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Pravastatin for the Prevention of Preeclampsia in High-Risk Pregnant Women

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Abstract

Preeclampsia complicates approximately 3–5% of pregnancies and remains one of the major causes of maternal and neonatal morbidity. It shares pathogenic similarities with adult cardiovascular disease as well as many risk factors. Attempts at prevention of preeclampsia using various supplements and classes of medications have failed or had limited success, and were not convincing enough to lead to widespread adoption of any particular strategy. Contrary to the experience with preeclampsia, prevention of cardiovascular mortality and other cardiovascular events in non-pregnant patients using 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, or statins, is widely accepted. Pravastatin, and other statins, have been shown to reverse various pathophysiological pathways associated with preeclampsia, such as angiogenic imbalance, endothelial injury, inflammation, and oxidative stress. These beneficial effects are likely to contribute substantially to preventing preeclampsia, and provide biological plausibility for the use of pravastatin in this setting. Pravastatin has favorable safety and pharmacokinetic profiles. In addition, animal studies and pregnancy human exposure data do not support teratogenicity claims for pravastatin. Therefore, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network started a pilot trial to collect maternal-fetal safety data and evaluate pravastatin pharmacokinetics when used as a prophylactic daily treatment in high-risk pregnant women (ClinicalTrials.gov identifier NCT01717586).

Introduction

Preeclampsia is a multisystem disorder that complicates 3-5% of pregnancies and remains one of the major causes of maternal and neonatal morbidities and mortality. (1) It is characterized by hypertension and proteinuria after 20 weeks of gestation, and it frequently leads to endothelial dysfunction and end organ damage. (1) Preeclampsia is associated with short-term and long-term maternal and fetal complications. For the mother, it may lead to eclamptic seizures, stroke, intracranial bleed, uncontrolled hypertension, renal failure, and hemolysis. It also predisposes the mother to hypertension, renal disease, ischemic heart disease, stroke, and premature death. For the fetus, it may lead to intrauterine growth restriction, placental abruption, and the short-term and long-term complications of prematurity; as well as predisposition to adult cardiovascular and metabolic disorders. (2)

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There is no effective prophylactic therapy, and delivery remains the only approach to preventing maternal morbidity and mortality. (1, 3) However, this is usually achieved at the expense of premature delivery and its associated morbidities.

ETIOLOGY OF PREECLAMPSIA

Although many mechanisms have been proposed for the pathogenesis of preeclampsia, abnormalities in the following processes have generally been well accepted: angiogenesis, endothelial injury, oxidative stress, and inflammation. (1)

Angiogenic Imbalance

Imbalances in proangiogenic and antiangiogenic factors are thought to play a role in preeclampsia. (4) Two anti-angiogenic factors, soluble Fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), have been shown to bind angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) in the circulation and suppress their effects. Over expression of these antiangiogenic factors results in a preeclampsia-like condition in animal models, and lowering the circulating levels of sFlt-1 below a critical threshold reverses pathological features of preeclampsia. In humans, both sFlt-1 and sEng are known to increase dramatically weeks prior to the onset of clinical manifestations of preeclampsia. (1, 4)

The angiogenic imbalance may represent a “final common pathway” responsible for the expression of the clinical features of preeclampsia. The trigger for the cascade of events leading to preeclampsia remains unknown and may include immunologic, inflammatory, or genetic susceptibilities. The end result is excessive release of vasoactive factors, cytokines, and maternal endothelial dysfunction, which then triggers the clinical stage of the maternal syndrome. (1)

Endothelial Dysfunction, Oxidative Injury, and Inflammation

There is evidence from several studies that preeclampsia is accompanied by endothelial injury. This injury results in abnormal vascular relaxation and platelet activation and is associated with inflammation and oxidative imbalance. (5) The activation of the inflammatory cascade that occurs in normal pregnancy is further exaggerated in preeclampsia. (6) Markers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP), are elevated in patients who later develop preeclampsia. (6) In addition, preeclampsia is associated with elevated cytokines such as tumor necrosis factor- α , interleukin-6 (IL-6), and IL-12. These activate the inflammatory cascade and increase free radical generation and oxidative stress, thus contributing to endothelial injury. (6)

In addition to the dyslipidemia associated with preeclampsia, studies have shown increased antibodies for the oxidized form of LDL (7) in patients with preeclampsia, which is consistent with oxidative stress and similar to changes noted in atherosclerotic disease. Moreover, preeclampsia is associated with suppression of the heme oxygenase-1 (HO-1)/carbon monoxide pathway. (8) HO-1 is an inducible enzyme with anti-inflammatory and cytoprotective properties, and has a protective effect against oxidative stress in the vascular system. (8)

IS PREECLAMPSIA A CARDIOVASCULAR DISEASE?

Although preeclampsia is unique to pregnancy, it shares biological and pathological similarities as well as many risk factors (e.g., obesity, diabetes, dyslipidemia, hypertension, etc) with adult cardiovascular diseases (CVD). (3) Endothelial dysfunction and inflammation are fundamental mechanisms for the initiation and progression of both

atherosclerosis (9) and preeclampsia. (1,4) In addition, preeclampsia is considered by many as either an early manifestation of CVD unmasked by the pregnancy, or a risk factor for future CVD. This association is demonstrated in studies that showed that a diagnosis of preeclampsia increases by 2-3 fold the patient's risk of hypertension, ischemic stroke and heart disease later in life. (2, 10) Moreover, the severity and gestational age at diagnosis of preeclampsia are important determinants of the risk of future CVD. Patients who had severe preeclampsia have higher risk compared to those who had mild disease (relative risk [RR] 5.4 95% confidence interval [CI] 4.0–7.3 for severe preeclampsia vs. RR 2.0 95% CI 1.8–2.2 for mild preeclampsia). (10) Similarly, the RR of death from CVD later in life is 9.54 (95% CI 4.5–20.26) if the preeclampsia occurred at less than 34 weeks compared to 2.14 (95% CI 1.29–3.57) for patients who had preeclampsia at term. (11)

CAN PREECLAMPSIA BE PREVENTED?

Numerous attempts at primary and secondary prevention of preeclampsia, using various supplements and medications, have failed. (3) Use of antihypertensive medications in women with chronic hypertension, who are at higher risk of preeclampsia, was found to better control severe hypertension, without decreasing the risk of preeclampsia. (12) Supplementation with fish oil, calcium, or antioxidant vitamins C and E did not show any benefit in reducing the rate of recurrence or severity of preeclampsia. (3,13,14) Low-dose aspirin, by selectively inhibiting the production of the vasoconstrictive thromboxane A₂ without affecting the vasorelaxant prostacyclin, was thought to protect the vasculature and prevent preeclampsia. However, the benefits of low-dose aspirin in preeclampsia prevention were not supported by multiple large randomized studies that included both high-risk and low-risk women. (3) Recently, the Perinatal Antiplatelet Review of International Studies Collaborative Group performed an individual patient meta-analysis of the effectiveness of antiplatelet agents (predominantly aspirin) for the prevention of preeclampsia. (15) They included 31 randomized trials involving 32,217 women, and found a small benefit in reducing the rate of preeclampsia [RR of developing preeclampsia 0.90 (95% CI 0.84-0.96)]. When the effect of aspirin was evaluated according to when it was started, a meta-analysis found that the benefit from low-dose aspirin was achieved only when it was started before 16 weeks gestational age, with no benefit if aspirin was started after that. (18)

Overall, the trials regarding preeclampsia prevention have been negative, contradictory, or not convincing enough to lead to widespread adoption of any particular strategy.

IS THERE A BIOLOGICAL PLAUSIBILITY OF USING STATINS FOR PREVENTION OF PREECLAMPSIA?

Contrary to the experience with preeclampsia, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, have been essential in primary and secondary prevention of cardiovascular mortality and other cardiovascular events through pleiotropic and lipid-lowering actions; and their use for these indications is widely accepted. The properties and mechanisms of action of statins make them highly promising candidates for the prevention of preeclampsia.

Using animal models of preeclampsia, we and others have shown that daily pravastatin administration to rodents destined to develop preeclampsia improved their abnormal vascular profile, lowered blood pressure, and restored angiogenic balance. In addition, pravastatin upregulated NOS3 expression in the vasculature, restored HO-1/CO balance, and prevented kidney injury. These benefits were observed without affecting maternal cholesterol levels and without any increase in rates of pup resorption, or differences in pup birth weights. (17-21) In fact, pravastatin prevented the growth restriction associated with

preeclampsia in these animal models. (21) The ability of pravastatin to restore the angiogenic balance is currently being tested in a proof of concept “StAmP trial” that is enrolling subjects in the UK (Statins to Ameliorate early onset Preeclampsia; www.controlled-trials.com; ISRCTN23410175).

Statins are also known to have anti-inflammatory properties and have been shown to decrease hs-CRP (37%) in parallel with the decrease in cardiovascular mortality and morbidities even in patients with normal cholesterol levels. (22) Statins also correct the imbalance in the Th1/Th2 cytokine responses observed in preeclampsia (statins decrease Th1 proinflammatory cytokines, such as TNF- α , IL-1, IL-2, IFN- γ , and increase Th2 anti-inflammatory cytokines such as IL-4, IL 10). (23) These and other pleiotropic actions on free oxygen radical formation, smooth muscle cell proliferation, and immunomodulatory effects, make statins highly promising candidates for the prevention and/or treatment of preeclampsia. However, attempts to prevent preeclampsia and other pregnancy complications based on pathophysiological pathways have previously failed. Therefore, pravastatin is far from clinical applicability before a definite benefit is shown in clinical trials.

TERATOGENICITY CONCERNS OF PRAVASTATIN

When statins were originally marketed in the 1980's, they were designated pregnancy category X. By definition, category X signifies that “studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.” (24) This classification was primarily based on the second half of the definition, namely that there were no indications that warrant use of a statin in pregnancy (no benefit to outweigh any risk). It was also partially based on the theoretical concern of potential teratogenicity secondary to inhibition of cholesterol synthesis during embryological development in pregnancy, in addition to small case series of teratogenic effects of the original statins in use at the time. (25) However, post-marketing surveillance of lovastatin and simvastatin (two lipophilic statins) published by Merck showed no relationship between early pregnancy statin exposure and adverse pregnancy outcome or congenital anomalies. Despite this, the X categorization was not questioned or adequately investigated because until now there was no reason to use statins in pregnancy. (25)

An increased risk of congenital malformations has not been seen with pravastatin. (25-29) The Medical Genetics branch of the National Institutes of Health reviewed 214 ascertained pregnancy exposures to statins that were reported to the U.S. Food and Drug Administration (FDA) from 1987 to 2001. Of the 70 evaluable cases reviewed in the final report, 20 cases of pravastatin exposure were included. No congenital malformations or adverse pregnancy outcomes occurred in the pravastatin exposed group. (26) Exploration of two large case-control studies of birth defects, the National Birth Defects Prevention Study and the Slone Epidemiology Center Birth Defects Study failed to show any link between statin exposure and a pattern of birth defects. (29) Moreover, a Canadian population based pregnancy registry that collected data on women exposed to statins and other cholesterol-lowering agents prior to pregnancy and in the first trimester showed no pattern, or increased rate, of congenital abnormalities in 288 women with live births. Moreover, no congenital anomalies were found in women exposed to pravastatin. (27) In addition, a prospective observational cohort study by the Motherisk program in Toronto did not find any malformation patterns or increased malformations in infants of 64 women with first trimester exposure to statins compared with women without exposure to known teratogens. (28)

Despite their limited size, the findings from these studies support the lack of teratogenicity of pravastatin. This may be expected because of pravastatin's unique pharmacokinetic properties. Pravastatin (446.52 kD) is rapidly absorbed after oral administration (Time to achieve maximal plasma levels is 1 - 1.5 hours), and has a short elimination half-life (1.77 hours). It is one of the most hydrophilic (polar) statins and a substrate of the efflux pump P-glycoprotein; thus expected to have limited ability for transplacental transfer. Moreover, pravastatin is one of the least potent inhibitors of HMG-CoA reductase when compared to other statins, and its inhibition is specific to hepatocytes. Pravastatin is cleared through both hepatic and renal routes, which reduces the need for dose reduction in case of liver/renal impairment; and CYP3A-dependent metabolism represents only a minor pathway in its elimination with no clinically important pharmacokinetic interactions between pravastatin and CYP3A inhibitors. (30) However, these data were obtained from nonpregnant women and men. In vitro placental transfer studies are currently under way to study the bidirectional transfer of pravastatin.

The other drawbacks from the previously mentioned pregnancy cohorts (26-28) include their limited sample size and the fact that most of them assessed statin exposure during the first trimester of pregnancy. For women who conceive while taking statins, the current recommendation is to discontinue treatment as soon as possible. Therefore, most of the statin-exposed patients in these cohorts discontinued statin use as soon as pregnancy was confirmed. The effects of long-term pravastatin use on fetal and neonatal health and growth in humans are unknown. Animal data are scarce and not consistent. Whereas, fetal sheep exposed to pravastatin in late gestation have a depressed cardiovascular and metabolic response to acute hypoxia in utero (31); data from murine models of preeclampsia, where pravastatin was administered daily throughout the pregnancy, show that pravastatin does not negatively impact fetal and pup growth. (17-21)

In summary, the available human and animal data do not support pravastatin being teratogenic. Were pravastatin to have significant benefit in pregnancy, then the category X designation would have to be critically reevaluated, given that there is no evidence of risk.

CONCLUSION

Multiple clinical trials, using various supplements and medications, failed to prevent preeclampsia or its complications. On the other hand, pravastatin was shown in various preclinical and clinical studies to (1) reverse the pregnancy-specific angiogenic imbalance associated with preeclampsia, (2) restore global endothelial health, and (3) prevent oxidative and inflammatory injury; actions that provide biological plausibility for the use of pravastatin in the prevention of preeclampsia. Despite its category X classification, pravastatin has not been shown to be teratogenic in animal and human cohort studies. In addition, data from the long term cardiovascular trials in non pregnant women and men suggest a favorable maternal safety and pharmacokinetic profiles. However, knowledge of pravastatin drug disposition during pregnancy is limited. Based on these, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network started a double blinded placebo controlled pilot trial to collect preliminary maternal-fetal safety data for pravastatin during pregnancy, and evaluate its pharmacokinetics when used as a prophylactic daily treatment in high-risk pregnant women ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01717586) Identifier NCT01717586). Data from this work will be used to set the foundation in establishing dosage and response information to be utilized in designing future clinical trials to evaluate pravastatin's effectiveness to prevent preeclampsia in this high-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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