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ORIGINAL RESEARCH ARTICLE

Pravastatin Versus Placebo in Pregnancies at High Risk of Term Preeclampsia

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BACKGROUND: Effective screening for term preeclampsia is provided by a combination of maternal factors with measurements of mean arterial pressure, serum placental growth factor, and serum soluble fms-like tyrosine kinase-1 at 35 to 37 weeks of gestation, with a detection rate of ≈75% at a screen-positive rate of 10%. However, there is no known intervention to reduce the incidence of the disease.

METHODS: In this multicenter, double-blind, placebo-controlled trial, we randomly assigned 1120 women with singleton pregnancies at high risk of term preeclampsia to receive pravastatin at a dose of 20 mg/d or placebo from 35 to 37 weeks of gestation until delivery or 41 weeks. The primary outcome was delivery with preeclampsia at any time after randomization. The analysis was performed according to intention to treat.

RESULTS: A total of 29 women withdrew consent during the trial. Preeclampsia occurred in 14.6% (80 of 548) of participants in the pravastatin group and in 13.6% (74 of 543) in the placebo group. Allowing for the effect of risk at the time of screening and participating center, the mixed-effects Cox regression showed no evidence of an effect of pravastatin (hazard ratio for statin/placebo, 1.08 [95% CI, 0.78–1.49]; *P*=0.65). There was no evidence of interaction between the effect of pravastatin, estimated risk of preeclampsia, pregnancy history, adherence, and aspirin treatment. There was no significant between-group difference in the incidence of any secondary outcomes, including gestational hypertension, stillbirth, abruption, delivery of small for gestational age neonates, neonatal death, or neonatal morbidity. There was no significant between-group difference in the treatment effects on serum placental growth factor and soluble fms-like tyrosine kinase-1 concentrations 1 and 3 weeks after randomization. Adherence was good, with reported intake of ≥80% of the required number of tablets in 89% of participants. There were no significant between-group differences in neonatal adverse outcomes or other adverse events.

CONCLUSIONS: Pravastatin in women at high risk of term preeclampsia did not reduce the incidence of delivery with preeclampsia.

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Editorial, see p 680

Preeclampsia is an important cause of maternal and perinatal mortality and morbidity. Although the adverse consequences of preeclampsia in terms of maternal and fetal/neonatal mortality and morbidity are more severe in preterm preeclampsia, with delivery at <37 weeks, than in term preeclampsia, the overall contribution to adverse outcome may be the same because term preeclampsia is 3 times as common as preterm pre-

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Clinical Perspective

What Is New?

- In this double-blind, placebo-controlled, randomized trial, pravastatin at a dose of 20 mg/d from 35^{+0} to 36^{+6} weeks of gestation until delivery among women identified as high risk for term preeclampsia did not reduce the incidence of preeclampsia.
- Pravastatin did not reduce the incidence of gestational hypertension, stillbirth, abruption, delivery of small for gestational age neonates, neonatal death, or neonatal morbidity.
- Pravastatin intake from 35^{+0} to 36^{+6} weeks of gestation until delivery was not associated with increased incidence of serious or nonserious adverse events.

What Are the Clinical Implications?

- Prophylactic administration of pravastatin in late pregnancy in women at high risk for preeclampsia is not useful in the prevention of preeclampsia.

eclampsia.[1–6] Preterm preeclampsia can to a great extent be predicted and prevented.[1,7–11] Screening at 11 to 13 weeks of gestation by a combination of maternal demographic characteristics and medical history with measurements of uterine artery pulsatility index, mean arterial pressure, and serum placental growth factor can predict ≈75% of cases of preterm preeclampsia but only 40% of cases of term preeclampsia at a 10% screen-positive rate.[1,7–9] Administration of aspirin (150 mg/d from 11–14 to 36 weeks of gestation) in the high-risk group reduces the rate of preterm preeclampsia by 60% to 70% but has no significant effect on term preeclampsia.[10,11] Therefore, term preeclampsia is neither predictable nor preventable by first-trimester screening and prophylactic pharmacological intervention.

Effective screening for term preeclampsia is provided by a combination of maternal factors with measurements of mean arterial pressure, serum placental growth factor, and serum soluble fms-like tyrosine kinase-1 (triple test) at 35 to 37 weeks of gestation, with a detection rate of ≈75% at a screen-positive rate of 10%.[12,13] One potentially beneficial pharmacological intervention for the high-risk group is the use of pravastatin, a hydrophilic, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor. The rationale for the use of statins to prevent preeclampsia is that these drugs are effective in primary and secondary prevention of mortality and morbidity in people with cardiovascular disease,[14,15] and both preeclampsia and cardiovascular disease are characterized by endothelial dysfunction and inflammation and share many risk factors.[16,17] The clinical onset of preeclampsia is preceded by an increase in serum soluble fms-like tyrosine kinase-1,[12,13,18,19] and there is some evidence that statins inhibit cytokine-mediated release of soluble fms-like tyrosine kinase-1.[20] Animal studies have demonstrated that overexpression of soluble fms-like tyrosine kinase-1 results in a preeclampsia-like condition,[21] and lowering the circulating levels of soluble fms-like tyrosine kinase-1 below a critical threshold reverses pathological features of preeclampsia.[22] A randomized study of pravastatin starting from 12 to 16 weeks until delivery in 10 pregnancies at high risk for preeclampsia reported no serious adverse events and very promising results in reducing the rate of preeclampsia; it was concluded that a major randomized study was necessary to examine efficacy.[23]

The randomized, controlled trial with pravastatin versus placebo for the prevention of preeclampsia trial was designed to test the hypothesis that, among women identified as high risk for term preeclampsia on the basis of the factors above, pravastatin at a dose of 20 mg/d from 35^{+0} to 36^{+6} weeks of gestation until delivery, compared with placebo, would result in halving of the incidence of delivery with preeclampsia.

METHODS

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Trial Design and Participants

This was a double-blind, placebo-controlled trial comparing pravastatin at a dose of 20 mg once per day with placebo from 35 to 37 until 41 weeks of gestation in women with singleton pregnancies at high risk of term preeclampsia. We conducted the trial at 10 maternity hospitals in England, Spain, and Belgium.

All women with a routine prenatal visit at 35^{+0} to 36^{+6} weeks of gestation in the participating hospitals were offered screening for preeclampsia by the same algorithm that combines maternal demographic characteristics and medical history, mean arterial pressure, and maternal serum placental growth factor and soluble fms-like tyrosine kinase-1.[24] Gestational age was determined by the measurement of fetal crown-rump length at 11 to 13 weeks or fetal head circumference at 19 to 24 weeks.[25,26] Maternal characteristics, medical history, and obstetric history were recorded, and maternal weight and height were measured. Mean arterial pressure was measured by validated automated devices and a standardized protocol.[27] Serum placental growth factor and soluble fms-like tyrosine kinase-1 concentrations were measured by an automated device (BRAHMS KRYPTOR compact PLUS, Thermo Fisher Scientific, Hennigsdorf, Germany). Quality control of screening and verification of adherence to protocol were performed by the Fundación para la Formación e Investigación Sanitaria for the sites in Spain and by the Fetal Medicine Foundation for sites in the United Kingdom and Belgium.

Inclusion criteria for the trial were age of ≥18 years, singleton pregnancy, live fetus at the 35- to 37-week scan, and high risk (≥1 in 20) for term preeclampsia. We excluded women who were unconscious or severely ill; those with learning difficulties

or serious mental illness; women with major fetal abnormality; women with planned delivery within 7 days of the randomization date; women with established preeclampsia; those with statin use within 28 days before randomization; women participating in another intervention study that influences the outcomes of this study; and those with contraindications for statin therapy (Data Supplement). Potential trial participants were given written information about the trial, and those who agreed to participate provided written informed consent.

Approval for the study was obtained in each country where the trial was conducted from the relevant Research Ethics Committee and competent authority. Funding organizations had no role in study design; collection, analysis, or interpretation of the data; or the writing and decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and analyses.

Calculation of Risk for Preeclampsia

Our approach for the calculation of risk for preeclampsia is based on a survival-time model for the gestational age at delivery with preeclampsia.[7] Every pregnant woman has a personalized distribution of gestational age at delivery with preeclampsia, which comes from the application of the Bayes theorem to combine a prior distribution, determined from maternal demographic characteristics and medical history, with likelihoods from biomarkers. In the previous model, the risk of development of preeclampsia is increased with advancing maternal age; increasing weight; Black and South Asian race; medical history of chronic hypertension, diabetes mellitus, and systemic lupus erythematosus or antiphospholipid syndrome; conception by in vitro fertilization; and family or personal history of preeclampsia. The risk for preeclampsia is decreased with increasing maternal height and in parous women with no previous preeclampsia. At 35 to 37 weeks of gestation, useful biomarkers for subsequent development of preeclampsia are mean arterial pressure and maternal serum placental growth factor and soluble fms-like tyrosine kinase-1.[12,13,24] The measured values for these biomarkers are expressed as multiples of the median after adjustment for gestational age, weight, race, method of conception, medical conditions, elements from the obstetric history associated with the individual on whom they are measured, and the instrument used for measurement. In pregnancies that develop preeclampsia, multiple of the median values of mean arterial pressure and soluble fms-like tyrosine kinase-1 tend to be higher and placental growth factor tends to be lower than in normal pregnancies. The effect sizes increase with increasing severity of the disease, quantified by the gestational age at delivery. The posterior distribution of gestational age at delivery with preeclampsia is obtained with the Bayes theorem by multiplying the previous probability density from maternal factors by the likelihood function from biomarker multiple of the median values.

Randomization and Study Group Assignment

Eligible women were randomly assigned in a 1:1 ratio with the use of a web-based system (Sealed Envelope, London, UK) to receive either pravastatin or placebo. In the random-sequence generation, there was stratification according to participating center. Pravastatin tablets were procured and overencapsulated by Mawdsley Brooks and Co (Salford, UK); a matched placebo capsule was also procured by Mawdsley Brooks and Co. Both pravastatin and placebo capsules were packaged, labeled, stored, and distributed by Mawdsley Brooks and Co.

The placebo capsules were identical to the pravastatin capsules in parameters such as size, thickness, physical properties, and appearance. After randomization, study participants were prescribed the investigational medicinal product and received instructions to take 1 capsule every day throughout the study and to stop taking capsules at 41 weeks of gestation or in the event of delivery, at the onset of labor, or 1 day before planned cesarean section.

Outcome Measures

The primary outcome measure was delivery with preeclampsia defined as per the American College of Obstetrics and Gynecology (Data Supplement).[28] There was a central adjudication process to establish the diagnosis of preeclampsia; all anonymized data in cases of suspected preeclampsia reported to the Fundación para la Formación e Investigación Sanitaria and by the Fetal Medicine Foundation were examined by 1 operator (A.S.) to determine whether the diagnosis was correct.

Secondary outcomes were adverse outcomes of pregnancy at any gestation and at or after 37 weeks of gestation, stillbirth or neonatal death, neonatal morbidity, neonatal therapy, and low birth weight.[29] The effect of pravastatin on serum placental growth factor and soluble fms-like tyrosine kinase-1 concentrations 1 and 3 weeks after the onset of treatment and the safety of pravastatin were assessed by creatine kinase concentrations in women with adverse muscle symptoms.

Adverse Events and Adherence

Adherence and adverse events were assessed and recorded at follow-up clinical visits at 36 to 38 and 39 to 40 weeks of gestation, at 6 weeks after delivery, and in 1 telephone interview at 37 to 39 weeks of gestation. Participants were encouraged to record any side effects or adverse events in a diary that was reviewed at each trial visit, and they were specifically asked about such events at the telephone interview.

Researchers assessed adherence by counting the capsules returned by participants at each visit and by the participants themselves at the telephone interview. The total number of capsules taken was calculated by subtracting the number of capsules returned from the number of capsules prescribed. Adherence was considered to be good if the reported intake of capsules was ≥80% of the total number that the participants should have taken between the date of randomization and the date of the 41 weeks' gestation or delivery if it occurred before 41 weeks.

Statistical Analysis

The sample size estimation was based on the assumption that screening at 35 to 36 weeks of gestation would detect 77% of cases of term preeclampsia at a screen-positive rate of 10%.[24] It was hypothesized that pravastatin would reduce the rate of preeclampsia by 50%, from 12% in the placebo group to 6% in the pravastatin group. Further details on sample size calculation are provided in the Data Supplement. We calculated that enrollment of 1020 participants would give the study a power of 90% to show a treatment effect at a 2-sided

α level of 5%. The target recruitment figure was inflated to 1120 to account for attrition.

Statistical analyses were performed on an intention-to-treat basis, and no interim analyses were performed. Kaplan-Meier estimates of the cumulative incidence of preeclampsia by treatment group, with deliveries without preeclampsia treated as censored observations, were produced. The primary comparison was a test of the treatment effect at the 2-sided 5% level in a mixed-effects Cox regression adjusting for the fixed effect of the risk of preeclampsia at screening and random effects for participating center. The proportional hazards assumption was examined through the analysis of residuals.

Prespecified subgroup analyses of the primary outcome were performed according to subgroups categorized by estimated risk of preeclampsia, history of pregnancy with preeclampsia, adherence, and antenatal aspirin intake. *P* values were reported for tests of interaction with treatment; these were obtained from a likelihood ratio test. No adjustments were made for multiple comparisons.

Binary outcomes were analyzed with log-binomial regression analysis. Measurements of placental growth factor and soluble fms-like tyrosine kinase-1 concentrations 1 and 3 weeks after the onset of treatment were tested with ANCOVA of the log-transformed concentrations adjusting for the baseline levels. Estimates and 95% CIs for treatment effects were produced. No adjustments were made for multiple comparisons.

The statistical software package R was used for data analyses.[30] The package coxme[31] was used for the mixed-effects Cox regression. The package logbin[32] was used for the log-binomial regression.

RESULTS

Trial Participants

Recruitment to the trial started in August 2018 and was completed in November 2019. A total of 29816 women with singleton pregnancies had screening, and 3490 (11.7%) were found to be at high risk, but 385 (11.0%) of them were excluded from recruitment to the trial because they did not fulfill the eligibility criteria (Figure 1). Of the 3105 eligible women, 1120 (36.1%) agreed and 1975 (63.9%) declined to participate in the trial. The maternal and pregnancy characteristics of women who agreed and those who declined participation in the trial are shown in Table I in the Data Supplement; the characteristics of the 2 groups were similar. After randomization, 29 (2.6%) women withdrew consent, which is lower than the anticipated attrition rate of 10%. The pravastatin and placebo groups were similar in baseline characteristics (Table 1).

Of the 29816 pregnancies screened, 108 women were lost to follow-up, 29 women withdrew consent, and 2 pregnancies were terminated. Follow-up data were available for the remaining 29677 (99.5%),

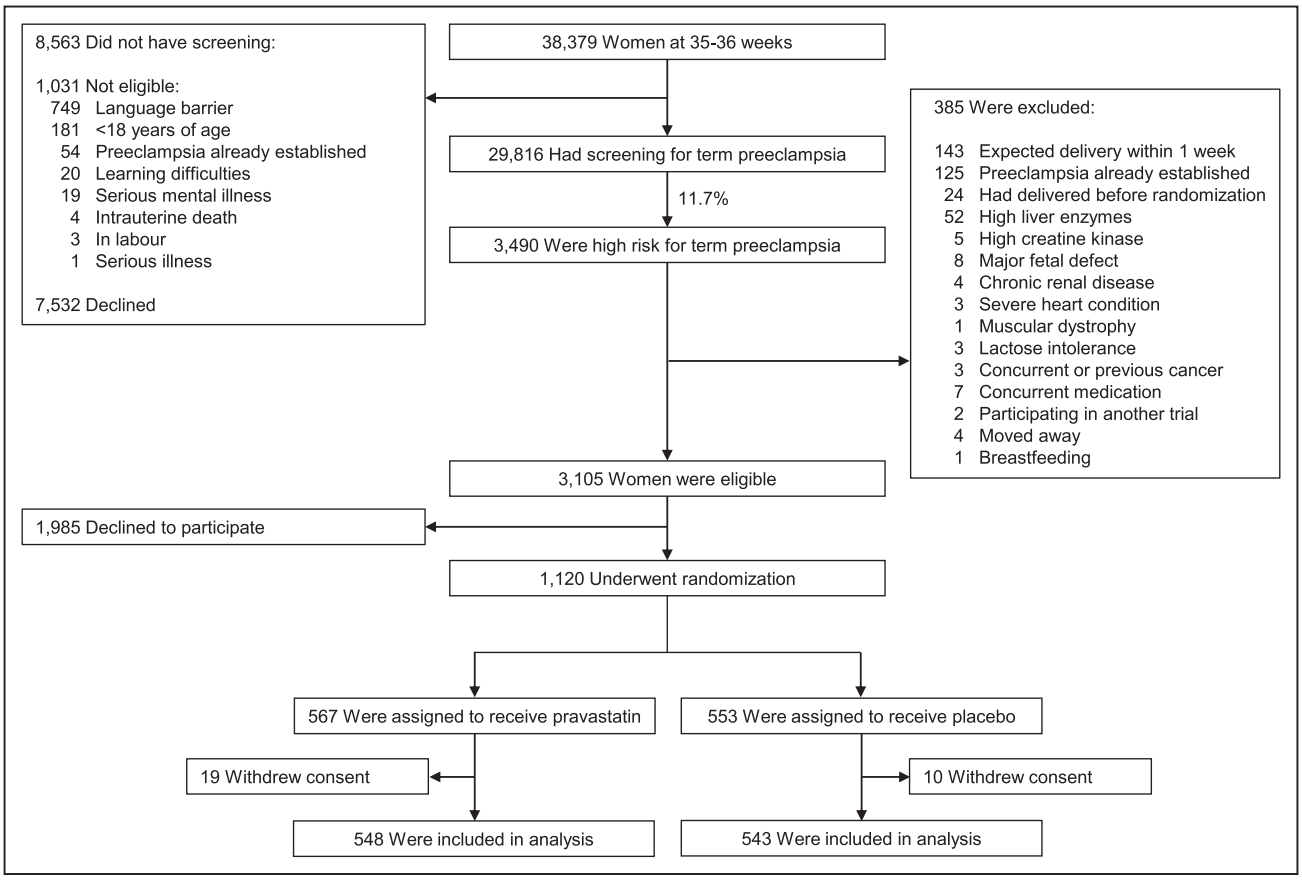

Figure 1. Screening, randomization, and follow-up.

Table 1. Characteristics of the Trial Participants*

Characteristic	Pravastatin group (n=548)	Placebo group (n=543)
Gestation at randomization, median (IQR), wk	35.9 (35.4–36.1)	35.9 (35.4–36.1)
Age, median (IQR), y	32.9 (28.6–36.9)	32.5 (28.0–36.8)
Body mass index, median (IQR), kg/m^2	30.5 (27.3–34.8)	30.9 (27.2–34.9)
Race or ethnic group, n (%)†		
White	392 (71.5)	402 (74.0)
Black	67 (12.2)	68 (12.5)
South Asian	68 (12.4)	47 (8.7)
East Asian	4 (0.7)	11 (2.0)
Mixed	17 (3.1)	15 (2.8)
Conception, n (%)		
Natural	513 (93.6)	509 (93.7)
In vitro fertilization	35 (6.4)	34 (6.3)
Cigarette smoker, n (%)	26 (4.7)	24 (4.4)
Mother had preeclampsia, n (%)	36 (6.6)	43 (7.9)
Medical history, n (%)		
Chronic hypertension	28 (5.1)	20 (3.7)
Systemic lupus erythematosus	3 (0.5)	2 (0.4)
Antiphospholipid syndrome	1 (0.2)	7 (1.3)
Diabetes type 1	3 (0.5)	2 (0.4)
Diabetes type 2	11 (2.0)	11 (2.0)
Obstetric history		
Nulliparous, n (%)	311 (56.8)	319 (58.7)
Multiparous without preeclampsia, n (%)	209 (38.1)	191 (35.2)
Multiparous with preeclampsia, n (%)	28 (5.1)	33 (6.1)
Interval from last pregnancy, median (IQR), y	3.9 (2.1–6.6)	3.1 (1.8–5.5)
Gestation at delivery of last pregnancy, wk	39.0 (38.0–40.0)	39.0 (38.0–40.0)
Treatment with aspirin 150 mg/d, n (%)	92 (16.8)	76 (14.0)
Screening for preeclampsia at 35–36 wk		
Mean arterial pressure, median (IQR), mm Hg	95.6 (91.3–100.2)	96 (91.8–100.2)
Multiple of the median	1.1 (1.0–1.1)	1.1 (1.0–1.1)
Serum placental growth factor, median (IQR) pg/mL	87.61 (58.53–131.03)	85.7 (54.8–133.8)
Multiple of the median	0.3 (0.2–0.5)	0.3 (0.2–0.5)
Serum soluble fms-like tyrosine kinase-1, median (IQR), pg/mL	4921 (3614–6831)	4929 (3677–6658)
Multiple of the median	2.2 (1.7–3.0)	2.2 (1.7–2.9)
Risk of preeclampsia, median (IQR)	1 in 8 (1 in 14–1 in 4)	1 in 9 (1 in 14–1 in 5)

IQR indicates interquartile range.
*There is a balance in baseline variables between the 2 groups.
†Race and ethnic group were self-reported.

and preeclampsia occurred in 720 cases (2.43% [95% CI, 2.25%–2.60%]). Screening performance is shown in Table II in the Data Supplement. With the exclusion of the 119 with preeclampsia at the time of screening, the detection rate for delivery with preeclampsia after screening was 75.0% (95% CI, 71.4%–78.5%) with a false-positive rate of 9.9% (95% CI, 9.6%–10.3%).

Primary Outcome

In the intention-to-treat population, preeclampsia occurred in 14.6% (80 of 548) of participants in the pravastatin group and in 13.6% (74 of 543) in the placebo group. Allowing for the effect of risk at the time of screening and participating center, the mixed-effects Cox regression showed no evidence of an effect of pravastatin (hazard ratio for statin/placebo, 1.08 [95%

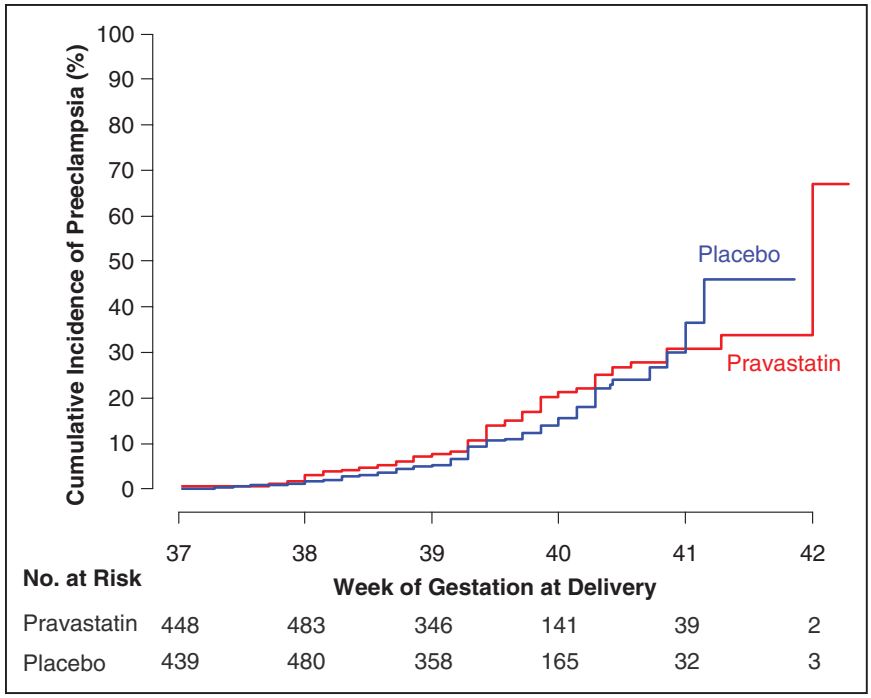

Figure 2. Kaplan-Meier plot of cumulative percentage of participants who delivered with preeclampsia.
Some women were randomized after 37 weeks of gestation, which explains why the numbers exposed to risks at 38 weeks are higher than those at 37 weeks.

CI, 0.78–1.49]; *P*=0.65). Kaplan-Meier estimates of the cumulative incidence of preeclampsia by treatment group with births from causes other than preeclampsia taken as censored observations are shown in Figure 2. There was no evidence of interaction among the effect of pravastatin, estimated risk of preeclampsia, pregnancy history, adherence, and aspirin treatment (Figure 3). Analysis of the per-protocol populations, with at least

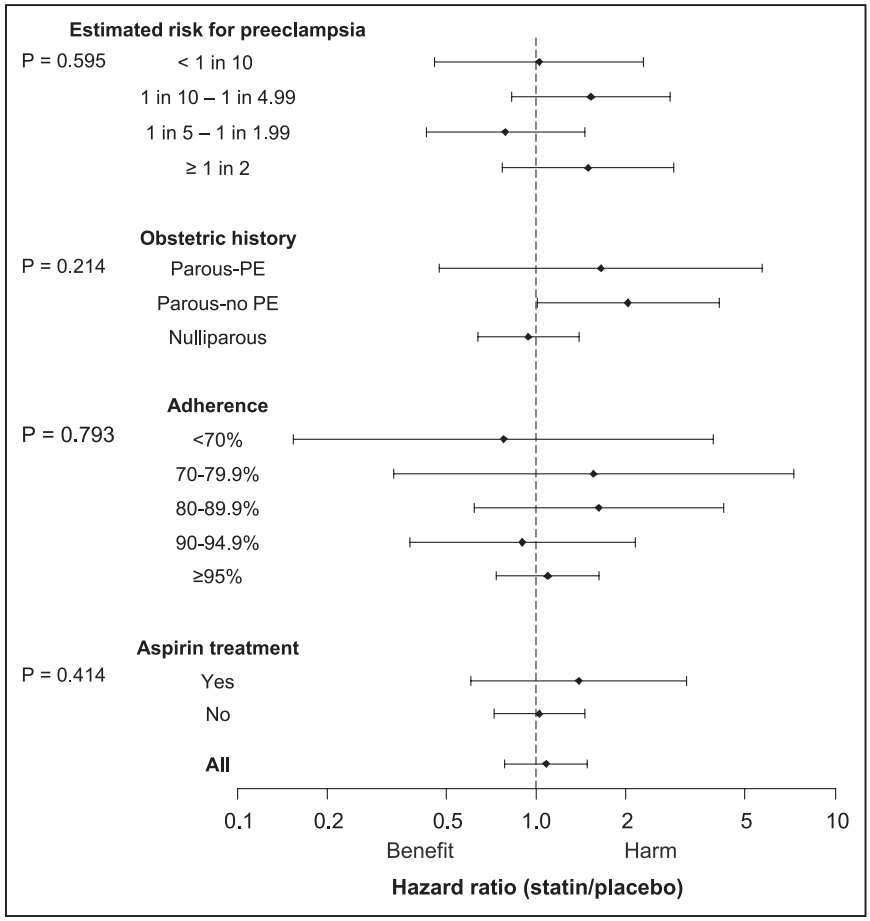

Figure 3. Subgroup analysis of hazard ratio (statin/placebo) with 95% CIs in different groups according to estimated risk for preeclampsia (PE), obstetric history, adherence, and aspirin treatment.
P values are given for the test of interaction with treatment.

80% compliance and with at least 80% compliance for at least 7 days, gave essentially the same conclusions.

Secondary Outcomes

The treatment effect for secondary outcomes, quantified as relative risks in the pravastatin group with 95% CIs, is shown in Table 2. There was no significant between-group difference in the incidence of any secondary outcomes. Kaplan-Meier estimates of the cumulative incidence of preeclampsia or gestational hypertension by treatment group are shown in Figure I in the Data Supplement. There was no significant between-group difference in the treatment effects on serum placental growth factor and soluble fms-like tyrosine kinase-1 concentrations 1 and 3 weeks after randomization (Table III and Figures II and III in the Data Supplement).

Table 2. Outcomes According to Trial Group

Outcome	Pravastatin group	Placebo group	Relative risk (95% CI)	*P* value
Group total, n	548	543		
Preeclampsia, n (%)	80 (14.6)	74 (13.6)	1.08 (0.78–1.49)*	0.65
Secondary outcomes				
Adverse outcomes at any gestation, n (%)				
Gestational hypertension	99 (18.1)	89 (16.4)	1.08 (0.83–1.40)	0.57
Preeclampsia or gestational hypertension	179 (32.7)	163 (30)	1.05 (0.89–1.23)	0.60
Small for gestational age <5th percentile	86 (15.7)	77 (14.2)	1.08 (0.81–1.43)	0.61
Stillbirth	0	0	…	
Abruption	1 (0.2)	2 (0.4)	…	
Composite of all the above	238 (43.4)	221 (40.7)	1.03 (0.90–1.17)	0.67
Group total, n	536	530		
Adverse outcomes at ≥37 wk, n (%)				
Preeclampsia	79 (14.7)	74 (14.0)	1.01 (0.76–1.33)	0.96
Gestational hypertension	99 (18.5)	86 (16.2)	1.12 (0.86–1.45)	0.41
Preeclampsia or gestational hypertension	178 (33.2)	160 (30.2)	1.06 (0.90–1.25)	0.48
Small for gestational age <5th percentile	83 (15.5)	76 (14.3)	1.06 (0.79–1.40)	0.71
Stillbirth	0	0	…	…
Abruption	1 (0.2)	2 (0.4)	…	…
Composite of all the above	234 (43.7)	218 (41.1)	1.03 (0.90–1.17)	0.70
Group total, n	548	543		
Neonatal outcomes, n (%)				
Small for gestational age <3rd percentile	65 (11.9)	55 (10.1)	1.00 (0.72–1.40)	1.00
Small for gestational age <10th percentile	118 (21.5)	116 (21.4)	0.99 (0.79–1.24)	0.93
Neonatal therapy, n (%)				
Intensive care unit admission	10 (1.8)	16 (2.9)	0.62 (0.28–1.35)	0.23
Ventilation with positive airway pressure or intubation	7 (1.3)	15 (2.8)	0.46 (0.19–1.13)	0.09
Composite of all the above	12 (2.2)	21 (3.9)	0.57 (0.28–1.14)	0.11
Neonatal morbidity, n (%)				
Respiratory distress syndrome	7 (1.3)	15 (2.8)	0.46 (0.19–1.13)	0.09
Intraventricular hemorrhage	0	1 (0.2)	…	…
Anemia	0	1 (0.2)	…	…
Necrotizing enterocolitis	0	0	…	…
Sepsis	1 (0.2)	1 (0.2)	…	…
Composite of all the above	8 (1.5)	15 (2.8)	0.53 (0.23–1.24)	0.14

Hazard ratios (pravastatin/placebo) were obtained from a mixed-effects Cox regression with fixed effects for risk and treatment group and random effects for participating center. Risk ratios were obtained from a log-binomial regression adjusted for risk.

*Hazard ratio (95% CI).

Adverse Events

In the pravastatin group, there was at least 1 serious adverse event in 2 cases (0.4%) and at least 1 adverse event in 112 (20.4%); respective frequencies for the placebo group were 6 (1.1%) and 103 (19.0%). There was no significant between-group difference in the incidence of these events (Table 3 and Table IV in the Data Supplement). Muscle pains or cramps developed in 6 patients in the pravastatin group and in 7 in the placebo group; creatine kinase concentrations were normal in all 13 cases.

Adherence

Adherence was ≥80% in 972 participants (89.1%). There were no significant between-group differences in the degree of adherence (Table V in the Data Supplement).

DISCUSSION

In this multicenter, randomized, placebo-controlled trial involving women with singleton pregnancies who were identified by means of screening at 35 to 37 weeks of gestation as being at high risk for term preeclampsia, the administration of pravastatin at a dose of 20 mg/d from 35 to 37 weeks of gestation until delivery did not reduce the incidence of delivery with preeclampsia compared with placebo. There was no evidence of interaction among the effect of pravastatin, estimated risk for preeclampsia, pregnancy history, adherence, and aspirin consumption. Adherence was good, with reported intake of ≥80% of the required number of tablets in 89% of participants. There was no significant between-group difference in the incidence of pregnancy complications or of adverse fetal or neonatal outcomes. However, the trial was not adequately powered for the secondary outcomes.

Table 3. Serious Adverse Events Among Trial Participants*

Serious adverse event	Pravastatin group (n=548)	Placebo group (n=543)
Maternal serious adverse events, n		
Rupture of uterus and bladder	0	1
Fetal structural defects, n		
Cleft palate and lip	1	0
Ventricular septal defect	1	0
Ventricular septal defect and atrial septal defect	0	1
Hip dysplasia	0	1
Hypospadias	0	2
Talipes equinovarus unilateral	0	1
At least 1 serious adverse event, n (%)	2 (0.4)	6 (1.1)
No serious adverse event, n (%)	546 (99.6)	537 (98.9)

*None of these serious adverse events were considered by the investigators to be associated with pravastatin or placebo.

The objective of this study was to investigate the prediction and prevention of term preeclampsia because we have previously reported that preterm preeclampsia can to a great extent be predicted by first-trimester screening and prevented with aspirin.[1,10] Similarly, we have previously reported that effective screening for term preeclampsia is not possible before 35 weeks of gestation.[12] In our study of nearly 30 000 pregnancies, screening for term preeclampsia identified 75% of subsequent deliveries with preeclampsia at a false-positive rate of 10%. This finding provides prospective confirmation of our screening model, which combines information from maternal demographic characteristics and medical history with measurements of mean arterial pressure, serum placental growth factor, and serum soluble fms-like tyrosine kinase-1.[12,13,24] In a previous study, we reported that at 35 to 37 weeks of gestation the triple test was superior to the alternative strategies of screening for imminent preeclampsia by placental growth factor alone[33] or the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor.[34] This method of screening could therefore be adopted in future studies investigating the potential value of alternative strategies for the prevention of term preeclampsia such as early delivery for the high-risk group.

The dose of 20 mg pravastatin per day was selected on the basis of previous evidence from an open-label trial in pregnant women with antiphospholipid syndrome who developed preeclampsia or fetal growth restriction between 21 and 30 weeks of gestation.[35] In the control group, all deliveries occurred preterm, and 4 of the 10 babies died, whereas in the group treated with pravastatin at 20 mg/d, all 11 babies were born close to full term and survived.[35]

Animal studies had suggested that a possible mechanism whereby pravastatin prevents preeclampsia is by inducing placental growth factor and lowering the circulating levels of soluble fms-like tyrosine kinase-1.[22,36] We found that pravastatin had no significant effect on serum levels of placental growth factor or soluble fms-like tyrosine kinase-1. Similarly, a previous trial in women with early-onset preeclampsia reported that pravastatin at 40 mg/d had no effect on the plasma levels of soluble fms-like tyrosine kinase-1.[37] It is possible that considerably higher doses and longer duration of treatment with pravastatin are needed to restore the balance in the circulating levels of angiogenic and antiangiogenic factors and thereby prevent the development of preeclampsia.

This was a large study in a high-risk population, but it could be argued that the study was underpowered because of the assumed effect size (50% reduction in incidence). However, the hazard ratio (statin/placebo) of 1.08 (95% CI, 0.78–1.49; P=0.65) shows no evidence of benefit and is in the direction of harm. The lower confidence limit of 0.78 means that substantial benefits from pravastatin can be ruled out.

Conclusions

This trial showed that, in women with singleton pregnancies at high risk of term preeclampsia, the administration of pravastatin at a dose of 20 mg/d from 35 to 37 weeks of gestation until delivery did not reduce the incidence of delivery with preeclampsia.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Definition of preeclampsia
Contraindications for statin therapy
Sample size calculation
Data Supplement Tables I–V
Data Supplement Figures I–III

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