Preeclampsia is a pregnancy-specific condition characterized by an imbalance of circulating angiogenic factors and new-onset hypertension. Although current treatment options are limited, recent studies suggest that pravastatin may improve angiogenic profile and reduce blood pressure in preeclampsia. We hypothesized pravastatin would restore angiogenic balance and reduce mean arterial pressure (MAP) in rats with reduced utero-placental perfusion pressure (RUPP)-induced hypertension. Pravastatin was administered intraperitoneally (1 mg/kg per day) in RUPP (RUPP+P) and normal pregnant rats (NP+P) from day 14 to 19 of pregnancy. On day 19, MAP was measured via catheter, conceptus data were recorded, and tissues collected. MAP was increased (P<0.05) in RUPP compared with NP dams, and pravastatin ameliorated this difference. Pravastatin attenuated decreased fetal weight and plasma vascular endothelial growth factor and the RUPP-induced increased soluble fms-like tyrosine kinase-1 when compared with NP dams. Pravastatin treatment did not improve angiogenic potential in RUPP serum and decreased (P<0.05) endothelial tube formation in NP rats. RUPP rats presented with indices of oxidative stress, such as increased placental catalase activity and plasma thiobarbituric acid reactive substances along with decreased plasma total antioxidant capacity compared with NP controls, and pravastatin attenuated these effects. MAP, fetal weight, vascular endothelial growth factor, and plasma soluble fms-like tyrosine kinase-1 were unchanged in NP+P compared with NP controls. The present data indicate that treatment with pravastatin attenuates oxidative stress and lowers MAP in placental ischemia-induced hypertension, but may have negative effects on circulating angiogenic potential during pregnancy. Further studies are needed to determine whether there are long-term deleterious effects on maternal or fetal health after pravastatin treatment during pregnancy-induced hypertension or preeclampsia. (Hypertension. 2013;61:1103-1110.)

Key Words: angiogenic factors ■ oxidative stress ■ pravastatin ■ preeclampsia

Preeclampsia is a pregnancy-specific condition characterized by new-onset hypertension, proteinuria, and intrauterine growth restriction and is a leading cause of maternal and fetal morbidity and mortality worldwide.1,2 Treatment options are currently lacking, and delivery of the placenta is the only effective treatment of preeclampsia, making it the leading cause of preterm delivery. Despite the significance of preeclampsia as a women’s health concern, the mechanisms underlying the pathogenesis of this condition are not well understood. Therefore, treatment of this condition remains a challenge.

In preeclampsia, impaired remodeling of the maternal uterine vasculature, leading to placental ischemia and inappropriate hypoxia, is believed to result in an angiogenic imbalance with increased soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased vascular endothelial growth factor (VEGF).3-5 This angiogenic imbalance, in concert with dysregulation of a variety of other inflammatory mediators, including the complement system, is thought to contribute to widespread maternal inflammation and oxidative stress ultimately resulting in endothelial dysfunction and high blood pressure.6,7 These characteristics of preeclampsia are also exhibited in animal models of preeclampsia.8-12 An area of intense investigation is identification of potential therapeutic strategies that may be directed toward the amelioration of maternal inflammation, oxidative stress, and endothelial dysfunction, which in turn will ameliorate hypertension and permit gestation to continue to term. To this end, recent interest has turned to the potential role of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, or statins, to promote vascular endothelial function and mitigate manifestations of preeclampsia. Recent studies have revealed that this class of drugs may have a number of pleiotropic effects that are independent of the modification of cholesterol metabolism, including antioxidant, antiinflammatory, and antiapoptotic effects both in vivo and in vitro.13,14
Although several recent studies have revealed the potential for 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors (ie, statins) to attenuate characteristics of preeclampsia present in several animal and cell culture models used to study pregnancy-induced hypertension,\(^{11,15-17}\) none of these experiments has used a model of preeclampsia in which angiogenic imbalance and hypertension arise spontaneously after placental ischemia, such as the reduced utero-placental perfusion pressure (RUPP) rat or baboon with uterine ischemia via partial uterine artery ligation.\(^{13,15}\) These studies have generally reported positive outcomes such as lowering blood pressure, increases of proangiogenic factors, and the promotion of vasculature function.\(^{12,15-17}\) Furthermore, these studies have not reported any deleterious effects in the fetus. However, statin use remains contraindicated during pregnancy because of unknown, but potentially teratogenic, effects on the fetus. Considering the substantial controversy regarding the putative role of statin use in pregnancy, there is need for further study on this matter. Therefore, the purpose of this study was to test the hypothesis that pravastatin administration would restore angiogenic balance, ameliorate oxidative stress, and attenuate high blood pressure in rats with RUPP-induced hypertension without any deleterious effects on fetal outcome.

**Methods and Apparatus**

**Animals**

Studies were performed in timed-pregnant Sprague-Dawley rats purchased from Charles River (Portage, MI). Animals were housed in a temperature-controlled room (23°C) with a 12:12 light:dark cycle. The experimental procedures in this study were performed strictly in accordance with National Institutes of Health guidelines for use and care of animals, and the protocols used in this study were approved by the Institutional Animal Care and Use Committee of the Universities of Minnesota and Oregon. On day 14 of gestation, rat dams were randomly assigned to RUPP (n=14), RUPP+pravastatin (RUPP+P; n=7), normal pregnant (NP; n=12), or NP+pravastatin (NP+P; n=7) control groups.

**RUPP Procedure and Determination of Mean Arterial Pressure**

RUPP procedure is a well-established model for studying the link between placental ischemia and hypertension in pregnant rat and has been described in detail previously.\(^{5,18}\) NP rats underwent a sham surgery, which included the midline incision and suture, on the same day of pregnancy. On days 14 to 19 of pregnancy, pravastatin was administered at a dose, 1 mg/kg per day (IP QD), that has previously been shown not to have adverse effects on lipid metabolism in Sprague-Dawley rats.\(^{9}\) Animals were instrumented on day 18 of gestation, and arterial pressure was determined via an indwelling catheter on day 19 of gestation as described previously.\(^{5,18}\)

**Conceptus Measurements**

After measurement of mean arterial pressure, dams were anesthetized with isoflurane and a midline ventral incision was made to isolate the abdominal aorta for plasma and serum collection as reported previously.\(^{5,18}\) Pups and placentas that seemed viable were excised with isoflurane and a midline ventral incision was made to isolate the abdominal aorta for plasma and serum collection as reported previously.\(^{5,18}\) Pups and placentas that seemed viable were excised with isoflurane and a midline ventral incision was made to isolate the abdominal aorta for plasma and serum collection as reported previously.\(^{5,18}\) Pups and placentas that seemed viable were excised with isoflurane and a midline ventral incision was made to isolate the abdominal aorta for plasma and serum collection as reported previously.\(^{5,18}\) Pups and placentas that seemed viable were excised with isoflurane and a midline ventral incision was made to isolate the abdominal aorta for plasma and serum 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were not smaller than that of the NP rats or the NP rats treated with pravastatin. Although there was a treatment effect by 1-way ANOVA for placental weight (data not shown), there were no significant differences among specific treatment groups when data were further analyzed with a Newman–Keuls post hoc test. Fetal resorptions were increased because of the RUPP procedure, and this was not altered by pravastatin (Figure 2B). Placental efficiency was decreased by RUPP and this was attenuated by treatment with pravastatin (Figure 2C). Heart weight (Figure 2D) was increased ($P<0.05$) in the RUPP rats compared with NP rats, and this was attenuated in the RUPP+P group. Pravastatin had no adverse effect on heart weight in the NP rats. Kidney weight was not different among any of the groups (data not shown).

### Circulating Factors
Figure 3A illustrates that plasma sFlt-1 was increased ($P<0.05$) in the RUPP compared with NP rats, and this was attenuated by treatment with pravastatin. Circulating levels of free VEGF were decreased ($P<0.05$) in the RUPP compared with the NP rats, and this was also attenuated by treatment with pravastatin (Figure 3B). Figure 3C shows that the sFlt-1:VEGF ratio, which was increased in RUPP compared with NP rats, was ameliorated by pravastatin treatment. There was no difference between NP and NP+P controls with respect to either sFlt-1 or VEGF. Figure 3D illustrates that TNF-$\alpha$ was not significantly increased in the RUPP compared with NP rats, but was increased in the RUPP+P rats compared with the NP controls. Serum total bilirubin was not different among the NP, RUPP, RUPP+P, and NP+P (1.40±0.27 versus 1.91±0.25 versus 1.10±0.21 versus 1.52±0.21 mg/dL).

### Total Antioxidant Capacity and Catalase Activity
Figure 4 illustrates that thiobarbituric acid reactive substances (Figure 4A) were increased ($P<0.05$) in the plasma of RUPP compared with NP rats, and this increase was attenuated ($P<0.05$) by treatment with pravastatin. Total antioxidant

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**Results**

### Mean Arterial Pressure
Figure 1 shows that RUPP resulted in increased arterial pressure compared with NP controls. RUPP rats treated with pravastatin had decreased blood pressure compared with untreated RUPP rats, but had blood pressure that was higher than the NP controls ($P<0.05$). Although the blood pressure of the NP rats treated with pravastatin was 6 mm Hg higher than the NP rats, it was not significantly different than any of the treatment groups.

### Conceptus and Maternal Morphometrics
Fetal weight was decreased in RUPP compared with NP dams (Figure 2A). Fetuses from RUPP rats treated with pravastatin

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**Figure 1.** Mean arterial pressure (MAP). Pravastatin decreased blood pressure compared with untreated reduced utero-placental perfusion pressure (RUPP) rats, but was higher than normal pregnant (NP) controls. Data are expressed as mean±SEM, $^*P<0.05$.

**Figure 2.** Fetal weight, fetal resorptions, placental efficiency, and heart weight.
Fetal weight (A) was decreased in reduced utero-placental perfusion pressure (RUPP) compared with normal pregnant (NP). Pravastatin administration resulted in fetuses that were not smaller than fetuses from NP dams or from NP dams treated with pravastatin. There was an increased number of fetal resorptions in the RUPP compared with the NP rats, and pravastatin had no effect in either group (B). Placental efficiency was decreased by RUPP, and this was ameliorated by pravastatin (C). Heart weight was increased by RUPP, and this was ameliorated by pravastatin (D). Data are expressed as mean±SEM, $^*P<0.05$. 

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**Figure 2A.** Fetal weight (g) in normal pregnant (NP) and reduced utero-placental perfusion pressure (RUPP) rats with and without pravastatin (P). Data are expressed as mean±SEM.

**Figure 2B.** Fetal resorptions in normal pregnant (NP) and reduced utero-placental perfusion pressure (RUPP) rats with and without pravastatin (P). Data are expressed as mean±SEM.

**Figure 2C.** Placental efficiency (Fetus/Plac) in normal pregnant (NP) and reduced utero-placental perfusion pressure (RUPP) rats with and without pravastatin (P). Data are expressed as mean±SEM.

**Figure 2D.** Heart weight (g) in normal pregnant (NP) and reduced utero-placental perfusion pressure (RUPP) rats with and without pravastatin (P). Data are expressed as mean±SEM.
capacity, shown in Figure 4B, was decreased ($P<0.05$) in plasma of RUPP compared with NP controls, and pravastatin attenuated ($P<0.05$) this difference in the treated RUPP rats. There was no difference between NP and NP+P controls. Figure 5 shows that placental catalase activity was increased ($P<0.05$) in RUPP compared with NP, and this was attenuated by treatment with pravastatin. Pravastatin had no effect on catalase activity in the NP placentas.

Western Blots for HO-1 and Heat Shock Proteins 27 and 70

No differences were found among any of the treatment groups in regards to placental expression of HO-1 (or HSP 32), HSP 27, or HSP 70 (data not shown). In addition, hepatic expression of HO-1 relative to $\beta$-actin was not altered because of pravastatin treatment among the NP, RUPP, RUPP+P, and NP+P (2.45±1.01 versus 3.12±1.27 versus 2.83±1.06 versus 3.23±0.90) groups.

Angiogenic Potential

Endothelial cell tubule formation was assessed as a measure of the angiogenic potential of serum from animals in each treatment group. Figure 6A shows that angiogenic potential as determined by the tube formation assay was decreased ($P<0.05$) in the RUPP compared with the NP rats. Despite the observed increase in VEGF and decrease in sFlt-1 in pravastatin treated animals (Figure 3A–3C), there was no improvement in endothelial tube formation in the treated RUPP+P rats. Moreover, we observed a decrease ($P<0.05$) in endothelial tube formation in the NP rats that were treated with pravastatin.
To determine whether pravastatin directly affected endothelial cell tube formation, we added 20 μmol/L pravastatin to serum collected from NP and RUPP rats. Figure 6B shows that the RUPP serum decreased (P<0.05) tube formation, but addition of pravastatin to either RUPP or NP serum did not result in a statistically significant change in tubule formation.

**Figure 6.** Effects of pravastatin on endothelial cell (EC) tube formation. A, EC tube formation was decreased in reduced utero-placental perfusion pressure (RUPP) rats compared with normal pregnant (NP) controls. Pravastatin treatment had no effect in RUPP rats and decreased EC tube formation in NP rats compared with NP controls. B, When 20 μmol/L pravastatin was added directly to NP and RUPP serum postmortem to determine whether there were direct effects on EC tube formation, EC tube formation was decreased in RUPPs compared with NPs controls. Pravastatin did not directly affect EC tube formation (RUPPs+P, NPs+P). Data are expressed as mean±SEM, *P<0.05.

**Cell Culture Studies**

To determine whether pravastatin had differential effects on trophoblast cells compared with endothelial cells, we treated BeWo and JAR cells with varying oxygen concentrations and pravastatin doses. BeWo cells secreted increased (P<0.05) concentrations of VEGF in hypoxic (1.5% O₂) conditions with and without pravastatin, and therefore the main statistical effect was a result of O₂ concentration (Figure 7A). In contrast, Figure 7B shows JAR cells decreased (P<0.05) VEGF secretion with pravastatin treatment and showed no effect of O₂ concentrations.

### Discussion

This study reports a combination of potentially positive and negative effects of pravastatin use during pregnancies with placental ischemia-related hypertension. Animal studies are required to investigate potential treatments for complications of pregnancy, but animal models often have limitations and ours is no different. Nevertheless, we believe that our rat model of placental ischemia-induced hypertension, which mimics many of the features of preeclampsia, is robust and contributes important findings to the volume of literature in this area.

Foremost, we report that pravastatin administration ameliorates RUPP-induced hypertension. Furthermore, we found that pravastatin increased circulating free VEGF concentrations and normalized sFlt-1:VEGF ratio, but did not restore angiogenic potential of the serum of these animals as determined by an endothelial tube formation assay. Although pravastatin treatment also improved markers of oxidative stress in the RUPP rats and resulted in no obvious adverse effects on fetal outcome, there was an increase in circulating TNF-α in the RUPP+P rats compared with the NP controls. Thus, the current study shows that pravastatin treatment during pregnancy may have effects that are specific to the concurrent presence of placental ischemia.

Our current findings are in agreement with previous studies reporting that pravastatin treatment has beneficial effects on blood pressure in hypertensive pregnant rodents.11,16 This is an important consideration as elevations in blood pressure are of primary concern in the treatment and management of preeclamptic patients. In addition, we also report that pravastatin treatment increased circulating free VEGF concentrations. Again, this is similar to other recent reports that have shown that pravastatin increases placental growth factor and VEGF in other models of pregnancy-induced hypertension11,16 or otherwise complicated pregnancies with angiogenic imbalance.25 We are presently unsure of the mechanism by which pravastatin increases VEGF in the pregnant rat, but it seems to be ischemia-dependent as the same dose did not increase VEGF concentrations in the NP rats. Furthermore, it remains unclear whether the alterations in VEGF attributable to pravastatin treatment presage the reduction in blood pressure or occur because of the alteration in blood pressure, and further studies are needed to clarify the mechanisms underlying these observations. Alternatively, previous work has shown that statins may stimulate endothelial nitric oxide synthase in endothelial cells29 and improve vascular function via increased NO or cGMP signaling.

We also observed a decrease in endothelial tube formation in human umbilical vein endothelial cells incubated with serum from both the RUPP and NP rats treated with pravastatin when compared with NP rats. Similarly, Frick et al27 reported endothelial cells treated directly with 10 μmol/L simvastatin formed fewer tubes compared with cells treated with 0.1 μmol/L simvastatin. In contrast, we performed an additional study using NP and RUPP serum with pravastatin added postmortem and did not observe any direct effects on tube formation. One possibility for the differences in these observations is that factors in the rat serum interfere with the direct effects of statins on tubule formation that has been reported previously.27 Alternatively, it is possible that TNF-α which we found to be increased by RUPP in the current study,
has a direct effect on tubule formation that is independent of pravastatin treatment. Further studies are being planned to evaluate this possibility.

Moreover, we also evaluated the effects of pravastatin on VEGF secretion from trophoblast cells in vitro at different oxygen concentrations and found differing effects depending on the cell type. In fusigenic BeWo cells we found that hypoxia increased VEGF expression, but that there was no effect of pravastatin on VEGF expression. In contrast, JAR cells decreased VEGF secretion with pravastatin treatment and showed no effect of O2 concentrations. Data are expressed as mean±SEM, *P<0.05.

Figure 7. Effects of oxygen concentration and pravastatin on vascular endothelial growth factor (VEGF) secretion by BeWo and JAR trophoblast cells. BeWo cells secreted increased (A) concentrations of VEGF in hypoxic (1.5% O2) conditions with and without pravastatin (Prav), thus the main statistical effect was attributable to O2 concentration. In contrast, JAR cells decreased (B) VEGF secretion with pravastatin treatment and showed no effect of O2 concentrations. Data are expressed as means±SEM, *P<0.05.

In addition to the beneficial effects of pravastatin treatment on blood pressure, there was no evidence of fetal distress attributable to pravastatin treatment in either RUPP or NP rats. We also observed the placental efficiency, which was decreased in the RUPP compared with NP rats, was restored by pravastatin treatment. This observation is in agreement with previous work showing improved placental development and VEGF expression in a transgenic mouse model of preeclampsia in which mice have a complement component C1q deficiency. However, our study only examined the effects of 1 dose of pravastatin. It is possible that other doses may have different effects.

In contrast to previous studies that have reported only positive outcomes associated with pravastatin use in models of preeclampsia and miscarriage, we report for the first time that pravastatin treatment is associated with potentially detrimental effects on maternal physiology. In contrast to previous studies that have reported improved endothelial function
in various models of preeclampsia and angiogenic imbalance in pregnancy, we observed that, despite increases in VEGF, pravastatin treatment did not improve endothelial tube formation in RUPP hypertensive rats. Moreover, we found that pravastatin treatment decreased the angiogenic potential of the serum from NP rats. As pravastatin did not alter VEGF expression in the NP rats, it seems that this effect is VEGF independent. In addition, a dose of pravastatin that was higher than the in vivo dose used in our studies did not have the same effect on endothelial tube formation when added to NP and RUPP serum postmortem. Thus it seems that pravastatin has a pregnancy-specific interaction with maternal cells that is not dependent on placental ischemia and results in an alteration in angiogenic potential of the maternal serum. This may represent an area of concern with respect to use of pravastatin during pregnancy and further studies are warranted to further evaluate this observation.

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Disclosures
None.

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**Novelty and Significance**

**What Is New?**

- In this study we report for the first time that pravastatin treatment reduced high blood pressure, attenuated oxidative stress, and restored angiogenic balance in the reduced utero-placental perfusion pressure rat, a robust model of preeclampsia. However, in contrast to previous reports we found that pravastatin treatment did not improve angiogenic potential in rats with placental ischemia-induced hypertension suggesting pravastatin use during pregnancy may have deleterious effects on maternal physiology.

**What Is Relevant?**

- There are currently no treatments available for women with preeclampsia except for delivery of the baby when necessary. Our findings provide important evidence that pravastatin treatment attenuates many symptoms of placental ischemia-induced hypertension including high blood pressure, angiogenic imbalance, and oxidative stress. Nevertheless, we also report pravastatin treatment may have negative effects on maternal physiology. Therefore, further consideration must be given to whether reported benefits of statin use in hypertensive pregnancies outweigh the potential risks.

**Summary**

Pravastatin treatment attenuates high blood pressure, angiogenic imbalance, and oxidative stress in placental ischemia-induced hypertension but may stimulate circulating antiangiogenic factors.
Pravastatin Attenuates Hypertension, Oxidative Stress, and Angiogenic Imbalance in Rat Model of Placental Ischemia-Induced Hypertension
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