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Propensity score analysis of low-dose aspirin and bleeding complications in pregnancy

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KEYWORDS: abruption; bleeding complications; gestational hypertension; low-dose aspirin; postpartum hemorrhage; pre-eclampsia; pregnancy; propensity score analysis

CONTRIBUTION

What are the novel findings of this work?
This propensity score analysis found that a documented clinician recommendation for low-dose aspirin (LDA) in pregnancy was associated with an increased risk for postpartum hemorrhage and placental abruption in a large, contemporary birth population. The number needed to harm with LDA was 1 in 79 for postpartum hemorrhage and 1 in 287 for placental abruption.

What are the clinical implications of this work?
More research into bleeding complications in pregnancy is needed before recommending LDA beyond the highest-risk pregnancies.

ABSTRACT

Objective *Low-dose aspirin (LDA) has been shown to reduce the risk of preterm pre-eclampsia and it has been suggested that it should be recommended for all pregnancies. However, some studies have reported an association between LDA and an increased risk of bleeding complications in pregnancy. Our aim was to evaluate the risk of placental abruption and postpartum hemorrhage (PPH) in patients for whom their healthcare provider had recommended prophylactic aspirin.*

Methods *This multicenter cohort study included 72 598 singleton births at 19 hospitals in the USA, between January 2019 and December 2021. Pregnancies complicated by placenta previa/accreta, birth occurring at less than 24 weeks' gestation, multiple pregnancy or those with data missing for aspirin recommendation were excluded. Propensity scores were calculated using 20 features spanning sociodemographic factors, medical history, year and hospital providing care. The association between LDA recommendation and placental abruption or PPH was estimated by inverse-probability treatment weighting using the propensity scores.*

Results *We included 71 627 pregnancies in the final analysis. Aspirin was recommended to 6677 (9.3%) and was more likely to be recommended for pregnant individuals who were 35 years or older ($P < 0.001$), had a body mass index of 30 kg/m^2 or higher ($P < 0.001$), had prepregnancy hypertension ($P < 0.001$) and who had a Cesarean delivery ($P < 0.001$). Overall, 1.7% of the study cohort (1205 pregnancies) developed preterm pre-eclampsia: 1.3% in the no-aspirin and 5.8% in the aspirin group. After inverse-probability weighting with propensity scores, aspirin was associated with increased risk of placental abruption (adjusted odds ratio (aOR), 1.44 (95% CI, 1.04–2.00)) and PPH (aOR, 1.21 (95% CI, 1.05–1.39)). The aOR translated to a number needed to harm with LDA of 79 (95% CI, 43–330) for PPH and 287 (95% CI, 127–3151) for placental abruption.*

Conclusions *LDA recommendation in pregnancy was associated with increased risk for placental abruption and for PPH. Our results support the need for more research into aspirin use and bleeding complications in pregnancy before recommending it beyond the highest-risk pregnancies.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

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INTRODUCTION

Low-dose aspirin (LDA) reduces the risk of preterm pre-eclampsia (PE) in singleton pregnancies identified as high risk by first-trimester screening using the Fetal Medicine Foundation (FMF) prediction model, an algorithm based on maternal risk factors, mean arterial pressure, uterine artery Doppler and serum biomarkers[1].

While the International Federation of Gynecology and Obstetrics (FIGO) recommends the combined FMF PE risk assessment at 11–14 weeks' gestation as the preferred approach to identify patients for LDA in pregnancy[2], the National Institute for Health and Care Excellence (NICE) in the UK and the United States Preventative Services Task Force (USPSTF) recommend using maternal factors only (one high-risk factor and two or more moderate-risk factors)[3–5]. In 2021, the USPSTF guidelines were expanded to include consideration of LDA for pregnant people even with one moderate-risk factor[5], which could result in 85% of the pregnant population in the USA being eligible for LDA[6].

Some authors have gone further, and made a case for LDA being recommended to all pregnant people irrespective of risk[7,8]. These recommendations are predicated on there being no trade off to universal prescription of aspirin in low-risk pregnancies. However, a Cochrane systematic review[9], an observational study from Sweden[10] and a recent small randomized controlled trial in low-risk nulliparous patients[11], have suggested there may be an association between aspirin use and an increased risk of bleeding complications for pregnant people and even for their infants[10].

Given the importance of aspirin safety as use increases in pregnancy, our objective was to use a propensity score analysis to evaluate the risk of bleeding complications in pregnancies where LDA was recommended compared to those where it was not.

METHODS

Setting and study design

This retrospective multicenter cohort study included data from 72 598 singleton births (between January 2019 and December 2021) at 19 hospitals in the USA participating in a perinatal quality-improvement program (Obstetrical Care Outcomes Assessment Program (OB-COAP)). Data were collected from the medical record by trained abstractors at each site, by direct acquisition from electronic medical record systems where feasible, and uploaded to a cloud-based database. More detailed information on chart abstraction and data-quality checks has been reported previously[12]. The Western–Copernicus Group Institutional Review Board (IRB) deemed research using deidentified OB-COAP data as exempt from IRB review.

Study population

The study population included singleton births occurring at or beyond 24 weeks' gestation. Multiple pregnancy and pregnancies with placenta accreta spectrum or placenta previa were excluded. Pregnancies with missing data for LDA recommendation ($n = 590$) were also excluded.

Race and ethnicity data were from self-reported entries in the medical record. The Economic Innovation Group's Distressed Community Index[13], which assigns quintiles of economic wellbeing of the area in which the patient lives, was used as a marker of socioeconomic status.

Exposure

The exposure was a recommendation for LDA during pregnancy documented in the medical record. In 2014 the USPSTF recommended LDA for prevention of PE in patients identified as at increased risk if they had one high-risk factor or two or more moderate-risk factors[4]. The guidance was updated[5] in September 2021, but most births in the current dataset occurred before this time and so clinical practice was likely based predominantly on the 2014 guidance. LDA dose and timing in pregnancy were not available in the database, but the American College of Obstetricians and Gynecologists (ACOG) recommends 81 mg aspirin per day, starting at 12 weeks' gestation and continuing until delivery[14].

Outcomes

The main outcomes of interest were postpartum hemorrhage (PPH) and placental abruption. Neonatal intracranial hemorrhage was investigated as a secondary outcome. All outcomes were based on a clinical diagnosis of the outcome in the medical record. ACOG defines PPH as blood loss of 1000 mL or more (including blood loss during delivery) or blood loss with signs or symptoms of hypovolemia, in the first 24 h after delivery[15,16]. ACOG defines placental abruption as separation of the placenta before birth and in the absence of placenta previa[15]. Stillbirth was defined as any antepartum or intrapartum fetal loss, and neonatal death included death within the first 28 days postnatally.

Statistical analysis

We examined the association between individual features and LDA using descriptive statistics and Fisher's exact test. We used logistic regression with robust standard errors and stabilized inverse-probability treatment weights to examine the association between LDA and outcome. Propensity scores were estimated using logistic regression. The 20 features used in the logistic regression and their definitions in the OB-COAP database are shown in Table S1.

A propensity score is an estimate of the probability that an individual will receive the exposure (recommendation for LDA) based on the individual's characteristics. We estimated this probability using logistic regression, with LDA as the outcome and individual characteristics as covariates. The logistic regression model was used to calculate a predicted probability (P) of receiving LDA for

each individual. Inverse-probability treatment weighting was used to create weightings that balance the differences between the LDA and non-LDA populations with respect to each of the covariates used in the logistic regression model. Individuals who received a LDA recommendation were weighted by $1/P$, while individuals who did not receive an LDA recommendation were weighted by $1/(1-P)$.

The reason for using this approach is that, in general, inverse-probability treatment weighting using the propensity score results in weighted populations that are balanced with respect to all of the individual covariates included in the propensity-score model, mimicking the balance expected if randomization was possible. However, unlike randomization, there is no guarantee that groups are balanced with respect to unmeasured covariates.

Continuous variables (age, body mass index, height) were categorized and included in the propensity-score model as discrete features. Missing values in features were included as a level of the feature. Inverse-probability weighted and unweighted *P*-values of features in the propensity score analysis are shown in Table S2. Balance in features was examined using standardized mean differences (SMD) separately for each level of each feature, and the propensity-score model was required to have a maximum absolute SMD of less than 0.1. To meet this standard, parity was included in the propensity-score model as an interaction term with age category, chronic hypertension and obesity.

Subanalyses were performed, stratifying the propensity score analyses by Cesarean *vs* vaginal delivery, by PE/gestational hypertension *vs* no PE/gestational hypertension and by prepregnancy hypertension *vs* no prepregnancy hypertension, in order to evaluate the possibility of heterogeneous effects of aspirin in these subgroups. All statistical analyses were conducted in R[17] version 4.02.

RESULTS

Of 71 627 singleton pregnancies in the final study cohort, LDA was recommended for 6677 (9.3%). Patients with a LDA recommendation were more likely to be 35 years or older (44.2% *vs* 20.8%; $P < 0.001$), have a body mass index of 30 kg/m^2 or higher (67.8% *vs* 55.4%; $P < 0.001$), have prepregnancy hypertension (20.4% *vs* 2.3%; $P < 0.001$), have prepregnancy diabetes (6.8% *vs* 1.2%; $P < 0.001$) and were less likely to be nulliparous (31.5% *vs* 41.8%; $P < 0.001$) compared to patients without an aspirin recommendation (Table 1). Patients living in the most affluent communities (Distressed Communities Index Quintile 1) were over-represented in the LDA group (Table 1). Gestational age at the first prenatal visit was available for 99.5% of the aspirin-recommendation group and was 16 weeks or later in 974 (14.6%).

More pregnancy complications were also observed in the aspirin group, including preterm PE (5.8% *vs* 1.3%; $P < 0.001$), term PE/gestational hypertension (24.0% *vs* 9.1%; $P = 0.001$) and Cesarean delivery (42.2% *vs* 28.3%; $P < 0.001$) (Table 2). The incidence of placental abruption was significantly higher in the aspirin compared to the no-aspirin group (1.3% *vs* 0.8%; $P < 0.001$) as was the incidence of PPH (9.6% *vs* 6.5%; $P < 0.001$). There was no significant difference in the rate of stillbirth/neonatal death within the first 28 postnatal days between the two groups (0.3% *vs* 0.4%; $P = 0.915$) (Table 2).

In the propensity score analysis, the adjusted odds ratio (aOR) for placental abruption in the aspirin compared to the no-aspirin group was 1.44 (95% CI, 1.04–2.00). The aOR for PPH was 1.21 (95% CI, 1.05–1.39) (Table 3). The odds for postpartum hemorrhage in the aspirin group were not statistically significant when stratified by mode of delivery (Cesarean or vaginal) (Table 3). There were only a small number of neonates with intracranial hemorrhage, individual cell sizes were too small to be reported, and the CIs were wide and crossed unity (OR, 1.28 (95% CI, 0.32–5.15)), consistent with the sample size being underpowered to evaluate this outcome.

In the subanalyses, after exclusion of patients who developed PE, the aOR for placental abruption remained significantly higher (1.51 (95% CI, 1.08–2.11)), but did not for PPH (1.07 (95% CI, 0.93–1.24)) (Table 4). When stratified by prepregnancy hypertension, the aOR for placental abruption (1.46 (95% CI, 1.03–2.07)) and for PPH (1.22 (95% CI, 1.05–1.42)) were significantly higher in the patients without prepregnancy hypertension, but not in those with a history of prepregnancy hypertension (Table 5). The aOR translated to a number needed to harm with LDA of 79 (95% CI, 43–330) for PPH and 287 (95% CI, 127–3151) for placental abruption.

The rate of Cesarean delivery was 42.2% in the aspirin group and 28.3% in the no-aspirin group (aOR, 1.21 (95% CI, 1.09–1.33)) (Table 2). After exclusion of patients with previous Cesarean delivery and exclusion of placental abruption, the rate of Cesarean was 25.9% in the aspirin and 18.0% in the no-aspirin group (aOR, 1.17 (95% CI, 1.04–1.33)).

DISCUSSION

Summary of key findings

In this study, LDA recommendation in pregnancy was associated with a 44% increase in the odds for placental abruption and a 21% increase in the odds for PPH, based on a propensity score analysis with inverse-probability treatment weighting for multiple factors. However, it should be noted that the absolute risk from aspirin is relatively small, with an estimated number needed to harm of 1 in 79 for PPH and 1 in 287 for placental abruption.

After exclusion of patients who developed PE, an increased risk persisted for placental abruption, but not for PPH. When stratified by prepregnancy hypertension, the odds for placental abruption and for PPH were significantly increased only in the patients without prepregnancy hypertension. Although not all of the subanalysis results were statistically significant, the

Table 1 Population characteristics of 71 627 singleton pregnancies, according to low-dose aspirin recommendation

Characteristic	*No low-dose aspirin (n = 64 950)*	*Low-dose aspirin (n = 6677)*	P
Maternal age (years)	30 (26–34)	34 (29–37)	< 0.001
Maternal age ≥ 35 years	13 531 (20.8)	2954 (44.2)	< 0.001
BMI (kg/m^2)	26.3 (22.9–31.2)	29.3 (24.4–35.3)	< 0.001
BMI ≥ 30 kg/m^2	35 958 (55.4)	4524 (67.8)	< 0.001
Nulliparous	27 154 (41.8)	2106 (31.5)	< 0.001
Prepregnancy hypertension	1502 (2.3)	1361 (20.4)	< 0.001
Prepregnancy diabetes	812 (1.2)	452 (6.8)	< 0.001
Previous preterm birth*	1601 (2.5)	340 (5.1)	< 0.001
Previous stillbirth	696 (1.1)	167 (2.5)	< 0.001
First prenatal visit ≥ 16 weeks	12 790 (19.7)	974 (14.6)	< 0.001
Data not in record	1173 (1.8)	36 (0.5)	
In-vitro fertilization	1819 (2.8)	555 (8.3)	< 0.001
Data not in record	240 (0.4)	2 (0.0)	
Smoker	6053 (9.3)	672 (10.1)	0.128
Data not in record	96 (0.1)	8 (0.1)	
Race			< 0.001
American Indian/Alaska native	911 (1.4)	91 (1.4)	
Asian	10 535 (16.2)	1119 (16.8)	
Black	3314 (5.1)	473 (7.1)	
Native Hawaiian/Pacific islander	1148 (1.8)	120 (1.8)	
White	32 796 (50.5)	3549 (53.2)	
Mixed race	968 (1.5)	85 (1.3)	
Other	8405 (12.9)	697 (10.4)	
Data not in record	6873 (10.6)	542 (8.1)	
Ethnicity			< 0.001
Hispanic	10 342 (15.9)	892 (13.4)	
Non-Hispanic	53 011 (81.6)	5757 (86.2)	
Data not in record	1597 (2.5)	28 (0.4)	
Distressed communities quintile†			< 0.001
1	24 473 (37.7)	3078 (46.1)	
2	17 412 (26.8)	1691 (25.3)	
3	8891 (13.7)	820 (12.3)	
4	9997 (15.4)	760 (11.4)	
5	3226 (5.0)	248 (3.7)	
Data not in record	951 (1.5)	80 (1.2)	
Hospital neonatal care level			< 0.001
I	7350 (11.3)	141 (2.1)	
II	14 207 (21.9)	1347 (20.2)	
III or IV	43 393 (66.8)	5189 (77.7)	

Data are given as median (interquartile range) or *n* (%). *Before 37 weeks' gestation. †1, most affluent; 5, least affluent. BMI, body mass index.

Table 2 Singleton pregnancy characteristics of 71 627 participants, according to low-dose aspirin recommendation

Characteristic	*No low-dose aspirin (n = 64 950)*	*Low-dose aspirin (n = 6677)*	P
Preterm PE	821 (1.3)	384 (5.8)	< 0.001
Term PE/GH	5921 (9.1)	1602 (24.0)	0.001
Preterm birth*	2936 (4.5)	356 (5.3)	0.003
Placental abruption	499 (0.8)	84 (1.3)	< 0.001
Postpartum hemorrhage	4202 (6.5)	643 (9.6)	< 0.001
Induction of labor	21 562 (33.2)	3012 (45.1)	< 0.001
Cesarean delivery	18 357 (28.3)	2815 (42.2)	< 0.001
Scheduled Cesarean delivery	10 026 (15.4)	1744 (26.1)	< 0.001
Spontaneous vaginal delivery	43 579 (67.1)	3649 (54.7)	< 0.001
Forceps or vacuum application during delivery	3206 (4.9)	220 (3.3)	< 0.001
Birth weight (g)	3370 (3058–3686)	3280 (2936–3620)	< 0.001
Small-for-gestational age†	5096 (7.8)	606 (9.1)	0.002
Stillbirth/neonatal death	234 (0.4)	23 (0.3)	0.915

Data are given as *n* (%) or median (interquartile range). *Before 37 weeks' gestation, not associated with pre-eclampsia (PE). †Less than 10th percentile. GH, gestational hypertension.

Table 3 Propensity score analysis according to low-dose aspirin recommendation in 71 627 singleton pregnancies

Outcome	*No low-dose aspirin (n = 64 950)*	*Low-dose aspirin (n = 6677)*	*OR (95% CI)*	*aOR (95% CI)*
Placental abruption	499 (0.8)	84 (1.3)	1.65 (1.30–2.08)	1.44 (1.04–2.00)
Postpartum hemorrhage	4202 (6.5)	643 (9.6)	1.54 (1.41–1.68)	1.21 (1.05–1.39)
Postpartum hemorrhage stratified by				
Vaginal delivery	2415/46 593 (5.2)	279/3862 (7.2)	1.42 (1.25–1.62)	1.22 (0.97–1.55)
Cesarean delivery	1787/18 357 (9.7)	364/2815 (12.9)	1.38 (1.22–1.55)	1.19 (1.00–1.40)

Data are given as *n* (%) or *n*/*N* (%), unless stated otherwise. aOR, adjusted odds ratio; OR, odds ratio.

Table 4 Study outcomes stratified by presence of pre-eclampsia (PE)/gestational hypertension (GH), according to low-dose aspirin recommendation in 71 627 singleton pregnancies

Outcome	*No low-dose aspirin (n = 64 950)*	*Low-dose aspirin (n = 6677)*	*OR (95% CI)*	*aOR (95% CI)*
Placental abruption				
No PE/GH	427/58 208 (0.7)	63/4691 (1.3)	1.84 (1.41–2.40)	1.51 (1.08–2.11)
PE/GH	72/6742 (1.1)	21/1986 (1.1)	0.99 (0.61–1.61)	1.12 (0.58–2.18)
Postpartum hemorrhage				
No PE/GH	3562/58 208 (6.1)	427/4691 (9.1)	1.54 (1.38–1.71)	1.07 (0.93–1.24)
PE/GH	640/6742 (9.5)	216/1986 (10.9)	1.16 (0.99–1.37)	1.18 (0.89–1.55)

Data are given as *n*/*N* (%), unless stated otherwise. aOR, adjusted odds ratio; OR, odds ratio.

Table 5 Study outcomes and Cesarean delivery stratified by presence of prepregnancy hypertension, according to low-dose aspirin recommendation in 71 627 singleton pregnancies

Outcome	*No low-dose aspirin (n = 64 950)*	*Low-dose aspirin (n = 6677)*	*OR (95% CI)*	*aOR (95% CI)*
Placental abruption				
No prepregnancy hypertension	481/63 448 (0.8)	67/5316 (1.3)	1.67 (1.29–2.16)	1.46 (1.03–2.07)
Prepregnancy hypertension	18/1502 (1.2)	17/1361 (1.2)	1.04 (0.54–2.03)	1.05 (0.51–2.17)
Postpartum hemorrhage				
No prepregnancy hypertension	4059/63 448 (6.4)	506/5316 (9.5)	1.54 (1.40–1.70)	1.22 (1.05–1.42)
Prepregnancy hypertension	143/1502 (9.5)	137/1361 (10.1)	1.06 (0.83–1.36)	0.94 (0.71–1.22)
Cesarean delivery				
No prepregnancy hypertension	17 626/63 448 (27.8)	2116/5316 (39.8)	1.72 (1.62–1.82)	1.31 (1.18–1.46)
Prepregnancy hypertension	731/1502 (48.7)	699/1361 (51.4)	1.11 (0.96–1.29)	1.08 (0.89–1.30)

Data are given as *n*/*N* (%), unless stated otherwise. aOR, adjusted odds ratio; OR, odds ratio.

direction of the effect of LDA was almost always towards higher risk for placental abruption and PPH.

Interpretation of study findings and comparison with existing literature

Strong evidence exists to support the role of LDA in reducing preterm PE in high-risk pregnancy[1,18]. Potential mechanisms include aspirin's role in inhibition of cyclo-oxygenase-1, reduction in thromboxane A2, decreasing platelet aggregation or through its anti-inflammatory properties[19,20]. Multiple clinical practice guidelines recommend LDA in pregnancy identified as high risk for PE, but vary in their strategies for identifying high risk[2–5,21,22]. Guidelines also vary in their recommendations for aspirin dosing and when to discontinue. FIGO guidance recommends 150 mg until 36 weeks' gestation[2], NICE recommends 75–150 mg until delivery[3] and the ACOG recommends 81 mg until delivery[14]. The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends discontinuation at 36 weeks' gestation and a dose of 150 mg of aspirin per day if high-risk status was determined by multivariate screening, and 100–162 mg per day if high-risk was identified by maternal risk factors and blood pressure[21]. The World Health Organization (WHO) recommends 75 mg per day with discontinuation at a locally defined gestational age[22].

Although there remains inconsistency among guidelines about the optimal dose of aspirin, one systematic review found no reduction in preterm or term PE with less than 100 mg of aspirin per day[18], and another reported a trend towards greater reduction in PE with higher doses of aspirin (≥ 75 mg)[9]. A secondary analysis of the Aspirin for Evidence-Based Pre-eclampsia Prevention (ASPRE) trial also demonstrated the relationship between compliance with LDA and reduction in preterm PE[23].

Whether a higher dose of aspirin or its continuation beyond 36 weeks' gestation could be risk factors for bleeding complications remains unclear.

This study adds to the literature supporting a possible association between LDA and bleeding complications in pregnancy. A previous propensity score analysis using Swedish birth data evaluated the association between any recorded use of LDA during pregnancy and bleeding complications[10]. Although the total population of 313 624 was considerably larger than in this study, aspirin exposure was documented in a smaller number of pregnancies ($n = 4088$). Any aspirin use during pregnancy was associated with a 23% increase in the odds for PPH, which was very similar to the findings in this study, but, unlike this study, the aOR for PPH remained statistically significant after exclusion of patients with PE[10]. An almost 10-fold increased odds for neonatal intracranial hemorrhage in the aspirin group was also reported in the Swedish study[10], but this study was underpowered to evaluate this.

A 2019 Cochrane systematic review reported a relative risk of 1.06 (95% CI, 1.00–1.12) for PPH and 1.21 (95% CI, 0.95–1.54) for placental abruption[9]. The authors concluded there was moderate evidence to support a relationship between LDA and these bleeding complications in pregnancy[9]. A 2018 meta-analysis by Roberge *et al.*[24] reported an increased risk of abruption or antepartum hemorrhage in patients taking 100 mg of aspirin who started it after 16 weeks' gestation compared to those who started it at or before 16 weeks. A subsequent meta-analysis also reported a trend towards increased risk of placental abruption, but only when aspirin was started after 16 weeks' gestation (relative risk, 1.20 (95% CI, 1.00–1.46))[25]. However, a 2021 USPSTF systematic review reported no statistically significant association between LDA and risk for PPH, placental abruption or newborn intracranial hemorrhage[26].

Two recent randomized controlled trials, the ASPRE trial[1] and the Low-Dose Aspirin in the Prevention of Preeclampsia in China (APPEC) trial[27], did not observe any bleeding issues related to LDA. In the ASPRE trial, which randomized participants to 150 mg of aspirin at 11–14 weeks' gestation, abruption without PE was a prespecified secondary outcome and was not significantly different in the aspirin group compared to the control group. PPH was not evaluated, and it should be noted that the ASPRE trial was underpowered for all of the secondary outcomes. In the APPEC trial, which randomized participants between 12 and 20 weeks' gestation to 100 mg of aspirin per day (discontinuing at 34 weeks' gestation), there was no statistically significant difference between the treatment and control groups for either PPH or abruption, although the reported incidence of abruption was high in both arms of the study. In contrast, Mone *et al.*[11], in a small randomized controlled trial, the Trial of feasibility and acceptability of routine-LDA *vs* Early Screening Test indicated aspirin for Pre-eclampsia Prevention (TEST study) reported a statistically significant, two-fold increase in the odds for antepartum bleeding and for PPH in patients prescribed 75 mg aspirin per day. Unlike the ASPRE and the APPEC trials, which both included participants who were identified as at increased risk for PE, the TEST study participants were low-risk nulliparous patients.

Strengths and limitations

The strengths of this study include the large contemporary cohort and the availability of granular clinical data from the medical record allowing propensity score matching on multiple variables, including markers of socioeconomic status. Limitations of this study include the lack of information about the dose of aspirin, when it was initiated and discontinued, and whether patients actually took aspirin. Tracking the use of LDA for prevention of PE is challenging because aspirin is available over the counter and is not always prescribed when it is recommended in pregnancy[28]. Aspirin exposure in this study was based on documentation of a recommendation from the clinician in the medical record, which has been identified by the Society for Maternal–Fetal Medicine as a quality metric for high-risk patients[28]. Recommendations by clinicians in this study were most likely based on the 2018 ACOG guidelines to prescribe a daily dose of 81 mg aspirin, ideally starting at 12–16 weeks' gestation and to continue until delivery[14]. For the 14.6% of the aspirin-recommendation group who had their first prenatal visit at ≥ 16 week's gestation, starting aspirin at or after 16 weeks' gestation might confer an increased risk of placental abruption[24]. A further limitation is the potential for unaccounted confounding despite propensity score matching; this could include prepregnancy health factors and previous pregnancy complications (for example, PPH) that were not available in the research dataset. Additionally, while prepregnancy hypertension and diabetes were accounted for, there was no indication of the severity of these conditions. The high rate of pregnancy complications, including PE, in the aspirin-recommendation group speaks to this being a very-high-risk patient group.

Clinical and research implications

The findings of this study are important because of increasingly liberal approaches to aspirin use in pregnancy and proposals for universal aspirin recommendation. Our findings, in conjunction with those of previous authors, suggest caution is needed before implementing LDA treatment in an unselected pregnant population. Further research is also needed to evaluate the optimal dose for aspirin and when to discontinue it in pregnancy, in the light of the possible association with bleeding complications.

Conclusions

LDA recommendation in pregnancy was associated with significantly higher risk for PPH and for placental abruption, even after excluding patients who developed

PE or had chronic hypertension. Our results support the need for more research into aspirin and bleeding complications in pregnancy before recommending LDA beyond the highest risk pregnancies.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Definitions of features in Obstetrical Care Outcomes Assessment Program database used for data collection and propensity score estimation

Table S2 Inverse-probability treatment weighted and unweighted *P*-values of features in propensity score analysis