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Vaginal progesterone to prevent preterm birth in pregnant women with a sonographic short cervix: clinical and public health implications

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Abstract

Vaginal progesterone administration to women with a sonographic short cervix is efficacious and safe intervention used to prevent preterm birth and neonatal morbidity and mortality. The clinical and public health implications of this approach in the United States have been critically appraised and compared to other therapeutic interventions in obstetrics. Vaginal progesterone administration to women with a transvaginal sonographic cervical length (CL) ≥ 25 mm before 25 weeks of gestation is associated with a significant and substantial reduction of the risk of preterm birth from <28 to <35 weeks of gestation, respiratory distress syndrome, composite neonatal morbidity and mortality, admission to the neonatal intensive care unit, and mechanical ventilation. These beneficial effects have been achieved in women with a singleton gestation, with or without a history of spontaneous preterm birth, and did not differ significantly as a function of CL (<10 mm, 10–20 mm, or 21–25 mm). The number of patients required for treatment to prevent one case of preterm birth or adverse neonatal outcomes ranges from 10 to 19 women. The number needed to screen for the prevention of one case of preterm birth before 34 weeks of gestation is 125 women, and 225 for the prevention of one case of major neonatal morbidity or neonatal mortality. Several cost-effectiveness and decision analyses have shown that the combination of universal transvaginal CL screening and vaginal progesterone administration to women with a short cervix is a cost-effective intervention that prevents preterm birth and associated perinatal morbidity and mortality. Universal assessment of CL and treatment with vaginal progesterone for singleton gestations in the United States would result in an annual reduction of approximately 30,000 preterm births before 34 weeks of gestation and of 17,500 cases of major neonatal morbidity or neonatal mortality. In summary, there is compelling evidence to recommend universal transvaginal CL screening at 18–24 weeks of gestation in women with a singleton gestation and to offer vaginal progesterone to

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those with a CL $\leq$ 25 mm, regardless of the history of spontaneous preterm birth, with the goal of preventing preterm birth and neonatal morbidity and mortality.

Keywords

biomarker; cervical length; cost-effectiveness; neonatal morbidity; pregnancy; prematurity; prevention; screening; singleton gestation; twin gestation; ultrasound

INTRODUCTION

Preterm birth affected 11.4% of all births in the United States in 2013;¹ it is the leading cause of neonatal and child mortality worldwide.^{2,3} Accumulating evidence suggests that preterm birth is a syndrome caused by multiple pathologic processes.^{4–7} A short cervix, traditionally defined as a transvaginal sonographic cervical length (CL) $\leq$ 25 mm in the mid-trimester of pregnancy, is a risk factor for preterm delivery. Untimely cervical ripening is one of the mechanisms of disease implicated in the etiology of the preterm parturition syndrome.^{5,7}

A prospective multicenter cohort study reported that women with a singleton gestation and a CL $\leq$ 25 mm at 22–24 weeks of gestation were more than six times more likely than women with a CL $>$ 40 mm to deliver spontaneously before 35 weeks of gestation.⁸ Today, a short cervix is a well-accepted risk factor for preterm birth^{9–12} and one of the strongest predictors of preterm birth in both singleton^{13–18} and twin^{17,19–22} gestations. In the absence of any intervention, an estimated 17% of infants born to mothers with a CL $\leq$ 25 mm before 25 weeks of gestation will die during the neonatal period or develop major neonatal complications such as respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, or neonatal sepsis.²³

Efficacy of vaginal progesterone in pregnant women with a short cervix

Progesterone, a key hormone for pregnancy maintenance, plays a role in the control of cervical ripening through several mechanisms, including the regulation of extracellular matrix metabolism,^{24–30} and anti-inflammatory effects.^{27,31–33} Progesterone also has other effects on the common pathway of parturition, which may contribute to the prevention of preterm birth in women with a short cervix.^{34–43}

The most powerful evidence of the efficacy of vaginal progesterone in the prevention of preterm birth derives from randomized clinical trials and individual patient meta-analyses. Fonseca et al⁴⁴ randomly assigned 250 women with a CL $\leq$ 15 mm at 20–25 weeks of gestation to receive vaginal progesterone capsules (200 mg/d) or a placebo at 24–34 weeks of gestation, and reported a significant reduction of 44% of the risk for spontaneous preterm birth before 34 weeks of gestation [relative risk (RR), 0.56; 95% confidence interval (CI), 0.36–0.86] and a non-significant decrease of 41% of the risk for major neonatal morbidity (RR, 0.59; 95% CI, 0.26–1.25). Hassan et al⁴⁵ reported a trial in which 458 women with a CL of 10–20 mm at 19–23 weeks of gestation were randomly selected to receive vaginal progesterone gel (90 mg/d) or a placebo at 20–23 to 36 weeks of gestation. The

administration of vaginal progesterone was associated with a significant reduction of the risk for preterm birth before 33 weeks of gestation (RR, 0.55; 95% CI, 0.33–0.92), respiratory distress syndrome (RR, 0.39; 95% CI, 0.17–0.92), and composite neonatal morbidity and mortality (RR, 0.57; 95% CI, 0.33–0.99).

In 2012, an individual patient data meta-analysis assessed the efficacy of vaginal progesterone to prevent preterm birth in asymptomatic women with a transvaginal sonographic CL ≥ 25 mm in the midtrimester.²³ A total of 775 women (723 with singleton gestations and 52 with twin gestations) and 827 infants (723 from singleton gestations and 104 from twin gestations) from five randomized controlled trials were included in the study. In addition to the two trials specifically designed to evaluate vaginal progesterone in women with a sonographic short cervix,^{44,45} the individual patient data meta-analysis included information from three trials that assessed the use of vaginal progesterone in women at high risk for preterm birth,^{46–48} which provided data for women with a CL of ≥ 25 mm before randomization. Treatment with vaginal progesterone was associated with a statistically significant reduction of the risk for preterm birth from <28 to <35 weeks of gestation, respiratory distress syndrome, composite neonatal morbidity and mortality, birthweight $<1,500$ g, admission to the neonatal intensive care unit, and requirement for mechanical ventilation. Importantly, the reduction of preterm birth before 33 weeks of gestation and of composite neonatal morbidity and mortality was demonstrated by women with no previous spontaneous preterm birth as well as by those with at least one previous spontaneous preterm birth.

Another important pre-specified subgroup analysis showed that the beneficial effects of vaginal progesterone did not differ significantly among women as a function of CL, which stratified patients into three groups: <10 mm, 10–20 mm, or 21–25 mm. The *P* values for the interaction effect of progesterone based on CL were non-significant (0.32 for preterm birth before 33 weeks of gestation and 0.93 for composite neonatal morbidity and mortality). The interpretation of these non-significant interaction *P* values is that the beneficial effects of vaginal progesterone for patients with a CL between 21–25 mm and <10 mm are not significantly different from those for patients with a CL of 10–20 mm.

The beneficial effects of vaginal progesterone in women with a singleton gestation and a CL ≥ 25 mm are shown in Table 1. Among women with a twin gestation and a CL ≥ 25 mm, the use of vaginal progesterone was associated with a significant 44% reduction of the risk of composite neonatal morbidity and mortality (adjusted RR, 0.56; 95% CI, 0.30–0.97) and a 30% non-significant reduction of the risk for preterm birth before 33 weeks of gestation (RR, 0.70; 95% CI, 0.34–1.44).²³ Similar results were recently reported in an individual patient data meta-analysis by Schuit et al,⁴⁹ which has been subject to editorial comment,⁵⁰ and in a randomized clinical trial among women with a twin gestation and a CL between 20–25 mm at 20–24 weeks of gestation (N=224).⁵¹

Public health implications

The number of patients needed to treat with vaginal progesterone to prevent one case of preterm birth before 33 weeks or adverse neonatal outcomes varies from 10–19 women (Table 1). This compares favorably to the numbers needed to treat by other obstetrical and

perinatal interventions such as magnesium sulfate to prevent eclampsia or cerebral palsy, aspirin to prevent preeclampsia, active management of the third stage of labor to prevent postpartum hemorrhage, and antenatal corticosteroids to prevent respiratory distress syndrome and neonatal death (Table 2).^{52–56}

During the late 1990s, Iams et al⁸ conducted a multicenter study in the United States and found that the prevalence of a CL ≥ 25 mm during the midtrimester in women with a singleton gestation 9%; Heath et al¹⁰ reported an 8% prevalence in a large cohort from the United Kingdom. At our institution, during the period of 2006 through 2015, the prevalence of a CL ≥ 25 mm was 8.9% (Edgar Hernandez-Andrade, MD, PhD, unpublished observations, June 28, 2015). Based on a prevalence of 8%, we calculated that the number of patients with a singleton gestation who need to be screened for a transvaginal sonographic CL to prevent one case of preterm birth before 34 weeks of gestation is 125 women, assuming that all patients with a CL ≥ 25 mm would receive vaginal progesterone (Table 1). The number of patients who need to be screened to prevent one case of major neonatal morbidity or neonatal mortality is 225 women.

Currently, there is strong evidence indicating that universal transvaginal sonographic CL screening and vaginal progesterone administration for women with a short cervix is a cost-effective intervention to prevent preterm birth and associated morbidity and mortality, regardless of the cutoff used to define a short cervix in the decision and economic analyses (≥ 15 mm,^{57–59} ≥ 20 mm,⁶⁰ ≥ 25 mm,^{57,61,62} 10–20 mm,⁶³ or 10–30 mm⁶⁴). Moreover, the analysis of Combs⁶⁵ provided compelling evidence that this strategy satisfies the 10 criteria that the World Health Organization considers to be a good screening test.

Using current national vital statistics,¹ we estimated that 303,613 women with a singleton gestation and a CL ≥ 25 mm would have been identified in the United States in 2013 if universal transvaginal sonographic CL screening had been implemented. Based on the results of the individual patient data meta-analysis,²³ if all the women with a CL ≥ 25 mm had received vaginal progesterone, then 30,545 preterm births occurring before 34 weeks of gestation (95% CI, 13,434–41,793) and 17,433 cases of major neonatal morbidity or neonatal mortality (95% CI, 3740–25,765) could have been prevented. Since the rate of preterm birth occurring before 34 weeks of gestation among singleton gestations was 2.72% ($n=103,228$),¹ the implementation of universal transvaginal sonographic CL screening and treatment with vaginal progesterone could contribute to a decrease of 30% (30,545/103,228) in the rate of preterm birth occurring before 34 weeks of gestation in the United States. Universal transvaginal sonographic screening for a short cervix and treatment with vaginal progesterone appears to be a relevant public health strategy when compared to universal screening for maternal group B streptococcal colonization and intrapartum antibiotic prophylaxis^{66,67} (Table 3).

Implications for practice

Professional organizations^{68,69} recommend performing a single transvaginal sonographic CL measurement at 18–24 weeks of gestation for women with a singleton gestation but without a previous preterm birth, and offering vaginal progesterone to those with a CL ≥ 20 mm. For those women with a singleton gestation who receive 17 α -hydroxyprogesterone caproate (17-

OHPC) due to a history of spontaneous preterm birth, an intervention typically started at 16–20 weeks of gestation, these organizations recommend performing serial transvaginal sonographic CL measurement at 16–23 weeks of gestation, offering a cervical cerclage to those whose cervix shortens to <25 mm,^{68,69} and continuing administration of 17-OHPC until 36 weeks of gestation.⁶⁸ Vaginal progesterone and 17-OHPC are not the same; they have different indications, pharmacologic properties, and profiles of efficacy and safety.⁷⁰ After a careful review of these recommendations and the existing literature, we consider that the following evidence was not taken into account when formulating these recommendations for practice:

1. The efficacy of vaginal progesterone is similar to that of cervical cerclage in the prevention of preterm birth and perinatal morbidity and mortality for women with a singleton gestation, previous preterm birth, and a CL of <25 mm, as demonstrated in an indirect comparison meta-analysis of individual patient data.⁷¹ Since cervical cerclage, a surgical procedure, requires anesthesia and is associated with an increased risk of maternal side effects (vaginal discharge, bleeding, and pyrexia) and cesarean delivery,⁷² we believe that these patients should be offered the option of medical treatment with vaginal progesterone, as there is equipoise between the two approaches. In addition, there is strong evidence indicating that vaginal progesterone is not associated with an increased risk of adverse maternal events or congenital anomalies when compared to either a placebo or no treatment.^{23,73,74}
2. At present, the recommendations of professional organizations restrict vaginal progesterone for patients who have a CL of ≥20 mm. This is largely based on the inclusion criteria used in the study by Hassan et al.⁴⁵ However, as previously mentioned, a pre-planned subgroup analysis derived from an individual patient data meta-analysis indicated that the effect of vaginal progesterone in the prevention of preterm birth was not affected by CL.²³ Indeed, vaginal progesterone was effective in reducing the risk of preterm birth before 33 weeks of gestation and composite neonatal morbidity and mortality among women with a CL measuring 21–25 mm, as demonstrated by non-significant interaction *P* values. Further trials would be desirable to confirm the beneficial effects of vaginal progesterone for women with a CL measuring 21–25 mm. However, it is unclear whether such trials would be forthcoming because agencies are likely to focus on more pressing questions, such as the efficacy of vaginal progesterone in patients with a twin gestation and a short cervix. Until such trials are conducted and reported, the findings of the individual patient data meta-analysis²³ provide the best available evidence to counsel patients and to inform physicians at this time.
3. In the United States, the professional organizations recommend offering 17-OHPC to women with a history of spontaneous preterm birth.^{68,69} These patients undergo serial sonographic examination of the cervix, and when a short CL is detected, the question of the optimal management emerges. The professional organizations proposed, under these circumstances, that a cervical cerclage should be offered^{68,69} and that 17-OHPC administration should be continued,⁶⁸

however, the latter issue is a subject of controversy. Two secondary analyses of a trial of ultrasound-indicated cerclage⁷⁵ reported that, among women with a singleton gestation, previous preterm birth, and s CL<25 mm, there were no significant differences in the rates of preterm birth at <37, <35, <32, and <28 weeks of gestation and of perinatal mortality among women who received 17-OHPC plus cerclage (n=47) and those who received 17-OHPC alone (n=52) or cerclage alone (n=101).^{76,77} However, the rates of preterm birth at <35, <32, and <28 weeks of gestation were lower among women who received 17-OHPC plus cerclage than among those who received 17-OHPC alone or cerclage alone. Because these secondary analyses may have been underpowered to detect significant differences in the outcome measures, it appears reasonable to consider the continuation of 17-OHPC administration among women who receive a cerclage.

4. If a patient with a singleton gestation and a history of preterm birth receiving 17-OHPC develops a sonographic short cervix (< 25 mm) and chooses treatment with vaginal progesterone, we see no reason to continue the administration of 17-OHPC. Firstly, although there are no randomized controlled trials that have compared the administration of 17-OHPC vs. 17-OHPC plus vaginal progesterone or 17-OHPC vs. vaginal progesterone alone, some data from the indirect comparison meta-analysis of individual patient data⁷¹ and one secondary analysis⁷⁶ of the trial of ultrasound-indicated cerclage suggest that the administration of vaginal progesterone alone has, at least, similar efficacy to 17-OHPC in the prevention of preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix. In fact, the rates of preterm birth at <37, <35, <32, and <28 weeks of gestation among women who received vaginal progesterone were 45%, 27%, 12%, and 8%, respectively,⁷¹ whereas the corresponding rates among women who received 17-OHPC alone were 60%, 39%, 21%, and 15%, respectively.⁷⁶ Secondly, the combined administration of 17-OHPC and vaginal progesterone would expose the mother and fetus to higher concentrations of progesterone in the absence of evidence that this is beneficial. Although vaginal progesterone is considered to have a high margin of safety,^{23,44,45,73,74,78} a fundamental principle of pharmacology in pregnancy is to administer the lowest efficacious dose. Clinicians should be aware that a randomized clinical trial compared the efficacy and safety of 200 mg and 400 mg doses daily of vaginal progesterone in women with a twin gestation under the belief that a higher dose may be required for a twin gestation.^{79,80} The administration of 400 mg of vaginal progesterone was associated with a higher frequency of intrahepatic cholestasis of pregnancy without evidence of efficacy. Therefore, discontinuation of 17-OHPC seems logical in a patient with a singleton gestation, previous spontaneous preterm birth, and a CL < 25 mm who chooses treatment with vaginal progesterone.
5. The guidelines of professional organizations recommend a single transvaginal sonographic CL measurement at 18–24 weeks of gestation for women with a singleton pregnancy and without a previous preterm birth, and serial transvaginal

sonographic CL measurement once every two weeks, starting at 16 weeks of gestation until 23 weeks of gestation, for women with a singleton pregnancy and previous preterm birth.^{68,69} The recommendation to perform serial transvaginal CL measurement is mainly based on a research protocol of a trial that assessed ultrasound-indicated cerclage in women with a singleton gestation, previous preterm birth, and a CL <25 mm.⁷⁵ However, there are no randomized controlled trials comparing the effectiveness of serial transvaginal sonographic CL measurement and cerclage versus a single transvaginal sonographic CL measurement and cerclage versus a single transvaginal sonographic CL measurement and cerclage in patients with a singleton gestation, previous spontaneous preterm birth, and a short cervix. In addition, a recent meta-analysis found that a single CL measurement obtained between 18–24 weeks of gestation is a better test to predict preterm birth than changes in CL over time.⁸¹ Finally, it should be noted that all randomized controlled trials that assessed the efficacy of vaginal progesterone in women with a short cervix performed only a single measurement of CL at 18–24 weeks of gestation, regardless of the history of spontaneous preterm birth.^{44,45} None of these studies considered the serial measurement of CL in at-risk and/or borderline CL cases.

In summary, the evidence is now compelling to recommend universal transvaginal sonographic CL screening at 18–24 weeks of gestation for women with a singleton gestation and to offer vaginal progesterone to those with a CL $\geq$ 25 mm, regardless of the history of spontaneous preterm birth, with the goal of preventing preterm birth and neonatal morbidity and mortality. Cerclage could be offered as an alternative to vaginal progesterone to women with previous spontaneous preterm birth and a CL $\geq$ 25 mm. However, the surgical placement of a cerclage requires anesthesia and is associated with adverse maternal events, while medical treatment with vaginal progesterone does not. In the absence of evidence that 17-OHPC adds benefit to women with previous spontaneous preterm birth and a short cervix who choose vaginal progesterone, we recommend that 17-OHPC be discontinued to reduce the risk of potential adverse events to the mother and fetus. On the other hand, if the patient elects to receive a cerclage, the recommendation of continuing the administration of 17-OHPC⁶⁸ appears to be reasonable based on the evidence described above. A new management scheme is presented in Figure 1. This approach can be modified as new evidence arises. A randomized controlled trial of vaginal progesterone for women with a twin gestation and a short cervix is urgently needed to clarify whether this intervention can reduce the rate of preterm birth.

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Figure 1.
Algorithm for use of vaginal progesterone in a singleton gestation with a short cervix.
*17-OHPC, 17 α -hydroxyprogesterone caproate

TABLE 1

Effect of vaginal progesterone administration on the risk for preterm birth and adverse neonatal outcomes for women with a singleton gestation and a cervical length ≥ 25 mm

Outcome	RR (95% CI)	NNT (95% CI)	NNS (95% CI) ^a
Preterm birth <35 weeks	0.67 (0.51–0.87)	11 (7–28)	138 (88–350)
Preterm birth <34 weeks	0.60 (0.44–0.82)	10 (7–23)	125 (88–288)
Preterm birth <33 weeks	0.56 (0.40–0.80)	11 (8–25)	138 (100–313)
Preterm birth <32 weeks	0.56 (0.38–0.82)	13 (9–32)	163 (113–400)
Preterm birth <30 weeks	0.59 (0.37–0.92)	19 (12–97)	238 (150–1213)
Preterm birth <28 weeks	0.51 (0.31–0.85)	19 (13–61)	238 (163–763)
Respiratory distress syndrome	0.47 (0.27–0.81)	18 (13–51)	225 (163–638)
Birthweight <1500 g	0.52 (0.34–0.81)	14 (10–35)	175 (125–438)
Admission to NICU	0.67 (0.50–0.91)	12 (8–46)	150 (100–575)
Major neonatal morbidity/neonatal mortality ^b	0.59 (0.38–0.91)	18 (12–81)	225 (150–1013)

CI, confidence interval; NICU, neonatal intensive care unit; NNS, number needed to screen; NNT, number needed to treat; RR, relative risk.

^a Assuming a prevalence of 8% for a cervical length ≥ 25 mm.

^b Occurrence of any of the following events: neonatal death, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, or neonatal sepsis.

TABLE 2

Comparison of vaginal progesterone administration for women with a singleton gestation and a short cervix to other interventions commonly used in obstetrics and perinatal medicine

Intervention	Target population	Adverse outcome to prevent	RR (95% CI)	NNT (95% CI)
Magnesium sulfate	Women with preeclampsia ²⁸	Eclampsia	0.41 (0.29–0.58) ⁵²	91 (75–127)
	Women at risk of preterm birth before 34 weeks of gestation ²⁹	Cerebral palsy	0.69 (0.55–0.88) ⁵³	52 (31–154)
Aspirin	All women ³⁰	Preeclampsia	0.90 (0.84–0.97) ⁵⁴	167 (104–556)
Active management of the third stage of labor	All women ³²	Postpartum hemorrhage >1000 ml	0.34 (0.14–0.87) ⁵⁵	62 (48–315)
		Blood transfusion	0.35 (0.22–0.55) ⁵⁵	53 (44–76)
Antenatal corticosteroids	Women at risk of preterm birth ³³	Respiratory distress syndrome	0.66 (0.59–0.73) ⁵⁶	11 (9–14)
		Neonatal death	0.69 (0.58–0.81) ⁵⁶	22 (16–36)
Vaginal progesterone	Women with a singleton gestation and a short cervix ¹⁹	Preterm birth before 33 weeks of gestation	0.56 (0.40–0.80) ²³	11 (8–25)
		Major neonatal morbidity/neonatal mortality	0.59 (0.38–0.91) ²³	18 (12–81)

CI, confidence interval; NNT, number needed to treat; RR, relative risk.

Table 3

Comparison of universal transvaginal sonographic screening for a short cervix and treatment with vaginal progesterone to universal screening for group B streptococcal colonization and intrapartum antibiotic prophylaxis

Characteristic	Cervical length in women with a singleton pregnancy at 18–24 weeks of gestation	GBS colonization in women at 35–37 weeks of gestation
Test	Transvaginal sonographic cervical length measurement	Vaginal-rectal culture
Risk factor	Cervical length ≤ 25 mm	Colonization with GBS
Prevalence of untreated risk factor	~8%	~24%
Adverse outcome	Major neonatal morbidity/neonatal mortality ^a	Early-onset neonatal GBS infection
Frequency of adverse outcome if risk factor is untreated	13.7%	2%
Treatment	Vaginal progesterone	Intrapartum antibiotic prophylaxis
Evidence base	IPD meta-analysis involving 775 women (vaginal progesterone vs placebo) ²³	Cochrane meta-analysis involving 488 women (antibiotics vs no treatment) ⁶⁷
Treatment effect	RR, 0.59; 95% CI, 0.38–0.91	RR, 0.17; 95% CI, 0.04–0.74
Number needed to treat	18	60
Number needed to screen	225	250
Potential number of adverse outcomes averted annually in the United States	~17,500	~5000

CI, confidence interval; GBS, group B streptococcus; IPD, individual patient data; RR, relative risk.

^aOccurrence of any of the following events: neonatal death, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, or neonatal sepsis.