Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis

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

STUDY DESIGN: Adjusted indirect metaanalysis of randomized controlled trials.

RESULTS: Four studies that evaluated vaginal progesterone vs placebo (158 patients) and 5 studies that evaluated cerclage vs no cerclage (504 patients) were included. Both interventions were associated with a statistically significant reduction in the risk of preterm birth at <32 weeks of gestation and composite perinatal morbidity and mortality compared with placebo/no cerclage. Adjusted indirect metaanalyses did not show statistically significant differences between vaginal progesterone and cerclage in the reduction of preterm birth or adverse perinatal outcomes.

CONCLUSION: Based on state-of-the-art methods 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 mid trimester, singleton gestation, and previous preterm birth. Selection of the optimal treatment needs to consider adverse events, cost and patient/clinician preferences.

Key words: birthweight, cervix, neonatal intensive care unit, perinatal mortality, perinatal morbidity, premature, prematurity, progestin, 17α-hydroxyprogesterone caproate, 17P

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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] (ie, 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 who is 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; a multiple causation model of a sonographic short cervix has been proposed (eg, a short cervix is syndromic in nature).[75,123,124] Such model would have biologic, diagnostic, prognostic, and therapeutic implications.[3,75] Indeed, patients may have a short cervix after diethylstilbestrol exposure in utero,[125-127] a cervical conization,[128-145] a loop electrosurgical excision 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 treat patients with a sonographic short cervix: (1) vaginal progesterone administration,[101-105] (2) cervical cerclage for patients with a history of preterm birth,[174-177] and (3) 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 <25 mm.[178]

Two independent randomized clinical trials[101,104] and an individual patient data (IPD) metaanalysis showed that vaginal progesterone decreases the rate of preterm delivery and neonatal morbidity/mortality in women with a sonographic short cervix.[105] This is the case for patients with or without a history of preterm birth.[105] The placement of a cervical cerclage appears to be indicated in patients with acute cervical insufficiency,[179-186] and perhaps, in some with a history of preterm birth and a sonographic short cervix of <25 mm.[174-177] Thus, there appear to be 2 interventions that may reduce the rate of preterm delivery in patients with a history of preterm birth and a cervix of <25 mm: vaginal progesterone administration or a cervical cerclage.

★ EDITORS' CHOICE ★

Recently, 2 professional organizations have recommended that cerclage may be considered for the treatment of women with a singleton gestation, previous spontaneous preterm birth, and a cervical length <25 mm at <24 weeks of gestation.[187,188] This recommendation was based mainly on an IPD metaanalysis of randomized controlled trials that show 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 metaanalysis demonstrated that vaginal progesterone administration to women with a sonographic short cervix (≤25 mm) in the mid trimester 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 with 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 (≤25 mm), singleton gestation, and previous spontaneous preterm birth.[105]

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 about the optimal choice of treatment.[189] Thus far, there are no randomized controlled trials comparing vaginal progesterone and cerclage directly. In the absence of this evidence, indirect metaanalysis has emerged as an accepted and valid method for the comparison of competing interventions with the use of a common comparator.[190-193]

We performed an adjusted indirect metaanalysis to compare the treatment effects of vaginal progesterone vs cerclage in asymptomatic women with a cervical length <25 mm in the mid trimester, singleton gestation and previous spontaneous preterm birth for the prevention of preterm birth. Previously, we had conducted an IPD metaanalysis to evaluate the efficacy of vaginal progesterone vs placebo in patients with such characteristics. Then, the summary estimates and measures of uncertainty were used together with those reported in the IPD metaanalysis that evaluated cerclage vs no cerclage[177] to perform the adjusted indirect comparison metaanalysis.

MATERIALS AND METHODS

The study was conducted based on a prospectively prepared protocol and is reported with the use of the Preferred Reporting Items for Systematic reviews and Metaanalyses (PRISMA) guidelines for metaanalyses of randomized controlled trials[194] and suggested guidelines for IPD[195] and indirect metaanalyses.[196]

Literature search

We searched MEDLINE, EMBASE, CINAHL, and LILACS (all from inception to October 31, 2012), the Cochrane Central Register of Controlled Trials (1960 to October 31, 2012; http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html), ISI Web of Science (1960 to October 31, 2012; http://www.isiknowledge.com), 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, McDon-

ald 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 mid trimester, singleton gestation, and previous spontaneous preterm birth at <37 weeks of gestation were allocated randomly to receive vaginal progesterone vs placebo/no treatment or cerclage vs no cerclage for the prevention of preterm birth. Trials were included if the primary aim of the study was to (1) prevent preterm birth in women with such characteristics; or (2) prevent preterm birth in women with other characteristics, but outcomes were available for patients with a prerandomization cervical length <25 mm in the mid trimester, singleton gestation, and previous preterm birth. Trials were excluded if they (1) were quasirandomized, (2) evaluated the interventions in women with only 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 dilation), or compared different cerclage techniques or outpatient cerclage vs inpatient cerclage, (6) compared cerclage with 17α-hydroxyprogesterone caproate, or (7) did not provide data for women with a cervical length <25 mm in the mid trimester, singleton gestation, and previous preterm birth.

All published studies that were deemed suitable were retrieved and reviewed independently by 2 authors (A.C-A. and R.R.) to determine inclusion. Disagreements were resolved through consensus.

Data collection

For the IPD metaanalysis that evaluated vaginal progesterone vs placebo, we contacted the corresponding authors to request access to the data. Authors were asked to supply anonymized data (without identifiers) about patient baseline characteristics, experimental intervention, control intervention, cointerventions, and prespecified outcome measures for every randomly assigned subject and were invited to become part of the collaborative group with joint authorship of the final publication. Data that were provided by the investigators were merged into a master database that had been constructed specifically for the review. Data were checked for missing information, errors, and inconsistencies by cross-referencing the publications of the original trials. Quality and integrity of the randomization processes were assessed by a review of the chronologic randomization sequence and pattern of assignment and the balance of baseline characteristics across treatment groups. Inconsistencies or missing data were discussed with the authors and corrections were made when deemed necessary. Finally, data were extracted for women with a cervical length <25 mm in the mid trimester, singleton gestation, and previous preterm births. A similar approach was used in the IPD metaanalysis by Berghella et al[177] that evaluated cerclage vs no cerclage.

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 mortality). 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), birthweight <1500 g and <2500 g, and admission to the neonatal intensive care unit (NICU).

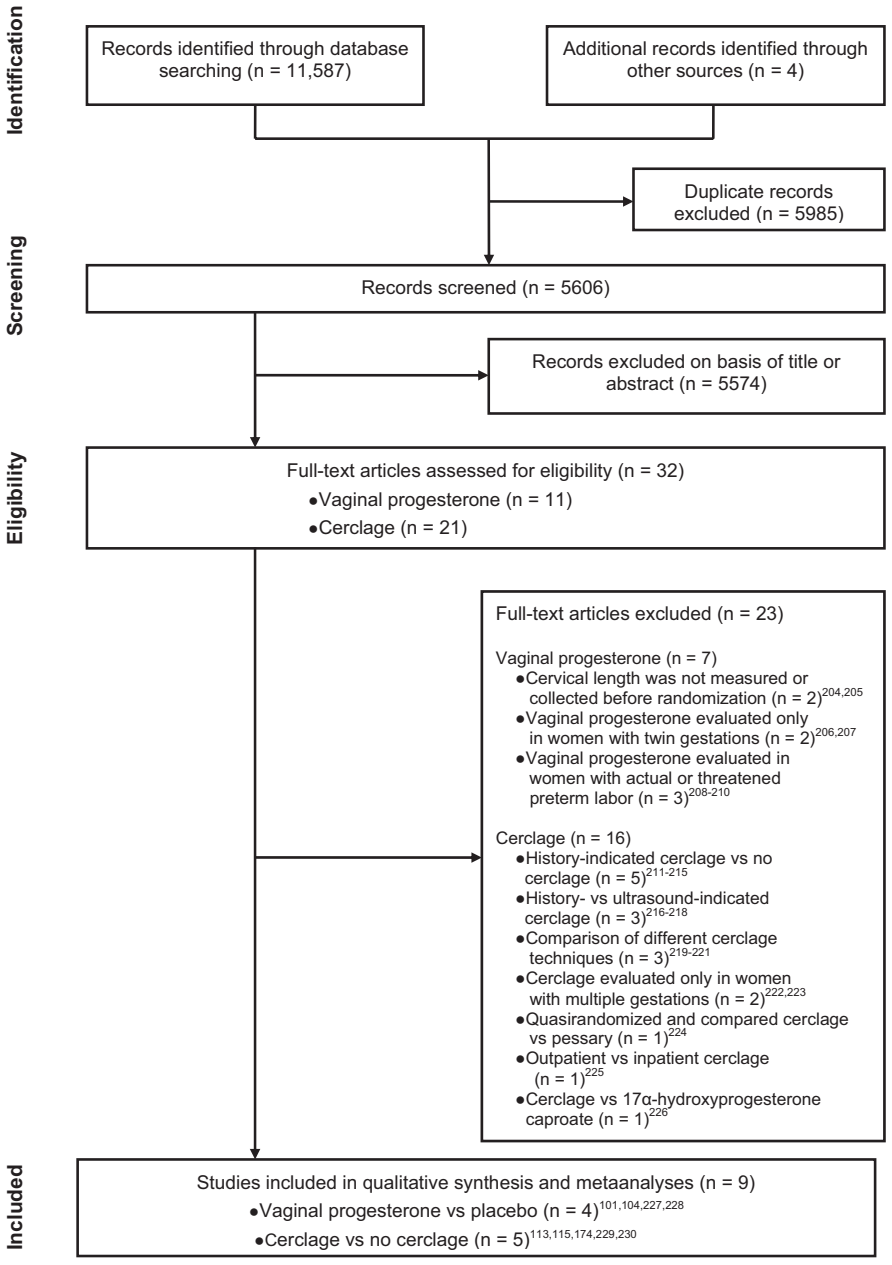
Assessment of risk of bias

The risk of bias in each included study was assessed by the use of the criteria recently outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[197] Seven domains that are related to the risk of bias were assessed in each included trial because 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* was 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 included trial was assessed individually by 2 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, which included 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, cer-

FIGURE
Study selection process



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clage 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 that assessed cerclage, data on proportions and relative risks (RRs) with 95% confidence intervals (CIs) for each outcome measure were extracted from the IPD metaanalysis 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 randomly assigned women and their fetuses/infants. For studies that assessed vaginal progesterone, IPD were combined in a 2-stage approach in which outcomes were analyzed in their original trial, then summary statistics were combined with the use of standard summary data metaanalysis techniques to give an overall measure of effect (summary RR with 95% CI).[198] A similar approach was used in the IPD metaanalysis of trials that evaluated cerclage vs no cerclage.[177] Heterogeneity of the results among studies was tested with the quantity I^2 in the IPD metaanalysis of vaginal progesterone vs placebo[199] and the Mantel-Haenszel Q statistics in the IPD metaanalysis of cerclage vs no cerclage. I^2 values of ≥50% or a probability value of < .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 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.[200] Publication and related biases were assessed visually by an examination of the symmetry of funnel plots and statistically by the use of the Egger test.[201] A probability value of < .1 was considered to indicate significant asymmetry.

The adjusted indirect comparison metaanalysis of vaginal progesterone vs cerclage was performed according to the most widely applied indirect comparison method by Bucher et al.[202] The Canadian Agency for Drugs and Technologies in Health[192] and others[190,193,203] 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 vs B and C vs B with the common comparator link B are used to yield an indirect comparison of A vs C. Because vaginal progesterone and cerclage have been compared with 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 2 metaanalyses into a RR (95% CI) that represented the difference between vaginal progesterone (p) and cerclage (c) as in the following equations:[192]

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

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

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 with the use of sensitivity analyses. A predefined sensitivity analysis was conducted by excluding patients who received progesterone in trials that evaluated cerclage vs no cerclage and patients who received a cerclage in studies that compared vaginal progesterone with placebo to explore the impact of these cointerventions on the effect size for preterm birth and perinatal mortality. This analysis was performed because it is unclear whether 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 the exclusion of trials with high risk of bias.

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

Informed consent was provided by the patients on 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 that were identified, the abstracts were reviewed, and 32 studies were retrieved because they were considered potentially relevant to this indirect metaanalysis. Twenty-three studies were excluded[204-226] (Figure). The remaining 9 trials met the inclusion criteria and provided data for 662 women with a cervical length of <25 mm at mid trimester, singleton gestation, and previous spontaneous preterm birth at <37 weeks of gestation.[101,104,113,115,174,227-230] Four studies evaluated vaginal progesterone vs placebo (158 women),[101,104,227,228] and 5 studies evaluated cerclage vs no cerclage (504 women).[113,115,174,229,230]

The main characteristics of studies that were included in this indirect comparison metaanalysis are presented in Table 1. All 4 studies that evaluated vaginal progesterone were double-blind, placebo-controlled trials.[101,104,227,228] None of the studies that assessed cerclage were double-blind. Seven trials (2 that evaluated vaginal progesterone[101,104] and all 5 that evaluated cerclage[113,115,174,229,230]) examined the interventions in women with a sonographic short cervix, 1 study evaluated the use of vaginal progesterone in women with a history of spontaneous preterm birth,[227] and the remaining study evaluated the use of vaginal progesterone in women with a previous spontaneous preterm birth, uterine malformations, or twin gestation.[228] Only 1 trial was designed specifically to evaluate the use of cerclage in women with a cervical length of <25 mm in the mid trimester, singleton gestation, and previous spontaneous preterm birth.[174] The primary outcome was preterm birth at <37 weeks of gestation for 1 trial,[228] <35 weeks of gestation for 2 trials,[113,174] <34 weeks of gestation for 2 trials,[101,115] <33 weeks of gestation for 2 trials,[104,230] ≤32 weeks of gestation for 1 trial,[227] and gestational age at delivery for the remaining study.[229]

Gestational age at cervical length screening varied between 14 and 25 weeks of gestation, although most studies performed screening at <25 weeks of gestation.[104,113,115,174,227-230] Of the 4 trials that evaluated vaginal progesterone, 2 used gel (90 mg/d),[104,227] 1 used capsules (200 mg/d),[101] and the other used suppositories (100 mg/d).[228] The treatment was initiated at 24 weeks of gestation in 2 trials,[101,228] between 20 and 23 weeks of gestation in 1 trial,[104] and between 18 and 22 weeks of gestation in the remaining study.[227] Two studies reported that participating women received study medication from enrollment until 34 weeks of gestation,[101,228] and 2 studies reported that medication was given from enrollment until 36 6/7 weeks of gestation.[104,227] In the study by Hassan et al,[104] 5 women received an emergency cerclage. Among the 5 trials that evaluated cerclage, 4 used the McDonald procedure,[113,115,174,229] and 1 used the Shirodkar technique.[230] Rescue cerclage in women who were allocated to the no cerclage group was allowed in 3 studies based on physical examination[174] or based on ultrasonographic cervical changes.[115,229] Prophylactic antibiotics and tocolytics were administered to most participating women in 3 studies,[115,229,230] whereas bed rest was recommended to all women who were recruited in 2 trials.[113,115] In the trial by Owen et al,[174] 99 women received 17α-hydroxyprogesterone caproate, and 1 woman received vaginal progesterone.[231]

All 9 studies that were included in the metaanalysis had adequate random sequence generation and allocation concealment, were free of selective outcome reporting, and had no obvious risk of other biases. In the 4 trials that evaluated vaginal progesterone, there was blinding of participants, health care providers, and outcome assessors. In the 5 trials that evaluated cerclage, study participants and health care providers were not blinded, and it was unclear whether outcome assessors were masked to intervention allocations after inclusion of patients into the study. However, we

TABLE 1
Characteristics of studies included in this systematic review

Study	Participating countries	Primary target population	Inclusion/exclusion criteria	Women with cervical length <25 mm, singleton gestation, and previous preterm birth, n		Gestational age at screening, wk	Intervention	Cointerventions	Primary outcome
				Intervention group	Control 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 mm 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/d) or placebo from 24-33 6/7 weeks of gestation	No	Spontaneous preterm birth <34 wk
O'Brien et al, 2007[227]	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 old, and a history of spontaneous singleton preterm birth at 20-35 wk of gestation in the immediately preceding pregnancy Exclusion: planned cervical cerclage, history of adverse reaction to progesterone, treatment with progesterone within 4 wk 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 that require 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/d) 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 wk
Cetingoz et al, 2011[228]	Turkey	Women at high risk of preterm birth	Inclusion: women with a least 1 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/d) or placebo from 24-34 wk of gestation	No	Preterm birth <37 wk

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(continued)

TABLE 1
Characteristics of studies included in this systematic review *(continued)*

Study	Participating countries	Primary target population	Inclusion/exclusion criteria	Women with cervical length <25 mm, singleton gestation, and previous preterm birth, n		Gestational age at screening, wk	Intervention	Cointerventions	Primary outcome
				Intervention group	Control group				
Hassan et al, 2011[104]	United States, Republic of Belarus, Chile, Czech Republic, India, Israel, Italy, Russia, South Africa, Ukraine	Women with a short cervix	Inclusion: women with a singleton pregnancy, transvaginal sonographic cervical length of 10-20 mm, and no signs or symptoms of preterm labor Exclusion: planned cerclage, acute cervical dilation, allergic reaction to progesterone, current or recent progestogen treatment within the previous 4 wk, 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	48	44	19-23	Vaginal progesterone gel (90 mg/d) or placebo from 20-23 to 36 6/7 weeks of gestation, rupture of membranes or preterm delivery, whichever occurred first	Emergency cervical cerclage (4 in vaginal progesterone group [8.3%] and 1 [2.3%] in placebo group)	Preterm birth <33 wk
Rust et al, 2001[229]	United States	Women with a short cervix	Inclusion: women with a singleton or multiple gestation and transvaginal sonographic dilation of the internal os with either membrane prolapse into the endocervical canal at least 25% of the total cervical length but not beyond the external os or a cervical length <25 mm Exclusion: membrane prolapse beyond the external os, any fetal lethal congenital or chromosomal anomaly, abruption placenta, unexplained vaginal bleeding, chorioamnionitis, persistent uterine activity with cervical change, or any other contraindication to a cerclage procedure	53	49	16-24	McDonald procedure with a single stitch of permanent monofilament or no cerclage	Clindamycin and indomethacin that were discontinued at approximately 24 hr after random assignment (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/clavulanic 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 wk and neonatal morbidity and mortality
To et al, 2004[230]	United Kingdom, Brazil, South Africa, Slovenia, Greece, Chile	Women with a short cervix	Inclusion: women with a singleton gestation and cervical length ≤15 mm	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 wk

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(continued)

TABLE 1
Characteristics of studies included in this systematic review *(continued)*

Study	Participating countries	Primary target population	Inclusion/exclusion criteria	Women with cervical length <25 mm, singleton gestation, and previous preterm birth, n		Gestational age at screening, wk	Intervention	Cointerventions	Primary outcome
				Intervention group	Control group				
			Exclusion: major fetal abnormalities, painful regular uterine contractions, history of ruptured membranes and cervical cerclage in situ, and dilated cervix during transvaginal sonography						
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 wk
Owen et al, 2009[116]	United States	Women with a short cervix, singleton gestation, and previous spontaneous preterm birth	Inclusion: women with a singleton gestation, at least 1 previous spontaneous preterm birth between 17-33 weeks of gestation, and mid trimester 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 mellitus) and cervical insufficiency that indicated cerclage in a previous 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 wk

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judged that assessment and measurement of most outcomes that were included in our review are considered objective in nature and were not likely to be influenced by a lack of blinding in the studies that evaluated cerclage. All but one study[104] had adequate handling of incomplete outcome data. Overall, all 9 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 of <25 mm in the mid trimester, singleton gestation, and previous spontaneous preterm birth was associated with a significant reduction in the risk of preterm birth at <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 either 1 case of preterm birth at <32 weeks of gestation or 1 case of composite perinatal morbidity/mortality was 7 (95% CI, 5−38 for preterm birth at <32 weeks of gestation and 5−69 for composite perinatal morbidity/mortality). The corresponding numbers needed to treat 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 who were allocated to cerclage had a statistically significant reduction in the risk of preterm birth at <37, <35, and <28 weeks of gestation and a birthweight of <1500 g when compared with those who were allocated to no cerclage.

Indirect comparison

Adjusted indirect comparison meta-analyses showed that, compared with

TABLE 2
Direct and indirect comparisons

Outcome	Direct comparisons: Vaginal progesterone vs placebo					Direct comparisons: Cerclage vs no cerclage					Indirect comparison: vaginal progesterone vs cerclage	
	Trials, n	Intervention, n/N (%)	Control, n/N (%)	Relative risk (95% CI)	Heterogeneity I^2, %	Trials, n	Intervention, n/N (%)	Control, n/N (%)	Relative risk (95% CI)	Heterogeneity, *P* value[a]	Relative risk (95% CI)	*P* value[b]
Primary outcomes												
Preterm birth <32 wk	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)	.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)	.86
Secondary outcomes												
Preterm birth <37 wk	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)	.94
Preterm birth <35 wk	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)	.98
Preterm birth <28 wk	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)	.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)	.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	4/196 (2.0)	0.28 (0.05–1.64)	> .10	1.79 (0.15–22.00)	.80
Necrotizing enterocolitis	4	0/75	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)	.90
Neonatal sepsis	4	0/75	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)	.78
Bronchopulmonary dysplasia	2	0/51	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)	.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)	.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)	.96
Admission to neonatal intensive care	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)	.84
Birthweight <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)	.93
Birthweight <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)	.93

[a] For the Mantel-Haenszel Q statistics (test of heterogeneity); [b] For the test of association; [c] Occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal mortality; [d] Occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, or bronchopulmonary dysplasia.

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TABLE 3
Sensitivity analysis of direct and indirect comparison metaanalyses

	Direct comparisons						Indirect comparison: vaginal progesterone vs cerclage	
	Vaginal progesterone vs placebo			Cerclage vs no cerclage				
Outcome	Intervention, n/N (%)	Control, n/N (%)	Relative risk (95% CI)	Intervention, n/N (%)	Control, n/N (%)	Relative risk (95% CI)	Relative risk (95% CI)	*P* value[a]
Preterm birth								
<32 wk	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)	.88
<28 wk	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)	.88
<35 wk	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)	.96
<37 wk	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)	.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)	.98

[a] For the test of association.

Conde-Agudelo. Vaginal progesterone vs cervical cerclage. Am J Obstet Gynecol 2013.

cerclage, treatment with vaginal progesterone was associated with a nonsignificant 29% reduction in the risk of preterm birth at <32 weeks of gestation (RR, 0.71; 95% CI, 0.34−1.49) and a 33% nonsignificant 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 the reduction of 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 that evaluated cerclage and those in whom a cerclage was placed in trials that evaluated vaginal progesterone (Table 3). Cervical cerclage, compared with 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 2 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 2 metaanalyses (admission to NICU and birthweight <2500 g in comparison of cerclage vs 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 mid trimester, 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 of gestation, a 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 of gestation, a 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 a birthweight of <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 in which patients who received progestogens (eg, 17α-hydroxyprogesterone caproate or vaginal progesterone), and cerclage were excluded.

Strengths and limitations of the study

Strengths of the study include (1) use of the most rigorous methodology for performing an indirect comparison metaanalysis of randomized controlled trials. Specifically, we applied the best available method to undertake the indirect comparisons, assessed the assumption of similarity of treatment effects using sensitivity analyses, evaluated statistical homogeneity, and reported the results following the recommended guidelines for this type of study; (2) indirect comparisons were performed by using data obtained from IPD metaanalyses[105,177] of 2 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 methodologic 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 metaanalyses; (8) the evidence of clinical and statistical homogeneity for most of the outcomes evaluated; (9) the sensitivity analysis, by excluding patients who received both progesterone and cerclage, was consistent with (and thus supportive of) our overall findings; and (10) the symmetric funnel plots suggesting absence of publication and related biases in our metaanalyses.

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 comparisons (14%), which may be more common with subjectively assessed outcomes, comparisons that include a lower number of trials in the analyses, and with statistically significant results from either direct or indirect comparisons.[232] A recent simulation study reported that indirect comparisons may be underpowered to determine treatment differences, particularly when there is a moderate-to-large between-study degree of heterogeneity.[233] In addition, the risk of overestimation could be high when the indirect comparison of interest relies on just 1 trial for 1 of the 2 direct comparisons. However, virtually all outcome measures that were included in our study were assessed objectively, and most of the direct metaanalyses had a low degree of statistical heterogeneity. Moreover, the comparisons of cerclage vs no cerclage and vaginal progesterone vs placebo relied mainly on 2 trials each (Owen et al[174] and Rust et al[229] for cerclage and Hassan et al[104] and Fonseca et al[101] for vaginal progesterone).

Another potential limitation of this indirect metaanalysis was that 20% of women in the control group of trials that evaluated cervical cerclage received 17α-hydroxyprogesterone caproate compared with none in the control group of trials that evaluated vaginal progesterone. This difference could potentially mean that the control groups, which were used as the common comparator, are not similar. Nevertheless, sensitivity analyses that were performed by excluding these patients showed no significant differences in the results that were obtained with overall metaanalyses. In addition, there is no evidence that 17α-hydroxyprogesterone caproate can decrease the risk of preterm birth in women with a short cervix.[234]

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 a previous spontaneous preterm birth should consider when selecting an optimal treatment for a sonographic short cervix in the mid trimester. The IPD metaanalysis by Romero et al[105] 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 metaanalysis by Berghella et al,[177] which evaluated cerclage vs no cerclage, did not provide data on adverse events, but the trial by Owen et al,[174] which contributed 60% of patients to that metaanalysis, reported that surgical and anesthetic complications that were associated with cerclage placement were uncommon. Nonetheless, a recently updated Cochrane review that assessed the use of cerclage in women with a singleton gestation who were 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).[235] The authors of that review speculated that the higher rates of cesarean delivery that were associated with cerclage could be due to biased diagnosis of failed induction or failure to progress in labor when clinicians knew 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 mid trimester, singleton gestation, and previous spontaneous preterm is by a direct comparison with a randomized controlled clinical trial. It is unknown whether such a trial will be forthcoming in the near future. We have performed a sample size calculation to estimate the number of patients who would be required to conduct such a trial. Assuming a reduction in the frequency of preterm birth at <32 weeks of gestation from 19.2% in the cerclage group to 12.0% in the vaginal progesterone group, 800 patients (400 per group) 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.

Currently, the American College of Obstetricians and Gynecologists recommends the administration of 17α-hydroxyprogesterone caproate for the prevention of preterm birth in women with a history of a spontaneous singleton preterm birth at <37 weeks of gestation.[236] Thus far, there are no randomized controlled trials that have compared 17α-hydroxyprogesterone caproate vs placebo, 17α-hydroxyprogesterone caproate vs vaginal progesterone, or 17α-hydroxyprogesterone caproate plus cerclage vs cerclage alone or 17α-hydroxyprogesterone caproate alone in women with a short cervix, singleton gestation, and previous spontaneous preterm birth for the prevention of preterm birth. A recently published secondary analysis of the trial by Owen et al[174] evaluated the efficacy of cerclage vs no cerclage in patients with a singleton gestation and previous spontaneous preterm birth who developed a short cervix (<25 mm) in the second trimester while receiving 17α-hydroxyprogesterone caproate.[237] Of the 99 women who received 17α-hydroxyprogesterone

caproate, 47 were allocated to have a cerclage, and 52 were allocated to the group who were treated without cerclage. The rates of preterm birth at <32, <28, <35, and <37 weeks of gestation among women who received 17α-hydroxyprogesterone caproate and a cerclage were 17%, 9%, 30%, and 49%, respectively. The corresponding rates among women who received 17α-hydroxyprogesterone caproate in the no cerclage group were 21%, 15%, 38%, and 60%, respectively. These outcome measures for preterm birth were not significantly different between the cerclage and no cerclage groups. The authors concluded that cerclage does not offer additional benefit for the prevention of preterm birth in women with a singleton gestation and a cervical length of <25 mm who are receiving 17α-hydroxyprogesterone caproate because of a previous preterm birth.

In our sensitivity analysis reported herein, we found that the frequency of preterm birth at <32, <28, <35, and <37 weeks of gestation in women with a singleton gestation, previous preterm birth, and a short cervix who received vaginal progesterone was 11%, 7%, 24%, and 44%, respectively. These data suggest that vaginal progesterone is at least similar in efficacy to the combination of 17α-hydroxyprogesterone caproate and cerclage in the prevention of preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a cervical length of <25 mm. Recently, a randomized clinical trial reported that 17α-hydroxyprogesterone caproate did not reduce the risk of preterm birth at <32, <35, and <37 weeks of gestation when compared with placebo in nulliparous women with a short cervix (<30 mm).[234] In addition, subgroup analyses did not demonstrate a benefit from 17α-hydroxyprogesterone caproate administration to women with a cervical length of <15 mm or 10-20 mm. Therefore, based on the totality of the current available evidence, we propose that women with a singleton pregnancy who have a history of singleton spontaneous preterm birth and have begun treatment with 17α-hydroxyprogesterone caproate between 16 and 20 weeks of gestation be followed with serial cervical length measurements using transvaginal sonography beginning at approximately 18 weeks and continuing every 2 weeks until 23 6/7 weeks. If cervical length is <25 mm, vaginal progesterone should be offered to the patient because this intervention has been proven to be effective in women with a short cervix and a history of preterm birth. If cervical length is 25-30 mm, these patients could be followed with additional ultrasound examinations because they may still benefit from vaginal progesterone. There is no evidence to support the continued administration of 17α-hydroxyprogesterone caproate in patients with a short cervix if vaginal progesterone is used. This approach would address the safety concerns that have been outlined by the Food and Drug Administration in the package insert of the commercially available form of 17α-hydroxyprogesterone caproate (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021945s000lbl.pdf) and the lack of evidence that this synthetic progestin would be effective if the patient is already receiving vaginal progesterone because of a history of preterm birth and a cervix of <25 mm.

The key finding of this study is that vaginal progesterone and cervical cerclage have similar efficacy for the prevention of preterm birth and adverse perinatal outcomes in patients with a short cervix and a 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.

The current recommendation that patients with a short cervix and a history of preterm birth should be treated with cervical cerclage must be revisited in light of the results of the present study. Medical treatment with vaginal progesterone can decrease the risks that are associated with anesthesia and a surgical procedure; therefore, it is important to disclose the availability of a non-surgical therapeutic choice to patients with a history of preterm birth and a short cervix. ■

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