

## Mini Review

# 17-Hydroxyprogesterone Caproate as a Potential Therapeutic to Add to the Management of Preeclampsia

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Submitted: 26 August 2015

Accepted: 15 October 2015

Published: 18 October 2015

ISSN: 2333-7079

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## Keywords

- Preeclampsia
- 17-hydroxyprogesterone caproate
- Blood pressure

## Abstract

Preeclampsia (PE) is a complex disorder, occurring during the third trimester of gestation characterized by hypertension with proteinuria, increased uterine artery resistance (UARI), elevated inflammatory cytokines and endothelial dysfunction during pregnancy. 17-hydroxyprogesterone caproate (17-OHPC), a synthetic hormone called progestogen or progestin, is already approved by US Food and Drug Administration (FDA) and used for the prevention of subsequent preterm labor not complicated by PE. There is limited information for the use of 17-OHPC to manage or treat preeclampsia. In fact, this progestin is not used in the management of PE and there are no studies, other than ours in recent years, evaluating the efficacy of 17-OHPC to improve symptoms of preeclampsia. Therefore, this mini review reflects on our preclinical experiments with the use of 17-OHPC for the management of preeclampsia (PE). We have recently published that PE is a state of progesterone deficiency. 17-OHPC administered on gestation day 18 (GD18) to Reduced Uterine Perfusion Pressure (RUPP) rats reduced renal and placental endothelin-1 (ET-1), TNF-alpha and IL-6, most recently, increased vascular endothelial nitric oxide synthase (eNOS) expression and nitrate-nitrite levels while improving blood pressure in response to placental ischemia. These data suggest that 17-OHPC improves pregnancy outcomes during placental ischemia and should be considered for addition to the management of PE.

## ABBREVIATIONS

PE: Preeclampsia; 17-OHPC: 17-hydroxyprogesterone caproate; FDA: US Food and Drug Administration; UARI: Uterine Artery Resistance Index; RUPP: Reduced Uterine Perfusion Pressure; ET-1: Endothelin-1; TNF-alpha: Tumor Necrosis Factor alpha; IL-6: Interleukin 6; eNOS: Nitric oxide synthase

## INTRODUCTION

## Pathophysiology of preeclampsia

Preeclampsia is characterized by blood pressure greater than 140/90 mmHg after the 20th weeks of gestation with proteinuria or thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms [1-3]. An important initiating event in PE is thought to be inadequate trophoblast invasion into the uterine spiral arteries which leads to placental ischemia and widespread maternal vascular endothelial dysfunction [3-6]. In addition, an increase in inflammatory cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), and interleukin-6 (IL-6) is associated with

endothelial dysfunction during preeclampsia [7-11]. Moreover, other mediators such as endothelin-1 (ET-1), enhanced of the anti-angiogenic factors Flt-1, agonistic auto antibodies to the angiotensin II type I receptor and decreased vasodilators such as nitric oxide (NO) have been shown play a role in the development of hypertension and intrauterine growth restriction (IUGR) in preeclamptic women [12-18].

In this review we refer specifically to 17-hydroxyprogesterone caproate (17-OHPC) use alone for the improvement of hypertension during pregnancy in our preclinical rat models of preeclampsia.

## Current obstetrical uses for 17-OHPC

Currently, the clinical management of PE is hydralazine with labetalol and most likely early delivery of the baby, which makes preeclampsia the leading cause for preterm labor and maternal and infant mortality and morbidity. In fact, when severe preterm PE develops during pregnancy prior to 34 weeks gestation, intravenously infused magnesium sulfate is initiated to slow disease progression and prevent maternal seizure [19,20]; potent

glucocorticoids are given to enhance fetal lung maturation, and anti hypertensives are used to prevent stroke [21]. Very often the maternal-fetal status does not permit continuation of pregnancy during the first 48-72 hours of maternal-fetal evaluation/stabilization and delivery becomes necessary.

At present, 17-hydroxyprogesterone caproate (17-OHPC) is currently the only medication with sufficient evidence to support its use for prevention of spontaneous recurrent preterm birth [22-25].

Preterm birth characterized by any delivery occurring before 37 weeks of gestation, is a public health problem that requires urgent action to protect the babies born too soon and improve perinatal outcome. [26]. Overall, the survival chances of the 15 million babies born preterm each year vary dramatically depending on where the babies are born and it is a leading cause of perinatal morbidity and mortality throughout the world [27].

17-OHPC is a synthetic hormone that interacts with progesterone receptors and causes relaxation of the uterus and slows contractions during preterm labor [24]. This progestogen can be administered weekly to patients diagnosed between 22-30 weeks of gestation to prolong pregnancy and increase the time to delivery which significantly improve prenatal outcomes. The US Food and Drug Administration (FDA) approved this medication in 2011 to reduce the risk of recurrent preterm birth in women with a singleton pregnancy with at least one prior premature delivery [28]. Combs et al demonstrated that prophylactic treatment with 17-OHPC during either twin or triplet pregnancies did not prolong gestation or reduce the neonatal morbidity [29, 30]. Furthermore, Lim et al showed that 17-OHPC did not change any of the parameters mentioned in Comb's study during multiple pregnancies [31]. In addition, 17-OHPC given weekly to nulliparous women with a short cervix did not reduce the frequency of preterm birth [32]. Rozenberg and colleagues demonstrated that the time to delivery and neonatal outcomes were not improved, nor worsened after 17-OHPC supplementation after preterm labor [33]. However, 17-OHPC is not used in the preterm births complicated by PE or in the management of this syndrome since there are no strong studies evaluating 17-OHPC to improve preeclampsia. The Cochrane Collaboration review showed that there is insufficient data to support the hypothesis that progesterone may be used for preventing PE and its complications [34]. Randomized trials using progesterone and other progestogens, oral and vaginal, for PE prevention or complications were inconclusive concerning its role in PE [35,36].

Therefore, the effects of 17-OHPC on pathophysiology of preeclampsia is the major focus for studies in our laboratory following the positive outcomes at the preclinical level with the use of 17-OHPC

### **Effects of 17- hydroxyprogesterone caproate on rat models of preeclampsia**

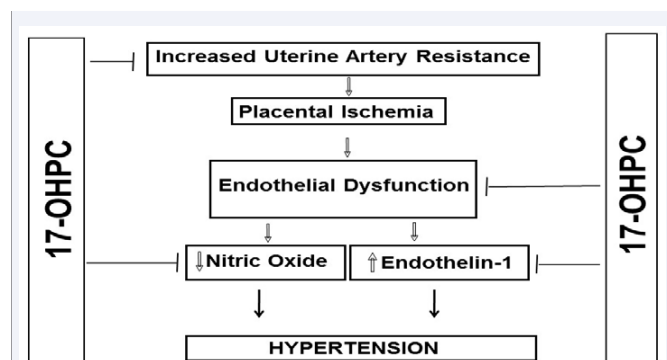
In order to study the specific mechanisms of 17-OHPC on the pathophysiology of preeclampsia, we have conducted several studies in animal models. We used the RUPP rat model, a well-accepted and established model for preeclampsia, and

the elevated cytokines rat model of preeclampsia. These studies were performed to test the central hypothesis, discussed in this mini review, that 17-OHPC could improve pregnancy outcomes in response to placental ischemia and elevated cytokines.

Previously, we have examined the hypothesis that progesterone in the form of 17-OHPC is a drug for treatment of hypertension in response to elevated TNF- $\alpha$  during pregnancy [37]. Our in vivo findings have demonstrated that the normal pregnant (NP) recipient rats implanted with a mini osmotic pump infusing TNF- $\alpha$  had higher mean arterial blood pressure (MAP,  $115 \pm 3$  mm Hg vs.  $97 \pm 2$  mm Hg,  $P < 0.01$ ) associated with a twofold increase in circulating levels of TNF- $\alpha$  ( $47 \pm 6$  pg/ml vs.  $23 \pm 7$ ) when compared with the control NP rats [37]. In addition, TNF- $\alpha$ -induced hypertensive rats significantly increased local production of ET-1 in the kidney, placenta, and vasculature [12]. Administration of 17-OHPC on day 18 of gestation decreased renal cortex prepro-ET-1 mRNA levels and significantly decreased MAP to  $100 \pm 4$  mm Hg ( $P < 0.01$ ) compared with TNF- $\alpha$ -induced hypertensive rats. These findings indicate that the antihypertensive effects of 17-OHPC might be via blunting of TNF- $\alpha$ -stimulated ET-1 synthesis in pregnant rats [37].

Additionally, we recently demonstrated that administration of 17-OHPC on GD 18 attenuated interleukin 6 (IL-6) induced hypertension during pregnancy. Furthermore, administration of 17-OHPC on GD 18 to IL-6 induced hypertensive rats attenuated circulating levels of AT1-AA ( $17 \pm 9$  bpm vs.  $4 \pm 0.8$  bpm,  $P < 0.05$ ) and significantly improved placental eNOS expression [38]. Importantly, these results were the first one to show that 17-OHPC could improve symptoms and outcomes by modulation of NO bioavailability.

We utilize the RUPP (reduced uterine perfusion pressure) rat model of PE which has been shown to exhibit endothelial dysfunction, marked increase in arterial blood pressure with lower birth weight, uterine artery resistance index (UARI), anti-angiogenic factors (sFlt-1), and endothelin 1 (ET-1), and AT1-AA, all characteristics which are associated with PE [4,14,39]. Our previous data demonstrated that 17-OHPC administered on gestation day 18 (GD18) to RUPP rats attenuated renal and placental ET-1 while improving blood pressure [40, 41]. Furthermore, 17-OHPC significantly decreased circulating IL-6 and TNF alpha in response to RUPP in pregnant rats. Our most recent studies have shown that while 17-OHPC improves inflammation, it also significantly improves uterine artery resistance index (UARI), increased vascular endothelial nitric oxide synthase (eNOS) expression and circulating levels of nitrate-nitrite in response to placental ischemia [42]. Therefore, beyond the anti-inflammatory effects of 17-OHPC, other mechanisms whereby 17-OHPC could improve blood flow is by decreasing ET-1 and increase NO bioavailability there by stimulating vasodilation. Importantly both vasodilation and anti-inflammatory actions of 17-OHPC could improve fetal and maternal outcomes during PE. Although, we did not observe any improvement on the pup weight [42], this may be due to the late term administration of 17-OHPC in gestation to RUPP rats. Pup weights were measured only 24 hours following injection in the aforementioned studies. Future studies will determine the effects of 17-OHPC administered earlier in gestation, thereby



**Figure 1** 17-hydroxyprogesterone caproate improves pathophysiology of preeclampsia in response to placental ischemia.

allowing a few days to determine if any beneficial effects on fetal weight occur. Nevertheless, these findings indicate that 17-OHPC improves important pathological mediators and improves maternal blood pressure response associated with PE.

Our recent study has suggested that preeclampsia may be a progesterone deficient state. We have published that PE women have lower circulating progesterone levels (15 ng/mL) compared to normal pregnant (NP) women (34 ng/mL,  $P < 0.013$ ) [41]. To further examine a direct effect of progesterone, we recently demonstrated that progesterone supplementation of human umbilical venous endothelial cells (HUVEC) significantly decreased ET-1 secretion following exposure to either RUPP serum or serum from PE women [41]. Together these studies suggest that the decreased circulating progesterone could exacerbate the vascular effect of soluble factors stimulated during preeclampsia to cause maternal endothelial activation. These findings indicate that progesterone could provide protection from soluble factors released in response to placental ischemia (Figure 1).

## CONCLUSION

Collectively, our data suggest the 17-OHPC has important anti-inflammatory and vasodilatory effects as mechanisms of protecting maternal endothelium from the activation by soluble circulating factors thereby resulting in the lowering of blood pressure and improved outcomes during PE. In conclusion, 17-OHPC supplementation improves cortical renal PPET-1 and blood pressure in response to elevated TNF- $\alpha$ ; improves circulating levels of AT1-AA, placental eNOS expression and hypertension in response to elevated IL-6; lastly 17 OHPC improves inflammation, renal and placental PPET-1, UARI, hypertension, eNOS expression and nitric oxide bioavailability in response to placental ischemia during pregnancy. Indeed, studies are needed to evaluate the use of 17-OHPC in a larger clinical trial to provide information about the safety and efficacy of this synthetic hormone during preeclampsia. Nevertheless, based on our preclinical evidence, we believe that 17-OHPC should be further considered for addition to the management of PE, especially severe preterm PE.

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Cite this article

Amaral LM, LaMarca B (2015) 17-Hydroxyprogesterone Caproate as a Potential Therapeutic to Add to the Management of Preeclampsia. *J Pharmacol Clin Toxicol* 3(4):1059.