high risk of pregnancy loss found that, compared with no treatment, cerclage was associated with a statistically significant increased risk of maternal fever (RR 2.39, 95% CI 1.35–4.23) and cesarean delivery (RR 1.19, 95% CI 1.01–1.40).²³⁶ The authors of this review speculated that higher rates of cesarean section associated with cerclage could be due to biased diagnosis of failed induction or failure to progress in labor when clinicians know that a woman had a cerclage earlier in pregnancy.

Implications for practice

The optimal method to compare the efficacy and safety of vaginal progesterone and cerclage in women with a sonographic short cervix in the midtrimester, singleton gestation, and a previous spontaneous preterm is by performing a direct comparison with a randomized controlled clinical trial. It is unknown if such trial will be forthcoming in the near future. We have performed a sample size calculation to estimate the number of patients required to conduct such a trial. Assuming a reduction in the frequency of preterm birth <32 weeks of gestation from 19.2% in the cerclage group to 12.0% in the vaginal progesterone group, 800 patients with such characteristics would be required for this study to have an 80% power with an alpha of 0.05. In the absence of such a trial, we believe that the findings of the current study provide the best available evidence to counsel patients and inform physicians at this time.

The key finding is that vaginal progesterone and cervical cerclage are equally effective for the prevention of preterm birth and adverse perinatal outcomes in patients with a short cervix and history of preterm birth. Given similar efficacy, therapeutic decision-making can be informed by reports about adverse events and cost-effectiveness of the interventions, as well as the patient and physician's preferences.

Acknowledgments

This research was supported, in part, by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services.

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Figure 1.
Study selection process

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TABLE 1

Characteristics of studies included

Study, year	Participating countries	Primary target population	Inclusion/exclusion criteria	No of women with CL <25 mm, singleton gestation, and previous preterm birth		Control group	Gestational age at screening (weeks)	Intervention	Cointerventions	Primary outcome
				Intervention group						
Vaginal progesterone compared with placebo										
Fonseca et al, 2007 ¹⁰¹	United Kingdom, Chile, Brazil, Greece	Women with a short cervix	Inclusion: women with a singleton or twin pregnancy and a sonographic cervical length 15. Exclusion: major fetal abnormalities, painful regular uterine contractions, a history of ruptured membranes, or cervical cerclage.	15	23	20–25	Vaginal progesterone capsule (200 mg/day) or placebo from 24 to 33 6/7 weeks of gestation	No		Spontaneous preterm birth <34 weeks
O'Brien et al, 2007 ²²⁸	United States, South Africa, India, Czech Republic, Chile, El Salvador	Women with a history of spontaneous preterm birth	Inclusion: women with a singleton pregnancy, 18–45 years of age, and a history of spontaneous singleton preterm birth at between 20 and 35 weeks of gestation in the immediately preceding pregnancy. Exclusion: planned cervical cerclage, history of adverse reaction to progesterone, treatment with progesterone within 4 weeks before enrollment, treatment for a seizure disorder, a psychiatric illness or chronic hypertension at the time of enrolment, history of acute or chronic congestive heart failure, renal failure, uncontrolled diabetes mellitus, active liver disorder, HIV infection with a CD4 count of <350 cells/mm ³ and requiring multiple antiviral agents, placenta previa, history or suspicion of breast or genital tract malignancy, history or suspicion of thromboembolic disease, Müllerian duct anomaly, major fetal anomaly or chromosomal disorder, or multifetal gestation.	9	13	16–22	Vaginal progesterone gel (90 mg/day) or placebo from 18–22 to 37 0/7 weeks of gestation, rupture of membranes or preterm delivery, whichever occurred first.	No		Preterm birth <32 weeks
Cetingoz et al, 2011 ²²⁹	Turkey	Women at high risk of preterm birth	Inclusion: women with a least one previous spontaneous preterm birth, uterine malformation or twin pregnancy. Exclusion: in-place or planned cervical cerclage, or serious fetal anomalies	3	3	20–24	Vaginal progesterone suppository (100 mg/day) or placebo from 24 to 34 weeks of gestation.	No		Preterm birth <37 weeks
Hassan et al, 2011 ¹⁰⁴	United States, Republic of Belarus, Chile, Czech Republic, India, Israel,	Women with a short cervix	Inclusion: women with a singleton pregnancy, transvaginal sonographic cervical length	48	44	19–23	Vaginal progesterone gel (90 mg/day) or placebo from 20–23 to	Emergency cervical cerclage (4 in vaginal progesterone group		Preterm birth <33 weeks

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Study, year	Participating countries	Primary target population	Inclusion/exclusion criteria	No of women with CL <25 mm, singleton gestation, and previous preterm birth			Gestational age at screening (weeks)	Intervention	Cointerventions	Primary outcome
				Intervention group	Control group					
Cerclage compared with no cerclage	Italy, Russia, South Africa, Ukraine United States	Women with a short cervix	between 10 and 20 mm, and without signs or symptoms of preterm labor. Exclusion: planned cerclage, acute cervical dilation, allergic reaction to progesterone, current or recent progesterogen treatment within the previous four weeks, chronic medical conditions that would interfere with study participation or evaluation of the treatment, major fetal anomaly or known chromosomal abnormality, uterine anatomic malformation, vaginal bleeding, or known or suspected clinical chorioamnionitis.	53	49	16–24	36 6/7 weeks of gestation, rupture of membranes or preterm delivery, whichever occurred first.	McDonald procedure with a single stitch of permanent monofilament or no cerclage	Clindamycin and indometacin which were discontinued at approximately 24 hours after randomization (both groups). Rescue cerclage (both groups)	Gestational age at delivery and neonatal morbidity
Althuisius et al, 2001 ¹¹⁵	The Netherlands	Women with a short cervix	Inclusion: women with a singleton gestation, risk factors and/or symptoms of cervical incompetence, and a cervical length <25 mm. Exclusion: fetal congenital/chromosomal anomalies, preterm rupture of membranes, membranes bulging into the vagina, or intrauterine infection.	14	12	14–23	McDonald procedure with braided polyester thread or no cerclage		Amoxicillin/clavula nic acid for 7 days and bed rest (both groups); two 100 mg suppositories of indomethacin (cerclage group). Rescue cerclage (no cerclage group)	Preterm birth <34 weeks, and neonatal morbidity and mortality
To et al, 2004 ²³¹	United Kingdom, Brazil, South Africa, Slovenia, Greece, Chile	Women with a short cervix	Inclusion: women with a singleton gestation and cervical length 15 mm. Exclusion: major fetal abnormalities, painful regular uterine contractions, history of ruptured membranes and cervical cerclage in situ, and dilated cervix during transvaginal sonography.	21	23	22–24	Shirodkar suture with mersilene tape or no cerclage		Prophylactic corticosteroids for fetal lung maturation (both groups); single dose of erythromycin (cerclage group)	Preterm birth <33 weeks

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Study, year	Participating countries	Primary target population	Inclusion/exclusion criteria	No of women with CL <25 mm, singleton gestation, and previous preterm birth			Intervention	Cointerventions	Primary outcome
				Intervention group	Control group	Gestational age at screening (weeks)			
Berghella et al. 2004 ¹¹³	United States	Women with a short cervix	Inclusion: women with a singleton or twin gestation and cervical length <25 mm or significant funneling (>25%). Exclusion: history-indicated prophylactic cerclage, last pregnancy delivered at term, major fetal anomaly, triplets or higher order pregnancy, previous inclusion in another trial, current drug abuse, or regular contractions leading to preterm labor after identification of abnormal cervix by ultrasonography.	14	17	14–23	McDonald procedure with mersilene tape or no cerclage	Bed rest (both groups)	Preterm birth <35 weeks
Owen et al, 2009	United States	Women with a short cervix, singleton gestation, and prior spontaneous preterm birth	Inclusion: women with a singleton gestation, at least 1 prior spontaneous preterm birth between 17 and 33 weeks of gestation, and midtrimester cervical length <25 mm. Exclusion: fetal anomaly, planned history-indicated cerclage for a clinical diagnosis of cervical insufficiency, and clinically significant maternal/fetal complications (eg, fetal red cell isoimmunization, treated chronic hypertension, insulin-dependent diabetes) and cervical insufficiency–indicated cerclage in a prior pregnancy.	148	153	16–22	McDonald procedure with nonabsorbable suture (braided tape) or no cerclage	17α-hydroxyprogesterone caproate (47 [31.8%] in cerclage group and 52 [34.0] in no cerclage group); vaginal progesterone (1 [0.7%] in no cerclage group). Rescue cerclage (no cerclage group)	Preterm birth <35 weeks

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Direct and indirect comparisons

TABLE 2

Outcome	Direct comparisons										Indirect comparison	
	Vaginal progesterone versus placebo					Cerclage versus no cerclage					Vaginal progesterone versus cerclage	
	No. of trials	Intervention n/N (%)	Control n/N (%)	RR (95% CI)	I ² (%)	No. of trials	Intervention n/N (%)	Control n/N (%)	RR (95% CI)	P value ^a	RR (95% CI)	P value ^b
Primary outcomes												
Preterm birth <32 weeks	4	9/75 (12.0)	24/83 (28.9)	0.47(0.24–0.91)	0	5	48/250 (19.2)	75/254 (29.5)	0.66 (0.48–0.91)	> .10	0.71 (0.34–1.49)	0.88
Composite perinatal morbidity/mortality ^c	4	7/75 (9.3)	20/83 (24.1)	0.43 (0.20–0.94)	0	5	39/250 (15.6)	63/254 (24.8)	0.64 (0.45–0.91)	> .10	0.67 (0.29–1.57)	0.86
Secondary outcomes												
Preterm birth <37 weeks	4	34/75 (45.3)	46/83 (55.4)	0.84 (0.61–1.14)	0	5	105/250 (42.0)	154/254 (60.6)	0.70 (0.58–0.83)	> .10	1.20 (0.84–1.72)	0.94
Preterm birth <35 weeks	4	20/75 (26.7)	35/83 (42.2)	0.66 (0.42–1.04)	0	5	71/250 (28.4)	105/254 (41.3)	0.70 (0.55–0.89)	> .10	0.94 (0.56–1.58)	0.98
Preterm birth <28 weeks	4	6/75 (8.0)	14/83 (16.9)	0.51 (0.22–1.18)	0	5	32/250 (12.8)	51/254 (20.1)	0.64 (0.43–0.96)	> .10	0.80 (0.31–2.02)	0.92
Respiratory distress syndrome	4	3/75 (4.0)	12/83 (14.5)	0.38 (0.13–1.07)	7	4	13/207 (6.3)	21/196 (10.7)	0.61 (0.32–1.19)	> .10	0.62 (0.18–2.16)	0.84
Grade III/IV intraventricular hemorrhage	4	1/75 (1.3)	3/83 (3.6)	0.50 (0.08–2.96)	8	4	0/207 (0.0)	4/196 (2.0)	0.28 (0.05–1.64)	> .10	1.79 (0.15–22.00)	0.80
Necrotizing enterocolitis	4	0/75 (0.0)	1/83 (1.2)	0.47 (0.02–10.32)	0	4	1/207 (0.5)	2/196 (1.0)	0.62 (0.08–4.67)	> .10	0.76 (0.02–31.49)	0.90
Neonatal sepsis	4	0/75 (0.0)	6/83 (7.2)	0.25 (0.05–1.37)	0	4	8/207 (3.9)	17/196 (8.7)	0.47 (0.21–1.05)	> .10	0.53 (0.08–3.35)	0.78
Bronchopulmonary dysplasia	2	0/51 (0.0)	1/47 (2.1)	0.31 (0.01–7.32)	0	1	7/135 (5.2)	6/127 (4.7)	1.10 (0.38–3.18)	> .10	0.28 (0.01–9.01)	0.58
Composite neonatal morbidity ^d	4	3/75 (4.0)	16/83 (19.3)	0.29 (0.11–0.81)	0	4	17/207 (8.2)	28/196 (14.3)	0.60 (0.34–1.06)	> .10	0.48 (0.15–1.53)	0.75
Perinatal mortality	4	5/75 (6.7)	7/83 (8.4)	0.73 (0.25–2.10)	0	5	22/250 (8.8)	35/254 (13.8)	0.65 (0.40–1.07)	> .10	1.12 (0.35–3.63)	0.96
Admission to NICU	4	11/75 (14.7)	33/83 (39.8)	0.39 (0.21–0.71)	0	4	57/207 (27.5)	67/196 (34.2)	0.63 (0.34–1.18)	< .10	0.62 (0.26–1.48)	0.84
Birth weight <2500 g	4	30/75 (40.0)	42/83 (50.6)	0.79 (0.55–1.13)	0	5	86/250 (34.4)	117/249 (47.0)	0.65 (0.42–1.00)	< .10	1.22 (0.69–2.14)	0.93
Birth weight <1500 g	4	8/75 (10.7)	18/83 (21.7)	0.53 (0.26–1.11)	0	5	42/250 (16.8)	66/249 (26.5)	0.64 (0.45–0.90)	> .10	0.83 (0.37–1.85)	0.93

CI, confidence interval; NICU, neonatal intensive care unit; RR, relative risk

^aP value for the Mantel-Haenszel Q statistics (test of heterogeneity)

^bP value for the test of association

^cOccurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal death

^dOccurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, or bronchopulmonary dysplasia

TABLE 3

Sensitivity analysis by excluding women who received progesterone in trials evaluating cerclage and patients who underwent a cerclage in trials evaluating vaginal progesterone

Outcome	Direct comparisons						Indirect comparison	
	Vaginal progesterone versus placebo			Cerclage versus no cerclage			Vaginal progesterone versus cerclage	
	Intervention n/N (%)	Control n/N (%)	RR (95% CI)	Intervention Control n/N (%)	Control n/N (%)	RR (95% CI)	RR (95% CI)	P value ^a
Preterm birth <32 weeks	8/71 (11.3)	24/82 (29.3)	0.44 (0.22–0.87)	40/203(19.7)	64/201 (31.8)	0.63 (0.45–0.88)	0.70 (0.33–1.50)	0.88
Preterm birth <28 weeks	5/71 (7.0)	14/82 (17.1)	0.46 (0.19–1.11)	28/203 (13.8)	43/201 (21.4)	0.65 (0.43–1.00)	0.71 (0.27–1.88)	0.88
Preterm birth <35 weeks	17/71 (23.9)	35/82 (42.7)	0.59 (0.37–0.95)	57/203 (28.1)	85/201 (42.3)	0.67 (0.51–0.88)	0.88 (0.51–1.52)	0.96
Preterm birth <37 weeks	31/71 (43.7)	46/82 (56.1)	0.80 (0.58–1.10)	82/203 (40.4)	123/201 (61.2)	0.67 (0.55–0.82)	1.19 (0.82–1.74)	0.94
Perinatal mortality	4/71 (5.6)	7/82 (8.5)	0.61 (0.20–1.91)	19/203 (9.4)	33/201 (16.4)	0.58 (0.35–0.98)	1.05 (0.30–3.64)	0.98

CI, confidence interval; RR, relative risk

^aP value for the test of association