Commentary

17-α Hydroxyprogesterone Caproate Immunology, a Special Focus on Preterm Labor, Preeclampsia, and COVID-19

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Abstract: 17-α hydroxyprogesterone caproate (17-OHPC) could alter the immune response and inflammation, specifically affecting the risk of preterm labor and preeclampsia. However, the exact immune and inflammatory effects of 17-OHPC remain hard to be identified. The current literature on 17-OHPC immune effects is limited and more research is needed to identify these mechanistic pathways. Further, coronavirus disease 2019 (COVID-19) infection in pregnancy involves heightened immune response, widespread inflammation and high rates of preterm labor and preeclampsia. Since the pathogenesis of preterm labor, preeclampsia and COVID-19 involves inflammation and altered immune response, it is important to explore the possible immune effects of 17-OHPC in pregnant women with COVID-19. This commentary article will explain the immune effects of 17-OHPC and their implications in preterm labor, preeclampsia and COVID-19.

Keywords: inflammation; 17-OHPC; preterm labor; preeclampsia; COVID-19

1. Introduction

17-α hydroxyprogesterone caproate (17-OHPC) is a synthetic form of the natural progestin (17-α hydroxyprogesterone) that is produced by the adrenal glands, and by fetal adrenal glands and the corpus luteum during pregnancy [1]. 17-OHPC was FDA approved in 2011 to be used in pregnant women with a history of a previous singleton preterm birth in an attempt to prevent spontaneous recurrent preterm labor [1,2]. The efficacy of 17-OHPC in preventing preterm birth remains controversial [3–7]. Despite the agreed generalizability of the original Meis trail that proved the efficacy and effectiveness of 17-OHPC in preterm birth prevention in the United States [4], a more recent confirmatory trial, the PROLONG study, failed to prove the effectiveness of 17-OHPC in preventing preterm birth in indicated women [3]. However, designs of both trials have been called into a question. The majority of participants in the PROLONG study were recruited from outside the United States with various races, ethnicities and possibly different access to health care systems than the United States which leads to questioning the effectiveness and generalizability of PROLONG results [5]. On the other hand, the incidence of preterm birth in the placebo group of the Meis trial was considered higher than expected and that was speculated to drive the statistically significant findings of the study (i.e., 17-OHPC was effective in preventing preterm birth) [4,8]. Despite the ongoing conversation on withdrawing 17-OHPC from the market, no decision has been made yet to prevent its current administration to women with prior singleton preterm birth in the United States [9].

2. Immune Effects of 17-OHPC and its Implication in Preterm Labor and Preeclampsia

Alteration of the immune response and involvement of inflammation has been postulated to be on the causal pathway of preterm labor initiation [8]. Failure of maternal immune tolerance has been described as one of the mechanisms of preterm labor initiation as the fetal-placental unit is considered a semi-allograft (i.e., derivative of paternal genes) against which maternal immune system can react and reject [10]. Involvement of immune

response in initiation of preterm labor is evidenced by weakening and rupture of fetal membranes in the presence of inflammatory cytokines [11], and high rates of preterm birth in women with autoimmune diseases [10]. Although the mechanism of action of 17-OHPC to affect the initiation of preterm labor is poorly understood, involvement of immune response may contribute. 17-OHPC was found to inhibit TNF-α and thrombin mediated fetal membranes weakening in an in vitro study that tested tissues of fetal membranes taken from term deliveries [12]. Additionally, 17-OHPC was suggested to stimulate cortisol synthesis from fetal adrenal glands with subsequent anti-inflammatory net effect in the tissues of the fetal-maternal interface that could eventually protect from preterm labor [8].

Nevertheless, the exact immune effects of 17-OHPC remains elusive. 17-OHPC failed to show a net anti-inflammatory role in number of studies [13]. In vitro, 17-OHPC was not found to decrease TNF-α in myometrial cells or downregulate decidual Toll-like receptor gene expression with or without lipopolysaccharide (LPS) exposure [14,15]. In pregnant mice, 17-OHPC failed to increase decidual Treg lymphocytes, decrease decidual macrophages, myometrial INF-γ and neutrophils, or systematic IL-1β [16]. 17-OHPC failed to prolong pregnancy in women with preterm birth who had non-inflammatory or severe inflammatory amniotic fluid [17]. In the same study, there was a non-statistically significant tendency to prolong gestation in women who had infectious intra-amniotic fluid with mild inflammation; however, this study used a small sample of a retrospective cohort after excluding women with preeclampsia and gestational diabetes [17]. 17-OHPC did not modulate the levels of cervical fluid cytokines (IL-6, IL-10 and TNF-α) in a small sample of overweight women with unadjusted markers of metabolic dysfunction (e.g., obesity, hypertension, diabetes) [18]. In the same study (Caritis et al.), women with early preterm birth (gestational age 16–23 weeks) had higher levels of inflammatory cytokines (IL-6, IL-10, and TNF-α) than women with preterm birth at 32–36 weeks [18]. The findings of Caritis et al. were consistent with the findings of Ashford and colleagues that women with preterm birth tend to have higher levels of cervico-vaginal cytokines than women with term birth [18,19]. Alternatively, 17-OHPC tended to accelerate preterm labor in women with low inflammatory score of non-infectious intra-amniotic fluid [20]. High dose of 17-OHPC (341 mg) did not affect number of cervical cytokines (IL-6, IL-8 and TNF-α) in pregnant women with threatened preterm labor [21]. In a small sample prospective study with unclear statistical analysis, 17-OHPC failed to reduce the number of inflammatory cytokines (IL-1α, IL-1β, IL-2, and IL-13) in vaginal wash specimens taken from pregnant women with history of preterm labor [22]. However, in the same study, a non-statistically significant tendency to attenuate the levels of some cytokines was found within the 17-OHPC exposed group after exclusion of some chronic inflammatory diseases [22].

Net anti-inflammatory effects of 17-OHPC found in number of studies [13]. In an experimental study, 17-OHPC successfully decreased the immune response of peripheral blood monocytes taken from a small sample of pregnant women [23]. In an animal study, 17-OHPC successfully decreased IL-1β and TNF-α that were previously increased after exposure to a chemotherapeutic agent [24]. 17-OHPC was reported to modestly prolong gestation in pregnant mice after inducing inflammation by LPS [25]. Further, progesterone and 17-OHPC improved neuronal function by inhibiting inflammation in animals [24,26,27]. The Anti-inflammatory role of 17-OHPC is further evidenced by the ability of 17-OHPC to attenuate the number of inflammatory cytokines in pregnant women. Regardless of systematic corticosteroid administration, a high dose of 17-OHPC (341 mg) decreased cervical IL-1β and attenuated cervical shortening in women with threatened pre-term labor after exclusion of women with diabetes, hypertension and autoimmune diseases [21]. 17-OHPC was shown to prolong the duration of pregnancy in women with preterm birth who had non-infectious mild inflammation by amniocentesis in small sample retrospective cohort study after excluding women with preeclampsia and gestational diabetes [17]. Furthermore, 17-OHPC was predicted to prolong gestation if administered to women with high inflammatory score of non-infectious intra-amniotic fluid with short mid-trimester cervix [20]. Adiposity and diabetes, are associated with higher rates of preterm birth with

the higher risk mainly driven by adiposity induced inflammation [10,28–30]. Most of the above-mentioned studies did not adjust for common inflammatory conditions that could affect the risk of preterm labor like diabetes, hypertension and obesity.

Preeclampsia, on the other hand, is associated with inflammation and altered immune response [31–33]. Among the many immunological causes of preeclampsia, it was thought that the disease is to be presumably driven by lack of exposure to paternal antigens and thus high reported rates of preeclampsia in primigravida patients which is further evidence of the benefits of immune-suppressing products in preeclampsia treatment [34]. Indeed, women with preeclampsia were reported to have high levels of inflammatory cytokines (e.g., TNF-α and the vasoconstricting endothelin) that subsequently lead to vasoconstriction and disrupt angiogenesis [35,36]. There exists evidence that 17-OHPC could mitigate hypertension and preeclampsia through, in part, immune response modulation in animal models [36–39]. The animal model of reduced uterine perfusion pressure (RUPP) in rats is a suitable medium to test the inflammatory changes induced by hypoxia, mimicking preeclampsia pathogenesis [37,39]. As a result of ischemia induction in RUPP rat model, several inflammatory cytokines were reported to be increased (e.g., CD4 T lymphocytes, TNF-α, and the anti-angiogenic soluble vascular endothelial growth factor receptor-1) whose levels were attenuated after exposure to 17-OHPC [37,38]. Additionally in animal models, 17-OHPC could improve blood pressure, increase nitric oxide, and decrease the activating antibody to angiotensin II type-I receptor, and therefore reversing the changes induced by ischemia or IL-6 [37,40].

Taken together, studies that tested the immune effects of 17-OHPC in preventing preterm labor showed inconsistent results with non-robust design or analysis, and therefore further prospective studies are needed to confirm these findings. Moreover, only animal studies reported that 17-OHPC can mitigate preeclampsia through immune modulation and thus more research is needed to test this hypothesis. Despite the inconsistent findings (in preterm labor studies) and shortage of evidence (in preeclampsia studies), the immune altering effects of 17-OHPC cannot be neglected.

3. The Possible Implications of 17-OHPC Immune Effects in Pregnant Women with COVID-19

COVID-19 infection is characterized by SARS-CoV-2 virus-induced widespread inflammation and cytokines storm that might involve many organs [41,42]. Specifically, COVID-19 in pregnancy is associated with adverse obstetrical outcomes with reports of high rates of preterm labor and preeclampsia or preeclampsia like syndrome, possibly through immune-altering effects [43–52]. There is a rising evidence of a causal relationship between COVID-19 infection during pregnancy and initiation of preterm labor [43,45,50]. Although most of pregnant women with COVID-19 infection, especially severe cases, are being medically induced to deliver in order to improve their respiratory functions, there is biological evidence that SARS-CoV-2 virus could cause uterine contractions by using uterine ACE-2 receptor to induce the production of vasoconstricting inflammatory agents in the setting of SARS-CoV-2 viremia [45].

Moreover, both COVID-19 and preeclampsia involve augmented inflammatory status that could impair the endothelium and vascular function, and the diagnosis of the two conditions may overlap in pregnancy [42,46,47]. It has been shown that SARS-CoV-2 could alter some of the markers and genes associated with preeclampsia and thus support a causal relationship between the two [53]. However, the interplay between COVID-19 infection during pregnancy and preeclampsia remains uncertain with suggestions that COVID-19 infection during pregnancy could alter the normal placental vasculature and present in a similar way as preeclampsia or worsen the course of preeclampsia [54]. While uncertainty remains on whether COVID-19 can cause preeclampsia or the presentation of the preeclampsia could simply be driven by COVID-19 widespread inflammatory injury, recent findings support a causal relationship between the two conditions [47,50,55].

Recent studies showed that pregnant women with COVID-19 had increased risk of preterm birth and could have 3–5 times the risk of preeclampsia among women with severe COVID-19 infection [48–50,52,56]. Given the similarities in the pathogenesis shared by preterm labor, preeclampsia and COVID-19 infection, which all involve inflammation and altered immune response, it is reasonable to think that 17-OHPC may affect the course of COVID-19 infection and its related obstetrical complications (preterm labor and preeclampsia) in pregnant women through altering the immune response and inflammation. Therefore, it is important to understand the potential immune altering effects of 17-OHPC in pregnant women with COVID-19.

4. Conclusions

17-OHPC could affect inflammation and the response of the immune system. Although the exact inflammatory and immune effects of 17-OHPC remain inconclusive, it was found to affect number of inflammatory markers including those related to preterm labor initiation and preeclampsia, which are both occurring in high rates in pregnant women with COVID-19 infection. Therefore, assuming an immune altering role of 17-OHPC in pregnant women with COVID-19 infection is reasonable with potential alteration in the course of COVID-19 infection during pregnancy, at least at the level of the associated obstetrical co-morbidities (preterm labor and preeclampsia). Further studies are warranted to understand the exact immune effects of 17-OHPC in pregnant women with preterm labor, preeclampsia and COVID-19 infection through large prospective studies with robust designs.

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