

The role of statins in the prevention of preeclampsia



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Introduction

Preeclampsia (PE) is a morbid multi-system hypertensive disorder that complicates 3% to 8% of pregnancies. In its severe form, PE may lead to maternal seizure, stroke, intracranial bleeding, coagulopathy, renal failure, pulmonary edema, and death. Fetal consequences may include growth restriction, stillbirth, and complications related to prematurity.¹ PE has been the focus of incredible efforts to understand, treat, and prevent its development, with limited success. Professional societies currently recommend low-dose aspirin for PE prevention despite its modest effect and the contradictory results of most large aspirin prevention trials.² Iatrogenic delivery, often preterm, remains the primary intervention to decrease maternal morbidity and mortality.

PE shares many pathophysiological features and risk factors with adult

Preeclampsia is a common hypertensive disorder of pregnancy associated with considerable neonatal and maternal morbidities and mortalities. However, the exact cause of preeclampsia remains unknown; it is generally accepted that abnormal placentation resulting in the release of soluble antiangiogenic factors, coupled with increased oxidative stress and inflammation, leads to systemic endothelial dysfunction and the clinical manifestations of the disease. Statins have been found to correct similar pathophysiological pathways that underlie the development of preeclampsia. Pravastatin, specifically, has been reported in various preclinical and clinical studies to reverse the pregnancy-specific angiogenic imbalance associated with preeclampsia, to restore global endothelial health, and to prevent oxidative and inflammatory injury. Human studies have found a favorable safety profile for pravastatin, and more recent evidence does not support the previous teratogenic concerns surrounding statins in pregnancy. With reassuring and positive findings from pilot studies and strong biological plausibility, statins should be investigated in large clinical randomized-controlled trials for the prevention of preeclampsia.

Key words: angiogenesis, cholesterol, cholesterol synthesis, hydroxymethylglutaryl-coenzyme A reductase inhibitors, lipoprotein, low-density lipoprotein, placental growth factor, pravastatin, preeclampsia, prevention, statins, soluble endoglin, soluble fms-like tyrosine kinase, vascular endothelial growth factor

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cardiovascular disease. Endothelial injury and inflammation underlie both PE and atherosclerosis. In addition, PE has been identified as an independent risk factor for cardiovascular disease later in life. A diagnosis of PE more than doubles the risk of future hypertension, ischemic heart disease, and stroke.^{3–6} When compared with patients who did not develop PE, the relative risk (RR) of developing cardiovascular disease later in life was 2.0 for patients with mild PE and 5.4 for patients with severe PE.⁷ Similarly, the RR of death from cardiovascular disease later in life was 2.1 for patients who had PE at term and 9.5 for patients who were delivered for PE before 34 weeks of gestation.⁸ Whether the association between PE and cardiovascular morbidity later in life is causal remains controversial. However, this relationship has led many experts to describe PE as an early manifestation of underlying cardiovascular disease predisposition, unmasked by the demands of pregnancy. Rather than causing future

cardiovascular disease, PE may represent a failed result of the maternal “stress test” that is pregnancy. As such, interventions known to decrease cardiovascular morbidity, such as statins, have garnered attention and recently shown promise in the prevention of PE. In this article, we review the use of statins and their role in the treatment and prevention of PE.

Statins for cardiovascular disease

Pharmacologic properties

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase is the enzyme responsible for the conversion of HMG-CoA to mevalonate in the mevalonic acid pathway of cholesterol biosynthesis. HMG-CoA reductase inhibitors, known as statins, competitively inhibit this rate-limiting enzyme resulting in decreased downstream production of cholesterol.⁹ Decreased intrahepatic cholesterol levels lead to increased expression of low-density lipoprotein (LDL) receptors and reuptake (and thus lowering) of circulating lipids.^{10–12} Decreasing

serum lipid levels has been found to prevent the development and progression of atherosclerotic cardiovascular disease, and statins remain among the most potent and widely used medications for lowering LDL cholesterol (LDL-C) and for primary and secondary cardiovascular protection.^{13,14}

First-generation statins, which include lovastatin, pravastatin, and fluvastatin, are the least potent. Second-generation statins include simvastatin and atorvastatin and are currently the most widely used. Third-generation statins, such as rosuvastatin, have the highest potency. Statins are also classified according to their hydrophilicity with pravastatin and rosuvastatin being hydrophilic and simvastatin, atorvastatin, and fluvastatin being lipophilic.¹⁵ Statins are absorbed rapidly following oral administration, and most are highly bound to plasma proteins. Lipophilic statins cross easily into hepatocytes and other cells through passive diffusion, whereas hydrophilic statins require active transport and are more hepatoselective.¹⁵

Principal effects

Until recently, statins were touted predominantly for their ability to decrease cholesterol concentrations and the progression of atherosclerosis.¹² The intensity of LDL-C reduction by statins is dependent on the dose and the individual statin used. High-intensity therapy (rosuvastatin 20–40 mg or atorvastatin 80 mg) leads to >50% reduction in LDL-C, moderate-intensity therapy (rosuvastatin 5–10 mg, atorvastatin 20–40 mg, pravastatin 40 mg, or simvastatin 20–40 mg) leads to 30% to 50% reduction in LDL-C, and low-intensity therapy (atorvastatin 10 mg, pravastatin 10–20 mg, or simvastatin 10 mg) leads to <30% reduction in LDL-C.^{16,17} Decreased atherosclerosis is supported by angiographic and magnetic resonance imaging studies, which reveal an increase in lumen diameter and slowing of stenosis with years of statin therapy.^{18–20} These findings also translate into improved clinical outcomes and reduced mortality and morbidity from cardiovascular disease. However, the benefits of statin therapy are not solely explained by

their lipid-lowering capabilities, and the exact mechanisms of cardiovascular benefit that extend beyond decreased lipoprotein levels are not completely understood. Although their lipid-lowering effect is well documented, the clinical benefits of statin therapy occur before and are disproportionately greater than the improvement in atherosclerotic disease burden. Patients often experience clinical improvement in markers of vascular disease as early as 6 months after initiating therapy.^{21,22} Factors thought to contribute to the benefits of statin therapy include reversal of endothelial dysfunction, decreased inflammation and thrombogenicity, and plaque stabilization, all of which can be seen shortly after beginning therapy.

Plaque stabilization

It is generally accepted that acute coronary events are often caused by disruption of lipid-rich atherosclerotic plaques. Infiltration of the collagen-deficient fibrinous cap of a plaque by inflammatory cells (macrophages, activated lymphocytes) leads to plaque disruption and the formation of a thrombus and potential vessel occlusion.^{23,24} Evaluation of human carotid plaques removed during endarterectomy revealed that statin therapy decreased plaque inflammation (as a result of decreased matrix metalloproteinase-2, macrophage, and T-cell levels) and increased plaque stability (by increase in metalloproteinase-1 inhibition and collagen content).²⁵ In addition, statin therapy has been found to decrease platelet reactivity and tissue factor expression by inflammatory cells.²³

Endothelial protection

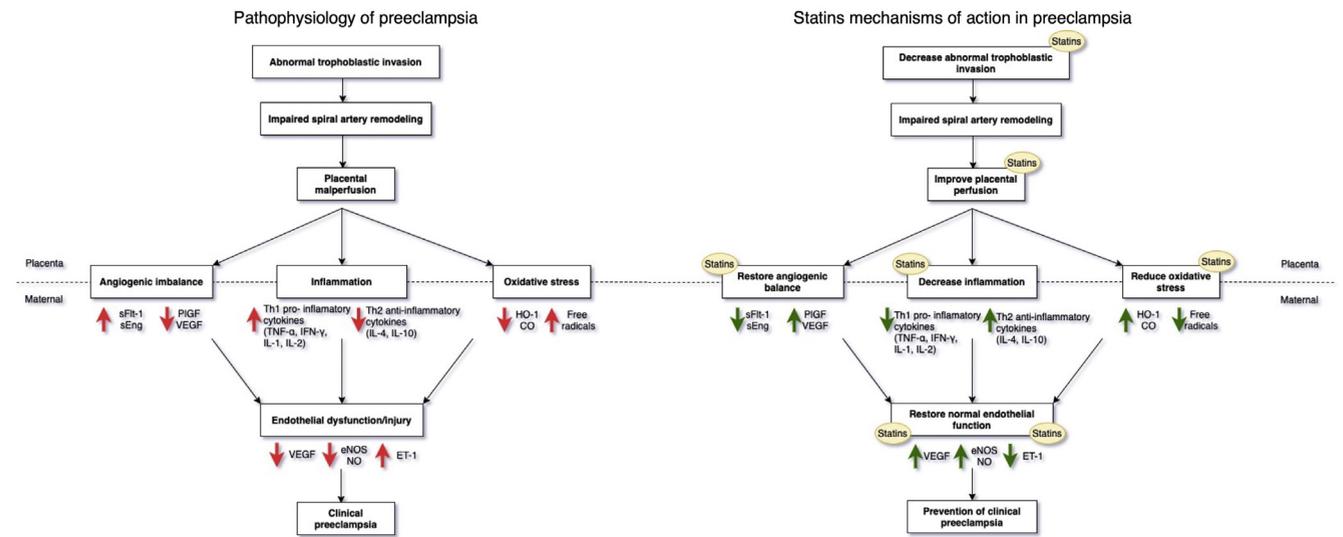
The endothelial layer separates the circulatory compartment from the vascular wall, and as such, it regulates the contractile and hemostatic functions of blood vessels. There is growing evidence to support that endothelial dysfunction, often involving reduced endothelial-derived nitric oxide (NO) production and endothelial activation resulting in the expression of cell surface leukocyte adhesion molecules, is causal in the development of cardiovascular disease.²⁶

Endothelium-dependent vascular relaxation is predominantly mediated by nitric oxide (NO), whereas endothelium-dependent vascular constriction is mediated by endothelin-1 (ET-1) and thromboxane-A₂. The balance between these endothelium-derived vasoactive substances determines the contractile state of a vessel.²⁶ In a study of 30 healthy adults with normal serum cholesterol, a single dose of 0.3 mg cerivastatin resulted in increased flow-mediated dilatation of the brachial artery within 3 hours of administration.²⁷ There is growing evidence that statin therapy amplifies the effect of other endothelium-dependent medications, increases blood flow, and reduces the density of surface adhesion molecules.²⁶ This is likely because of statin's ability to up-regulate endothelial nitric oxide synthase (eNOS) expression, which increases NO production and promotes vessel relaxation. Statins have also been found to restore the function of eNOS in pathologic conditions and increase the expression of tissue-type plasminogen activator and decrease the expression of potent vasoconstrictor ET-1.²⁶ In addition, statins have been found to promote the proliferation, migration, and survival of circulating endothelial progenitor cells, which are important for angiogenesis and endothelial restoration after injury.²⁶

Decreased inflammation

Markers of inflammation, most notably high-sensitivity C-reactive protein (hs-CRP), are elevated in patients with atherosclerosis and can help predict the risk of cardiac events and progression of cardiovascular diseases.²⁸ Statin therapy has been found to decrease hs-CRP levels independent of lipid levels, an effect seen within 14 days.²⁹ However, the mechanism behind the decrease in inflammatory markers is not well understood. It has been reported that some (though not all) statins selectively inhibit an important inflammatory cell adhesion protein, $\alpha_L\beta_2$ integrin (also referred to as lymphocyte function-associated antigen 1, or integrin LFA-1).^{30,31} Statin therapy has in addition been found to affect immune cell signaling. Interferon gamma plays an important role in the

FIGURE
Pathophysiology of preeclampsia and effect of statins



CO, carbon monoxide; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; HO-1, heme oxygenase-1; IL-1, interleukin 1; INF- γ , interferon gamma; NO, nitric oxide; PIGF, placental growth factor; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; Th2, T helper cell 2; TNF- α , tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

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immune response by stimulating immune cells to express major histocompatibility complex class II (MHC-II) proteins, which in turn activate T lymphocytes. There is evidence that statins directly inhibit the interferon gamma-mediated induction of MHC-II expression leading to a decrease in T-cell activation.³² Through the inhibition of T-cell activation and adhesion molecule expression, statins decrease the presence of inflammatory cytokine-releasing immune cells (monocytes, macrophages, lymphocytes) in the endothelium.²⁶

Statins for preeclampsia

Pathophysiology of preeclampsia

The pathogenesis of PE, although not completely understood, is believed to be a 2-stage process, originating early in pregnancy with abnormal cytotrophoblast invasion and remodeling of the spiral arterioles during early placenta development.³³ Although the exact trigger remains unknown, it is generally accepted that a combination of genetic, environmental, and immunologic factors plays an important role in the early stage.³⁴ These changes ultimately culminate in an angiogenic imbalance, coupled with widespread maternal

endothelial dysfunction, oxidative stress, and exaggerated inflammation. These promote systemic endothelial dysfunction and result in vasoconstriction, end-organ ischemia, and the clinical signs and symptoms of PE (Figure).

Angiogenesis refers to the physiological process by which new blood vessels form from preexisting vessels, whereas vasculogenesis refers to the process by which vessels are formed from angioblast precursor cells. The human placenta undergoes both angiogenesis and vasculogenesis during fetal development and pseudovasculogenesis, the process by which placental cytotrophoblast cells convert from an epithelial phenotype to an endothelial phenotype. Normal placental development depends on a balance between pro- and anti-angiogenic factors that promote angiogenesis and normal endothelial function. An imbalance in angiogenic placental mediators, with excessive release of vasoactive factors, has been linked to the development of PE and is thought to be a critical feature to its etiology.³⁵ Both soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng) are 2 anti-angiogenic factors that have been found to neutralize and inhibit the effects of

circulating proangiogenic mediators, such as vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) (Figure). In animal models, overexpression of sFlt-1 results in a PE-like condition, which is reversed by lowering sFlt-1 levels below a critical threshold.³⁴ In humans, both of these antiangiogenic factors are known to increase dramatically several weeks before the onset of clinical manifestations.^{34,36,37}

Exaggeration of the inflammatory cascade is also a feature of PE and is manifested by reversal of the T helper cell 1 (Th1) and T helper cell 2 (Th2) responses (increase in Th1 proinflammatory cytokines, such as tumor necrosis factor alpha [TNF- α], interleukin 1 [IL-1], IL-2, and interferon gamma, and decrease in Th2 anti-inflammatory cytokines such as IL-4 and IL-10). The increase of proinflammatory cytokines, along with a vasoconstrictive imbalance in vasoactive mediators, exacerbates oxidative stress and leads to endothelial injury. Furthermore, PE is associated with the suppression of the heme oxygenase-1 (HO-1) and carbon monoxide pathways, which have antiinflammatory, antioxidant, and

vasoprotective properties.³⁴ Endothelial injury can also trigger a cascade of inflammatory and immunogenic processes similar to the endothelial dysfunction seen in atherosclerotic vascular disease. Interestingly, increases in circulating free radicals caused by increased cytokine activity lead to the oxidation of LDL, another finding similar to atherosclerotic cardiovascular disease.³⁸

Statins for prevention of PE: biological plausibility

The properties and mechanisms of action of statins make them highly promising candidates for the prevention and/or treatment of PE. Statins up-regulate eNOS, promoting NO production in the vasculature.^{39,40} They also promote VEGF and PlGF releases, reduce sFlt-1 and sEng concentrations, and up-regulate the transcription and expression of HO-1 in endothelial and vascular smooth muscles.^{41–43} Activation of the HO-1/CO pathway by statins has been found, in some but not all studies, to suppress the production of sFlt-1.⁴⁴ Statins are also known to have antiinflammatory properties and have been shown to decrease hs-CRP even in patients with normal cholesterol levels.⁴⁵ They are also known to up-regulate Th2 antiinflammatory cytokine production and down-regulate Th1 proinflammatory cytokine production (Table 1, Figure).⁴⁶ These immunomodulatory and antiinflammatory effects, along with other pleiotropic actions on free oxygen radical formation and smooth muscle cell proliferation, make statins highly promising candidates for the prevention and treatment of PE.

Preclinical studies

The ability of statins to reverse pathophysiological pathways associated with PE and to ameliorate its phenotype was evaluated in several preclinical studies using tissue cultures and different rodent models of PE. Initial studies using pre-eclamptic villous explants and a mouse model of PE reported that simvastatin therapy increased endothelial HO-1 activity, which, in turn, promoted VEGF and PlGF releases and decreased sFlt-1

levels.⁴⁸ Other studies using primary endothelial cells, purified cytotrophoblast cells, and placental explants obtained from women with preterm PE reported that pravastatin decreased sFlt-1 and increased endothelial, but not placental, sEng secretion⁴⁹ and that it was not dependent on up-regulation of HO-1. Moreover, the ability of pravastatin to decrease sFlt-1 concentrations using pravastatin-perfused human placental cotyledons and placental explants was only observed under hypoxic conditions, with no alterations of placental physiological functions under normoxic conditions.⁴⁷ Finally, pravastatin was also found to reduce the secretion of endothelin-1 and sFlt-1 in human umbilical vein endothelial and uterine microvascular cells.⁵⁰

Although some studies reported that simvastatin may be a more potent inhibitor of sFlt-1 secretion when compared with pravastatin or rosuvastatin,⁵¹ most studies using murine PE models evaluated pravastatin, probably because of its more favorable pregnancy profile. Using an adenoviral overexpression of the sFlt-1 model, we and others reported that pravastatin improved vascular reactivity by decreasing sFlt-1 and sEng levels and up-regulating eNOS in the vasculature.^{42,52} In addition, pravastatin up-regulated the expression of VEGF and PlGF and a pro-survival or antiapoptotic mitogen-activated protein kinase pathway in the placenta.⁵³ Various other models of PE, including a CBA/J×DBA/2 model of immunologic-mediated PE,⁵⁴ complement component 1q deficiency (C1q^{-/-}),⁵⁵ and lentiviral vector-mediated placenta-specific sFlt-1 overexpression,⁴³ reaffirmed that pravastatin restored angiogenic balance, lowered blood pressure, prevented kidney damage (decreased albuminuria, glomerular endotheliosis, and fibrin deposition), improved glomerular and placental blood flow, restored trophoblast invasiveness, and prevented fetal growth restriction (FGR).^{15,43,54,55}

Human studies

Earlier reports found that, when given to women with preterm PE, pravastatin use

was associated with improvement in blood pressure, reduction in sFlt-1 serum concentrations, and improved pregnancy outcomes.⁴⁸ In addition, pravastatin improved angiogenic profiles and prevented fetal demise in a case report of patients with massive perivillous fibrin deposition in the placenta.⁵⁶ A pilot double-blind, placebo-controlled PE prevention trial using pravastatin, conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Obstetric-Fetal Pharmacology Research Units Network, randomized women with a history of previous PE that required preterm delivery before 34 weeks of gestation to either 10 mg of oral pravastatin or placebo from 12 to 16 weeks until delivery. Of note, 25% of participants were also taking low-dose aspirin, with no difference between the 2 groups. Maternal and neonatal outcomes were overall more favorable in women randomized to pravastatin than in women randomized to placebo, with reduced rates of PE (0% vs 40%), severe features of PE, and indicated preterm delivery before 37 weeks of gestation (10% vs 50%). Women receiving pravastatin had increased serum PlGF and decreased sFlt-1 and sEng levels compared with those who received placebo, although the differences did not reach statistical significance. In addition, there were no differences in rates of side effects (with myalgia and headache being the most common), congenital anomalies, or adverse events between the groups.⁵⁷ Maternal blood concentrations of liver (alanine and aspartate transaminases) and muscle (creatine kinase) enzymes were not increased with pravastatin therapy. More importantly, birthweight, gestational age at delivery, and neonatal intensive care unit admissions tended to be better in the pravastatin group, although without statistical significance (Table 2). A second cohort of the trial randomized women to 20 mg pravastatin or placebo and revealed similar findings (unpublished data).

The use of pravastatin as a therapeutic agent was also evaluated in a prospective study of 21 women with antiphospholipid syndrome (APLS) and

TABLE 1
Mechanisms and effects of statins by cell type

Cell types	Mechanisms	Effects
Placental trophoblast cells ^{41–43}	Increased VEGF and PlGF Increased HO-1 Decreased sFlt-1 and sEng	Decreased inflammation Improved vascular reactivity
Platelets ^{15,26}	Inhibition of platelet adhesion Decreased TXA ₂	Decreased thrombosis
Monocytes and macrophages ^{15,26,31}	Inhibition of T-cell adhesion, activation, and release of proinflammatory cytokines	Decreased inflammation
Endothelial progenitor cells ^{15,26}	Increased mobilization of stem cells	Improved neovascularization and reendothelialization
Endothelial cells ^{15,39,40}	Increased eNOS Decreased ET-1 Increased VEGF Decreased PAI-1 Decreased ROS	Improved endothelial function Decreased oxidative stress Decreased vasoconstriction Decreased inflammation Improved angiogenesis
Vascular smooth muscle cells ⁴⁷	Decreased AT1 receptor expression Decreased ROS	Decreased vasoconstriction

AT-1, angiotensin II receptor type 1; eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; HO-1, heme oxygenase-1; PAI-1, plasminogen activator inhibitor-1; PlGF, placental growth factor; ROS, reactive oxygen species; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor; TXA₂, thromboxane A₂.

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poor pregnancy outcomes. All patients received low-dose aspirin and low-molecular-weight heparin per local standard of care, were observed closely throughout pregnancy, and were assigned to pravastatin (20 mg) or standard of care when they developed PE and/or intrauterine growth restriction. Compared with patients in the control cohort, those who received pravastatin had improved uterine artery Doppler velocimetry, had lower blood pressure (130/89 mm Hg [interquartile range (IQR), 125–130/85–90] vs 160/98 mm Hg [IQR, 138–180/90–110]), and delivered infants with higher birthweight (2390 g [IQR, 2065–2770] vs 900 g [IQR, 580–1100]), at a more advanced gestational age (36 weeks [IQR, 35–36] vs 26.5 weeks [IQR, 26–32]).⁵⁸ Moreover, the Statins to Ameliorate Early Onset Pre-Eclampsia (StAmP) trial randomized women with early-onset PE (24–31 weeks of gestation) to pravastatin 40 mg or placebo.⁵⁹ The difference in sFlt-1 levels between the pravastatin (n=27) and placebo (n=29) groups was 292 pg/mL (95% confidence interval [CI], 1175–592; *P*=.5) 3 days after randomization and 48 pg/mL (95% CI, 1009–913; *P*=.9) 14 days after

randomization. Subjects who received pravastatin had a similar gestational latency after randomization when compared with subjects who received placebo (hazard ratio, 0.84; 95% CI, 0.50–1.40; *P*=.6) with a median time to delivery of 9 days (IQR, 5–14) in the pravastatin group and 7 days (IQR, 4–11) in the placebo group. Overall, pravastatin use was not associated with a reduction in maternal plasma sFlt-1 levels, prolongation of pregnancy, or other pregnancy outcomes. However, despite its negative results and limitations, the StAmP trial confirmed several findings that support the safety of pravastatin use in high-risk pregnancies.⁶⁰ In addition, the effect of pravastatin in pregnancy with early-onset FGR was evaluated in a nonrandomized controlled study conducted in Spain. Women with early-onset FGR at ≤28 weeks' gestation were offered a dose of pravastatin 40 mg daily (n=19). A control group (n=19) was matched to the treatment group for gestational age; maternal, obstetrical, and Doppler findings; and angiogenic factors.⁶¹ Treatment with pravastatin was associated with substantial improvement in angiogenic

profile. In addition, latency from diagnosis to delivery was extended by 16.5 days, median newborn birthweight was increased by 260 g, and the rate of PE decreased from 47.4% to 31.6%. However, these clinical findings were not statistically significant.

Although these 4 studies offer insight into the potential role of statins for PE, they are limited by sample size and are conflicting in their design and findings (Table 3). Specifically, the StAmP trial was limited by the timing of the primary outcome, small sample size, slow recruitment, and study medication noncompliance, and neither the StAmP trial nor the NICHD pilot trial was powered for maternal or fetal outcomes. Furthermore, similar to the use of aspirin for PE and progesterone for preterm birth, medications effective in prevention may not necessarily prove effective in treatment. As such, there are other currently active trials that aim to evaluate the utility of pravastatin in preventing PE and other hypertensive disorders in various high-risk groups. Future investigations should include randomized-controlled trials (RCTs) evaluating different statins, doses of pravastatin for both prevention and

TABLE 2

Summary of results of safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women

Variable	10-mg cohort	
	Placebo (n = 10)	Pravastatin (n = 10)
Use of low-dose aspirin	3 (30)	2 (20)
Heartburn	3 (30)	4 (40)
Musculoskeletal pain	1 (10)	4 (40)
Maternal, fetal, or infant death	0	0
Rhabdomyolysis	0	0
Liver injury	0	0
Myopathy (weakness without increase in CK)	0	0
Congenital anomalies	2	2
Preeclampsia (any)	4 (40)	0
Preeclampsia with severe features	3 (30)	0
Gestational age at delivery (wk)	36.7±2.1	37.7±0.9
Indicated preterm delivery at <37 wk	5 (50)	1 (10)
Indicated preterm delivery at <34 wk	1(10)	0 (0)
Total cholesterol at 34 to 37 wk (mg/dL)	252±27	207±31
LDL cholesterol at 34 to 37 wk (mg/dL)	130.8±46.7	90.4±21.9
Birthweight (g)	2,877±630	3,018±260
Highest level of care routine nursery	5 (50)	8 (80)
NICU length of stay ≥48 h	3 (30)	0

CK, creatine kinase; LDL, low-density lipoprotein; NICU, neonatal intensive care unit.

Adapted from Costantine et al.⁵⁷

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treatment, and study populations for which statin therapy may be beneficial.

Statin use in pregnancy

Fetal effects

Cholesterol is an important part of the cell membrane, bile acids, and steroid hormone synthesis. It is essential for normal fetal development. This is evidenced by the congenital malformations that result from genetic aberrations in cholesterol synthesis. Therefore, 6 of 7 known mutations related to cholesterol biosynthesis are extremely rare and often lethal. The seventh, and most common, is the result of a defect in the final step of cholesterol synthesis in which dehydrocholesterol is converted to cholesterol by 7-dehydrocholesterol reductase. This results in a disorder known as Smith-Lemli-Opitz syndrome, which is

manifested by derangements in growth, microcephaly, mental retardation, and multiple congenital anomalies, including abnormal facial features, cleft palate, heart defects, fused digits, polydactyly, and underdeveloped external genitalia in males.

Cholesterol synthesis occurs predominantly in the liver and is mediated by the rate-limiting enzyme HMG-CoA reductase. Lipoproteins carry cholesterol throughout the human body and facilitate cholesterol transport across the syncytiotrophoblast of the placenta, which expresses LDL receptors. Although there is a physiological increase in serum lipid concentrations during normal pregnancy, maternal cholesterol supply is of minimal importance to the developing fetus as 80% of fetal cholesterol is produced endogenously.^{62,63} This is supported by

the fact that fetuses with Smith-Lemli-Opitz syndrome have very low cholesterol concentrations and are not rescued by the normal maternal cholesterol levels. It is also supported by studies reporting that women with abetalipoproteinemia or hypobetalipoproteinemia and those consuming low cholesterol diets have lower maternal serum cholesterol levels yet do not experience increased adverse fetal or pregnancy outcomes.^{64,65} In the presence of normal fetal sterol synthesis, maternal cholesterol supply is of minimal importance.⁶²

Given the well-known lipid-lowering effects of statins, there has been historic concern surrounding their use in pregnancy. In 2015, the US Food and Drug Administration implemented the Pregnancy Lactation Labeling Rule, which required that drug manufacturers replace the previous pregnancy letter categorization (ie, A, B, C, D, and X) with a summary of product information discussing the use of the drug in pregnant women, dosing, potential risks, and registry availability. Before this change, statins were assigned to category X because it was felt that there was “no benefit to outweigh the potential risk.” This was also based on the case reports and animal studies from the 1980s, which reported teratogenicity with high doses of statins (namely, lovastatin) in rats.⁶⁶ Although the teratogenicity of statins, especially pravastatin, has largely been debunked, they remain contraindicated in pregnancy. This is primarily because of theoretical concerns and a lack of data supporting an indication for their use in pregnancy.⁶⁷ Several cohorts (Table 4) of women exposed to statins during pregnancy did not indicate increased teratogenicity or other adverse pregnancy outcomes. However, most of the statin-exposed patients in these cohorts discontinued statin use as soon as pregnancy was confirmed. In an analysis of Medicaid claims from the United States of more than 800,000 pregnant women, including 1152 exposed to statins in the first trimester of pregnancy, and after controlling for confounders (particularly preexisting diabetes) and conducting a propensity score matching, there was no increased risk of congenital

TABLE 3
Summary of human studies evaluating pravastatin for preeclampsia

Study	Author	Year	Country	Design	Sample size	Dose	Primary outcome	Major findings
Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial	Costantine et al ⁵⁷	2016	United States	Pilot randomized placebo-controlled trial	20	10 mg	Maternal-fetal safety and pharmacokinetic parameters of pravastatin during pregnancy	Pravastatin group found reduced rates of preeclampsia (0% vs 40%), severe features of preeclampsia, and indicated preterm delivery before 37 wk (10% vs 50%)
Pravastatin improves pregnancy outcomes in obstetrical antiphospholipid syndrome refractory to antithrombotic therapy	Lefkou et al ⁵⁸	2016	Greece	Nonrandomized control trial	21	20 mg	Uteroplacental blood hemodynamics, progression of preeclampsia features, and fetal or neonatal outcomes	Pravastatin group found improved uterine artery Doppler velocimetry, lower blood pressure (130/89 mm Hg vs 160/98 mm Hg), higher birthweight (2390 g vs 900 g), later delivery (36 wk vs 26.5 wk)
Pravastatin for early-onset preeclampsia: a randomized, blinded, placebo-controlled trial	Ahmed et al ⁵⁹	2020	United Kingdom	Proof of principle randomized placebo-controlled trial	56	40 mg	Difference in mean plasma sFlt-1 levels over the first 3 days following randomization	Pravastatin use was not associated with reduction in maternal plasma sFlt-1 levels (difference of 292 pg/mL [95% CI, 1175–592; <i>P</i> =.5]), prolongation of pregnancy, or other pregnancy outcomes
Evaluating the effect of pravastatin in early-onset fetal growth restriction: a nonrandomized and historically controlled pilot study	Mendoza et al ⁶¹	2020	Spain	Pilot nonrandomized controlled trial	38	40 mg	Doppler progression, sFlt-1 and PIGF values, and pregnancy outcomes	Pravastatin group found improvement in angiogenic profile, greater gestational latency (by 16.5 d), greater birthweight (by 260 g), and decreased rates of preeclampsia (31.6% vs 47.4%)

CI, confidence interval; PIGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1.

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TABLE 4
Summary of major studies assessing the risk of congenital anomalies with the use of statins in pregnancy

Study	y	Study type	Population or exposure	Statin (n)	Control (n)	Congenital anomalies
Edison et al ⁶⁸	2004	Case series	Ascertained reports of exposure to statin reported to the FDA (1987–2001)	n=70; pravastatin (20)	None	22 reports of congenital anomalies, none with pravastatin
Ofori et al ⁶³	2007	Population-based registry	Statin use within 1 y before and during pregnancy (1997–2003)	n=64; pravastatin (12)	Use of statins only before conception (1 y to 1 mo) (67)	Exposed vs nonexposed: 4.7% vs 10.5%; aOR, 0.36 (95% CI, 0.06–2.18). No anomalies with pravastatin
Taguchi et al ⁶⁹	2008	Prospective observational cohort	Pregnant women exposed to statins and contacting the Motherisk teratology information service (1998–2005)	n=64; pravastatin (6)	No exposure to known teratogens (64)	Exposed vs nonexposed: 2.2% vs 1.9%; <i>P</i> =.93
Winterfeld et al ⁷⁰	2013	Multicenter observational prospective	Pregnant women exposed to statins and contacting the European teratology information services (1990–2009)	n=249; pravastatin (32)	Exposure to agents known to be nonteratogenic (249)	Exposed vs nonexposed: 4.1% vs 2.7%; OR, 1.5 (95% CI, 0.5–4.5)
Bateman et al ⁷¹	2015	Cohort	Women with live birth, from US Medicaid data (2000–2007)	n=1152; pravastatin (75)	No statin use in the first trimester (propensity score matched group)	Exposed vs nonexposed: 6.3% vs 3.6%; aOR, 1.04 (95% CI, 0.85–1.37)
Costantine et al ⁶⁷	2016	Randomized trial	Women with history of previous preeclampsia that required preterm delivery before 34 wk, randomized to 10 mg pravastatin vs placebo between 12 and 16 wk	Pravastatin (10)	Placebo (10)	One fetus in the pravastatin group had hypospadias, and another had coarctation of the aorta (diagnosed postnatally), whereas in the placebo group, 1 fetus had polydactyly, and another had ventriculomegaly
Lefkou et al ⁵⁸	2016	Nonrandomized trial	Women with antiphospholipid syndrome and poor obstetrical history	Pravastatin (11)	Patients receiving standard of care (10)	N/A (no reports of congenital anomalies)
McGrogan et al ⁷²	2017	Cohort	Women using statins before or during the first trimester (1992–2009)	n=281; pravastatin (8)	No statin use (2643)	Exposed vs nonexposed: 3.2% vs 2.8%, OR ^a , 1.6 (95% CI, 0.72–3.64)
Ahmed et al ⁵⁹	2020	Randomized trial	Women with early-onset preeclampsia, randomized to 40 mg pravastatin vs placebo	Pravastatin (30)	Placebo (32)	N/A (no detectable adverse effects on the short-term health of offspring)

aOR, adjusted odds ratio; CI, confidence interval, FDA, Food and Drug Administration; N/A, not applicable; OR, odds ratio.

^a Unadjusted OR calculated from data in report.

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malformation (adjusted odds ratio, 1.07; 95% CI, 0.85–1.37) or any pattern of anomalies or propensity for select organ systems with the use of statins.⁷¹ A 2016 systematic review that included 16 clinical studies (5 case series, 3 cohort series, 3 registry-based studies, 1 RCT, and 4 other systematic reviews) found no relationship between statin use in pregnancy and congenital anomalies.⁶⁷ Similarly, the more recent cohort and registry-based studies, which controlled for risk factors, did not find statins to be teratogenic.⁶⁷ Therefore, it is prudent to interpret the early case series with caution as they did not adjust for confounders and were limited by selection bias.⁶⁷ Moreover, data from the recent pilot human trials, in which pravastatin was used for a much longer duration outside the first trimester of pregnancy, support its safety in pregnancy. In the US pilot trial, there were no increased rate of congenital anomalies and similar concentrations of cord blood markers for neurologic injury, cholesterol, steroidogenic hormones, and liver enzymes between neonates born to women who were assigned to pravastatin and placebo. In addition, all newborns exposed to pravastatin passed either an auditory brain stem response or otoacoustic emission test before being discharged from the hospital after birth.⁵⁷ Similarly, the StAmP trial reported no detectable adverse effects on the short-term health of the offspring,⁵⁹ and the APLS cohort reported improved neonatal outcomes among those born to mothers who received pravastatin compared with those born to mothers who received placebo.⁵⁸

These reassuring findings support the lack of teratogenicity of pravastatin and could be related to its low affinity for lipid environments and reduced permeability to extrahepatic tissues, specifically the embryo, and thus low potential for adverse effect on cholesterol biosynthesis in the developing fetus.⁶³ Pravastatin remains one of the least potent statins with high hepato-selectivity and limited transfer across the placenta.^{73–75} The limited transplacental transfer of pravastatin is supported by its hydrophilicity and its action as a substrate to placental efflux transporters.⁷⁶ This was

confirmed in the US pilot study and the StAmP trial in which most neonates exposed to pravastatin in utero had pravastatin concentrations below the lowest level of quantification of the assay.^{57,59,77}

Maternal effects

The safety and side effects profiles of statins have been studied extensively in the nonobstetrical population. In general, statins are considered safe and well tolerated, especially pravastatin. Pooled data from large RCTs in nonpregnant patients have reassured clinicians that serious adverse effects of pravastatin, most notably liver injury and rhabdomyolysis, are extremely rare. Of note, 3 long-term placebo-controlled trials of pravastatin (the West of Scotland Coronary Prevention Study, the Cholesterol and Recurrent Events Study, and the Long-term Intervention with Pravastatin in Ischemic Disease Study) collectively included 19,592 patients randomized to a dose of pravastatin 40 mg daily or placebo and accumulated more than 112,000 person-years of exposure. During 5 years of exposure, the rates of marked elevations of aminotransferases were low and similar between the 2 groups (<1.2%).^{21,78,79} In an indirect comparison meta-analysis, which included 159,458 patients, Alberton et al⁸⁰ assessed the adverse events associated with multiple different statins. They found that in pravastatin-exposed patients, the rate of adverse events (rhabdomyolysis, increased aminotransferases, and asymptomatic 10-fold increase in creatine kinase) was <2%. This finding is consistent with other large, long-term studies. In these trials, the most common reasons for discontinuation were mild, nonspecific gastrointestinal adverse effects. Myalgia is also a common symptom associated with pravastatin use and ranges in incidence from 0.6% to 10.9%.⁸¹ Studies regarding the interaction of pravastatin with other medications did not include pregnant women, and the effects of pregnancy on such interactions are unknown. Outside of pregnancy, statins are known to interact with erythromycin, niacin, cyclosporine, fibrates, bile acid

resins, clarithromycin, and cimetidine.⁸² An additional benefit of pravastatin over other statins is that it is the least diabetogenic.⁸³

Data regarding maternal safety of pravastatin use in pregnancy are limited to the more recent trials and cohorts, which revealed similar rates of adverse and serious adverse events between the pravastatin and placebo groups with the most common adverse effect among patients who received pravastatin in the US pilot study being heartburn and musculoskeletal pain. Of note, there were no reports of rhabdomyolysis or liver injury.^{57,59}

After oral administration, pravastatin is chemically degraded in the stomach, and a fraction of the intact drug is then rapidly absorbed in the small intestine, delivered to the liver via the portal vein, and then actively transported into hepatocytes. Most of the pravastatin following hepatic uptake is excreted into bile and eventually reenters the enterohepatic circulation, leading to relatively low systemic availability. Active pravastatin that survives first-pass metabolism is then distributed systemically and, outside of the liver and kidneys, is largely confined to the extracellular space.⁷⁵ As such, pravastatin was not found in adult cerebrospinal fluid and is thought to have limited ability to cross the blood-brain barrier.⁷⁵ Moreover, the pharmacokinetics of pravastatin are not significantly changed by renal or hepatic dysfunction, making it appealing for use with PE.⁷⁵

Data on the effects of pregnancy on pravastatin pharmacokinetics are limited to the US pilot trial. The apparent half-life of pravastatin was estimated to be 2 to 3 hours in pregnancy and not different from postpartum values. Similarly, pravastatin C_{max} , pravastatin T_{max} , and fraction of the drug excreted unchanged in urine are consistent with those previously reported in nonpregnant subjects. However, it appears that there is an increase in apparent oral clearance and a decrease in pravastatin area under the curve in pregnancy compared with after birth, predominantly related to the increase in renal clearance during pregnancy.

Conclusion

PE is a common hypertensive disorder of pregnancy associated with considerable maternal and fetal morbidities. With suboptimal preventive and limited therapeutic strategies and in view of its biological plausibility and the reassuring pilot studies, pravastatin poses as a potential agent for the prevention of PE. Although promising, these preventive benefits, along with the potential role of statin therapy in the treatment of PE, must be investigated in larger RCTs. ■

REFERENCES

- Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. *Physiology (Bethesda)* 2009;24:147–58.
- American College of Obstetricians and Gynecologists. ACOG Practice Bulletin no. 202: gestational hypertension and preeclampsia. *Obstet Gynecol* 2019;133:e1–25.
- Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ* 2007;335:974.
- van Pampus MG, Aarnoudse JG. Long-term outcomes after preeclampsia. *Clin Obstet Gynecol* 2005;48:489–94.
- Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. *JAMA* 2005;294:2751–7.
- Leon LJ, McCarthy FP, Direk K, et al. Preeclampsia and cardiovascular disease in a large UK pregnancy cohort of linked electronic health records: a CALIBER study. *Circulation* 2019;140:1050–60.
- McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;156:918–30.
- Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension* 2010;56:166–71.
- Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science* 2001;292:1160–4.
- Ness GC, Zhao Z, Lopez D. Inhibitors of cholesterol biosynthesis increase hepatic low-density lipoprotein receptor protein degradation. *Arch Biochem Biophys* 1996;325:242–8.
- Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005;46:1855–62.
- Blaaha MJ, Martin SS. How do statins work?: changing paradigms with implications for statin allocation. *J Am Coll Cardiol* 2013;62:2392–4.
- Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012;380:581–90.
- Rosenson RS. Rosuvastatin: a new inhibitor of HMG-coA reductase for the treatment of dyslipidemia. *Expert Rev Cardiovasc Ther* 2003;1:495–505.
- Esteve-Valverde E, Ferrer-Oliveras R, Gil-Aliberas N, Baraldès-Farré A, Llubra E, Alijotas-Reig J. Pravastatin for preventing and treating preeclampsia: a systematic review. *Obstet Gynecol Surv* 2018;73:40–55.
- Bittner VA. The new 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. *Circulation* 2019 [Epub ahead of print].
- Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2019;139:e1082–143.
- Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344:633–8.
- Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583–92.
- Corti R, Fayad ZA, Fuster V, et al. Effects of lipid-lowering by simvastatin on human atherosclerotic lesions: a longitudinal study by high-resolution, noninvasive magnetic resonance imaging. *Circulation* 2001;104:249–52.
- Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349–57.
- Furberg CD, Byington RP, Crouse JR, Espeland MA. Pravastatin, lipids, and major coronary events. *Am J Cardiol* 1994;73:1133–4.
- Ambrose JA, Martinez EE. A new paradigm for plaque stabilization. *Circulation* 2002;105:2000–4.
- Schartl M, Bocksch W, Koschyk DH, et al. Use of intravascular ultrasound to compare effects of different strategies of lipid-lowering therapy on plaque volume and composition in patients with coronary artery disease. *Circulation* 2001;104:387–92.
- Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation* 2001;103:926–33.
- Wolfrum S, Jensen KS, Liao JK. Endothelium-dependent effects of statins. *Arterioscler Thromb Vasc Biol* 2003;23:729–36.
- Omori H, Nagashima H, Tsurumi Y, et al. Direct in vivo evidence of a vascular statin: a single dose of cerivastatin rapidly increases vascular endothelial responsiveness in healthy normocholesterolaemic subjects. *Br J Clin Pharmacol* 2002;54:395–9.
- Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *Lancet* 1997;349:462–6.
- Plenge JK, Hernandez TL, Weil KM, et al. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. *Circulation* 2002;106:1447–52.
- Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med* 2001;7:687–92.
- Frenette PS. Locking a leukocyte integrin with statins. *N Engl J Med* 2001;345:1419–21.
- Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. *Nat Med* 2000;6:1399–402.
- Redman CW, Sargent IL. Latest advances in understanding preeclampsia. *Science* 2005;308:1592–4.
- Costantine MM, Cleary K; Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric–Fetal Pharmacology Research Units Network. Pravastatin for the prevention of preeclampsia in high-risk pregnant women. *Obstet Gynecol* 2013;121:349–53.
- Bdolah Y, Sukhatme VP, Karumanchi SA. Angiogenic imbalance in the pathophysiology of preeclampsia: newer insights. *Semin Nephrol* 2004;24:548–56.
- Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med* 2004;350:672–83.
- Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med* 2006;355:992–1005.
- Branch DW, Mitchell MD, Miller E, Palinski W, Witztum JL. Pre-eclampsia and serum antibodies to oxidized low-density lipoprotein. *Lancet* 1994;343:645–6.
- Endres M, Laufs U, Huang Z, et al. Stroke protection by 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors mediated by endothelial nitric oxide synthase. *Proc Natl Acad Sci U S A* 1998;95:8880–5.
- Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation* 1998;97:1129–35.
- Grosser N, Hemmerle A, Berndt G, et al. The antioxidant defense protein heme oxygenase 1

is a novel target for statins in endothelial cells. *Free Radic Biol Med* 2004;37:2064–71.

42. Costantine MM, Tamayo E, Lu F, et al. Using pravastatin to improve the vascular reactivity in a mouse model of soluble fms-like tyrosine kinase-1-induced preeclampsia. *Obstet Gynecol* 2010;116:114–20.

43. Kumasawa K, Ikawa M, Kidoya H, et al. Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. *Proc Natl Acad Sci U S A* 2011;108:1451–5.

44. Ahmed AS, Cudmore MJ. Can the biology of VEGF and haem oxygenases help solve preeclampsia? *Biochem Soc Trans* 2009;37:1237–42.

45. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.

46. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol* 2006;6:358–70.

47. Balan A, Szaingurten-Solodkin I, Swissa SS, et al. The effects of pravastatin on the normal human placenta: lessons from ex-vivo models. *PLoS One* 2017;12:e0172174.

48. Cudmore M, Ahmad S, Al-Ani B, et al. Negative regulation of soluble Flt-1 and soluble endoglin release by heme oxygenase-1. *Circulation* 2007;115:1789–97.

49. Brownfoot FC, Tong S, Hannan NJ, et al. Effects of pravastatin on human placenta, endothelium, and women with severe preeclampsia. *Hypertension* 2015;66:687–97; discussion 445.

50. de Alwis N, Beard S, Mangwiro YT, et al. Pravastatin as the statin of choice for reducing pre-eclampsia-associated endothelial dysfunction. *Pregnancy Hypertens* 2020;20:83–91.

51. Brownfoot FC, Tong S, Hannan NJ, Hastie R, Cannon P, Kaitu'u-Lino TJ. Effects of simvastatin, rosuvastatin and pravastatin on soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin (sENG) secretion from human umbilical vein endothelial cells, primary trophoblast cells and placenta. *BMC Pregnancy Childbirth* 2016;16:117.

52. Fox KA, Longo M, Tamayo E, et al. Effects of pravastatin on mediators of vascular function in a mouse model of soluble Fms-like tyrosine kinase-1-induced preeclampsia. *Am J Obstet Gynecol* 2011;205:366.e1–5.

53. Saad AF, Kechichian T, Yin H, et al. Effects of pravastatin on angiogenic and placental hypoxic imbalance in a mouse model of preeclampsia. *Reprod Sci* 2014;21:138–45.

54. Ahmed A, Singh J, Khan Y, Seshan SV, Girardi G. A new mouse model to explore therapies for preeclampsia. *PLoS One* 2010;5:e13663.

55. Singh J, Ahmed A, Girardi G. Role of complement component C1q in the onset of

preeclampsia in mice. *Hypertension* 2011;58:716–24.

56. Chaiworapongsa T, Romero R, Korzeniewski SJ, et al. Pravastatin to prevent recurrent fetal death in massive perivillous fibrin deposition of the placenta (MPFD). *J Matern Fetal Neonatal Med* 2016;29:855–62.

57. Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. *Am J Obstet Gynecol* 2016;214:720.e1–17.

58. Lefkou E, Mamopoulos A, Dagklis T, Vosnakis C, Rouso D, Girardi G. Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. *J Clin Invest* 2016;126:2933–40.

59. Ahmed A, Williams DJ, Cheed V, et al. Pravastatin for early-onset pre-eclampsia: a randomized, blinded, placebo-controlled trial. *BJOG* 2020;127:478–88.

60. Costantine MM. Author's reply re: pravastatin to ameliorate early onset pre-eclampsia: promising but not there yet. *BJOG* 2020;127:775–6.

61. Mendoza M, Ferrer-Oliveras R, Bonacina E, et al. Evaluating the effect of pravastatin in early-onset fetal growth restriction: a nonrandomized and historically controlled pilot study. *Am J Perinatol* 2020 [Epub ahead of print].

62. Woollett LA. Maternal cholesterol in fetal development: transport of cholesterol from the maternal to the fetal circulation. *Am J Clin Nutr* 2005;82:1155–61.

63. Ofori B, Rey E, Bérard A. Risk of congenital anomalies in pregnant users of statin drugs. *Br J Clin Pharmacol* 2007;64:496–509.

64. McMurry MP, Connor WE, Goplerud CP. The effects of dietary cholesterol upon the hypercholesterolemia of pregnancy. *Metabolism* 1981;30:869–79.

65. Connor WE, Cerqueira MT, Connor RW, Wallace RB, Malinow MR, Casdorph HR. The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. *Am J Clin Nutr* 1978;31:1131–42.

66. Minsker DH, MacDonald JS, Robertson RT, Bokelman DL. Mevalonate supplementation in pregnant rats suppresses the teratogenicity of mevinolinic acid, an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme a reductase. *Teratology* 1983;28:449–56.

67. Karalis DG, Hill AN, Clifton S, Wild RA. The risks of statin use in pregnancy: a systematic review. *J Clin Lipidol* 2016;10:1081–90.

68. Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. *Am J Med Genet A* 2004;131:287–98.

69. Taguchi N, Rubin ET, Hosokawa A, et al. Prenatal exposure to HMG-CoA reductase

inhibitors: effects on fetal and neonatal outcomes. *Reprod Toxicol* 2008;26:175–7.

70. Winterfeld U, Allignol A, Panchaud A, et al. Pregnancy outcome following maternal exposure to statins: a multicentre prospective study. *BJOG* 2013;120:463–71.

71. Bateman BT, Hernandez-Diaz S, Fischer MA, et al. Statins and congenital malformations: cohort study. *BMJ* 2015;350:h1035.

72. McGrogan A, Snowball J, Charlton RA. Statins during pregnancy: a cohort study using the General Practice Research Database to investigate pregnancy loss. *Pharmacoepidemiol Drug Saf* 2017;26:843–52.

73. Zarek J, DeGorter MK, Lubetsky A, et al. The transfer of pravastatin in the dually perfused human placenta. *Placenta* 2013;34:719–21.

74. Nanovskaya TN, Patrikeeva SL, Paul J, Costantine MM, Hankins GD, Ahmed MS. Transplacental transfer and distribution of pravastatin. *Am J Obstet Gynecol* 2013;209:373.e1–5.

75. Hatanaka T. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. *Clin Pharmacokinet* 2000;39:397–412.

76. Afrouzian M, Al-Lahham R, Patrikeeva S, et al. Role of the efflux transporters BCRP and MRP1 in human placental bio-disposition of pravastatin. *Biochem Pharmacol* 2018;156:467–78.

77. Costantine MM. Pravastatin to ameliorate early-onset pre-eclampsia: promising but not there yet. *BJOG* 2020;127:489.

78. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301–7.

79. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001–9.

80. Alberton M, Wu P, Druyts E, Briel M, Mills EJ. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. *QJM* 2012;105:145–57.

81. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;19:403–14.

82. Bristol-Myers Squibb. Pravachol (pravastatin sodium) [Package inserts]. 2016. Available at: https://packageinserts.bms.com/pi/pi_pravachol.pdf. Accessed May 29, 2020.

83. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. *BMJ* 2013;346:f2610.