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REVIEW

Critical appraisal of the efficacy, safety, and patient acceptability of hydroxyprogesterone caproate injection to reduce the risk of preterm birth

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Abstract: Prevention of preterm delivery is a major desiderate in contemporary obstetrics and a societal necessity. The means to achieve this goal remain elusive. Progesterone has been used in an attempt to prevent preterm delivery since the 1970s, but the evidence initially accumulated was fraught by mixed results and was based on mostly underpowered studies with variable eligibility criteria, including history of spontaneous abortion as an indication for treatment. More recent randomized controlled clinical trials restimulated the interest in progesterone supplementation, suggesting that progesterone may favorably influence the rate of preterm delivery. Preterm delivery is a complex disorder and consequently it is unlikely that one generalized prevention strategy will be effective in all patients. Further, an additional impediment in accepting progesterone as the "magic bullet" in the prevention of preterm delivery is that its mechanism of action is not fully understood and the optimal formulations, route of administration, and dose have yet to be established. We have concerned ourselves in this review with the most recent status of 17 alpha-hydroxyprogesterone caproate (17OH-PC) supplementation for prevention of preterm delivery. Our intention is to emphasize the efficacy, safety, and patient acceptability of this intervention, based on a comprehensive and unbiased review of the available literature. Currently there are insufficient data to suggest that 17OH-PC is superior or inferior to natural progesterone. Based on available evidence, we suggest a differential approach giving preferential consideration to either 17OH-PC or other progestins based on obstetric history and cervical surveillance. Progestin therapy for risk factors other than a history of preterm birth and/or a short cervix in the current pregnancy is not currently supported by the published evidence. The experience to date with 17OH-PC indicates that there are population subgroups that may be harmed by administration of 17OH-PC. Therefore, extending the use of 17OH-PC to unstudied populations or for indications that are not evidence-based is inadvisable outside of a research protocol.

Keywords: preterm delivery, prevention, 17 alpha-hydroxyprogesterone caproate, efficacy, safety, acceptability

Introduction

Use of progestins has recently re-emerged as a pharmacologic strategy to improve pregnancy outcomes in women at risk for preterm birth. Endogenous steroid hormones have long been known to regulate endocrine pathways during pregnancy. Estrogens have effects that can both help sustain pregnancy and terminate it by initiating labor. Some of the pregnancy-maintaining effects of estrogens result from their ability to promote synthesis of progesterone.[1] However, progesterone is the steroid hormone mainly responsible for maintaining the pregnancy through a variety of phases, including morphologic changes to the cervix and myometrium, inhibition of uterine contractions,

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and downregulation of the immune system both systemically and at the maternal-fetal interface.[2,3]

The use of exogenous progestins has been advocated for prevention of preterm delivery for almost 40 years. A number of trials have been conducted with conflicting results, and the aggregated body of knowledge lacks reliably reproducible and generalizable evidence of benefit. Interpretation of the available data is particularly difficult because different forms and doses of progestins have been used in disparate study populations. The formulations almost exclusively used have been either natural progesterone (administered either orally or vaginally) or the synthetic progestin 17 alpha-hydroxyprogesterone caproate (17OH-PC) administered intramuscularly. We reviewed the prevention of preterm birth using progestins in 2009[4] and the reader is referred to that publication for a broad overview. The purpose of this review was to update and organize, in an evidence-based format, the information relating exclusively to 17OH-PC.

We searched MEDLINE for all publications between January 1966 and March 2013 for articles reporting on progestin use in pregnancy. We used the following search terms: "progesterone", "17-alpha hydroxyprogesterone caproate", "pregnancy", and "preterm delivery". Additional limits were not placed. All articles retrieved from this search were reviewed for the outcome of interest. We selected reports that examined progestin use in relation to preterm delivery and any other articles commenting specifically on 17OH-PC.

Efficacy of hydroxyprogesterone caproate

Preterm delivery is a complex problem with varied and incompletely elucidated pathogenic pathways. Consequently, it is unlikely that one generalized interventional approach will be effective in all patients. Indeed, administration of supplemental progesterone is far from being a universal panacea in the fight against preterm delivery. A limiting factor of progesterone prophylaxis is that the current indications for this intervention are based on risk factors for preterm delivery (prior preterm delivery and/or short cervix). However, 50% of women destined to have a preterm delivery will have no identifiable risk factors.[5] When given in a low-risk study population (n = 168) that was not selected on the basis of risk factors for preterm delivery, 17OH-PC administered as a weekly 1000 mg intramuscular dose was ineffective in reducing the rate of preterm birth.[6] Based on limited data, it appears that progesterone supplementation should not be used as a primary prevention strategy in the general low-risk obstetric population; currently it is only recommended for secondary prevention to reduce the impact of previously expressed risk factors.

The single greatest risk factor for preterm delivery is a history of prior unexplained spontaneous preterm birth.[7] Studies over the last four decades have found that the synthetic progestin 17OH-PC is effective at prolonging pregnancy in some women with singleton pregnancies and previous premature delivery.[8] However, in spite of the prolongation of pregnancy, statistically significant reductions in perinatal mortality and neonatal morbidity have not been consistently demonstrated. While the timing of birth is important in and of itself for the purpose of investigative hypotheses, prolonging the duration of gestation may not always be in the mother's or the baby's best interest. For example, a baby delivered at 35 weeks' gestation may not necessarily fare better than a baby delivered at 33 weeks if spontaneous delivery was delayed as a result of an intervention that maintained the fetus in an unfavorable environment. The assumption that a greater gestational age at birth automatically translates into a lower risk of neonatal complications may be incorrect. Across studies, definitive evidence for tangible benefits such as increased birth weight, decreased neonatal morbidity, or improved childhood outcomes is inconclusive. Thus, it remains unclear whether 17OH-PC prophylaxis results in improved overall perinatal clinical outcome, and the same conclusion is true for other forms of progestins (vaginal or oral).[9]

In 2011, the US Food and Drug Administration (FDA) approved the use of 17OH-PC injections traded under the name Makena™ (KV Pharmaceutical, St Louis, MO, USA) for reducing the risk of recurrent preterm birth in women with a singleton pregnancy. 17OH-PC is also available on an individual limited basis in a pharmacy compounded form, although the FDA has recently stated that it recommends that practitioners prescribe the FDA-approved drug rather than a compounded drug unless the prescribing practitioner has determined that a compounded product is necessary for the particular patient and would provide a significant difference for the patient as compared with the commercially available FDA-approved drug product. The FDA further emphasized that it is applying its normal enforcement policies for compounded drugs to compounded 17OH-PC.[10] This has resulted in many compounding pharmacies ceasing to supply compounded 17 OH-PC. Makena and compounded 17OH-PC contain the same active (17OH-PC) and inactive (castor oil) ingredients, but only Makena contains preservatives (benzyl benzoate and benzyl alcohol). The FDA has previously approved 17OH-PC for use in pregnant women and the agent was marketed as Delalutin™ (Bristol-Myers

Squibb, New York, NY, USA) from 1956 for the treatment of recurrent and threatened abortions. In 2000, the FDA withdrew the approval at the request of the holder of the New Drug Application because the company was no longer marketing the drug.

According to the available data, 17OH-PC prevents approximately one third of recurrent preterm births. While this is encouraging from an individual standpoint, the public health impact is somewhat limited given that only 15% of preterm deliveries occur in women with a prior preterm birth.[11] It has been estimated that if all pregnant women with a history of spontaneous preterm delivery could receive prophylactic progesterone supplementation, the overall preterm delivery rate in the US would be reduced by approximately 2%.[11] Furthermore, the approximately 30% reduction estimate is based on the findings of pooled data from some of the largest reported randomized controlled trials of 17OH-PC, and it is possible that the enriched control population rate (as high as 54.9% in the trial reported by the Maternal-Fetal Medicine Units Network[12]) may have led to an overestimated benefit. If the risk reduction in real life conditions is lower than one third, the overall impact may be less.

In high-risk women with a history of spontaneous preterm delivery, the responsiveness to 17OH-PC is variable and may be genetically influenced. It has been suggested that single nucleotide polymorphisms in the progesterone receptor may play a role, causing women with certain genotypes to actually have an increased risk of preterm delivery when given 17OH-PC.[13] Another potentially important factor impacting the response to 17OH-PC is gestational age at the previous preterm delivery. Based on a secondary analysis of a randomized clinical trial, the benefit from 17OH-PC supplementation may be limited to those women who experienced a prior spontaneous birth before 34 weeks' gestation.[14] This might reduce the universal applicability of 17OH-PC in women with a prior preterm birth because only one third of preterm deliveries occur before 34 weeks' gestation.[15]

Cervical shortening in the mid-trimester is another significant risk factor for preterm delivery in both low-risk and high-risk populations.[16] 17OH-PC was not shown to be more effective than placebo in reducing the rate of preterm delivery in a randomized trial of 657 nulliparous women with a short cervix (<3 cm) at 16–22 weeks' gestation.[17] There are no randomized trials evaluating 17OH-PC in women with prior preterm delivery and a short cervix. The only applicable data are derived from a secondary analysis of a randomized clinical trial evaluating the impact of cerclage. This analysis did suggest that 17OH-PC may be associated with a reduction in previable birth but there was no significant effect on later preterm deliveries.[18] Vaginal progesterone, on the other hand, has been shown in several randomized trials in asymptomatic women with a short cervix to be associated with as much as a 38%–44% reduction in the risk for preterm delivery and neonatal death.[16,19] The individual randomized trials of vaginal progesterone in women with a short cervix did not demonstrate a reduction in the rate of recurrent spontaneous preterm delivery, but the number of such patients enrolled in these studies was small (15%–21% of total enrollment).[16,19] A subsequent individual patient data meta-analysis, allowing increased statistical power, concluded that patients with a history of preterm birth and a short cervix in the current pregnancy may benefit from vaginal progesterone.[20] However, at this time, the evidence available does not support the addition of vaginal progesterone to 17OH-PC or the substitution of 17OH-PC with vaginal progesterone if a short cervix is identified in a woman with prior preterm birth who is already on 17OH-PC. After evaluating the data from the largest available study of vaginal progesterone,[18] the FDA concluded that the study did not meet the statistical significance generally expected to support the approval of a new product. Compared with the overall efficacy in the trial, the efficacy in the US subgroup was relatively limited, indicating the need for additional investigation.[21] At this time, a short cervix does not constitute an FDA-approved indication for progesterone supplementation in pregnancy.

Currently, there are insufficient data to suggest that 17OH-PC is superior or inferior to natural progesterone. However, it is important to note that the chemical and biochemical properties of 17OH-PC and natural progesterone differ in some important ways.[22] 17OH-PC does not inhibit contractions of human myometrial cells in vitro, whereas progesterone does, presumably acting through nongenomic receptors after preliminary metabolization.[23] The synthetic derivative 17OH-PC is resistant to metabolism by traditional steroid-transforming enzymes, and is thus unlikely to replicate all of the actions of natural progesterone. 17OH-PC is not a prodrug, and is not cleaved to 17 alpha-hydroxyprogesterone,[24] a metabolite of progesterone already endogenously produced by the placenta in large amounts.[25] The only metabolism observed with 17OH-PC is oxidation by cytochrome P450 3A in hepatocytes to monohydroxy, dihydroxy, and trihydroxy derivatives, with unknown resulting activity.[26] The metabolism of 17-OH-PC is inhibited significantly, but with large individual variability, by the endogenous steroids, in particular progesterone.[27] This relative metabolic stability of 17OH-PC ensures a long half-life

(7.8 days) and allows for less frequent dosing in clinical practice compared with natural progesterone.

In spite of the fact that 17OH-PC binds to progesterone receptors with lower affinity than progesterone, both of these substances have similar potency in activating progesterone regulated target genes in cells throughout the classic hormone-hormone receptor pathway.[28] There are several clinical trials underway investigating direct comparisons of 17OH-PC and progesterone. The only published results to date are from Saudi Arabia. In a study of 518 pregnant women with a history of preterm delivery and a normal length cervix who were randomized to either 90 mg vaginal progesterone gel daily or 250 mg of intramuscular 17OH-PC weekly, vaginal progesterone was associated with a significantly lower percentage of preterm delivery before 34 weeks' gestation (16.6% versus 25.7%).[29]

Progestin therapy for risk factors other than a history of preterm birth and/or a short cervix in the current pregnancy is not currently supported by the published evidence. Progestins do not delay delivery in women with multiple gestation, suggesting that a distinct underlying mechanism of early parturition is present in these women, and that this mechanism is unresponsive to progestins.[30–32] This argument is supported by in vitro data showing that progesterone does not inhibit stretch-induced mitogen-activated protein kinase activation or gene expression in myometrial cells.[33] Even in selected asymptomatic twin pregnancy populations with a short cervix (representing a combination of risk factors for preterm delivery), prophylactic 17OH-PC did not appear to be beneficial either in a secondary analysis of a large randomized trial,[34] or in an open-label randomized controlled trial.[35] In the latter investigation, a higher dose of 17OH-PC than in previous clinical trials was used (intramuscular 17OH-PC 500 mg twice weekly) to address theoretical concerns about the higher volume of drug distribution in twin compared with singleton pregnancies. This was presumably in response to a report that plasma concentration of 17OH-PC is 40% lower in multiple pregnancies than in singleton pregnancies when the same dosage regimen is employed.[36] Despite this dose adjustment, 17OH-PC had no beneficial impact and the rate of preterm delivery before 32 weeks in the treatment group was twice that of the control group. A planned ancillary study to the Maternal-Fetal Medicine Units Network's randomized trial of 17OH-PC in twins[37] also suggested that women with higher plasma concentrations of 17OH-PC had earlier gestational age at delivery.[36] The authors have also found evidence for early systemic inflammation based on maternal plasma C-reactive protein concentration in women receiving 17OH-PC.[36] Similarly concerning, when studied in a randomized placebo-controlled study of 81 triplet pregnancies, 17OH-PC supplementation was associated with an increase in mid trimester pregnancy loss.[38] The negative results seen in multiple pregnancies are not influenced by chorionicity or mode of conception. The experience to date with 17OH-PC indicates that there are population subgroups that may be harmed by administration of 17OH-PC. Therefore, extending the use of 17OH-PC to unstudied populations or for indications that are not evidence-based is inadvisable outside of a research protocol.

Progesterone therapy in patients in established labor, or those manifesting spontaneous rupture of membranes, uterine contractions, or advanced painless cervical dilatation, cannot be expected to be effective.[39] In a small randomized, placebo-controlled trial involving 69 women with premature rupture of membranes at 20–30 weeks' gestation, weekly injections of 17OH-PC did not prolong gestation.[40] Several other studies have investigated the use of 17OH-PC in women who remained undelivered after an episode of preterm labor. In one such study, 60 women were randomized to treatment with 17OH-PC 341 mg twice weekly (a dose more than double the routinely used regimen) versus observation. A reduced rate of preterm delivery was observed in women who received 17OH-PC (odds ratio 0.15; 95% confidence interval 0.04–0.58).[41] However, in a larger randomized study using an even higher dose of 17OH-PC (500 mg twice weekly), the treatment had no effect on the incidence of preterm delivery.[42] Higher doses of 17OH-PC were used in these studies based on the assumption that increased drug exposure would be necessary to stop an ongoing pathologic process. Further, in an observational study, administration of 17OH-PC was not associated with a decrease in shortening of cervical length over time.[43] Thus, at this time, the available evidence is insufficient to recommend 17OH-PC, at any dose, for maintenance tocolysis.

It is not clear whether 17OH-PC provides additional benefit to women with a cerclage in place. One randomized, placebo-controlled study of 17OH-PC and cerclage in women with at least two preterm deliveries or mid trimester losses has shown benefit.[44] In this study, there was a significant reduction in the preterm delivery rate from 37.8% to 16.1%. In a more recent secondary analysis of data from a randomized trial evaluating cerclage, those women with a prior spontaneous preterm birth, a short cervix in the current pregnancy, and a cerclage in place, did not benefit significantly from addition of 17OH-PC.[18] The same conclusion was reached in a retrospective cohort study of singleton gestation with

a history of preterm delivery and a cerclage in place in the current pregnancy.[45]

Although there is no supporting evidence suggesting an additive effect of cerclage when 17OH-PC is already being given for accepted indications, some clinicians would still consider offering this intervention if cervical shortening is noted, particularly if the cervical length falls below 20–15 mm.[46] Of note, a randomized trial comparing cerclage versus 17OH-PC in pregnant women with a short cervix (<25 mm) demonstrated that in those women where the cervical length was <15 mm, cerclage was more effective than 17OH-PC at preventing preterm delivery.[47]

Safety of hydroxyprogesterone caproate

Exogenous 17OH-PC crosses the human placenta efficiently[48] and the drug is detectable in both maternal and fetal blood for at least 44 days after the last injection. Even when 17OH-PC doses are administered as much as a week apart, plasma concentrations of the drug continue to increase with repeat injection. This is because 17OH-PC is slowly released from the castor oil depots and maternal fat.[49] Plasma concentration of 17OH-PC shows considerable individual variation at the same dosing regimen and obese women tend to have lower plasma concentrations. The maximum concentration reported after administration of 17OH-PC was 0.07 μM in maternal plasma[50] and 0.02 μM in cord blood.[51] The therapeutic concentration of 17OH-PC has not been determined and the variable dosages used in the different clinical trials were based on speculation and theoretical assumptions rather than pharmacokinetic parameters.

Progesterone metabolites have been reported to play a role in the pathogenesis of intrahepatic cholestasis of pregnancy. A rise in the serum concentration of progesterone metabolites has been associated with impaired biliary excretion and subsequent accumulation of bile acids.[52] Elevated serum transaminase activity has been reported in pregnant women treated with oral micronized progesterone,[53] and withdrawal of treatment has frequently led to improvement in transaminase levels.[54] The synthesis of endogenous progesterone during normal pregnancy is between 250 mg and 500 mg per day,[54] and concern has been expressed that exogenous progesterone supplementation may impose an additional load on the hepatic transport of sulfated metabolites. In the 1980s and 1990s, oral micronized progesterone was widely used in France at doses of 900–1200 mg daily for women at risk for preterm delivery. The practice was stopped when secondary hepatic effects, including cholestasis of pregnancy, were reported at a higher rate in treated women.[55] In a prospective observational study (n = 50), cholestasis of pregnancy occurred in 64% of women receiving progesterone versus 36% in untreated women.[54] In addition, the diagnosis was made earlier in the treatment group (31 weeks) than in the untreated group (34 weeks). Hepatic effects were not monitored in the clinical trials utilizing 17OH-PC. Doses as high as 2000 mg of 17OH-PC per week have been used in clinical practice with no reported maternal or fetal adverse effects,[56] and doses of 1000 mg weekly have not been shown to affect maternal adrenal function or levels of endogenous steroid hormones.[57]

17OH-PC is inactivated by gastric passage when given by mouth. Compared with orally administered progesterone, progestins given by the vaginal or intramuscular route avoid the hepatic first-pass effect and for this reason may be associated with less hepatic dysfunction. Despite this, some French authors recommend monthly monitoring of serum liver transaminases and bilirubin levels even in patients treated with 17OH-PC.[58]

Both adult and fetus have a similar capacity to metabolize 17OH-PC. The presence of an active efflux process for 17OH-PC in fetal hepatocytes prevents accumulation of 17OH-PC or its metabolites in these cells, minimizing the risk of adverse effects. Inhibition of taurocholate transport by 17OH-PC has been observed in fetal hepatocytes, but only at concentrations of at least 0.5 μM. The measured levels of 17OH-PC in cord blood (maximum 0.02 μM)[51] are lower, suggesting that the likelihood of inhibition of bile transport in the fetus is small.

With regard to other possible maternal side effects, retrospective data suggest that 17OH-PC exposure might be associated with an increased risk of gestational diabetes.[59,60] However, in a more recent secondary analysis of a prospective cohort study, the rates of gestational diabetes were similar between women who did and did not receive 17OH-PC.[61] Isolated case reports in the literature have also referred to the development of transient Parkinsonism[62] and autoimmune dermatitis,[63] apparently related to treatment with 17OH-PC.

In utero exposure to progestins has not been associated with an increased risk of congenital anomalies, with the possible exception of hypospadias.[64] This possible association has been reported for progestins in general, but not for 17OH-PC specifically. The risk is limited to exposure to progestins prior to 11 weeks' gestation, and thus is not relevant to administration of 17OH-PC for preterm birth prophylaxis. In addition, 17OH-PC recommended for use after 16 weeks'

gestation is unlikely to cause hypospadias because formation of the phallus is completed before 16 weeks. Currently, no data suggest a link between congenital anomalies and 17OH-PC exposure in humans or mice.[65,66] A report from 2005 indicated that exposure to 17OH-PC during embryogenesis in rats, at doses similar to those prescribed in humans, may affect the reproductive potential of adult male rats.[67] However, a more recent extended multigenerational and developmental toxicity study in rats did not corroborate the earlier report.[68] Although extrapolation of rodent data to humans is difficult, a cautious approach would support initiation of 17OH-PC therapy only after completion of the first trimester of pregnancy. A North American cohort study of 24,000 pregnancies, with 649 offspring who were exposed to 17OH-PC and followed up to a mean of 11.5 years of age, showed no increase in congenital anomalies.[66] A population-based, case-control study of 318 women treated with parenteral 17OH-PC in the first trimester also showed no detectable teratogenic risk.[69]

The available human developmental data are limited to one study showing no impairment in developmental progress at a mean of 4 years of follow-up.[70] This study obviously does not include pubertal or reproductive development and does not answer other long-term safety questions. More data are needed to assess definitively the safety of the mother and child exposed to 17OH-PC during pregnancy.

Concern has been expressed about a potential safety signal reported as a statistically insignificant increase in pregnancy loss, fetal death, and early preterm birth following exposure to 17OH-PC in the second trimester.[71,72] A similar signal for embryo-fetal toxicity had been observed in rhesus monkeys at equivalent human doses,[73] but no published data provide a rationale for this observed difference in miscarriage and stillbirth rates. A protective action of 17OH-PC on the same outcomes, ie, miscarriage and stillbirth, has been reported by others,[18] highlighting the need for further investigation to evaluate the validity of the expressed concerns. Currently there is such a study underway, with proposed enrollment of more than 1,700 subjects, and is expected to provide more definitive data about the safety of 17OH-PC (clinicaltrials.gov).

Acceptance of hydroxyprogesterone caproate

Prophylactic progestin supplementation is generally initiated at 16 weeks' gestation and continued through 36 weeks of gestation. However, according to a retrospective analysis, later initiation of 17OH-PC prophylaxis, between 21 and 26 weeks' gestation, is as effective as initiation between 16 and 20 weeks.[74] On the other hand, early discontinuation, before 32 weeks, appears to increase the risk of recurrent late preterm delivery.[75]

In randomized trials, reported side effects have been injection site pain (35%), injection site swelling (17%), urticaria (12%), pruritus (8%), nausea and vomiting (6%), and injection site nodule (4%).[15] Clinical trials in the People's Republic of China of Injectable No 1 (250 mg 17OH-PC and 5 mg estradiol valerate), a once-a-month contraceptive, have shown that the side effects are few and acceptability is high, even with long-term use.[76]

Conclusion

The lack of reproducible and generalizable evidence of benefit on neonatal and childhood outcomes, combined with considerable uncertainty about the mechanism of action of exogenous progestins, contribute to ongoing debate. Critics question the relative biological activity of exogenous progestins given the fact that maternal plasma progesterone concentrations are already high in the absence of any exogenous hormone, and point out that weekly injections of 17 OH-PC do not significantly alter the underlying maternal levels.[77] Exogenous prophylactic injections do not impact the concentration of salivary progesterone either.[78] Salivary progesterone is a reflection of the biologically active free progesterone in serum.

It has been postulated that progesterone may decrease the risk of preterm delivery through suppressive effects on the immune responses in pregnancy[79] and by antagonizing the proinflammatory actions of estrogen.[80] This hypothesis has not been supported in an experimental mouse model where natural progesterone proved ineffective in decreasing the incidence of inflammation-induced preterm parturition.[81] It is possible that progestins may manifest different anti-inflammatory properties in humans, but any possible action is not believed to be exerted through anti-inflammatory mechanisms involving downregulation of nuclear factor-kappa B.[82] The exact pathway via which progestins suppress the inflammatory influences leading to parturition remains a key unanswered question. Adding to the mystery is the recent report in a murine model that neither vaginal progesterone nor 17OH-PC has any effect on pathways known to be involved in uterine contractility/quiescence or cervical remodeling.[83]

Future scientific efforts should place specific emphasis on establishing the optimal formulation, route of administration, and dosage for prophylactic administration of progestin.

Other issues still incompletely appreciated pertain to the optimal target population for use of prophylactic progestin, as well as long-term safety. 17OH-PC is part of the available armamentarium for outcome modification in pregnant women with a singleton pregnancy and a history of spontaneous preterm delivery. Its use should be limited to evidence-supported indications, without speculative propositions outside of approved trial settings.

Disclosure

The authors report no conflicts of interest in this work.

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