**Pravastatin versus Placebo in Pregnancies at High Risk of Term Preeclampsia**

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## ABSTRACT

**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 detection rate of about 75%, at 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 1,120 women with singleton pregnancies at high-risk of term preeclampsia to receive pravastatin, at a dose of 20 mg per day, 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% (80/548) participants in the pravastatin group and in 13.6% (74/543) in the placebo group. Allowing for the effect of risk at the time of screening and participating centre, the mixed effects Cox regression showed no evidence of an effect of pravastatin; hazard ratio (statin/placebo) 1.08 (95% confidence interval: 0.78, 1.49; p=0.65). There was no evidence of interaction between the effect of pravastatin, estimated risk of preeclampsia, previous 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% or more 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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## CLINICAL PERSPECTIVE

### WHAT IS NEW?

- In this double-blind placebo-controlled randomised trial, pravastatin at a dose of 20 mg per day, 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 non-serious 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. 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 three times as common as preterm preeclampsia.[1-6] Preterm preeclampsia can to a great extent be predicted and prevented.[1,7-11] Screening at 11-13 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 about 75% of cases of preterm preeclampsia, but only 40% of cases of term preeclampsia, at 10% screen positive rate.[1,7-9] Administration of aspirin (150 mg/day from 11-14 weeks of gestation to 36 weeks) in the high risk group reduces the rate of preterm preeclampsia by 60-70%, but has no significant effect on term preeclampsia.[10,11] Therefore, term preeclampsia is

neither predictable nor is it 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 35-37 weeks of gestation, with detection rate of about 75%, at 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 for prevention of 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 they 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 over expression 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 randomised study of pravastatin starting from 12-16 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 randomised controlled trial with pravastatin versus placebo for prevention of preeclampsia trial was designed to test the hypothesis that, among women identified as high risk for term preeclampsia based on the factors above, pravastatin at a dose of 20 mg per day, from $35^{+0}$ to $36^{+6}$ weeks of gestation until delivery, as compared with placebo, would result in halving the incidence of delivery with preeclampsia.

# METHODS

## 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 35-37 weeks of gestation until 41 weeks 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 which 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 11-13 weeks or fetal head circumference at 19-24 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 (FFIS) for the sites in Spain and by the Fetal Medicine Foundation for sites in the UK and Belgium.

Inclusion criteria for the trial were: age 18 years or older; singleton pregnancy; live fetus at the 35-37 weeks' scan; high-risk (≥1 in 20) for term preeclampsia. Exclusion criteria were: women who were unconscious or severely ill, those with learning difficulties or serious mental illness; major fetal abnormality; planned delivery within 7 days of randomization date; women with established preeclampsia; statin use within 28 days prior to randomization; women participating in another intervention study that influences the outcomes of this study and those with contraindications for statin therapy (see the Supplementary Appendix).

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, 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 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 Bayes theorem to combine a prior distribution, determined from maternal demographic characteristics and medical history, with likelihoods from biomarkers. In the prior model the risk of development of preeclampsia is increased with advancing maternal age, increasing weight, Black and South Asian racial origin, 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 35-37 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 (MoM) 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, MoM 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 using Bayes theorem by multiplying the *prior* probability density from maternal factors by the likelihood function from biomarker MoM 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 and in the random-sequence generation there was stratification according to participating center. Pravastatin tablets were procured and over-encapsulated by Mawdsley Brooks and Co; 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, Salford, UK.

The placebo capsules were identical to those of the pravastatin in parameters such as size, thickness, physical properties and appearance. After randomization, study participants were prescribed the investigational medicinal product, received instructions to take one 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 one 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 (see the Supplementary Appendix).[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 (FFIS) and by the Fetal Medicine Foundation were examined by one operator (AS) to determine if 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 and neonatal morbidity, neonatal therapy, 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 safety of pravastatin 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 36-38 and 39-40 weeks of gestation and at 6 weeks post-delivery and in one telephone interview at 37-39 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.

We assessed adherence by researchers 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 participants should have taken between the date of randomization and the date of the 41 weeks gestation or delivery if this occurred prior to 41 weeks.

## STATISTICAL ANALYSIS

The sample size estimation was based on the assumption that screening at 35-36 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 Supplementary Appendix. We calculated that enrolment of 1,020 participants would give the study a power of 90% to show a treatment effect at a two-sided alpha level of 5%. The target recruitment figure was inflated to 1,120 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 two-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 was performed according to subgroups categorized by estimated risk of preeclampsia, history of previous 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 analysed using 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 using analysis of covariance of the log-transformed concentrations adjusting for the baseline levels. Estimates and 95% confidence intervals 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 29,816 singleton pregnancies had screening and 3,490 (11.7%) were found to be at high-risk, but 385 (11.0%) of these were excluded from recruitment to the trial because they

did not fulfil the eligibility criteria (Fig. 1). Of the 3,105 eligible women, 1,120 (36.1%) agreed and 1,975 (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 S1 in the Supplementary Appendix; the characteristics of the two 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 29,816 pregnancies screened, 108 were lost to follow-up, 29 withdrew consent and 2 were terminated. Follow-up data were available for the remaining 29,677 (99.5%) and preeclampsia occurred in 720 cases (2.43%, 95% confidence interval, 2.25% to 2.60%). Screening performance is shown in Table S2 in the Supplementary Appendix. Excluding the 119 with preeclampsia at the time of screening, the detection rate for delivery with preeclampsia following screening was 75.0% (95% confidence interval, 71.4 to 78.5%) with a false positive rate of 9.9% (95% confidence interval, 9.6% to 10.3%).

**PRIMARY OUTCOME**

In the intention to treat population, preeclampsia occurred in 14.6% (80/548) participants in the pravastatin group and in 13.6% (74/543) in the placebo group. Allowing for the effect of risk at the time of screening and participating centre, the mixed effects Cox regression showed no evidence of an effect of pravastatin; hazard ratio (statin/placebo) 1.08 (95% confidence interval, 0.78 to 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 Fig. 2. There was no evidence of interaction between the effect of pravastatin, estimated risk of preeclampsia, previous pregnancy history, adherence and aspirin treatment (Fig. 3). Analysis of the per-protocol populations, with at least 80% compliance and with at least 80% compliance for at least seven days, gave essentially the same conclusions.

### SECONDARY OUTCOMES

The treatment effect for secondary outcomes, quantified as relative risks in the pravastatin group with 95% confidence interval 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 Fig. S1 in the Supplementary Appendix. 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 S3 and Fig. S2 and S3 in the Supplementary Appendix).

### ADVERSE EVENTS

In the pravastatin group there was at least one serious adverse event in 2 (0.4%) cases and at least one 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 S4 in the Supplementary Appendix). Muscle pains or cramps developed in six patients in the pravastatin group and in seven in the placebo group; creatine kinase concentrations were normal in all 13 cases.

### ADHERENCE

Adherence was ≥80% in 972 (89.1%) of the participants. There were no significant between-group differences in the degree of adherence (Table S5 in the Supplementary Appendix).

## DISCUSSION

In this multicenter, randomized, placebo-controlled trial involving women with singleton pregnancies who were identified by means of screening at 35-37 weeks of gestation as

being at high risk for term preeclampsia, the administration of pravastatin at a dose of 20 mg per day from 35-37 weeks of gestation until delivery did not reduce the incidence of delivery with preeclampsia than that with placebo. There was no evidence of interaction between the effect of pravastatin, estimated risk for preeclampsia, previous pregnancy history, adherence and aspirin consumption. Adherence was good, with reported intake of 80% or more 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.

The objective of this study was to investigate 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 by use of 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 thousand pregnancies screening for term preeclampsia identified 75% of subsequent deliveries with preeclampsia, at false positive rate of 10%. This finding provides prospective conformation 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 35-37 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 soluble fms-like tyrosine kinase-1 to placental growth factor ratio.[34] This method of screening could therefore be adopted in future studies investigating the potential value of alternative strategies for prevention of term preeclampsia, such as early delivery for the high-risk group.

The dose of 20 mg of 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 and / 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 per day 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 per day 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 anti-angiogenic 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) 1.08 (95% confidence interval: 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.

In conclusion, 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 per day from 35 to 37 weeks of gestation until delivery did not reduce the incidence of delivery with preeclampsia.

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**Supplementary material:** Definition of preeclampsia, Contraindications for statin therapy, Tables S1-S4, Figure S1.

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## FIGURE LEGENDS

**Figure 1.** Screening, Randomization and Follow-up.

**Figure 2.** Kaplan–Meier Plot of Cumulative Percentage of Participants Who Delivered with Preeclampsia.

Footnote: 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.

**Figure 3.** Subgroup Analysis of Hazard Ratio (statin/placebo) with 95% Confidence Intervals in Different Groups According to Estimated Risk for Preeclampsia, Obstetric History, Adherence and Aspirin Treatment. P values are given for the test of interaction with treatment.

**Table 1.** Characteristics of the Trial Participants.*

| Characteristic | Pravastatin Group (N=548) | Placebo Group (N=543) |
|---|---|---|
| Gestation at randomization – wk. Median (IQR) | 35.9 (35.4 - 36.1) | 35.9 (35.4 - 36.1) |
| Age – yr. Median (IQR) | 32.9 (28.6 - 36.9) | 32.5 (28.0 - 36.8) |
| Body mass index – kg/m$^2$. Median (IQR) | 30.5 (27.3 - 34.8) | 30.9 (27.2 - 34.9) |
| Race or ethnic group – no. (%)† | | |
| 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 – no. (%) | | |
| Natural | 513 (93.6) | 509 (93.7) |
| In vitro fertilization | 35 (6.4) | 34 (6.3) |
| Cigarette smoker – no. (%) | 26 (4.7) | 24 (4.4) |
| Mother had preeclampsia – no. (%) | 36 (6.6) | 43 (7.9) |
| Medical history – no. (%) | | |
| 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 mellitus type 1 | 3 (0.5) | 2 (0.4) |
| Diabetes mellitus type 2 | 11 (2.0) | 11 (2.0) |
| Obstetrical history – no. (%) | | |
| Nulliparous | 311 (56.8) | 319 (58.7) |
| Multiparous without preeclampsia | 209 (38.1) | 191 (35.2) |
| Multiparous with preeclampsia | 28 (5.1) | 33 (6.1) |
| Interval from last pregnancy – yr. Median (IQR) | 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 150mg/day – no. (%) | 92 (16.8) | 76 (14.0) |
| Screening for preeclampsia at 35-36 weeks | | |
| 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) |

* There is a balance on baseline variables between the two groups. IQR denotes interquartile range.

† Race and ethnic group were self-reported.

**Table 2.** Outcomes according to Trial Group.

| Outcome | Pravastatin Group (N=548) | Placebo Group (N=543) | | P value |
|---|---|---|---|---|
| **Primary outcome** | | | **Hazard ratio (95% CI)** | |
| Preeclampsia, no. (%) | 80 (14.6) | 74 (13.6) | 1.08 (0.78 - 1.49) | 0.65 |
| | | | | |
| **Secondary outcomes** | | | **Relative risk (95% CI)** | |
| Adverse outcomes at any gestation, no. (%) | | | | |
| 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 <5$^{th}$ 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 |
| | | | | |
| | **Pravastatin Group (N=536)** | **Placebo Group (N=530)** | **Relative risk (95% CI)** | |
| Adverse outcomes at ≥37 wk, no. (%) | | | | |
| 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 <5$^{th}$ 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 |
| | | | | |
| | **Pravastatin Group (N=548)** | **Placebo Group (N=543)** | **Relative risk (95% CI)** | |
| Neonatal outcomes, no. (%) | | | | |
| Small for gestational age <3$^{rd}$ percentile | 65 (11.9) | 55 (10.1) | 1.00 (0.72 - 1.40) | 1.00 |
| Small for gestational age <10$^{th}$ percentile | 118 (21.5) | 116 (21.4) | 0.99 (0.79 - 1.24) | 0.93 |
| Neonatal therapy, no. (%) | | | | |
| 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, no. (%) | | | | |
| 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) | - | - |
| Necrotising 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 |

CI = confidence interval

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 centre. Risk ratios were obtained from a log binomial regression adjusted for risk.

**Table 3.** Serious adverse events among trial participants. *

| **Serious adverse event** | **Pravastatin Group (N=548)** | **Placebo Group (N=543)** |
|---|---|---|
| | | |
| **Maternal serious adverse events** | | |
| Rupture of uterus and bladder | 0 | 1 |
| | | |
| **Fetal structural defects** | | |
| 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 one serious adverse event, no. (%)** | 2 (0.4) | 6 (1.1) |
| **No serious adverse event, no. (%)** | 546 (99.6) | 537 (98.9) |

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