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Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU High-Risk Aspirin Study

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Abstract

OBJECTIVE—Early initiation of low-dose aspirin (LDA) may reduce preeclampsia risk. We sought to determine whether LDA was beneficial when initiated <17w0d, within a trial of high-risk women enrolled <26w0d.

STUDY DESIGN—Secondary analysis of the Maternal-Fetal Medicine Units High-Risk Aspirin study, including women enrolled <17w0d, randomized to LDA (60 mg day^{-1}) or placebo with chronic hypertension (CHTN, $n = 186$), diabetes ($n = 191$) or prior preeclampsia ($n = 146$). The primary outcome was preeclampsia at any time in pregnancy, secondary outcomes were early preeclampsia (<34w0d), late preeclampsia ($\geqslant$34w), small for gestational age (SGA; neonatal birthweight <10th %) and composite (early preeclampsia or SGA). Outcomes were compared by exact X^2-tests.

RESULTS—Baseline characteristics were similar between treatment groups. Aspirin was associated with a lower rate of late-onset preeclampsia $\geqslant$ 34w (17.36% vs 24.42%, $P = 0.047$), with a 41% reduction in women with CHTN (18.28% vs 31.18%, $P = 0.041$). There were no other significant differences in the outcome.

CONCLUSION—Aspirin initiated <17w0d reduced the risk for late-onset preeclampsia by 29% supporting the practice of early initiation of aspirin in high-risk women.

INTRODUCTION

Preeclampsia, which affects 2.8% of the pregnancies worldwide,[1,2] remains a major cause of maternal and fetal morbidity. The exact etiology of preeclampsia remains uncertain and there is currently no clear prevention strategy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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In pregnancies complicated by preeclampsia and intrauterine growth restriction, shallow vascular invasion of maternal spiral arteries limits transformation of maternal vasculature into high-volume low-resistance vessels, which leads to subsequent uteroplacental under perfusion. It is hypothesized that placental blood flow may be further decreased by a combination of factors, including activation of the coagulation cascade, platelet aggregation and endothelial dysfunction, thought to be mediated in part by an imbalance of prostacyclin and thromboxane A2.[3–5] In vascular conditions such as chronic hypertension (CHTN), a baseline increase in the systemic inflammation is also thought to predispose women to the development of preeclampsia.[6]

As a modulator of platelet function and inflammation, aspirin given in low doses (60 to 150 mg)[7] has been studied as a potential target for the prevention of preeclampsia and fetal growth restriction. In low doses, aspirin selectively decreases thromboxane A2 (a mediator of vasoconstriction and platelet aggregation) without significantly affecting prostacyclin levels (which have a smooth muscle-relaxing effect). Aspirin also inhibits platelet aggregation.[7–9]

The gestational age at which low-dose aspirin (LDA) is initiated may be crucial to the reduction in preeclampsia risk. In the High-Risk Aspirin (HIRA) Study performed by the Maternal-Fetal Medicine Units (MFMU) Network in 1998 in which women were enrolled up to 26w, there was no reduction in preeclampsia risk with LDA.[10] Subsequent meta-analyses suggested that LDA is effective only when initiated at 16 weeks of gestation or less.[7,11]

Within the large, well-designed MFMU HIRA, we sought to validate the hypothesis that LDA serves a protective role against preeclampsia when initiated prior to 17w0d, and to further characterize which women most benefit from LDA prophylaxis in pregnancy.

METHODS

This is a secondary analysis of the MFMUs Network HIRA, approved by the Colorado Multiple Institutional Review Board. The HIRA trial was a randomized placebo-controlled trial performed at 12 medical centers within the United States (1991 to 1995) designed to determine whether LDA initiated at 13 to 26 weeks improved the pregnancy outcome in women at high risk for preeclampsia.[10]

Within the released HIRA dataset, we identified women enrolled prior to 17w0d who met criteria for enrollment based on preexisting diabetes mellitus, CHTN or a history of preeclampsia in a previous pregnancy. Chronic hypertension was defined by the use of an anti-hypertensive agent, or a resting blood pressure $\geqslant$ 140/90 mm Hg on two occasions at least 4 h apart, either prior to pregnancy or during pregnancy prior to 20 weeks gestation. Women with hypertension and diabetes were included in the diabetes group. A history of preeclampsia was determined by review of the medical record (with new onset proteinuria and hypertension), or an oral history of preeclampsia with delivery prior to 37 weeks. Further details of enrollment criteria and exclusion criteria are published.[10] After providing informed consent, women were randomized to receive aspirin (60 mg) or placebo daily.

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Our primary outcome was preeclampsia at any time point in pregnancy. Our secondary outcomes were late-onset preeclampsia (delivery on or after 34w0d), early-onset preeclampsia (delivery <34w0d), delivery of a small for gestational age neonate (SGA, <10%) or a composite outcome (early preeclampsia or SGA). The criteria for preeclampsia were those used in the original study. Preeclampsia was defined as the development of hypertension (either systolic blood pressure $\geqslant$ 140 mm Hg or diastolic blood pressure $\geqslant$ 90 mm Hg on two occasions at least 4 h apart) plus one of the following: proteinuria, thrombocytopenia or pulmonary edema. Proteinuria was defined as a 24-h urine collection with $\geqslant$ 300 mg or a dipstick test with 2+ proteinuria ($\geqslant$100 mg dl^{-1}) on two occasions at least 4 h apart, without any evidence of a urinary tract infection. Thrombocytopenia was defined as a platelet count of <100 000 mm^{-3}. Eclamptic seizures and HELLP also satisfied the diagnostic criteria for preeclampsia. In women with preexisting hypertension or proteinuria, the criteria for diagnosis of preeclampsia differed slightly, as previously described.[10] An infant was considered small for gestational age at birth if its weight was below the 10th percentile for gestational age based on normative birth weights for singletons.[10,12]

Demographics characteristics and outcome variables were compared using exact X^2-tests for categorical variables, and *t*-tests for continuous measures. Outcome comparisons were performed for the entire study group, and within each subgroup using the exact X^2-test (diabetes mellitus, CHTN and history of preeclampsia). Significance was defined as alpha of 0.05.

RESULTS

Within the HIRA study group, 523 women initiated LDA prior to 17w0d, including 186 women with CHTN, 191 with diabetes and 146 with a history of preeclampsia in a prior pregnancy. Within the original analysis, outcome data could not be obtained on 1% of women in each of the aspirin and placebo groups.[10] Demographic characteristics did not differ among aspirin and placebo groups. (Table 1)

The overall rate of preeclampsia was 25%. There was no significant difference in our primary outcome of preeclampsia at any time in pregnancy between the aspirin and placebo groups (22.26% vs 27.52%, $P = 0.164$). (Table 2) Among our secondary outcomes of late preeclampsia ($\geqslant$34w), early preeclampsia (<34w), SGA and the composite (early preeclampsia or SGA), only the rate of late preeclampsia was significantly reduced by aspirin use (17.36% vs 24.42%, $P = 0.047$). (Table 2)

When the analysis was repeated by subgroup (CHTN, diabetes mellitus, and history of preeclampsia in a prior pregnancy), a significant benefit of aspirin was seen only in women with CHTN (18.28% vs 31.18%, $P = 0.041$). In women with a history of preeclampsia in a prior pregnancy, the risk for fetal SGA was 60% lower with LDA (6.41% vs 14.71%), although this difference did not reach significance ($P = 0.086$).

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DISCUSSION

Within this large randomized-controlled MFMU trial (HIRA), LDA initiated prior to 17 weeks reduced the risk for late-onset preeclampsia (⩾34w) in women at increased risk for preeclampsia. This result was driven primarily by the effect seen in women with CHTN. Given the relative safety of LDA in pregnancy,[13,14] our findings support early initiation of LDA for women at risk for preeclampsia, particularly those with CHTN.

Our results differed from the original MFMU HIRA study which found no reduction in preeclampsia risk with LDA. The difference in our results is likely because of the timing of enrollment. Although the original study enrolled women up to 26 weeks gestational age, the current analysis included women enrolled prior to 17w0d. The importance of early initiation of LDA is supported by two more recent meta-analyses which found a protective benefit of LDA only when initiated at 16 weeks of gestation or less (but not after).[7,11] The reason LDA was not associated with improvement in preeclampsia risk in the original analysis may have been the inclusion of patients enrolled from 17 to 26 weeks gestation. Although the mechanism by which LDA reduces the risk of preeclampsia is uncertain, it is hypothesized that LDA improves the balance between thromboxane A2 and prostacyclin, protecting against thromboxane-mediated vasoconstriction and abnormal coagulation within the placenta.[4] The protective benefit of LDA seen in early pregnancy may be lost with the switch in placental vascular development from proliferation to endothelial remodeling at mid-gestation.[15] In addition, the original MFMU trial included women with multiple pregnancies. We did not include women with multiple pregnancies secondary to our presumption that the pathophysiology of preeclampsia in multiple pregnancies is likely related to a relatively large placental size[16] (rather than from early abnormalities in placental development leading to placental ischemia later in pregnancy).

We expected to see a reduction in our secondary outcome of early preeclampsia prior to 34 weeks, based on prior studies suggesting that early LDA use was associated with a reduction in severe preeclampsia[7] and preeclampsia prior to 34w.[13] We did not find a reduction in our primary outcome of preeclampsia overall or ‘early’ preeclampsia (<34w), although many cases of preeclampsia diagnosed after 34w in this analysis may have been severe as the distinction between mild and severe preeclampsia was not made within the original study. Instead we found a reduction in ‘late’ preeclampsia (with delivery after 34 weeks), which coincides with a growing body of evidence distinguishing early vs late preeclampsia, including differing risk factors,[17] patterns of vascular remodeling,[18] placental pathology[19] and first trimester metabolomic signatures.[20] The reduction in late but not early preeclampsia differs from a recent meta-analysis in which early initiation of aspirin was associated with a reduction in early but not late preeclampsia; that analysis defined early preeclampsia as delivery as <37w (compared with <34w in the current analysis).[21]

We expected to see a reduction in our secondary outcome of growth restriction based on meta-analysis data suggesting a reduction in SGA birthweights with initiation of LDA at 16 weeks of gestation or less[7] and the common theory that preeclampsia and SGA originate from early abnormalities in early placental development. LDA did not improve SGA without our analysis overall; women with a history of preeclampsia in a prior pregnancy had a 60%

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lower rate of SGA in the LDA group, although this finding did not reach statistical significance. Although small sample sizes may have affected our analysis, it is conceivable that LDA does not protect against growth restriction; this conclusion was reached by a number of prior studies.[10–14,22,23]

When we evaluated the effects of early LDA on pregnancy outcome by enrollment subgroup, only women with CHTN appeared to benefit from LDA (with reduction in late preeclampsia risk). The benefit of LDA may be because of the early improvement in spiral artery remodeling during early placental development, or alternately because of the modulation of the heightened systemic inflammation seen in patients with chronic vascular conditions such as hypertension, which is thought to predispose women to the development of preeclampsia.[6] In pregnant women with CHTN, there is greater reactivity within the platelet thromboxane A2 pathway,[23] a pathway which is modulated by LDA,[24] supporting the biologic plausibility of our findings. The limited number of patients in the early preeclampsia group (21 overall, including nine women with CHTN) may have limited our power to determine whether aspirin was beneficial against this outcome.

The strength of this study lies in the analysis of data from a single large randomized-controlled trial, as the hypothesis that early initiation of LDA improves outcome was previously based on meta-analyses of smaller studies with differing methodologies.[7,13] The multicentered randomized nature of the trial improves generalizability, although we had a larger proportion of African-American women (>50%) than the general population. Our results were limited by the retrospective nature of this analysis which did not allow us to distinguish potentially relevant outcomes (such as mild vs severe preeclampsia, and constitutionally small vs pathologically small neonatal growth parameters). In addition, we faced sample size limitations within our subgroup analyses owing to the restriction in gestational age at enrollment to <17w0d. This may have affected the clinical comparability of our subset analyses. Current gaps in our knowledge include the mechanism of LDA in reducing the risk of preeclampsia, and the means to efficiently and effectively identify women who may benefit early from LDA prophylaxis.

In summary, LDA reduced the risk of late-onset preeclampsia in high-risk women when initiated early in pregnancy. To optimize pregnancy outcome in women at increased risk for preeclampsia (particularly those with CHTN), our findings support initiation of LDA prior to 17w0d. These findings may be useful for the development of subsequent management guidelines by the American College of Obstetricians and Gynecologists, which currently recommends LDA only in women with a history of preeclampsia in a prior pregnancy.[25]

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Table 1

Characteristics of study participants by treatment group

Characteristic	Aspirin *n* = 265	Placebo *N* = 258	*P*-value
Age, mean (s.e.), years	26.7 (0.38)	27.5 (0.36)	0.107
Enrollment subgroup			
Diabetes	94 (35.47)	97 (37.60)	0.723
Chronic hypertension	93 (35.09)	93 (36.05)	
Preeclampsia in a prior pregnancy	78 (29.43)	68 (26.36)	
Gestational age at randomization, mean (s.e.), days	106 (0.49)	106 (0.50)	0.684
Proteinuria, mean (s.e.)			
<300 mg per 24 h	69 (70.41)	59 (67.82)	0.751
⩾ 300 mg per 24 h	29 (29.59)	28 (32.18)	
Gravidity			
1	42 (15.85)	42 (16.28)	0.906
2+	223 (84.15)	216 (83.72)	
Parity (deliveries>20 weeks)			
0	70 (26.42)	62 (24.03)	0.547
1+	195 (73.58)	196 (75.97)	
Number of miscarriages, mean (s.e.)	0.52 (0.06)	0.48 (0.06)	0.651
History of smoking			
No	211 (79.62)	203 (78.99)	0.729
Quit at pregnancy	17 (6.42)	21 (8.17)	
Yes	37 (13.96)	33 (12.84)	
Total years of regular school, mean (s.e.)	12.1 (0.14)	12.0 (0.17)	0.572
BMI, mean (s.e.)			
<18.5	4 (1.52)	4 (1.56)	0.583
18.5–24.9	86 (32.58)	71 (27.63)	
25–29.9	52 (19.70)	61 (23.74)	
30+	122 (46.21)	121 (47.08)	
Predominant race			
White	94 (35.47)	96 (37.21)	0.558
Hispanic	21 (7.92)	22 (8.53)	
Black	150 (56.60)	138 (53.49)	
Other	0 (0.00)	2 (0.78)	
Infant birthweight, mean (s.e.), grams	3159 (50.05)	3144 (50.22)	0.832
Sex of infant			
Male	136 (51.32)	124 (48.06)	0.485
Female	129 (48.68)	134 (51.94)	

Abbreviation: BMI, body mass index (kg/M*M). Results are presented as n (%) unless otherwise stated. We used a t-test for continuous data and X^2-test for categorical data.

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Table 2

Differences in pregnancy outcomes with early initiation of low-dose aspirin

Outcome	Aspirin	Placebo	*P*-value
Overall	*N* = 265	*N* = 258	
Preeclampsia	59 (22.26)	71 (27.52)	0.164
'Late' preeclampsia, delivery ⩾ 34w	46 (17.36)	63 (24.42)	0.047
'Early' preeclampsia, delivery <34w	13 (4.91)	8 (3.10)	0.293
SGA	15 (5.66)	23 (8.91)	0.152
Composite: 'early' preeclampsia or SGA	25 (9.43)	28 (10.85)	0.591
Diabetes mellitus	*N* = 94	*N* = 97	
Preeclampsia	17 (18.09)	21 (21.65)	0.537
'Late' preeclampsia, delivery ⩾ 34w	12 (12.77)	18 (18.56)	0.272
'Early' preeclampsia, delivery <34w	5 (5.32)	3 (3.09)	0.443
SGA	3 (3.19)	3 (3.09)	0.969
Composite: 'early' preeclampsia or SGA	7 (7.45)	6 (6.19)	0.729
Chronic hypertension	*N* = 93	*N* = 93	
Preeclampsia	23 (24.73)	32 (34.41)	0.148
'Late' preeclampsia, delivery ⩾ 34w	17 (18.28)	29 (31.18)	0.041
'Early' preeclampsia, delivery <34w	6 (6.45)	3 (3.23)	0.305
SGA	8 (8.60)	11 (11.83)	0.468
Composite: 'early' preeclampsia or SGA	13 (13.98)	12 (12.90)	0.83
History of preeclampsia	*N* = 78	*N* = 68	
Preeclampsia	19 (24.36)	18 (26.47)	0.77
'Late' preeclampsia, delivery ⩾ 34w	17 (21.79)	16 (23.53)	0.803
'Early' preeclampsia, delivery <34w	2 (2.56)	2 (2.94)	0.889
SGA	4 (5.13)	9 (13.24)	0.086
Composite: 'early' preeclampsia or SGA	5 (6.41)	10 (14.71)	0.1

Abbreviations: SGA, small for gestational age; w, weeks. We compared outcomes using exact X^2-test. Results are presented as n (%). We used X^2-test.