ORIGINAL ARTICLE

Is low-dose aspirin therapy to prevent preeclampsia more efficacious in non-obese women or when initiated early in pregnancy?

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Abstract

Objective: Late timing of intervention and maternal obesity are potential explanations for the modest effect of aspirin for preeclampsia prevention. We explored whether low-dose aspirin (LDA) is more effective in women at increased risk when initiated before 16 weeks’ gestation or given to non-obese women.

Methods: Secondary analysis of a trial to evaluate LDA (60 mg/d) for preeclampsia prevention in high-risk women. Participants were randomized to LDA or placebo between 13 and 26 weeks. We stratified the effect of LDA on preeclampsia by (a) timing of randomization (<16 or ≥16 weeks gestation) and (b) body mass index (BMI) class (non-obese and obese). The Breslow–Day test for homogeneity was used to assess for variations in effect of LDA across gestational age and BMI groups.

Results: Of 2503 women, 461 (18.4%) initiated LDA <16 weeks. LDA effect was not better when initiated <16 weeks (RR: 0.93, 95% CI: 0.67–1.31) versus ≥16 weeks (RR: 0.90, 95% CI: 0.75–1.08), (p value for interaction = 0.87). Similarly, LDA effect was not better in non-obese (RR: 0.91, 95% CI: 0.7–1.13) versus obese women (RR: 0.89, 95% CI: 0.7–1.13), (p value for interaction = 0.85).

Conclusion: LDA for preeclampsia prevention was not more effective when initiated <16 weeks or used in non-obese women at risk for preeclampsia. No particular subgroup of women was more or less likely to benefit from LDA therapy.

Keywords

Aspirin, gestational age, obesity, preeclampsia, prevention

Introduction

Preeclampsia affects 5–8% of pregnancies and results in significant maternal and neonatal morbidity and mortality [1]. While the exact mechanism leading to preeclampsia remains unclear, endothelial dysfunction and activation of the coagulation system seems to play a role [2]. Therefore, multiple prior studies have evaluated anti-platelet agents, in particular, low-dose aspirin (LDA) therapy, for the prevention of preeclampsia. While some studies have demonstrated benefit [3–5], others have shown no effect of LDA in both low-risk, healthy women as well as in women at high risk for preeclampsia [6–8]. Meta-analyses of relevant trials suggest modest benefits (10–20% reduction or less in preeclampsia or other outcomes) [9,10]. Potential reasons to explain these mixed findings include late timing of initiation of therapy (after the first half of pregnancy) and the small dose (e.g. 50–150 mg) for participants in some studies.

In particular, the Cochrane review found a reduction in the risk of preeclampsia was similar for women randomized before 20 weeks gestation and those randomized after 20 weeks. In addition, the risk reduction was greater for women treated with >75 mg aspirin per day [RR: 0.64 (95% CI: 0.51–0.8)] compared with <75 mg/d [RR: 0.88 (95% CI: 0.81–0.95)] [9]. A second meta-analysis of individual patient data (PARIS) showed that no particular subgroup benefited more or less when aspirin was initiated before or after 20 weeks gestation or at doses < or >75 mg/d [10]. In contrast, the meta-analysis by Bujold et al. evaluated the effect of earlier initiation of LDA and found a 50% reduction in preeclampsia [RR: 0.47 (95% CI: 0.34–0.65)] when initiated <16 weeks gestation [11]. Over one-half of pregnant US women are overweight or obese, and excessive maternal weight is associated with a 2–5-fold increased risk of developing preeclampsia [1,12–14]. Since the daily prophylactic dose of aspirin evaluated is typically small, maternal obesity is a biologically plausible reason for the observed small or lack of benefit with respect to some clinical trials. Obesity is associated with a larger volume of distribution, increased liver blood flow and a state of glomerular hyperfiltration, all of which may impact drug metabolism and elimination [15].
In addition, obese patients have shown higher clearance values for drugs metabolized via cytochrome P450 CYP2C19, which is a mediator induced in the metabolism of aspirin [15,16].

A previous randomized placebo-controlled trial by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network evaluated the efficacy of LDA (60 mg/d) therapy for preeclampsia prevention in high-risk gravidas. No significant reduction in the incidence of preeclampsia was observed in the LDA therapy group [6]. However, these women were randomized at 13–26 weeks gestation (mean of 20 weeks), and their mean body mass index (BMI) was 29.8.

Given the potential implications of BMI and timing of initiation, we evaluated the hypotheses that LDA therapy may be more effective than placebo for preeclampsia prevention when initiated before 16 weeks versus later in gestation or when used in normal weight versus overweight or obese women.

Methods

We performed a secondary analysis of data from the aforementioned MFMU trial designed to evaluate the efficacy of LDA (60 mg/d) therapy for preeclampsia prevention in four groups of high-risk gravidas: pregestational diabetes, chronic hypertension, multiple gestations or prior preeclampsia. In the primary trial, 2539 women were enrolled from 1991 to 1995 and randomized to LDA (60 mg/d) versus placebo [6]. The database has been released to individual study sites, and IRB waiver was obtained at our institution. Participants received assigned treatment daily from randomization until delivery. Preeclampsia was defined as the development of hypertension (either a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg on two separate occasions at least four hours apart) plus one of the following in women who did not have hypertension or proteinuria at baseline: proteinuria (300mg in a 24-h collection or two dipstick-test results of ≥ 2+), thrombocytopenia (platelet count ≤ 100,000 per cubic millimeter) or pulmonary edema. The diagnosis of preeclampsia was also made in the presence of eclamptic convulsions or HELLP syndrome [6]. In women who had normal blood pressure but proteinuria at base line, the diagnosis of preeclampsia required the presence of thrombocytopenia, a serum aspartate aminotransferase concentration of ≥ 70 U per liter, or hypertension accompanied by either severe headaches, epigastric pain or a sudden increase in proteinuria (either five times the base-line value or twice base-line if the base-line value exceeded 5 g per 24 h) [6].

The effect of LDA on outcomes was compared separately for women who initiated treatment prior to 16 weeks versus those who initiated treatment at or beyond 16 weeks gestational age (GA), consistent with the study by Bujold et al. [11]. In addition, women were stratified by BMI (kg/m²) at randomization into two groups: non-obese women with BMI < 30 and obese women with BMI ≥ 30. Considering that weight is not perfectly correlated with BMI and that many drugs are given by weight-based dosing, rather than BMI-based dosing, we stratified by weight at randomization into two groups (< 200 pounds and ≥ 200 pounds). The incidence and relative risk of preeclampsia were compared by aspirin status within each sub-group.

Similar analyses were performed for both GA at randomization and BMI separately. We compared categorical variables using the chi-square test and continuous variables using the student t-test. In additional analyses, we compared BMI categories < 25, 25–29.9, 30–34.9 and ≥ 35 and examined interaction between aspirin use and BMI, weight and GA at randomization as continuous variables. The incidence, relative risk and 95% confidence interval relating the outcomes of interest to aspirin supplementation status within each subgroup were computed. For each outcome, the Breslow–Day test for homogeneity was used to estimate if there was a difference in treatment effect (aspirin versus placebo). Correlation coefficients were calculated to determine the relationship between aspirin and the continuous variables of BMI (1 kg/m²), weight (pound) and GA at enrollment (day). For all outcomes, a p value less than 0.05 was considered to indicate statistical significance. Analyses were performed using SAS software, version 9.2 (Cary, NC).

Results

A total of 2539 women were enrolled in the original trial, and outcome data were available for 2503 women. Of them, 461 (18.4%) initiated LDA therapy prior to 16 weeks’ GA with a mean GA of 14.5 weeks, while 2042 (81.6%) initiated LDA after 16 weeks with a mean GA of 21.4 weeks. There were 1254 (50.1%) women who received LDA and 1249 (49.9%) who received placebo with the treatment assignment similar in both GA groups. Baseline maternal characteristics at randomization between treatment groups stratified by GA at initiation are listed in Table 1. Women who received placebo in the early GA sub-group were more likely to be married compared to those who received aspirin therapy (p = 0.004). Otherwise, there were no significant differences between the two groups.

Similarly, for the effect of aspirin by BMI subgroup, of the 2503 women available in the cohort, outcome data were missing for 36 women and 24 were missing values for BMI, leaving 2479 women for analysis. There were 1243 women who received LDA and 1236 who received placebo. There were 1512 non-obese (mean BMI = 23.7) and 967 obese (mean BMI = 37.7) women. Patient characteristics at randomization between treatment groups within BMI categories are listed in Table 2; the mean GA at initiation of therapy was approximately 20 weeks.

The effect of LDA on preeclampsia by GA at initiation is listed in Table 3. Earlier, GA at initiation did not increase the effect of LDA on the risk of preeclampsia (Breslow–Day p value = 0.87). The results remained unchanged when the analyses were repeated separately for each of the four high-risk groups (all p values for homogeneity > 0.10) (shown in supplementary Table 1). There was no significant interaction between GA as a continuous variable and aspirin therapy (p = 0.39); i.e. as GA at randomization decreased, aspirin was not more beneficial.

As shown in Table 3, the effect of LDA on the risk of preeclampsia did not vary by BMI group: BMI < 30 (RR: 0.91, 95% CI: 0.7–1.13), BMI ≥ 30 (RR: 0.89, 95% CI: 0.7–1.13) and aspirin was not more beneficial in the non-obese
Table 1. Baseline characteristics between treatment groups within gestational age categories.

| GA < 16 weeks (n = 461) | GA ≥ 16 weeks (n = 2042) |
|-------------------------|-------------------------|
| Aspirin (n = 225)       | Aspirin (n = 1029)      |
| Placebo (n = 236)       | Placebo (n = 1013)      |
| **p value**             | **p value**             |
| Mean age (yr)*          | Mean age (yr)*          |
| 26.5 ± 6.2              | 26.6 ± 6.3              |
| 27.6 ± 6.2              | 26.6 ± 6.3              |
| Primigravida            | Primigravida            |
| 39 (17.3%)              | 196 (19.1%)             |
| 39 (16.5%)              | 192 (19.0%)             |
| Race                    | Race                    |
| Black                   | Black                   |
| 132 (58.7%)             | 594 (57.7%)             |
| Hispanic                | Hispanic                |
| 14 (6.2%)               | 112 (10.9%)             |
| White/other             | White/other             |
| 79 (35.1%)              | 323 (31.4%)             |
| BMI*                    | BMI*                    |
| 29.3 ± 8.1              | 29.0 ± 8.5              |
| Smoker                  | Smoker                  |
| 34 (15.1%)              | 180/1027 (17.5%)        |
| Alcohol                 | Alcohol                 |
| 4/223 (1.8%)            | 35/1021 (3.4%)          |
| GA at randomization (week)* | GA at randomization (week)* |
| 14.5 ± 1.0              | 21.4 ± 3.2              |
| High school or greater  | High school or greater  |
| 170 (75.6%)             | 726 (70.6%)             |
| Married                 | Married                 |
| 76 (33.8%)              | 405 (39.4%)             |
| GDM                     | GDM                     |
| 22 (9.8%)               | 89 (8.7%)               |
| Diabetes                | Diabetes                |
| 76 (33.8%)              | 154 (15.0%)             |
| Chronic hypertension    | Chronic hypertension    |
| 71 (31.6%)              | 310 (30.1%)             |
| Multiple gestation      | Multiple gestation      |
| 20 (8.9%)               | 318 (30.9%)             |
| Prior preeclampsia      | Prior preeclampsia      |
| 58 (25.8%)              | 247 (24.0%)             |

*Mean ± SD.
GA = gestational age and GDM = gestational diabetes mellitus.

Table 2. Baseline characteristics between treatment groups within BMI categories.

| BMI < 30 (n = 1512) | BMI ≥ 30 (n = 967) |
|----------------------|---------------------|
| Aspirin (n = 756)    | Aspirin (n = 487)   |
| Placebo (n = 756)    | Placebo (n = 480)   |
| **p value**          | **p value**         |
| Mean age (year)*     | Mean age (year)*    |
| 25.6 ± 6.2           | 28.1 ± 6.1          |
| 26.0 ± 6.3           | 27.9 ± 6.1          |
| Primigravida         | Primigravida        |
| 167 (22.1%)          | 65 (13.4%)          |
| 151 (20.0%)          | 76 (15.8%)          |
| Race                 | Race                 |
| Black                | Black                |
| 398 (52.7%)          | 325 (66.7%)         |
| Hispanic             | Hispanic             |
| 80 (10.6%)           | 44 (9.0%)           |
| White/other          | White/other         |
| 278 (36.8%)          | 118 (24.2%)         |
| BMI*                 | BMI*                 |
| 23.7 ± 3.3           | 37.5 ± 6.8          |
| Smoker               | Smoker               |
| 135/755 (17.9%)      | 75/486 (15.4%)      |
| Alcohol              | Alcohol              |
| 23/751 (3.1%)        | 16/482 (3.3%)       |
| GA at randomization (week)* | GA at randomization (week)* |
| 20.4 ± 3.9           | 19.8 ± 3.9          |
| High school or greater | High school or greater |
| 528 (69.8%)          | 360 (73.9%)         |
| Married              | Married              |
| 297 (39.3%)          | 177 (36.3%)         |
| GDM                  | GDM                  |
| 25 (3.3%)            | 83 (17.0%)          |
| Diabetes             | Diabetes             |
| 154 (20.4%)          | 75 (15.4%)          |
| Chronic hypertension | Chronic hypertension |
| 153 (20.2%)          | 224 (46.0%)         |
| Multiple gestation   | Multiple gestation   |
| 254 (33.6%)          | 81 (16.6%)          |
| Prior preeclampsia   | Prior preeclampsia   |
| 195 (25.8%)          | 107 (22.0%)         |

*Mean ± SD.
GA = gestational age and BMI = body mass index.

Table 3. Effect of low-dose aspirin on the incidence of preeclampsia stratified by timing of initiation and BMI in high-risk women.

| Incidence of preeclampsia | Aspirin (N = 1254) | Placebo (N = 1249) | Relative risk (95% CI) | Breslow–Day p value |
|---------------------------|--------------------|--------------------|------------------------|---------------------|
| < 16 weeks                | 49/225 (21.8%)     | 55/236 (23.3%)     | 0.93 (0.67–1.31)       | 0.87                |
| ≥ 16 weeks                | 182/1029 (17.7%)   | 199/1013 (19.6%)   | 0.90 (0.75–1.08)       | 0.85                |
| BMI < 30                  | 131/756 (17.3%)    | 144/756 (19.1%)    | 0.91 (0.7–1.13)        | 0.85                |
| BMI ≥ 30                  | 97/487 (19.9%)     | 108/480 (22.5%)    | 0.89 (0.7–1.13)        | 0.85                |

GA = gestational age and BMI = body mass index.
(p value for interaction = 0.85). When BMI was further stratified into the four sub-categories, LDA was not more effective in lower BMI groups (p value for interaction = 0.25) (Supplementary Table 2). The results remained unchanged when the analyses were repeated separately for each of the four high-risk groups (all p values for homogeneity ≥ 0.05) (Supplementary Table 3). To further investigate whether a more beneficial effect exists when overweight patients are considered separately from the other groups, we examined the interaction between aspirin use and weight. The effect of LDA on the risk of preeclampsia did not vary by group: weight < 200 pounds (RR: 1.0, 95% CI: 0.8–1.2), weight ≥ 200 pounds (RR: 0.7, 95% CI: 0.5–1.0) (p value for interaction = 0.12; Supplementary Table 4). There was no significant interaction between BMI or weight as a continuous variable and aspirin therapy (p = 0.77 and p = 0.68, respectively).

**Discussion**

The findings of this secondary analysis do not support our hypotheses that prophylactic LDA may be more beneficial for preeclampsia prevention if initiated at an earlier GA (<16 weeks) or when used in non-obese as opposed to overweight or obese women.

Regarding GA at initiation, our observations are consistent with the Cochrane review which showed little evidence of difference in the incidence of preeclampsia in studies with LDA initiated prior to 20 weeks compared to those studies initiated at 20 weeks or greater GA [9]. In addition, the PARIS meta-analysis did demonstrate an overall 10% decrease in the incidence of both preterm birth and preeclampsia with prophylactic LDA; similarly, there was no additional benefit of LDA when started before 20 weeks’ gestation [10].

Our findings are in contrast with the meta-analysis by Bujold et al., which found benefit of LDA therapy when initiated <16 weeks gestation (RR: 0.47, 95% CI: 0.34–0.65), while a more modest non-significant reduction was seen in studies that started therapy after 16 weeks gestation (RR: 0.81, 95% CI: 0.63–1.03) [11]. This study, however, included a high-risk population heavily weighted toward women with abnormal uterine artery Dopplers [17].

In addition, two more recent meta-analyses by Roberge et al. show that LDA administered at or prior to 16 weeks gestation reduces the risk of preterm preeclampsia (RR: 0.11, 95% CI: 0.04–0.33) as well as severe preeclampsia (RR: 0.22, 95% CI: 0.08–0.57), but not mild preeclampsia (RR: 0.98, 95% CI: 0.42–2.33) or preeclampsia, which develops at term (RR: 0.81, 95% CI: 0.33–1.96 [18,19]). Due to sample size limitations, we did not specifically examine early onset preeclampsia or severe preeclampsia as outcomes.

There is little in the literature regarding the effect of LDA therapy according to BMI status. Obese women are at increased risk for the development of preeclampsia [12,14,20]. In addition, obesity and preeclampsia share similar pathophysiological features including endothelial dysfunction, oxidative stress and an increased state of inflammation [12,21]. Thus, while it is plausible that non-obese women may benefit the most from LDA therapy from a dose-distribution perspective, alternatively, it is also possible that obese women could benefit disproportionately considering the pathogenesis. The meta-analysis of individual patient data (PARIS) did not assess the effect of LDA on BMI subgroups, since BMI data were often missing from the original trials [22]. Although our study is likely underpowered to detect a statistically significant difference, the relative risks of the subgroups do not suggest even a trend towards better efficacy of LDA in the non-obese or normal weight women suggesting that using a higher dose of aspirin is unlikely to be more beneficial.

Overall, in women at high-risk of developing preeclampsia, the effect of LDA therapy on the incidence of preeclampsia (any) does not appear to be enhanced by earlier initiation (prior to 16 weeks GA) or absence of obesity with doses of aspirin as low as 60 mg. Although not statistically significant, the results for the subgroups of GA and BMI (RR: 0.9–0.93) do suggest modest benefits of low dose aspirin consistent with those reported in large meta-analyses.

The main limitation of this study is the fact that it is a secondary analysis of a trial that was not designed originally to evaluate these particular interactions. Thus, the power to fully delineate small interactions is limited. Although the likelihood of a chance finding is increased, we did not observe any significant interactions. Individual patient data meta-analyses evaluating the role of BMI and outcomes such as early onset preeclampsia and severe preeclampsia are needed to further clarify the role of timing of therapy and obesity.

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**Declaration of interest**

The authors report no declarations of interest.

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