OBSTETRICS

Prevention of preterm birth with vaginal progesterone or 17-alpha-hydroxyprogesterone caproate: a critical examination of efficacy and safety

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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

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]

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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 progestogen 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 process of an intervention 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 progestogens 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 chorioamniotic 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 progestogens is within the liver. Caritis et al[19] 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 progestogens 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 progestogens 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 progestogens. 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