OBSTETRICS

# Obesity and laboratory aspirin resistance in high-risk pregnant women treated with low-dose aspirin

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**BACKGROUND:** Low-dose aspirin is used for preeclampsia prevention in high-risk women, but the precise mechanism and optimal dose are unknown. Evidence suggests that an imbalance in prostacyclin and thromboxane $A_2$ ($TXA_2$) plays a key role in the pathogenesis of preeclampsia. Aspirin has a dose-dependent effect blocking production of $TXA_2$, a potent stimulator of platelet aggregation and promoter of vasoconstriction. Incomplete inhibition of platelet aggregation, designated aspirin resistance, can be reduced by increasing the aspirin dose. Evidence in the nonobstetric literature suggests that aspirin resistance may be more common among patients with a high body mass index.

**OBJECTIVE:** To investigate the association of obesity on platelet-derived thromboxane inhibition in high-risk women treated with low-dose aspirin.

**MATERIALS AND METHODS:** This was a secondary analysis of a prospective multi-centered study investigating the effect of low-dose aspirin (60-mg) administration in women at high risk for preeclampsia. Maternal serum $TXB_2$ (an indirect measure of $TxA_2$) levels were drawn at 3 time points: randomization (13−26 weeks' gestation), second trimester (at least 2 weeks after randomization and 24−28 weeks' gestation), and third trimester (34−38 weeks' gestation). Patients were included in the analysis if a $TXB_2$ level was recorded at randomization and at least 1 time point thereafter. Patients were stratified by body mass index category and treatment arm. Median $TXB_2$ levels were calculated at each time point, as well as rates of complete $TXB_2$ inhibition (<0.01 ng/mL). A multivariate logistic regression analysis was performed to generate odds ratios (OR) for complete $TXB_2$ inhibition by body mass index category, adjusting for maternal age, race, high-risk group at randomization, nulliparity, and rate of randomization less than 16 weeks' gestation.

**RESULTS:** A total of 1002 patients were included in the analysis, 496 (49.5%) and 506 (50.5%) in the low-dose aspirin and placebo groups respectively. There were substantial decreases in $TXB_2$ levels among low-dose aspirin-treated women in all body mass index categories. In contrast, women assigned to placebo did not show a marked decrease in $TXB_2$ levels after randomization, and obese women had higher median $TXB_2$ levels in both the second (16.5, interquartile range [IQR] 8.0−31.8 vs 14.0, IQR 6.9−26.7, ng/mL; $P = .032$) and third (15.7, IQR 7.6-28.5 vs 11.9, IQR 4.6-25.9, ng/mL; $P = .043$) trimesters. When comparing among stratified body mass index low-dose aspirin groups, women with class III obesity had the lowest odds of undetectable $TXB_2$ levels in the second trimester (adjusted odds ratio [aOR], 0.33; 95% confidence interval [CI], 0.15−0.72) and third trimester (aOR, 0.30; 95% CI, 0.11−0.78) as well as at both time points (aOR, 0.09; 95% CI, 0.02−0.41).

**CONCLUSION:** High-risk obese women receiving low-dose aspirin for the prevention of preeclampsia have lower rates of complete inhibition of $TXB_2$. These data suggest that an increase in aspirin dosing or frequency may be necessary in this population.

**Key words:** body mass index, obesity, platelet aggregation, preeclampsia thromboxane B2

Preeclampsia is a multi-system disorder that is a major contributor to adverse maternal and neonatal outcomes.[1] Although the etiology of preeclampsia is multifactorial, an imbalance of thromboxane $A_2$ ($TXA_2$) and prostacyclin ($PGI_2$) has been identified and is thought to play a key role in the pathogenesis of preeclampsia.[2] $TXA_2$ is a potent stimulator of platelet aggregation and promotor of vasoconstriction, whereas $PGI_2$ is a vasodilator.[3] Elevated concentrations of $TXA_2$ may explain some of the clinical manifestations of preeclampsia, such as hypertension and reduced uteroplacental blood flow.[4,5]

Aspirin is a dose-dependent cyclooxygenase (COX) inhibitor, which at doses between 60 and 150 mg per day irreversibly and selectively acetylates COX-1, which in turn leads to a preferential decrease in $TXA_2$ with minimal change in $PGI_2$ levels, leading to decreased vascular tone and platelet reactivity.[6-9] As a result, the use of LDA in the primary prevention of preeclampsia has been studied over several decades and is now recommended by many professional organizations.[10-12] However, the optimal dose of LDA remains unknown.

Laboratory aspirin resistance is defined as the failure of aspirin to inhibit platelet thromboxane $A_2$ production.[13,14] The incidence of aspirin resistance varies widely in the literature, from 5% to 40%, as it is largely dependent on the population studied and the laboratory method used for identification.[15] Several tests have been proposed to detect aspirin resistance, including light transmission aggregometry, platelet function analyzers, as well as serum and urinary thromboxane metabolites.[16] However, the production of serum thromboxane $B_2$ ($TXB_2$), the stable metabolite of $TXA_2$, is largely dependent on platelet COX-1 (aspirin's therapeutic target) and has therefore been used as an indirect measure of the inhibitory effects of low-dose aspirin on platelets.[17]

Obesity is recognized as an important risk factor for preeclampsia, and evidence suggests that LDA may be less effective in this population.[18] There are several

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## AJOG at a Glance

### Why was this study conducted?

To investigate the association of obesity and platelet thromboxane production using longitudinal serum thromboxane $B_2$ levels in high-risk pregnant women receiving low dose-aspirin vs placebo for prevention of preeclampsia.

### Key findings

Obese women receiving placebo had higher median thromboxane $B_2$ concentrations in both the second and third trimesters compared with nonobese women. In patients receiving low-dose aspirin, the rates of complete inhibition of thromboxane $B_2$ production were substantially reduced in obese individuals. This reduction was particularly evident in women with class III obesity in a stratified logistic regression analysis controlling for confounders.

### What does this add to what is known?

These data confirm prior reports in the nonobstetric literature regarding reduced effectiveness of low-dose aspirin to inhibit platelet thromboxane production in obese individuals, and suggest that increased aspirin dosing or frequency may be necessary in this population.

potential mechanisms to explain this phenomenon, including increased platelet reactivity, increased platelet turnover, reduced bioavailability of LDA, as well as higher levels of oxidative stress and inflammation in obese individuals.[18-20]

Given the increased rates of aspirin resistance in obese individuals, the traditional LDA doses of 60−81 mg available in the United States may be insufficient to fully suppress $TXA_2$ production in this population. Using a large prospectively collected data set from a previously published, multi-centered, randomized, controlled trial, we sought to evaluate the effect of obesity on rates of complete thromboxane inhibition in women at high risk for preeclampsia who were receiving LDA.[21]

## Materials and Methods

This was a secondary analysis of the National Institute of Child Health and Human Development (NICHD) Maternal−Fetal Medicine Units Network double-blind, randomized, placebo-controlled trial investigating the use of daily LDA (60 mg) for the prevention of preeclampsia in women at high risk for preeclampsia. Each participating center received institutional review board approval at their respective institutions. The current study uses a publicly available de-identified data set and is considered exempt by the institutional review board at The Ohio State University Wexner Medical Center. Detailed methods used in this trial have been previously published.[21] Briefly, this trial was performed at 13 centers and identified pregnant women with 1 of the following high risk factors for preeclampsia: pregestational diabetes requiring insulin, chronic hypertension, multifetal gestation, or history of preeclampsia in a previous pregnancy. Chronic hypertension was diagnosed by documentation of antihypertensive drug therapy or a blood pressure of ≥140/≥90 mm Hg taken on 2 occasions at least 4 hours apart, either before pregnancy or before entry into the study. Multifetal gestation was documented by ultrasound examination before enrollment. Previous preeclampsia was determined by medical records or, in the absence of a record, an oral history of preeclampsia that resulted in delivery before the 37th gestational week. Women with multifetal gestations were ineligible for the study if they also had preexisting diabetes mellitus, chronic hypertension, or proteinuria. Women with a history of preeclampsia and current proteinuria were also ineligible. Women with both diabetes and hypertension were included in the diabetes group. The primary outcome of the original study was preeclampsia defined as hypertension (systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg) in the setting of proteinuria. Proteinuria was defined as either a 24-hour urine ≥300 mg of total protein or 2+ protein by urine dipstick ≥2 times over 4 hours apart.

Women were enrolled between 13 and 26 weeks' gestation and were assessed for compliance with 1 week of placebo tablets. Women who successfully took 5 or more placebo tablets were then randomized to receive either 60 mg of aspirin or placebo. They were instructed to continue taking the tablets daily unless delivery occurred or unless they were diagnosed with preeclampsia. Patient compliance with the study drug was assessed by a combination of pill counts and interviews.

Maternal serum thromboxane $B_2$ $TXB_2$, the stable metabolite of $TXA_2$, was measured longitudinally at three time points during the original trial: randomization (13−26 weeks' gestation), second trimester (at least 2 weeks after randomization and at 24−28 weeks' gestation), and third trimester (34−38 weeks' gestation). Patients were included in the current analysis if they had a $TXB_2$ level drawn at randomization and a $TXB_2$ level in the second or third trimester or both.

The study population was stratified by obese (body mass index [BMI] ≥30 kg/m$^2$) and nonobese (BMI <30 kg/m$^2$) women. The primary outcome was the rate of complete $TXB_2$ inhibition, defined as undetectable $TXB_2$ levels <0.01 ng/mL. Secondary outcomes were rates of preeclampsia at any gestational age and preeclampsia with preterm delivery <37 weeks in women with and without undetectable $TXB_2$ levels.

Stata Statistical Software, Release 15 (StataCorp LLC, College Station, TX) was used for all statistical analyses. Baseline demographics were compared between the placebo and LDA groups. Categorical data were compared using the $\chi^2$ or Fisher exact test where appropriate. Continuous data were assessed for normality with the Shapiro−Wilk test and subsequently found to be nonparametric. The Wilcoxon rank-sum test was used to compare continuous data between groups. The median and interquartile range (IQR) for thromboxane levels were calculated for each time point: at randomization, in the

**TABLE 1**
**Population demographics**

| | ASA group (n = 496) | | | Placebo group (n = 506) | | |
|---|---|---|---|---|---|---|
| | BMI <30 n = 297 | BMI ≥30 n = 199 | *P* value | BMI <30 n = 311 | BMI ≥30 n = 195 | *P* value |
| Age, median year (IQR) | 24 (20-30) | 27 (22-33) | <.01 | 25 (21-30) | 27 (23-32) | .01 |
| Race | | | .01 | | | <.01 |
| White | 116 (39.1) | 47 (23.6) | | 133 (42.8) | 53 (27.2) | |
| Black | 156 (52.5) | 139 (69.9) | | 150 (48.2) | 125 (64.1) | |
| Hispanic | 24 (8.1) | 13 (6.5) | | 26 (8.4) | 16 (8.2) | |
| Other | 1 (0.3) | 0 (0.0) | | 2 (.6) | 1 (0.5) | |
| Enrollment group | | | <.01 | | | <.01 |
| Diabetes | 64 (21.6) | 31 (15.6) | | 74 (23.8) | 25 (12.8) | |
| cHTN | 58 (19.5) | 97 (48.7) | | 66 (21.2) | 91 (467) | |
| Twins | 88 (29.6) | 29 (14.6) | | 87 (28.0) | 34 (17.4) | |
| Prior preE | 87 (29.3) | 42 (21.1) | | 84 (27.0) | 45 (23.1) | |
| Nulliparity | 99 (33.3) | 50 (25.1) | .05 | 94 (30.2) | 41 (21.0) | .02 |
| Smoking | 50 (16.8) | 33 (16.6) | .94 | 54 (17.4) | 30 (15.4) | .56 |
| Preeclampsia | 56 (18.9) | 42 (21.1) | .54 | 66 (21.2) | 47 (24.1) | .45 |
| Preeclampsia <37 wk and PTD | 34 (12.4) | 14 (8.2) | .17 | 35 (12.5) | 17 (10.3) | .49 |
| Randomized ≤16 wk | 57 (19.2) | 57 (28.6) | .01 | 65 (20.9) | 36 (18.5) | .50 |
| % of Pills taken, median (IQR) | 94.4 (85.7-98.9) | 94 (86.7-98.7) | .90 | 93.3 (84.3-98.0) | 94.3 (85.7-99.4) | .13 |

All other data is presented as N (%)

*cHTN*, chronic hypertension; *IQR*, interquartile range; *preE*, preeclampsia; *PTD*, preterm delivery.

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second trimester, and in the third trimester. A multivariate logistic regression was performed to generate adjusted odds ratios (aOR) for complete $TXB_2$ inhibition in the second trimester, third trimester, or both time points comparing BMI categories of normal weight (BMI <25 kg/m$^2$), overweight (BMI 25−29.9 kg/m$^2$), class I and class II obesity (BMI 30−39.9 kg/m$^2$), and class III obesity (BMI ≥40 kg/m$^2$) adjusting for maternal age, black race, high-risk group at randomization, nulliparity, and randomization <16 weeks' gestation.

Thromboxane concentrations were determined using a radioimmunoassay of its stable metabolite, $TXB_2$. Maternal blood samples were analyzed and documented at the time of the original trial. The specifics of the assay used has been previously described.[22] Briefly, both the $TXB_2$ antibody/standard and tritiated $TXB_2$ were obtained from PerSeptive Diagnostics, Inc (Cambridge, MA) and New England Nuclear (Dupont Research, Wilmington, DE), respectively. The standard curve ranged from 0.78 to 400 pg, with a lower detection concentration limit of 1.68 pg. The intra- and interassay variation were reported as 7.2% and 14.7% respectively. The cross-reactivity for other eicosanoids including prostaglandin $E_2$, prostaglandin $F_{2\alpha}$, and 6-keto-prostaglandin $F_{1\alpha}$ was reported to be <0.01%.[23]

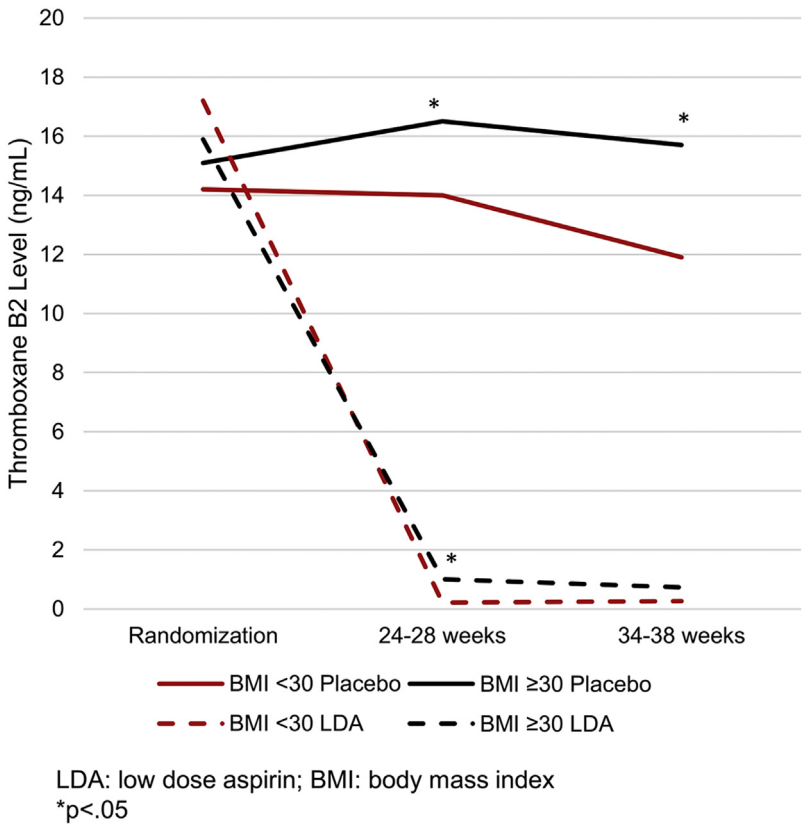
## Results

Of the original 2539 women who were randomized, 1002 had a $TXB_2$ level drawn at randomization and at least 1 time point afterward available for analysis. Of these, 496 and 506 women were in the LDA and placebo groups, respectively. In the LDA group, women who were obese were more likely to be older, of black race, randomized <16 weeks' gestation, and to have chronic hypertension as the reason for randomization. Compliance with the study drug was high among all groups, with the median percentage of pills taken between 93% and 94%. Population demographics are presented in Table 1.

There were no differences between $TXB_2$ levels at the time of randomization in either the LDA or placebo group. Women assigned to LDA had substantially lower median $TXB_2$ levels after randomization regardless of BMI, but obese women had statistically significant higher levels at 24−28 weeks (1.0, IQR 0.0−11.9 vs 0.21, IQR 0.0−9.1, ng/mL; $P = .03$). In contrast, women assigned to placebo did not show a marked decrease in $TXB_2$ levels after randomization, and obese women had higher median $TXB_2$ levels in both the second (16.5, IQR 8.0−31.8 vs 14.0, IQR 6.9−26.7, ng/mL; $P = .03$) and third (15.7, IQR 7.6−28.5 vs 11.9, IQR 4.6−25.9, ng/mL; $P = .04$) trimesters (Figure 1).

Obese women assigned to LDA had statistically significant lower rates of undetectable $TXB_2$ levels in the second trimester (39.4% vs 30.2%; $P = .04$), but

**FIGURE 1**
**Longitudinal thromboxane $B_2$ levels by treatment group and body mass index (BMI) category**

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not during the third trimester (41.4% vs 32.9%; $P = .12$). However, obese patients were substantially less likely to have undetectable levels of $TXB_2$ at both time points (30.6% vs 17.7%; $P = .010$). Regardless of BMI, women assigned to placebo had very low rates of undetectable $TXB_2$ levels at either time point individually (second trimester: 0.0% vs 1.6%; $P = 0.148$; third trimester: 4.4% vs 7.1%; $P = .31$) and at both time points (0.5% vs 3.0%; $P = .06$).

When comparing between the stratified BMI LDA groups, women with class III obesity had the lowest odds of undetectable $TXB_2$ levels in the second trimester (aOR, 0.33; CI, 0.15–0.72) and third trimester (aOR, 0.30; CI, 0.11–0.78) as well as at both time points (aOR, 0.09; CI, 0.02–0.41). The highest rates of undetectable $TXB_2$ levels were in the normal weight group, but remained under 50% for each time point (Table 2).

Finally, there were no differences in rates of preeclampsia in women receiving LDA with undetectable $TXB_2$ levels in the second trimester (17.2% vs 20.8%; $P = .34$), third trimester (16.4% vs 19.7%; $P = .46$), or at both time points (16.5% vs 17.5%; $P = .83$). Similarly, there were no differences in rates of preeclampsia with delivery less than 37 weeks in women with undetectable $TXB_2$ levels in the second trimester (9.9% vs 9.2%; $P = .71$), third trimester (4.5% vs 7.4%; $P = .27$), or at both time points (5.1% vs 6.3%; $P = .83$).

## Comment

### Main Findings

This secondary analysis of women at high risk for preeclampsia indicates that obese women have higher median $TXB_2$ levels and lower rates of complete $TXB_2$ inhibition when receiving LDA. This is especially true in women with class III obesity. Furthermore, obese women who are not receiving LDA have higher median $TXB_2$

**TABLE 2**
**Complete inhibition of thromboxane $B_2$, by body mass index and treatment group**

| | Normal weight n = 182 | Overweight n = 115 | Class I/II obesity n = 139 | Class III obesity n = 60 |
|---|---|---|---|---|
| $TxB_2$ undetectable at 24–28 wk | 83 (45.9) | 33 (29.2) | 46 (33.8) | 12 (21.4) |
| aOR (CI) | referent | 0.42 (0.25-0.74) | 0.55 (0.33-0.95) | 0.33 (0.15-0.72) |
| $TxB_2$ undetectable at 34–38 wk | 50 (44.6) | 27 (36.5) | 37 (39.0) | 8 (19.1) |
| aOR (CI) | referent | 0.63 (0.33-1.2) | 0.72 (0.38-1.4) | 0.30 (0.11-0.78) |
| $TxB_2$ undetectable at both time points | 41 (36.9) | 15 (20.8) | 21 (22.8) | 2 (5.3) |
| aOR (CI) | referent | 0.39 (0.18-0.84) | 0.48 (0.23-0.99) | 0.09 (0.02-0.41) |

Adjusted for age, high-risk group at randomization, race, nulliparity, and rate of randomization <16 weeks' gestation. Normal weight: BMI ≤25 kg/m$^2$; Overweight: BMI 25-29.9 kg/m$^2$; Class I/II Obesity: BMI 30-39.9 kg/m$^2$; Class III Obesity: BMI ≥40 kg/m$^2$.

*aOR*, adjusted odds ratio; *BMI*, body mass index; *CI*, confidence interval; *LDA*, low-dose aspirin; *Ref*, referent; *$TxB_2$*, thromboxane $B_2$.

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levels in both the second and third trimesters.

## Clinical Implications

Serum $TXB_2$ is a direct measure of the capacity of platelets to synthesize $TXA_2$ and is a highly specific test for monitoring aspirin's effect on COX-1–dependent thromboxane production.[24] The optimal reduction in serum $TxB_2$ to achieve inhibition of platelet COX-1 to obtain antiplatelet efficacy varies within the literature and is not well established.[9,25,26] However, several studies have examined the effects of LDA on serum $TXB_2$ levels and have described a nonlinear relationship between inhibition of serum $TXB_2$ and inhibition of platelet aggregation.[9,27] These results suggest that nearly complete suppression of the biosynthetic capacity of platelets to produce $TXA_2$ is required in order to have a measurable impact on thromboxane-dependent platelet function. These data informed the choice of complete serum $TXB_2$ inhibition (<0.01 ng/mL) as the primary endpoint in this study, and this cutoff is consistent with that in existing literature investigating the clinical implications of $TXB_2$.[28]

Although this study demonstrates a significant difference in rates of complete inhibition of $TXB_2$ in women stratified by BMI who were receiving LDA, there were no differences seen in overall rates of preeclampsia or preeclampsia with preterm delivery at less than 37 weeks in those with and without undetectable $TXB_2$ levels. This finding is consistent with a previous publication investigating the association of $TXB_2$ levels and incidence of preeclampsia using the same data set.[22] Although this may appear to invalidate the use of complete $TXB_2$ inhibition as a primary endpoint, there are several reasons that might explain this negative finding. Meta-analyses have indicated that LDA is most effective when initiated at less than 16 weeks' gestation, when doses greater than 100 mg are used, and when preterm rather than term preeclampsia is a studied outcome.[10,29] In the current analysis, fewer than one-fourth of the women assigned to LDA were randomized at less than 16 weeks' gestation; there were very few women who experienced preeclampsia with preterm delivery; and an aspirin dose of 60 mg was used, which may have led to the low rate of complete $TXB_2$ inhibition seen in this cohort. Overall, these data are likely underpowered for the outcome of preeclampsia.

Prior literature investigating laboratory-defined aspirin resistance found that doses as low as 20 mg daily were sufficient to cause maximal thromboxane inhibition, but this analysis was performed in healthy individuals without cardiac disease.[18] In obese individuals, bio-inactivation of aspirin has been shown to be increased after first-pass metabolism.[30] As a result, there is decreased systemic aspirin exposure, leading to an impaired ability to inhibit COX-1 in megakaryocytes and ultimately allowing newly formed platelets to remain uninhibited.[8] In addition, both pregnancy and obesity are associated with increased platelet turnover, further exacerbating platelet hyperreactivity in obese pregnant women.[31,32]

It is possible that increased frequency of aspirin dosing would be more effective than just increased dose.[33] A study investigating the recovery of COX-1 activity by measuring serial serum $TXB_2$ levels demonstrated a linear increase in $TXB_2$ production between 12 and 24 hours after aspirin administration. Increased BMI was the only factor associated with accelerated $TXB_2$ recovery in patients with and without diabetes. Twice-daily dosing of aspirin reversed the abnormal $TXB_2$ recovery in both groups.[31] In patients with essential thrombocytopenia, a condition also with accelerated platelet turnover, there is a high rate of incomplete $TXB_2$ inhibition with once-daily aspirin dosing. In this population, increasing the frequency of dosing from once to twice daily (100 mg) was substantially more effective at suppressing $TXB_2$ production than doubling the daily dose from 100 mg to 200 mg.[34] Furthermore, vascular safety of dosing at these concentrations has been demonstrated, with no effect on in vivo biosynthesis of $PGI_2$.[35]

## Strengths and Weaknesses

Strengths and limitations of this study are inherent to a secondary analysis of previously collected data. Specifically, the original cohort analyzed in this study was recruited between 1989 and 1992. This may decrease generalizability, but there has been a substantial increase in the prevalence of obesity over time, which makes exploration of the effectiveness of LDA in this population a salient topic.[36] Also, many women did not have $TXB_2$ levels drawn throughout the study or did not have a complete set of longitudinal $TXB_2$ levels available for analysis. It is possible that there are inherent differences in patients who did and did not receive $TXB_2$ surveillance. Finally, the dose of aspirin used in this trial is lower than what is used in current clinical practice, and it is not known whether differences in $TXB_2$ inhibition would persist among BMI groups with increased dosing. However, this analysis is performed on prospectively collected data from a large cohort of high-risk women, with rigid data and safety monitoring in addition to well-defined study outcomes and high study drug compliance.

## Conclusion and Future Research Implications

Overall, the literature supports a physiologic basis for increased rates of aspirin resistance in an obese pregnant population. However, further study is needed to investigate the pharmacokinetics and safety of both increased dosing and frequency of aspirin use in obese pregnant women. In addition, further investigation into specific patient characteristics as well as alternative etiologic pathways associated with the development of preeclampsia (ie, clinical treatment failure) despite complete suppression of $TXB_2$ could potentially individualize patient care in high-risk populations.

In conclusion, in this study, high-risk obese pregnant women receiving LDA for the prevention of preeclampsia had lower rates of complete inhibition of $TXB_2$. These data suggest that increased aspirin dosing or frequency may be necessary in this population. ■

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