The only class of medication to demonstrate significant reductions repeatedly in the rate of early preterm birth are progestogens, natural progesterone or the synthetic 17-hydroxyprogesterone caproate (17-OHPC).1,2 Published guidelines have provided recommendations regarding their use.3-5 These agents are prescribed in asymptomatic patients who are at increased risk for spontaneous preterm birth that was determined by obstetric history or a sonographic short cervix. The risk for recurrent preterm birth varies depending on the gestational age at previous delivery, number of previous preterm births, whether an intervening term delivery has occurred, and the classification of the previous preterm birth as either spontaneous or indicated.6-9 The risk for preterm birth based on the cervical length also varies based on the gestational age a short cervix is identified and the population in which the measurement is obtained.10-12 Defining an optimal strategy for preterm birth prevention based on a risk factor or a biomarker for a presumed pathophysiologic process (a decline in progesterone action) or both can improve the risk-benefit ratio, lower health care costs, and enhance translation of scientific findings along particular paths.13,14

Progestogens are the first drugs to demonstrate reproducibly a reduction in the rate of early preterm birth. The efficacy and safety of progestogens are related to individual pharmacologic properties of each drug within this class of medication and characteristics of the population that is treated. The synthetic 17-hydroxyprogesterone caproate and natural progesterone have been studied with the use of a prophylactic strategy in women with a history of preterm birth and in women with a multiple gestation. Evidence from a single large comparative efficacy trial suggests that vaginal natural progesterone is superior to 17-hydroxyprogesterone caproate as a prophylactic treatment in women with a history of mid-trimester preterm birth. Progestogen therapy is indicated for women with this highest risk profile based on evidence from 2 trials. A therapeutic approach based on the identification of a sonographic short cervix has been studied in several phase III trials. Independent phase III trials and an individual patient metaanalysis suggest that vaginal progesterone is efficacious and safe in women with a singleton and a short cervix. Two trials that tested 17-hydroxyprogesterone caproate in women with a short cervix showed no benefit. No consistent benefit for the prophylactic or therapeutic use of progestogens has been demonstrated in larger trials of women whose pregnancies were complicated by a multiple gestation (twins or triplets), preterm labor, or preterm rupture of membranes. Unfortunately, several large randomized trials in multiple gestations have identified harm related to 17-hydroxyprogesterone caproate exposure, and the synthetic drug is contraindicated in this population. The current body of evidence is evaluated by the Grading of Recommendations Assessment, Development, and Evaluation guidelines to derive the strength of recommendation in each of these populations. A large confirmatory trial that is testing 17-hydroxyprogesterone caproate exposure in women with a singleton pregnancy and a history of preterm birth is near completion. Additional study of the efficacy and safety of progestogens is suggested in well-selected populations based on the presence of biomarkers.

Key words: 17-OHPC, adverse event, biomarker, cervical length, early preterm birth, history of preterm birth, metaanalysis, multiple gestation, pharmacodynamics, progestogens, safety, short cervix, twin gestation

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J. M. O’Brien was involved in studies of progesterone gel treatment for preterm birth prevention sponsored by a maker of progesterone gel; he served on Advisory Boards and as Consultant for Watson Pharmaceuticals, a company with a financial interest in marketing vaginal progesterone gel for preterm birth prevention; he and others are listed in a patent on the use of progesterone compounds to prevent preterm birth (USA Patent Number 7884093: Progesterone for the Treatment and Prevention of Spontaneous Preterm Birth). He has received other patents and has applications pending for devices to treat obstetrical patients including populations at increased risk for preterm birth. He has not received any funds from a royalty agreement or licensing of any patent to date nor has his university. He was involved in studies as a principal investigator published in 2011 and 2007.

D.F. Lewis was a principal investigator in a study testing vaginal progesterone published in 2007 sponsored by Columbia Laboratories.

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Drug development pathways initially have focused on selecting candidate compounds by generating an animal model of disease or by defining molecular responses to exposures. Subsequent phase I and II studies provide information regarding pharmacokinetics, dose response, initial safety observations, and the potential to alter clinically meaningful endpoints (see Glossary of terms). Ideally, phase III trials should then evaluate efficacy and safety in a well-selected candidate population to yield significant improvement in the best chosen, clinically important outcome. After efficacy is validated (often by replication), the indication for use may be expanded by additional trials that consider the effectiveness and safety profile of the intervention. This sequence for drug development was not used when exploring the efficacy of progestogens to prevent preterm birth; indeed, this systematic approach has been used rarely in obstetrics. Hence, interventions in obstetrics should undergo more frequent reevaluation while being implemented into clinical practice. This review addresses the efficacy and safety of progesterone use, given recent experimental observations regarding pharmacodynamics and the evolving understanding of risk-benefit provided from trials and metaanalysis.

Glossary

Phase I trial
A study early in the development aimed to describe pharmacokinetics, suggest optimal dose, identify remarkable harms/frequent adverse events, or establish the feasibility of treatment.

Phase II trial
A study aimed to estimate the activity of the drug (explore surrogate endpoints), compare dosing schedules to alter pharmacodynamics, or provide an estimate for demonstrating significant differences in clinically important endpoints.

Phase III trial
A study aimed to demonstrate superiority of an intervention (over placebo or other comparator) to alter clinically important endpoints or noninferiority (an intervention is no worse than another by a specified margin), in conjunction with an aim to better define the frequency of adverse events or harm. To accomplish both aims, phase III studies most commonly have a sample size in the hundreds or thousands.

Pharmacodynamics
The identification of any changes within the body that are related to a drug exposure.

Efficacy
This is a function of a test article under idealized circumstances in which the exposure is more controlled by investigators who include stricter inclusion and exclusion criteria, standardized provider skill assessment or testing, and uniform response to clinical circumstances. This determination is potentially a product of phase III trials.

Effectiveness
This is a function of a test article under clinical use conditions. This determination is potentially a product of trials with pragmatic design features that include limited exclusion criteria and few restrictions on additional therapies in response to clinical circumstances.

Pharmacodynamics and their implications for treatment
The mechanism of action for supplemental progesterogens to improve pregnancy outcome likely relies on increased interaction between progesterone receptors and their ligands. Presumably, the enhanced receptor-ligand interaction alters ≥1 hormone-mediated physiologic properties aimed at meeting the dynamic functional demands placed on tissues of the reproductive tract during pregnancy. Each tissue of the reproductive tract, the chorionicamnionic membranes, and the fetus express progesterone receptors with potential physiologic activities.15-17 The potential to augment cellular and tissue functions that are mediated by progesterone receptors beyond that achievable by the hormone that is produced from the preterm placenta alone has been termed the progestogen hypothesis.18

If increasing the bioavailability of progesterone for its receptors within the reproductive tract is the therapeutic target, then this goal may be realized through supplementation that increases concentration within these target tissues or by reduction of progesterone degradation. Therefore, a potential alternative site of action for progesterogens is within the liver. Caritis et al19 reported a linear, highly significant positive correlation between serum 17-OHPC concentration and serum progesterone concentration ($R^2 = 0.46; P < .0001$). An association between 17-OHPC exposure and an increased serum progesterone concentration has also been observed in 2 animal models, 1 of which was a primate model (both $P < .01$).20,21 Furthermore, 17-OHPC and progesterone have been shown to competitively interact with the cytochrome P450 3A4 enzyme (CYP 3A4) in human liver microsome preparations.22 Of note, supplemental progesterogens do not act to increase the placental production of progesterone or cross-react with other steroid hormone receptors.19,23 Therefore, data support 2 potential sites of action for progesterogens to enhance the progesterone receptor-ligand interaction; however, each strategy may have different capabilities to alter progesterone actions within the reproductive tract.

Both progesterone and 17-OHPC have been shown to alter progesterone receptor and cellular activity, but the relative binding affinity of 17-OHPC for nuclear progesterone receptors A and B is only 26-30% that of natural progesterone.23-25 This lower binding affinity raises the question whether this synthetic drug can act with equal efficacy as natural progesterone to influence receptor-mediated activities directly within the reproductive tract. In addition to the pharmacologic properties of these drugs and their site of action, other factors influence treatment response to progesterogens. The population that is treated is the most important consideration because a variation in response to these agents has been demonstrated in different populations. Furthermore, within populations, individual patient
characteristics appear to alter the effectiveness of this treatment strategy. In support of the latter construct, Manuck et al.\textsuperscript{26} demonstrated a variable response to 17-OHPC exposure, based on the progesterone receptor genotype.

In an informative experiment in a pregnant murine model, Nold et al.\textsuperscript{20} assessed differences in gene transcription after supplemental progesterone or 17-OHPC exposure in select pathways that are implicated in the pathophysiology of preterm delivery. The effects of 17-OHPC and progesterone in the cervix and myometrium were assessed. These investigators found progesterone, but not 17-OHPC, had a treatment effect that was localized to the cervix. Specifically, defensin-1, an antimicrobial peptide, was significantly up-regulated by supplemental progesterone exposure. These data suggest that a potential relationship exists among mucosal integrity, inflammation, cervical remodeling, spontaneous preterm labor, and this treatment.

A detailed series of experiments that tested the immune response to supplemental progestogens was performed recently by Furcron et al.\textsuperscript{22} in a pregnant murine model. These investigators also observed that vaginal progesterone, but not 17-OHPC, was associated with beneficial effects. The immune response to natural progesterone alone resulted in a significant increase in the proportion of decidual CD4\textsuperscript{+} Tregs, a reduction in the proportion of macrophages in decidual tissues, and a reduction of active MMP-9\textsuperscript{+} cells in the cervix. Furthermore, vaginal progesterone was shown to protect against endotoxin-induced preterm birth (effect size, 50%; \( P = .0008 \)). Although additional study of supplemental progestogens is needed, current evidence suggests that the alteration in the immune response is an important mechanism of action for these agents.

A paucity of experimental data is available to describe the effects of supplemental progestogens on human tissues at preterm gestational ages. The treatment response to a dose of supplemental progestogens may differ throughout gestation because placental production of the hormone varies so remarkably based on gestational age.\textsuperscript{28} A study by Ruddock et al.\textsuperscript{29} incubated myometrial strips that were obtained from term cesarean deliveries with different progestogens. Progesterone treatment was found to induce relaxation of the smooth muscle; 17-OHPC exposure stimulated myometrial activity. Another study from term cesarean deliveries by Kumar et al.\textsuperscript{30} noted that exposure to progesterone significantly reduced membrane weakening.

In summary, the experimental observations in human tissue and animal models demonstrate that (1) sites of action within the reproductive tract and liver are possible after exposure to these distinct progestogens, (2) the cervix or decidua are likely primary targets to prevent preterm birth by these agents, but other activities are possible, and (3) natural progesterone may be the superior progestogen to alter gene transcription and cellular physiologies to vary the immune response to prevent spontaneous preterm birth.

Clinical trial data that has assessed pharmacodynamic responses to supplemental progestogens has focused on cervical length measurement. A planned secondary analysis of the largest trial to date measured cervical length at enrollment and at 28 weeks gestation in asymptomatic singletons.\textsuperscript{31} The difference in measurement at these time-points was significantly smaller, and the cervical length at 28 weeks gestation was significantly longer in women who were treated with progesterone. A slower rate of cervical change was also demonstrated in a randomized trial testing a higher dose of 17-OHPC (682 mg/wk) in a symptomatic population with an episode of preterm labor.\textsuperscript{32} However, 2 retrospective studies that evaluated prophylactic treatment with 250 mg/wk of 17-OHPC did not identify a treatment effect on cervical length.\textsuperscript{33,34} Regarding myometrial activity, a large observational study demonstrated a significant increase in contraction frequency after exposure to 17-OHPC, whereas natural progesterone exposure has been shown to significantly decrease contraction frequency.\textsuperscript{35,36} Therefore, clinical data also suggest that these 2 compounds should not be considered equivalent regarding their actions on the reproductive tract functions.\textsuperscript{37}

**Is there evidence of superiority between progestogens?**

Given its results, the phase III study by Meis et al.\textsuperscript{38} stimulated design and execution of numerous additional large trials that tested progestogens in a variety of populations. A significant reduction in recurrent preterm birth (36.3% vs 54.9%; relative risk [RR], 0.66 [95% confidence interval (CI), 0.54–0.81]) was demonstrated with exposure to 17-OHPC in addition to fewer deliveries at <35 weeks gestation (20.6% vs 30.7%; RR, 0.67 [95% CI, 0.48–0.93]). Although this trial demonstrated efficacy, several concerns have been identified that include an imbalance between study groups, patient selection and generalizability of its conclusions because of the higher rate of preterm birth in the placebo group compared with other prospective observational studies, and the vehicle (castor oil) for this progestogen. Despite randomization, the women in the placebo group had a significantly higher mean number of previous preterm births (1.6 ± 0.9 vs 1.4 ± 0.7; \( P = .007 \)) and a significantly greater percentage of these women had >1 previous preterm delivery before enrollment (41.2% vs 27.7%; \( P = .004 \) by chi square based on data presented). A confirmatory phase III trial was required by the Food and Drug Administration (FDA) for its current conditional approval, given these concerns. This study has a planned enrollment of 1707 women and is intended to replicate the efficacy of 17-OHPC as a prophylactic treatment in women with a history of preterm birth. (The PROLONG Trial-clincialtrials.gov/ct2/show/NCT01004092) This study will also better assess the safety of the drug in singleton gestations, given its planned sample size.

The FDA has also evaluated vaginal progesterone that is indicated for women with a sonographic short cervix.\textsuperscript{39} The marketing of natural progesterone indicated for this biomarker was
Pregnancy duration was in favor of natural progesterone by Kaplan-Meier analysis ($P = .0023$). Finally, the number of neonatal intensive care unit admissions was lower with progesterone (15.4% vs 25.7%; $P = .006$). This study found that the efficacy of vaginal progesterone was superior to 17-OHPC in the prevention of recurrent preterm birth in a higher risk, compliant population.

One potential explanation for decreased efficacy of the synthetic drug is that 630 mg/week of natural progesterone was administered vs 250 mg/week of 17-OHPC. In support of this concern, Caritis et al.\textsuperscript{45} found that the women in the lowest quartile of serum 17-OHPC concentration had higher rates of recurrent preterm birth. These data suggest, for singletons, that the optimal dose of 17-OHPC has not been identified and may vary based on factors such as body mass index, coexisting drug exposures, or innate differences in hepatic metabolism that may alter the serum concentration of this synthetic progestogen and/or natural progesterone.\textsuperscript{45,46}

If monitoring serum 17-OHPC concentration is ultimately deemed necessary to optimize treatment, then intramuscular dosing of this synthetic drug will be more difficult and costly. The vaginal route of drug delivery likely results in a greater concentration of supplemental progesterone within the uterus and cervix compared to serum, if vaginal absorption during pregnancy is similar to nonpregnant women.\textsuperscript{47,48}

The comparative efficacy study by Maher et al.\textsuperscript{44} also addresses a potential misperception that these individual progestogens are exclusively efficacious in particular populations that are at risk. Because both of these progestogens are members of the same class of drugs, most likely ultimately targeting changes in cellular and tissue physiology that are mediated via similar receptors, natural progesterone has the potential to alter outcomes in patients who are at risk like 17-OHPC. Clinical trials that have applied a prophylactic strategy in women with a history of preterm birth likely have enrolled heterogeneous groups of women with differing pathways that led to their birth histories which may explain some variation in trial findings. The negative progesterone trial by O’Brien et al.\textsuperscript{42} was not powered to assess efficacy in the subpopulation of women with a history of mid-trimester preterm birth and selection bias that was related to cervical length measurement at enrollment likely reduced the number of women who could respond to the intervention.

**Indications for vaginal progesterone and 17-OHPC**

A history of preterm birth, a sonographic short cervix, or both clinical problems have served to provide indication for this intervention.\textsuperscript{49} As noted previously, women at highest risk with a history of mid-trimester preterm birth should undergo prophylaxis with a progestogen. However, women with a history of later spontaneous preterm birth in the third trimester may not require this intervention. O’Brien et al.\textsuperscript{42} and DeFranco et al.\textsuperscript{50} evaluated treatment response in the largest randomized trial performed to date in singletons. In this study, prevention of recurrent preterm birth was not demonstrated with progesterone treatment based on historic factors alone, but a treatment response was identified when cervical length was used to stratify the population.\textsuperscript{45} This investigation identified a therapeutic effect to prolong gestation in women with a history of preterm birth who had a cervical length of $\leq 30\text{ mm}$ ($n = 116; P = .04$). Therefore, women with a history of spontaneous preterm birth in the third trimester who undergo cervical surveillance and have a cervical length $>30\text{ mm}$ may not benefit because a positive treatment response has not been replicated for this subpopulation.

The importance of cervical length in defining the indication for treatment in asymptomatic patients has been verified by 2 other phase III trials that tested a universal screening strategy. Fonseca et al.\textsuperscript{41} and Hassan et al.\textsuperscript{51} demonstrated that treatment indicated for a sonographic short cervix can reduce the rate of early preterm birth in women who...
undergo a universal screening strategy by transvaginal ultrasound scanning. Romero et al also quantified a 42% reduction using this strategy in an individual patient-level metaanalysis. Unfortunately, 2 large trials that tested 17-OHPC in asymptomatic women with a short cervix did not identify benefit in groups with either a high-risk or low-risk profile for preterm birth.\textsuperscript{52,53} Furthermore, the study by Grobman et al\textsuperscript{52} did not observe a therapeutic effect in the subpopulation of low-risk women with the shortest cervical lengths, <15 mm. Rozenberg et al\textsuperscript{54} also did not demonstrate benefit with 17-OHPC exposure in a randomized trial of symptomatic patients with a short cervix. Therefore, vaginal progesterone appears to be the superior progestogen for women with a sonographic short cervix. Other biomarkers in concert with cervical length measurement ultimately may facilitate a better definition for treatment indication and of treatment response.

The most confident conclusion that can be made from randomized trials that have been performed to date is that prophylactic progestogen exposure in women with a multiple gestation in unselected cohorts is ineffective and potentially harmful when 17-OHPC is used as the intervention.\textsuperscript{55-65} Numerous phase III trials have all failed to demonstrate positive results for their primary endpoints. Further study of a prophylactic strategy with vaginal progestosterone in multiples without risk stratification is not warranted.

Other populations with negative results from larger trials include symptomatic cohorts with preterm contractions or premature rupture of the membranes.\textsuperscript{66,67} However, 2 meta-analyses that synthesized data from smaller trials have suggested progestogens may be beneficial in symptomatic populations with preterm labor.\textsuperscript{68,69} Additional larger trials are necessary to better assess the efficacy of supplemental progestosterone in women with preterm labor; treatment is not recommended in symptomatic populations until such studies are performed.

A summary of clinical investigations to date is presented in the Box. Three important constructs regarding an indication for treatment are derived from the present data: (1) defining an indication for treatment primarily based on a biomarker in the ongoing pregnancy is likely optimal to basing therapy solely on obstetric history for the majority of patients, except for those at highest risk (a previous mid-trimester spontaneous preterm birth), (2) vaginal natural progesterone appears superior to 17-OHPC for efficacy in asymptomatic patients with a short cervix, and (3) women with a multiple gestation and symptomatic patients do not respond to this therapeutic strategy like asymptomatic singleton cohorts. The strength of recommendation for the use of progestogens to prevent preterm birth is based on the Grading of Recommendations Assessment, Development, and Evaluation guidelines (Box), and the present review is the first to assess this treatment strategy using these suggested guidelines.\textsuperscript{70}

Prophylactic treatment may be considered and offered to women with a singleton pregnancy and who have a history of preterm birth in the third trimester, based on the single study by Meis et al\textsuperscript{38} while awaiting confirmatory phase III data. Additional trials of progestogens are needed to assess (1) the comparable efficacy between progestogens to validate the findings of Maher et al, (2) whether dosing should be increased at differing gestational ages such as the start of the third trimester to improve efficacy, and (3) safety.

**Are vaginal progesterone and 17-OHPC equally safe?** Therapeutics aimed to prevent preterm birth such as tocolytics have limited efficacy once symptoms develop, necessitating earlier interventions. Current indications for supplemental progestogens to prevent preterm birth include populations that will most probably deliver at term. Consequently, a high margin of safety is required because these medications will be administered to pregnant women who are not experiencing potential benefit but who are undergoing a prolonged exposure.

The FDA review of 17-OHPC raised a safety concern based on the data from the trial by Meis et al.\textsuperscript{31} The Agency performed a survival analysis that generated Kaplan-Meier curves for the control and intervention groups that documented a cross-over event (Figure). The FDA has required labeling that acknowledges an increase in miscarriage was observed with this treatment from this trial. An early metaanalysis supported safety concerns related to the synthetic, as have more recent reviews, especially in women with a multiple gestations.\textsuperscript{72,73} In a secondary analysis derived from patients who were enrolled in the trial by Meis et al,\textsuperscript{38} an increased risk for preterm birth was observed in subpopulations that were discriminated by progesterone receptor genotype. Manuck et al\textsuperscript{26} demonstrated that particular haplotype blocks (Rs503362/rs666553 and Rs578029/rs666553) were associated with an adjusted odds ratio >10 for preterm birth <32 weeks gestation with exposure to 17-OHPC in the white/Hispanic subpopulation (adjusted odds ratio, 13.98 [95% CI, 1.27–153.32] and 16.19 [95% CI, 1.27–206.77], respectively). Differences were observed by race in this study, and further pharmacogenomic investigation of treatment response by race is needed.

Larger studies and metaanalyses have documented harm with exposure to progestogens, particularly in subpopulations at greater risk (Table). A trial level metaanalysis by Sotiriadis et al\textsuperscript{65} quantified a risk for harm related to 17-OHPC exposure in multiple gestations (RR, 1.21; 95% CI, 1.03–1.43), for a composite outcome of death and severe morbidity. The number needed to harm was 31 (95% CI 17–167). A recently published participant-level metaanalysis validated this concern for increased adverse outcomes.\textsuperscript{56} This study by Schuit et al\textsuperscript{66} found women who initiated 17-OHPC treatment at <24 weeks gestation had a higher rate of adverse outcomes (82/518 (16%) vs control subjects 60/512 (12%); RR, 1.4; 95% CI, 1.26–1.5). A significant
Increase in composite adverse outcome was also identified in the subgroup with a longer cervix, >25 mm, at enrollment. This metaanalysis concluded that 17-OHPC should not be prescribed to women with a multiple gestation. Therefore, evidence for harm should be incorporated into prescribing decisions, and a mechanistic assessment of safety concerns should direct further research. The safety of 17-OHPC exposure in this population can also be evaluated by application of the Bradford Hill criteria to the body of evidence.\(^1\) One of these 9 criteria includes evaluation of dose response. The duration of pregnancy in multiples has been related significantly inversely to the serum 17-OHPC concentration, (hazard ratio, 1.14; \(P = .001\)).\(^1\) A dose-response for adverse outcomes in multiple gestations is also suggested by comparison of trials that tested 17-OHPC. The largest trial to date

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**BOX**

**Proposed Grading of Recommendations Assessment, Development, and Evaluations for supplemental progestogens and the suggested superior agent\(^a\)**

I. **History indicated:** prophylactic therapy in an asymptomatic, singleton pregnancy in women with a history of spontaneous preterm birth indicated: Prior mid trimester spontaneous preterm birth — superior agent: natural progesterone. Studied agents included 17-OHPC, which is an option.

   Reproducible evidence is observed. Secondary analysis by Spong et al\(^5\) of the trial by Meis et al\(^3\) identified efficacy for this subpopulation. Validation for efficacy is provided from evidence of superiority of natural progesterone compared with 17-OHPC, Maher et al\(^4\) (assumes 17-OHPC exposure in this trial would not cause harm). Therapy should be initiated at 15-20 weeks gestation. Validation of natural progesterone being superior is needed by additional highly powered pragmatic trials. Grade 1B

   **Considered:** Prior spontaneous preterm birth at 28-36 weeks gestation — studied agents: synthetic 17-OHPC and natural progesterone

   Efficacy with 17-OHPC treatment is suggested from a single phase III trial by Meis et al\(^3\), but remarkable heterogeneity is present in metaanalysis (Cochrane review\(^9\)). The largest trial testing vaginal progesterone did not demonstrate benefit in this population, but the prevalence of a short cervix was relatively low in this study. Objective data, particularly cervical length, likely serves to better guide therapy in this subpopulation based on data from DeFranco et al\(^6\) (later). The superior progestogen optimizing both efficacy and safety in this subpopulation has not been defined clearly. If treated, therapy should begin at 15-20 weeks gestation. Additional dose-ranging and safety studies are also needed. Insufficient evidence from phase III trials for strongest recommendation. Grade 2B

II. **Biomarker-based indication for therapy in a singleton pregnancy**

   A. **Short cervix: asymptomatic, mid trimester, 19-24 weeks gestation**

      **Indicated:** Cervical Length \(< 20 \text{ mm}$$

      **Reproducible evidence for efficacy from phase III trials, (Hassan et al\(^5\) and Fonseca et al\(^4\)). The superior agent is suggested because of negative trials/secondary analysis by several groups. Safety and efficacy in patients with the shortest of cervical lengths, \(< 10 \text{ mm}$$, may be the subject for additional study to define optimal intervention, particularly if fetal membranes are exposed or intrauterine infection is suspected. The efficacy of treatment at longer cervical lengths, such as 21-25 mm, also requires validation in much larger trials; however, metaanalysis by Romero et al\(^6\) has suggested potential benefit. Grade 1A

      **Considered:** history of spontaneous preterm birth with a short cervix

      **Indicated:** Cervical length \(\leq 30 \text{ mm}$$ — studied agent: natural progesterone

      Based on evidence for pregnancy prolongation from a phase III trial over the continuum of cervical length by DeFranco et al\(^6\) and a participant-level metaanalysis by Romero et al\(^6\). The utilization of this criterion may be limited to those undergoing cervical surveillance. The efficacy of treatment at cervical lengths \(> 20 \text{ mm}$$ in this subpopulation requires validation in phase III trials. Insufficient evidence for strongest recommendation. Grade 2B

   B. A short cervix with symptomatic preterm labor, premature rupture of membranes, or at later gestational ages

      **No indication at present and safety concerns exist from experimental and animal data.**

      Further investigation reserved for carefully monitored, phase III randomized trials. A single phase III trial, Martinez de Tejada et al\(^5\), demonstrated possible harm in women who are diagnosed with preterm labor exposed to progesterone. Grade 2B

   C. Biochemical biomarker or other sonographic finding as an indication or exclusion for therapy

      **No indication or exclusion for treatment based on objective biochemical findings or other evidence of a potentially altered physiology has been identified and validated.**

III. **Multiple gestations**

   **Contraindicated in unselected populations:** 17-OHPC should not be further investigated or prescribed in multiples because of identified safety findings in an individual participant data metaanalysis by Schuit et al\(^5\). Grade 1B

   Subpopulations with an objective biomarker for decidual/placental dysfunction have not been studied adequately with natural progesterone. Also, 2 individual participant level metaanalyses have suggested that a short cervix at \(< 24 \text{ weeks}$$ gestation in asymptomatic patients may provide an indication worthy of study. Because of the presence of risk, treatment is not recommended until additional phase III trials have been performed in such candidate subpopulations that are stratified by biomarkers.

\(^a\) Level of recommendation is based on data that were derived preferentially from phase III trials with the application of the Grading of Recommendations Assessment, Development, and Evaluation criteria. O’Brien. Progestogen safety and efficacy to prevent preterm birth. Am J Obstet Gynecol 2016.
in multiples that evaluated prophylactic 17-OHPC was performed by Lim et al who used a dose of 250 mg/wk. These investigators found a significant increase in severe respiratory distress with exposure to the synthetic (RR, 1.55; 95% CI, 1.01—2.37). A study by Senat et al used a dose of 500 mg 17-OHPC twice per week in women with a twin gestation and a short cervix. They unfortunately observed a 2.4-fold increase in early preterm birth at <32 weeks gestation in the intent-to-treat analysis (24/82 (29%) treated vs 10/79 (12%) control; \(P = .007\)). A significant increase in perinatal mortality rate and a composite adverse outcome of stillbirth plus respiratory distress were associated with treatment.\(^7\)

Other phase III trials in multiple gestations have suggested potential benefit rather than harm with exposure to progestogens. Norman et al\(^5\) observed a reduction in cesarean delivery and operative vaginal delivery with progestrone use. Rode et al\(^6\) demonstrated a reduction in emergency cesarean delivery and a significant reduction in birthweight of <1500 g in their monochorionic subgroup. Subpopulations at greater risk for suspected decidual/placental pathophysiologic conditions may be appropriate for future study with natural progesterone. Of interest, the only trial that did not identify harm with exposure to 17-OHPC in a twin gestation, the PROGESTWIN trial, recently found a significant increase in birthweight, a decrease in frequency of birthweight <1500 g, and a decrease in composite neonatal morbidity with treatment.\(^7\) The mean gestational age at delivery for the placebo group was 34.6 ± 3.8 weeks gestation in this study, which could indicate a higher risk profile of participants that deserves further evaluation.

Whether asymptomatic patients with a multiple gestation and short cervix (<24 weeks gestation) could benefit from supplemental progesterone has been suggested by 2 participant-level metaanalyses and a recently published randomized trial.\(^4\) El-refaie et al\(^7\) randomly assigned 250 women with a cervical length of 20-25 mm between 20-24 weeks of gestation. The rates of respiratory distress syndrome, mechanical ventilation, and early neonatal death were reduced significantly with treatment. However, a retrospective study by Brubaker et al\(^8\) suggested caution in this population because of safety concerns. Given the safety profile of progestogen exposure in multiples, additional phase III trials are necessary, and any future trial should assess treatment response thoroughly by interrogating multiple biomarkers.

Structural teratogenicity has not been observed with early exposure to progestogens.\(^7\) Mechanisms for harm related to exposure later in gestation will likely involve alteration of progesterone receptor activity. Because these receptors are located within the central nervous system of the developing fetus, functional abnormalities such as behavioral teratogenicity requires further investigation. Basic science investigations have raised plausible concerns for such developmental abnormalities particularly for the synthetic drug.\(^8\) However, to date, no longer term adverse harms have been identified after exposure to either of these medications, but the data are limited.\(^8\)

Based on present data that were derived from phase III trials and metaanalysis, natural progesterone appears to be the safer progestogen, but plausible concerns for adverse outcomes with exposure remain. Safety for an intervention in any obstetric population is more probable when natural agents are administered at doses that yield exposures within boundaries observed in human reproduction.\(^\) Robust dose-response studies have yet to be performed and should be designed carefully. Also, this treatment strategy undoubtedly will be applied to other populations who are at risk for adverse events, such as women with an episode of preterm labor. Animal data have demonstrated the potential for adverse events, which include death, when supplemental progestogens are administered in models for preterm labor.\(^8\) Of concern, a recent trial in symptomatic women with an episode of preterm labor demonstrated that supplemental natural progesterone was associated with a significant increase in spontaneous preterm birth at <34 weeks gestation (74/180 (40%) vs 48/168 (29%) RR, 1.4; 95% CI, 1.04—1.88; \(P = .03\) per protocol analysis).\(^8\) Hence, in symptomatic women, biomarkers that augment cervical assessment, particularly those that describe infectious/inflammatory pathways, may be essential to help guide safer exploration of the efficacy of supplemental progestogens.

Risk/benefit and cost of progestogen use

Vaginal progesterone indicated for a sonographic short cervix is the first drug to demonstrate reproducible efficacy for the prevention of early preterm birth in independent phase III trials. The number of patients needed to screen to prevent 1 early preterm birth (<34 weeks gestation) has been estimated as 125 (95% CI, 88–288), and the number needed to screen to prevent a case of major neonatal morbidity/death has been quantified as 225 (95% CI, 150—1013; calculated for treatment of women with a cervical length of ≤25 mm).\(^6\) The proposed indications in the Box for progestogen use mimic the maturation of indication observed with cervical cerclage by focusing more on cervical length than obstetric
### Summary of statistically significant harms in published randomized trials after exposure to 17-hydroxyprogesterone caproate or progesterone

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug (dose)</th>
<th>Significant finding at secondary analysis</th>
<th>Data and/or significance</th>
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<td>Increased previable delivery</td>
<td>13/168 (8%) 17-OHPC vs 0/75 (0%); $P = .01$</td>
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<tr>
<td></td>
<td></td>
<td>Increased perinatal death</td>
<td>19/168 (11%) 17-OHPC vs 2/75 (3%); $P = .05$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase in birthweight &lt;1500 grams</td>
<td>91/212 (43%) 17-OHPC vs 46/183 (25%); relative risk, 1.7 (95% confidence interval, 1.1–2.7)</td>
</tr>
<tr>
<td><strong>Twins</strong></td>
<td></td>
<td>Shorter duration of pregnancy</td>
<td>Kaplan-Meier; $P = .02$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase in birthweight &lt;2500 grams</td>
<td>195/320 (61%) 17-OHPC vs 70/156 (45%); $P = .009$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Birthweight, grams</td>
<td>$2321 \pm 523$ 17-OHPC vs $2469 \pm 543$; $P = .03$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oxygen use at 28 days</td>
<td>9/308 (3%) 17-OHPC vs 0/150; $P = .03$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe respiratory distress syndrome in neonates</td>
<td>82/681 (12%) 17-OHPC vs 51/674 (8%); relative risk, 1.55 (95% confidence interval, 1.01–2.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Earlier gestational age of membrane rupture, weeks</td>
<td>$31.1 \pm 6.1$ 17-OHPC vs $33.9 \pm 4.0$; $P = .04$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased preterm birth &lt;32 weeks gestation</td>
<td>24/82 (29%) 17-OHPC vs 10/83 (12%); $P = .007$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Earlier gestational age at delivery</td>
<td>$34^{+6}$ ($31^{+4.3}$–$36^{+3}$) 17-OHPC vs $35^{+3}$ ($34^{+6}$ to $36^{+6}$); $P = .029$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased perinatal mortality rate</td>
<td>$9/158$ (6%) 17-OHPC vs 1/154 (0.6%); $P = .02$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Composite adverse outcome of stillbirth plus respiratory distress</td>
<td>55/160 (34%) 17-OHPC vs 34/154 (22%); $P = .016$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative correlation between 17-Hydroxyprogesterone caproate concentration and gestational age at delivery</td>
<td>Hazard ratio 1.14; $P = .001$; $R^2 = .49$</td>
</tr>
<tr>
<td><strong>Singletons</strong></td>
<td></td>
<td>Women with particular polymorphisms for progesterone receptors may have increased frequency of preterm birth with exposure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>rs503362 (white/Hispanic &lt;32 weeks)</td>
<td>Adjusted odds ratio, 13.98 (95% confidence interval, 1.27–153.32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>rs578029 (white/Hispanics &lt;32 weeks)</td>
<td>Adjusted odds ratio, 16.19 (95% confidence interval, 1.27–206.77)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Symptomatic women with preterm labor, spontaneous preterm birth &lt;34 weeks gestation</td>
<td>74/180 (40%) progesterone vs 48/168 (28.6%); $P = .03$</td>
</tr>
</tbody>
</table>

17-OHPC, 17-hydroxyprogesterone caproate.

Intramuscular therapy with 17-OHPC has the advantage to document compliance that is important for treatment response. Additional large pragmatic trials may better define the comparative effectiveness of these drugs as they are used in clinical practice. Methods to enhance compliance with vaginal treatment are needed. However, the treatment response to 17-OHPC appears to vary based on the gestational age of the previous preterm birth, whether a term birth has occurred, maternal weight, and serum concentration. Such a variable response explains, in part, the substantial heterogeneity that was noted in the Cochrane review of progestogens to prevent recurrent early preterm birth.

Results from the confirmatory PROLONG trial are expected relatively soon. This trial will enroll women at 16-20 weeks gestation with a history of spontaneous preterm birth (20-36 weeks gestation) and prophylactically expose them to either weekly 17-OHPC (250 mg) or placebo. Because of its estimated sample size of approximately 1700 participants, this trial will be important in defining the direction for progestogen treatment. A positive trial with evidence of safety will validate the approach and emphasize prophylaxis for women with a history of preterm birth that occurred over a wide gestational age range (20-36 weeks). The PROLONG trial may also find that benefit is limited to a select subpopulation such as those with a history of mid-trimester preterm birth. However, a negative trial should not negate the therapeutic benefits that have been identified with vaginal progesterone because these progestogens are different drugs with differing pharmacodynamics. Given the importance of this trial, its results should be forwarded to the obstetric community as early as possible.

Progestogen treatment indicated for a short cervix is cost-effective. An updated investigation by Werner et al. again demonstrated the cost-effectiveness of this treatment strategy. Further savings are possible by the avoidance of treatment in women with a history of third-trimester preterm birth and who have the longest cervical lengths. Cost-benefit has become more germane because the compounding of 17-OHPC is being curtailed by the FDA. Although the FDA has responsibility for the marketing of products in the United States, professional organizations in obstetrics have a greater influence on practice. Most medications in obstetrics that demonstrate efficacy (eg, corticosteroids for fetal lung maturity, magnesium for neuroprotection, and others) are not approved by the FDA. Practice guidelines that address newer interventions, such as progestogen use, should be reassessed frequently because the development of therapeutics in obstetrics rarely proceeds along common regulatory pathways, which increases uncertainty. Select basic principles for the assessment of efficacy are common to the application of the Grading of Recommendations Assessment, Development, and Evaluation guidelines and the evaluation of new drugs by the FDA. Such evaluations temporarily may influence the practice of obstetrics differently; however, the inevitable direction for therapeutics in obstetrics is toward a better appreciation of pathophysiologic conditions, better targeting of pathophysiologies through the use of biomarkers, and use of the safest treatments. Remarkably, the first intervention to demonstrate a significant reduction reproducibly in early preterm birth in phase III trials fulfills these important objectives. Recent data that evaluated the pharmacodynamics, safety, and efficacy of progestogens provides important new information regarding the optimal use or avoidance of these medications that should alter current recommendations.

REFERENCES


96. Spong CY, Meis PJ, Thom EA, et al. Progesterone for prevention of recurrent preterm...