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Impact of Aspirin Supplementation for Pre-Eclampsia Prevention on Neonatal Outcomes

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ABSTRACT

Introduction. Pre-eclampsia negatively affects pregnancy. In 2018, the American College of Obstetricians and Gynecologists (ACOG) updated their low dose aspirin (LDA) supplementation recommendation to include pregnant women at moderate risk for pre-eclampsia. In addition to the potential benefit of LDA supplementation for delaying or preventing pre-eclampsia, LDA supplementation can affect neonatal outcomes. The association of LDA supplementation was studied with six neonatal outcomes in a sample of mostly minority pregnant women from Hispanic and Black race/ethnicities that included those of low, moderate, and high-risk designation for pre-eclampsia.

Methods. This was a retrospective study of 634 patients. The main predictor variable was maternal LDA supplementation for six neonatal outcomes: NICU admission, neonatal readmission, one- and five-minute Apgar scores, neonatal birth weight (BW), and hospital length of stay (LOS). Demographics, comorbidities, and maternal high- or moderate-risk designation were adjusted for per ACOG guidelines.

Results. High-risk designation was associated with neonatal increased rate of NICU admission (OR: 3.80, 95% CI: 2.02, 7.13, $p < 0.001$), LOS ($B = 0.15$, $SE = 0.04$, $p < 0.001$), and decreased BW ($B = -442.10$, $SE = 75.07$, $p < 0.001$). No significant associations were found with LDA supplementation or moderate-risk designation for NICU admission, readmission, low one- and five-minute Apgar scores, BW, and LOS.

Conclusions. Clinicians recommending maternal LDA supplementation should be aware that LDA supplementation did not appear to provide any benefits for the above neonatal outcomes.

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INTRODUCTION

Pre-eclampsia affects approximately 4.6% of pregnancies worldwide.[1] In 2013, the American College of Obstetricians and Gynecologists (ACOG) recommended supplementation with low-dose aspirin (LDA) for pregnant women at high risk for pre-eclampsia to delay or prevent pre-eclampsia.[2] In 2018, ACOG updated their LDA supplementation recommendation to include pregnant women at moderate risk for pre-eclampsia. Meta-analyses on the benefits of LDA supplementation for patients at risk for development of pre-eclampsia revealed a 10% to 30% reduction in the risk of pre-eclampsia.[3,4]

In addition to the potential benefit of LDA supplementation for delaying or preventing pre-eclampsia, LDA supplementation can affect neonatal outcomes.[5-7] A meta-analysis revealed that LDA was associated with decreased risk for low birth weight.[5] Although LDA supplementation did not affect neonatal intensive care unit (NICU) admission, it decreased length of stay for those admitted to the NICU.[6] Furthermore, LDA supplementation was associated with decreased incidence of low five-minute Apgar scores.[7]

When studying how LDA supplementation can affect neonatal outcomes, it is important to consider relevant demographic and comorbid covariates that can affect neonatal outcomes. Increased maternal age was associated with increased NICU admission.[8] There was conflicting evidence on the impact of maternal age on neonatal birth weight with some showing increased risk of low birth weight in women greater than 35 years,[9] while others showed an increased risk of fetal macrosomia in women greater than 35 years.[10] With regard to race/ethnicity, in a sample of mothers with preexisting chronic hypertension, Hispanic and non-Hispanic Black mothers were more likely to have neonatal NICU admissions, low five-minute Apgar score, and decreased birth weight as compared to non-Hispanic White patients.[11]

Smoking in pregnancy has been implicated in fetal growth restriction,[12] low one-minute Apgar and five-minute Apgar scores,[13] increased risk for NICU admission, and increased length of hospital stay.[14] Maternal body mass index (BMI) and its relationship with neonatal birth weight is multidirectional with BMI greater than 23.7 showing an association with large for gestational age and fetal macrosomia versus BMI greater than 31 showing an association with growth restriction.[15] Maternal obesity also was associated with increased risk for low five-minute Apgar scores and higher NICU admission rates.[16,17] Maternal diabetes in pregnancy was associated with increased neonatal birth weight, increased rates of NICU admission, and increased length of hospital stay,[18,19] but not associated with one-minute and five-minute Apgar scores.[20] Maternal hypertension in pregnancy was associated with lower neonatal birth weight,[21] low one-minute and five-minute Apgar scores,[22] higher rates of NICU admission,[23] and longer length of neonatal stay in hospital.[23]

The latest ACOG guidelines for LDA supplementation included approximately 23% of pregnant women as eligible for LDA supplementation which included not only those at high-risk designation for pre-eclampsia, but also those at moderate-risk.[24] It would be useful to study how LDA supplementation affects neonatal outcomes for these women now eligible for LDA supplementation. In addition, LDA supplementation appeared to have a varied impact among different race/ethnicities, as LDA supplementation reduced recurrent pre-eclampsia in Hispanic women but not in Black women.[25] Furthermore, we are unaware of any studies on LDA supplementation and its association with the neonatal outcomes for hospital length of stay (LOS), hospital readmission, and one-minute Apgar score. Thus, the association of LDA supplementation was studied with the six neonatal outcomes of LOS in hospital, NICU admission, hospital readmission, birth weight, one-minute Apgar score, and five-minute Apgar score in a sample of mostly minority pregnant women from Hispanic and Black race/ethnicities.

METHODS

This was a retrospective study of 634 patients at a public county hospital in Long Island, a suburb of New York City, from January 2018 through April 2021. The study included patients who delivered at this hospital and who met ACOG criteria for aspirin prophylaxis for either moderate risk or high risk of developing pre-eclampsia. The study excluded patients with pre-existing coagulation disorder, cardiac disease, chronic pulmonary disease, chronic hepatic disease, thrombocytopenia, or thyroid disorder. The study was conducted ethically and was approved by the hospital Institutional Review Board. A waiver of informed consent was obtained due to the retrospective nature of the study.

Inclusion criteria for high or moderate risk of developing pre-eclampsia was established based upon the ACOG and United States Preventative Service Task Force (USPSTF) guidelines.[26] High risk is defined as having one or more of: a personal history of pre-eclampsia, multifetal gestation, pre-existing renal disease, autoimmune disease, pre-existing type I or II diabetes, and/or pre-existing chronic hypertension. Moderate risk is defined as having two or more of: first pregnancy, maternal age 35 years or older, pre-pregnancy BMI greater than 30, family history of pre-eclampsia, and/or low socioeconomic status.

The main predictor variable was maternal LDA supplementation (no/yes). Demographic variables were maternal age (years) and maternal race/ethnicity (White, Black, Hispanic, other). Comorbidity variables were pre-pregnancy BMI (kg/m^2), and pre-pregnancy smoker, gestational diabetes, gestational hypertension, and pre-eclampsia; all measured as no versus yes.

The primary outcome variable was NICU admission (no/yes). Secondary outcome variables were one-minute Apgar score (≥ 7 versus < 7), five-minute Apgar score (≥ 7 versus < 7), birth weight (grams), neonatal hospital LOS (days), and neonatal hospital readmission within six weeks of discharge (no/yes). Sample size for the two outcome variables of hospital readmission and LOS were only 512 of the total sample due to misplaced pediatric census records during facility reorganization required for the COVID-19 pandemic.

Mean and standard deviation were used to describe the continuous variables. Frequency and percentage were used to describe the categorical variables. Analysis of variance compared the continuous variables. The Pearson chi square test compared the categorical variables except when expected cell size was < 5 where the Fisher's exact test was used. LOS was logarithmic transformed due to presence of skewness. All variables statistically significant in the univariate comparisons between those with and without maternal LDA supplementation from the demographic, comorbidity, and risk designation variables were included as covariates in the multivariate linear regression or logistic regression analyses. This is the typical approach used to statistically adjust for variables that differ between the main predictor variable groups in an observational study that has a number of potential confounder variables. All p values were two tailed with alpha level of $p < 0.05$. IBM SPSS Statistics version 28 was used for the analyses (IBM Corporation, Armonk, NY, 2021).

RESULTS

Comparisons of study groups for the sample characteristics are listed in Table 1. The significant differences observed between those that received aspirin compared to those that did not were a greater mean age ($p < 0.001$), a greater percentage of Blacks ($p < 0.001$), a greater mean BMI ($p < 0.001$), a greater percentage diagnosed with pre-eclampsia ($p < 0.001$), and a greater percentage of those at high-risk for pre-eclampsia ($p < 0.001$).

Table 2 shows univariate comparisons for the outcomes. Mean birth weight significantly differed ($p = 0.02$) where those who received aspirin had a lower mean than those who did not receive aspirin. Mean LOS significantly differed ($p = 0.01$) where those who received aspirin had a greater mean than those who did not receive aspirin. One-minute Apgar score, five-minute Apgar score, NICU admission, and hospital readmission did not differ significantly between those who received and did not receive aspirin.

Table 3 shows the multivariate logistic regression analyses for NICU admission and hospital readmission. Receiving aspirin was not associated significantly with NICU admission. Among the covariates adjusted for in the analysis, increased age was associated significantly with decreased odds for NICU admission ($p = 0.01$) while being high risk for pre-eclampsia was associated significantly with increased odds for NICU admission ($p < 0.001$). Receiving aspirin was not associated significantly with hospital readmission. None of the covariates adjusted for in the analysis was associated significantly with hospital readmission.

Table 4 shows the multivariate logistic regression analyses for low one-minute and five-minute Apgar scores. Receiving aspirin was not associated significantly with low Apgar scores at one-minute or five-minutes. None of the covariates adjusted for in the analysis was associated significantly with low one-minute or five-minute Apgar scores.

Table 5 shows the multivariate linear regression analysis for birth weight and LOS. Receiving aspirin was not associated significantly with birth weight. Among the covariates adjusted for in the analysis, increased BMI was associated significantly ($p = 0.003$) with increased birth weight. Pre-eclampsia ($p = 0.003$) and antepartum high risk for pre-eclampsia ($p < 0.001$) were associated significantly with decreased birth weight. Receiving aspirin was not associated significantly with LOS. Among the covariates adjusted for in the analysis, pre-eclampsia ($p = 0.01$) and antepartum high risk for pre-eclampsia ($p < 0.001$) were associated significantly with increased LOS.

Table 1. Comparisons of sample characteristics.

Variable	No Aspirin M (SD) or # (%) (n = 527)	Yes Aspirin M (SD) or # (%) (n =107)	p Value
Age (years) [mean]	30.4 (6.72)	33.4 (6.20)	< 0.001
Race/Ethnicity			
White	27 (5.1)	1 (0.9)	< 0.001
Black	98 (18.6)	40 (37.4)	
Hispanic	365 (69.3)	63 (58.9)	
Other	37 (7.0)	3 (2.8)	
Smoker (yes)	16 (3.0)	3 (2.8)	1.00
Body Mass Index (kg/m^2) [mean]	29.7 (6.59)	32.3 (7.94)	< 0.001
Gestational Diabetes (yes)	83 (15.7)	25 (23.4)	0.06
Gestational Hypertension (yes)	58 (11.0)	11 (10.3)	0.83
Pre-eclampsia (yes)	87 (16.5)	33 (30.8)	< 0.001
At Risk			
No risk	198 (37.6)	8 (7.5)	< 0.001
Moderate risk	261 (49.5)	27 (25.2)	
High risk	68 (12.9)	72 (67.3)	

Note: M = mean, SD = standard deviation. Fisher's exact test conducted for race/ethnicity and smoker due to expected cell size < 5.

Table 2. Univariate comparisons for the outcomes.

Variable	No Aspirin M (SD) or # (%) (n = 527)	Yes Aspirin M (SD) or # (%) (n = 107)	p Value
NICU Admission (yes)	96 (18.2)	27 (25.2)	0.09
Hospital Readmission (yes)	31 (7.5)	7 (7.0)	0.86
Apgar 1 (< 7) (yes)	49 (9.3)	10 (9.3)	0.99
Apgar 5 (< 7) (yes)	18 (3.4)	1 (0.9)	0.22
Birth Weight (grams) [mean]	3,165.2 (593.05)	3,006.9 (718.36)	0.02
Length of Stay (days) [mean]	5.2 (5.71)	7.7 (9.81)	0.01

Note: M = mean, SD = standard deviation. NICU = neonatal intensive care unit. Sample size for Apgar 1 and Apgar 5 = 633. Sample size for readmission and length of stay = 512. Fisher's exact test conducted for Apgar 5 due to expected cell size < 5.

Table 3. Multivariate logistic regression analyses for neonatal intensive care unit admission and hospital readmission.

Variable	NICU OR (95% CI)	p Value	Readmission OR (95% CI)	p Value
Aspirin (yes)	0.95 (0.52, 1.76)	0.88	0.74 (0.27, 2.06)	0.56
Age (years)	0.96 (0.93, 0.99)	0.01	1.00 (0.95, 1.05)	0.95
Race/Ethnicity				
White	1.00		1.00	
Black	0.58 (0.22, 1.54)	0.28	4.80x107 (<0.001, --)	1.00
Hispanic	0.63 (0.26, 1.52)	0.30	2.01x108 (<0.001, --)	1.00
Other	0.59 (0.18, 1.89)	0.37	5.07x107 (<0.001, --)	1.00
BMI (kg/m^2)	0.97 (0.94, 1.00)	0.08	0.99 (0.94, 1.05)	0.73
Pre-eclampsia (yes)	1.46 (0.89, 2.38)	0.13	1.27 (0.55, 2.96)	0.58
At Risk				
No risk	1.00		1.00	
Moderate risk	1.51 (0.90, 2.55)	0.12	1.29 (0.56, 2.80)	0.56
High risk	3.80 (2.02, 7.13)	<0.001	2.00 (0.71, 5.62)	0.19

Note: OR = odds ratio, CI = confidence interval. NICU = neonatal intensive care unit. Nagelkerke R Square: NICU = 0.08, Readmission = 0.07. There were no multicollinearity concerns.

Table 4. Multivariate logistic regression analyses for low Apgar 1 and Apgar 5 scores.

Variable	Apgar 1 OR (95% CI)	p Value	Apgar 5 OR (95% CI)	p Value
Aspirin (yes)	0.80 (0.33, 1.94)	0.63	0.28 (0.03, 2.53)	0.26
Age (years)	1.00 (0.96, 1.04)	0.87	0.98 (0.91, 1.05)	0.58
Race/Ethnicity				
White	1.00		1.00	
Black	2.53 (0.55, 11.64)	0.24	1.72 (0.20, 14.85)	0.62
Hispanic	1.10 (0.25, 4.90)	0.90	0.79 (0.10, 6.42)	0.83
Other	1.05 (0.16, 6.81)	0.96	<0.001 (<0.001, --)	1.00
BMI (kg/m^2)	1.00 (0.96, 1.04)	0.90	1.01 (0.95, 1.09)	0.70
Pre-eclampsia (yes)	1.70 (0.91, 3.17)	0.09	1.54 (0.53, 4.47)	0.43
At Risk				
No risk	1.00		1.00	
Moderate risk	0.76 (0.40, 1.44)	0.39	0.98 (0.35, 2.73)	0.96
High risk	0.85 (0.35, 2.04)	0.71	0.58 (0.10, 3.35)	0.55

Note: OR = odds ratio, CI = confidence interval. Nagelkerke R Square: Apgar 1 = 0.04, Apgar 5 = 0.06. There were no multicollinearity concerns.

Table 5. Multivariate linear regression analyses for birth weight and length of stay.

Variable	Birth Weight B (SE)	p Value	Length of Stay B (SE)	p Value
Aspirin (yes)	82.03 (73.90)	0.27	0.03 (0.04)	0.51
Age (years)	1.63 (3.57)	0.65	0.001 (0.002)	0.71
Race/Ethnicity				
White	Reference		Reference	
Black	36.84 (123.55)	0.77	-0.13 (0.08)	0.09
Hispanic	78.93 (115.34)	0.49	-0.14 (0.07)	0.052
Other	61.98 (145.49)	0.67	-0.15 (0.09)	0.08
BMI (kg/m^2)	10.83 (3.63)	0.003	0.001 (0.002)	0.56
Pre-eclampsia (yes)	-183.14 (60.84)	0.003	0.08 (0.03)	0.01
At Risk				
No risk	Reference		Reference	
Moderate risk	10.48 (56.10)	0.85	0.05 (0.03)	0.14
High risk	-442.10 (75.07)	<0.001	0.15 (0.04)	< 0.001
Constant	2,810.54 (179.64)	<0.001	0.61 (0.11)	< 0.001

Note: B = unstandardized beta, SE = standard error. Adjusted R square: Birth weight = 0.09, Length of stay = 0.06. There were no multicollinearity concerns.

DISCUSSION

In our multivariate analyses, LDA supplementation was not associated significantly with NICU admission, hospital readmission, low one-minute Apgar score, low five-minute Apgar score, birth weight, or LOS. Antepartum high-risk for pre-eclampsia was associated significantly with increased NICU admission rates, increased LOS, and decreased birth weight. Increased age was associated significantly with decreased NICU admission. Increased BMI was associated significantly with increased birth weight. Pre-eclampsia was associated significantly with decreased birth weight and increased LOS.

No significant association of LDA supplementation was found with NICU admission. This finding was similar to that reported by others.[6] It was reassuring to note that LDA supplementation for pre-eclampsia delay or prevention did not have the negative impact of increased neonatal NICU admission rates. This study adds to the literature for the current time-period where greater numbers of women, including those of moderate risk for pre-eclampsia, are engaging in LDA supplementation

No significant association was found for LDA supplementation with neonatal hospital readmission. Neonates admitted to the NICU have lower rates of readmission to the hospital than neonates admitted to the nursery.[27] An intensive care environment experience offers more benefits than LDA supplementation when it comes to neonatal readmissions.

No significant association was found for LDA supplementation with low one-minute and five-minute Apgar scores. A previous meta-analysis found LDA supplementation was associated with decreased incidence of low five-minute Apgar scores.[7] Our findings for LDA supplementation differed from this pattern. Our sample had small numbers of those with low five-minute Apgar scores and was insufficient for determining statistical significance.

No significant association was found for LDA supplementation with birth weight. Aspirin supplementation starting in early pregnancy can reduce the incidence of fetal growth restriction.[5] This benefit, however, was not protective in women with a history of prior small for gestational age (SGA) neonate even in the setting of pre-eclampsia.[28] It is possible that our sample may have included patients who initiated care later on in their pregnancy and this may have diminished the impact of LDA supplementation on birth weight. Furthermore, the majority of the patients who were prescribed LDA supplementation were at high risk for developing pre-eclampsia and those same factors determining their high-risk status were associated with SGA. Our analysis may inadequately control for the impact of prior history of SGA neonate on subsequent neonatal birth weight despite LDA prophylaxis.

No significant association was found of LDA supplementation with neonatal hospital LOS. There was no known literature on LDA supplementation and neonatal hospital LOS. However, LDA supplementation was associated with decreased LOS for those admitted to the NICU.[6] Our findings for LDA supplementation for neonatal hospital LOS differed from this pattern. LDA supplementation may offer an observed clinical benefit in an intensive care environment but not in a typical hospital care environment.

High-risk designation was associated significantly with increased NICU admission rates, increased hospital LOS, and decreased birth weight but not with hospital readmission and low one-minute and five-minute Apgar scores. Moderate-risk designation was not associated significantly with any of the six neonatal outcomes. The USPSTF performed a systemic review of risk factors for development of pre-eclampsia and classified chronic hypertension, history of pre-eclampsia, multifetal gestation, renal disease, autoimmune disease, and

type 1 or 2 diabetes as markers of high risk designation for mothers at elevated risk of developing pre-eclampsia.[29] Our study supported previously reported results that found pregnancies complicated by multiple gestation, diabetes, and hypertension were predictive of NICU admission.[30] Similarly, our findings were congruent with literature reporting increased LOS in neonates of patients with high risk comorbidities.[31] Our observations agreed with other reports that birth weight was impacted negatively by hypertensive disorders,[21] maternal diabetes, pre-existing maternal disease, and multifetal gestations.[32] Conversely, low Apgar scores seemed to be impacted more so by neonatal, intrapartum, and delivery factors rather than maternal comorbidities, which can be a reason why our study did not show an association between high-risk designation and low one- and five-minute Apgar scores.[33]

A strength of our study was the inclusion of mostly Hispanic and Black ethnicities with moderate-risk and high-risk for pre-eclampsia, which accounted for only a small proportion of prior studies of LDA supplementation for pre-eclampsia prevention. This study had several limitations. First, it could not be determined if those prescribed LDA supplementation adhered to treatment recommendations. Second, the timing of LDA supplementation from 12 to 16 weeks of gestational age is ideal for pre-eclampsia prevention.[2,7] Our retrospective study did not have any standardized gestational age at which LDA supplementation began and included patients starting LDA supplementation at gestational ages different from recommended timing. Third, as this was an observational study, many potential confounders were controlled that differed between those with and without LDA supplementation. It was possible that there was inadequate controllability. Future research should consider a randomized clinical trial to determine any possible benefits of LDA supplementation on neonatal outcomes.

In conclusion, no association of LDA supplementation was found with NICU admission, hospital readmission, low one-minute Apgar score, low five-minute Apgar score, birth weight, and LOS. While we found no improved neonatal outcomes, it was important to note there were no increased adverse outcomes. Clinicians who are recommending maternal LDA supplementation should be aware that LDA supplementation did not appear to provide any benefits for these neonatal outcomes.

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