Khalil Asma (Orcid ID: 0000-0003-2802-7670)

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

V. Souter[1], I. Painter[1], K. Sitcov[1] and A. Khalil[2]

[1]Foundation for Health Care Quality, Seattle, WA, USA

[2]Fetal Medicine Unit, St George's Hospital, St George's University of London, UK.

Corresponding author: Vivienne Souter, MD

Email address: vsouter@qualityhealth.org

Mailing Address: Foundation for Health Care Quality, 705 Second Avenue, Suite 410, Seattle, WA 98104, USA.

Short title: Aspirin and bleeding complications

Keywords

Low dose aspirin; preeclampsia; pregnancy; bleeding complications; propensity score analysis; abruption; postpartum hemorrhage; gestational hypertension

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.27472

Contribution

What are the novel findings of this work?

This propensity score analysis found that a documented clinician recommendation for low dose aspirin 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 low dose aspirin 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 low dose aspirin beyond the highest-risk pregnancies.

ABSTRACT

Objectives: Low dose aspirin 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 low dose aspirin 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 U.S. hospitals (between January 2019 and December 2021). Pregnancies complicated by placenta previa/accreta, births occurring at less than 24 weeks' gestation, multiple pregnancies, or missing data 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 low dose aspirin recommendation and placental abruption or postpartum hemorrhage was estimated by inverse probability weighting using the propensity scores.

Results: We included 71,627 pregnancies in the final analysis. Aspirin was recommended to 6,677 (9.3%) and was more likely to be recommended for pregnant individuals who were older ($p<0.001$), had a higher body mass index (BMI) ($p<0.001$), had pre-pregnancy hypertension ($p<0.001$), and who did not have a spontaneous vaginal birth ($p<0.001$). Overall, 1,205 (1.7%) of the study cohort developed preterm preeclampsia: 1.3% in the no aspirin and 5.7% in the aspirin group. After inverse probability weighting with propensity scores, aspirin was associated with increased risk of placental abruption (adjusted OR 1.44; 95% CI 1.04, 2.00) and postpartum hemorrhage (adjusted OR 1.21; 95% CI, 1.05,1.39). The 'number needed to harm' with low dose aspirin was 1 in 79 (95% CI 1 in 43, 1 in 330) for postpartum hemorrhage and 1 in 287 (95% CI 1 in 127, 1 in 3151) for placental abruption.

Conclusions: Low dose aspirin recommendation in pregnancy was associated with increased risk for placental abruption and for postpartum hemorrhage. Our results support the need for more research into aspirin and bleeding complications in pregnancy before recommending it beyond the highest risk pregnancies.

INTRODUCTION

Low dose aspirin reduces the risk of preterm preeclampsia in singleton pregnancies identified as at 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 preeclampsia risk assessment at 11-14 weeks' gestation as the preferred approach to identify patients for low dose aspirin in pregnancy,[2] the National Institute for Health and Care Excellence 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 low dose aspirin for pregnant people even with one moderate risk factor,[5] which could result in 85% of the pregnant population in the US being eligible for low dose aspirin.[6]

Some authors have gone further and made a case for low dose aspirin 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 low dose aspirin was recommended compared to those where it was not.

METHODS

Setting and Design

This retrospective multicenter cohort study included data from 72,598 singleton births (between January 2019 and December 2021) at 19 U.S. hospitals 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 and 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 previously reported.[12] The Western-Copernicus Group Institutional Review Board (WCG IRB) deemed research using de-identified OB COAP data as exempt from IRB review.

Study population

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

Race and ethnicity were from self-reported entries in the medical record. The Economic Innovation Group's Distressed Community Index (https://eig.org/distressed-community), which assigns quintiles of economic well-being of the area in which the patient lives, was used as a marker of socioeconomic status.[13]

Exposure

The exposure was a recommendation for low dose aspirin during pregnancy documented in the medical record. In 2014 the USPSTF recommended low dose aspirin for prevention of preeclampsia 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 in September 2021,[5] but most of the

births in the current dataset occurred before this time and so clinical practice was likely based predominantly on the 2014 guidance. Low dose aspirin dose and timing in pregnancy were not available in the database but the USPSTF recommends 81mg aspirin per day starting between 12 and 16 weeks' gestation and continuing until delivery.[4,5]

Outcomes

The main outcomes of interest were postpartum hemorrhage and placental abruption. Neonatal intracranial hemorrhage was also investigated as a secondary outcome. All outcomes were based on a clinical diagnosis of the outcome in the medical record. The American College of Obstetricians and Gynecologists (ACOG) defines postpartum hemorrhage as blood loss of 1000ml or more (including blood loss during the delivery) or blood loss with signs or symptoms of hypovolemia, in the first 24 hours after delivery.[14,15] ACOG defines placental abruption as separation of the placenta before birth and in the absence of placenta previa.[14] Stillbirths were defined as any antepartum or intrapartum fetal loss and neonatal deaths included deaths within the first 28 days postnatally.

Statistical Analysis

We examined associations between individual features and low dose aspirin using descriptive statistics and Fisher's exact test. We used logistic regression with robust standard errors and stabilized inverse probability weights to examine associations between LDA and outcomes. 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 Supplementary Table 1. 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 (IPTW) 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 an LDA recommendation were weighted by 1/p, while individuals who did not receive an LDA recommendation were weighted by 1/(1-p).

The reason to use this approach is that, in general, IPTW 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 features (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 Supplementary Table 2. 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. Parity was included in the propensity score model as an interaction term with age category, chronic hypertension, and obesity to meet this standard.

Sub-analyses were performed stratifying the propensity score analyses by cesarean versus vaginal birth, by preeclampsia versus no preeclampsia, and by pre-pregnancy hypertension versus no pre-pregnancy hypertension, in order to evaluate the possibility of heterogeneous effects of aspirin in these subgroups. All analyses were conducted in R version 4.02[16]

RESULTS

Of 71,627 singleton births in the final study cohort, low dose aspirin was recommended for 6,677 (9.3%). Patients with a low dose aspirin recommendation were more likely to be 35 years or older (44.2% versus 20.8%; p<0.001), have a BMI or 30kg/m^2 or higher (67.8% versus 55.4%; p<0.001), have pre-pregnancy hypertension (20.4% versus 2.3%; p<0.001), and have pre-pregnancy diabetes (6.8% versus 1.2%; p<0.001), and less likely to be nulliparous (31.5% versus 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 low dose aspirin group (Table 1). Gestational age at the first prenatal visit was available for 99.5% of the aspirin recommendation group and was at 16 weeks' gestation or later in 833 (12.5%)

More pregnancy complications were also observed in the aspirin group including preterm preeclampsia (5.8% versus 1.3%; p<0.001), term preeclampsia / gestational hypertension (24.0% versus 9.1%; p=0.001), and cesarean birth (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% versus 0.8%, p<0.001) as was the incidence of postpartum hemorrhage (9.6% versus 6.5%; p<0.001). There was no significant difference in the rate of stillbirth / neonatal death within the first 28 days between the two groups (0.34% versus 0.36%; p=0.915) (Table 2).

In the propensity score analysis, the adjusted odds of placental abruption in the aspirin compared to the no aspirin group were 1.44 (95% CI 1.04, 2.00). The adjusted odds of postpartum hemorrhage were 1.21 (95% CI 1.05,1.39) (Table 3). The increased odds for placental abruption in the aspirin group remained statistically significant irrespective of the mode of delivery (cesarean or vaginal birth) (Table 3). There was only a small number of neonates with intracranial hemorrhage, individual cell sizes were too small to be reported, and the confidence intervals 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 sub-analyses, after exclusion of patients who developed preeclampsia, the adjusted odds for placental abruption remained significantly higher (aOR 1.51; 95% 1.08, 2.11) but the adjusted odds for postpartum hemorrhage did not (aOR 1.07; 95% CI 0.93, 1.24) (Table 4). When stratified by pre-pregnancy hypertension, the adjusted odds ratios for placental abruption (aOR 1.46; 95% CI 1.03, 2.07) and for postpartum hemorrhage (aOR 1.22; 95% CI 1.05, 1.42) were significantly higher in the patients *without* pre-pregnancy hypertension but not in those with a history of pre-pregnancy hypertension (Table 5). The number needed to harm with low dose aspirin was 1 in 79 (95% CI 1 in 43, 1 in 330) for postpartum hemorrhage and 1 in 287 (95% CI 1 in 127, 1 in 3151) for placental abruption.

The rate of cesarean birth was 42.2% in the aspirin group and 28.3% in the no aspirin group (aOR 1.21; 1.09, 1.33). After exclusion of patients with previous cesarean births and exclusion of placental abruptions, 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 our study, low dose aspirin recommendation in pregnancy was associated with a 44% increase in the odds for placental abruption and a 21% increase in the odds for postpartum hemorrhage, based on a propensity score analysis with inverse probability 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 postpartum hemorrhage and 1 in 287 for placental abruption. After exclusion of patients who developed preeclampsia, an increased risk persisted for placental abruption but not for postpartum hemorrhage. When stratified by pre-pregnancy hypertension, the odds for placental abruption and for postpartum hemorrhage were significantly increased only in the patients *without* pre-pregnancy hypertension. Although not all of the subanalysis results were statistically significant, the direction of the effect of low dose aspirin was almost always towards higher risk for placental abruption and postpartum hemorrhage.

Interpretation of study findings and comparison with existing literature

Strong evidence exists to support the role of low dose aspirin in reducing preterm preeclampsia in high risk pregnancies.[1,17] 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.[18,19] Multiple clinical practice guidelines recommend low dose aspirin in pregnancies identified as at high risk for preeclampsia but vary in their strategies for identifying high risk.[2-5,20,21] Guidelines also vary in their recommendations for aspirin dosing and when to discontinue it. FIGO guidance recommends 150mg until 36 weeks' gestation,[2] NICE recommends 75-150mg until delivery,[3] and the USPSTF recommends 81mg until delivery.[4,5] The International Society for the Study of Hypertension in Pregnancy recommends discontinuation at 36 weeks' gestation and a dose of 150mg of aspirin per day if high risk status was determined by multivariate screening and 100-162mg per day if high risk identified by maternal risk factors and blood

pressure.[20] The World Health Organization recommends 75mg per day with discontinuation at a locally defined gestational age.[21]

Although there remains inconsistency among guidelines about the optimal dose of aspirin, one systematic review found no reduction in preterm or term preeclampsia with less than 100mg of aspirin per day,[17] and another reported a trend towards greater reduction in preeclampsia with higher doses of aspirin (>=75mg).[9] A secondary analysis of the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial also demonstrated the relationship between compliance with low dose aspirin and reduction in preterm preeclampsia.[22] Whether a higher dose of aspirin or its continuation beyond 36 weeks' gestation could be risk factors for bleeding complications, remains unclear.

Our study adds to the literature supporting a possible association between low dose aspirin and bleeding complications in pregnancy. A previous propensity score analysis using Swedish birth data evaluated the association between any recorded use of low dose aspirin during pregnancy and bleeding complications.[10] Although the total population of 313,624 was considerably larger than our study, aspirin exposure was documented in a smaller number of pregnancies (4088 versus 6677). Any aspirin use during pregnancy was associated with a 23% increase in the odds for postpartum hemorrhage which was very similar to the findings in our study but, unlike our study, the adjusted odds ratio for postpartum hemorrhage remained statistically significant after exclusion of patients with pre-eclampsia.[10] An almost 10-fold increased odds for neonatal intracranial hemorrhage in the aspirin group was also reported in the Swedish study[10] but our 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 postpartum hemorrhage 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 low dose aspirin and these bleeding complications in pregnancy.[9] A 2018 meta-analysis by Roberge et al reported an increased risk of abruption or antepartum hemorrhage in patients taking 100mg of aspirin who

started it after 16 weeks' gestation compared to those who started it before 16 weeks.[23] A subsequent meta-analysis also reported a trend towards increased risk of placental abruption but only when aspirin was started at after 16 weeks' gestation (relative risk 1.20; 95% CI, 1.00 – 1.46).[24] However, a 2021 USPSTF systematic review reported no statistically significant association between low dose aspirin and risk for postpartum hemorrhage, placental abruption, or newborn intracranial hemorrhage.[25]

Two recent randomized controlled trials, the ASPRE trial and the Low Dose Aspirin in the Prevention of Preeclampsia in China (APPEC) trial did not observe any bleeding issues related to low dose aspirin. In the ASPRE trial, which randomized participants to 150mg of aspirin at 11 to 14 weeks' gestation, abruption without preeclampsia was a pre-specified secondary outcome and was not significantly different in the aspirin compared to the control group. Postpartum hemorrhage 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 100mg of aspirin per day (discontinuing at 34 weeks' gestation), there was no statistically significant difference between the treatment and control groups for either postpartum hemorrhage or abruption, although the reported incidence of abruption was high in both arms of the study.[1,26] In contrast, Mone et al, in a small randomized controlled trial, the 'Trial of feasibility and acceptability of routine-low dose aspirin versus 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 postpartum hemorrhage in patients prescribed 75mg aspirin per day.[11] Unlike the ASPRE and the APPEC trials which both included participants who were identified as at increased risk for pre-eclampsia, the TEST study participants were low risk nulliparous patients.

Strengths and limitations

The strengths of the 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 our 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 low dose aspirin for prevention of preeclampsia is challenging because aspirin is available over the counter and is not always prescribed when it is recommended in pregnancy.[27] Aspirin exposure in our 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.[27] Recommendations by clinicians in this study were most likely based on the 2014 US guidelines to prescribe a daily dose of 81mg starting at 12-16 weeks' gestation and to continue aspirin until delivery.[4,5] For the 12.5% of the aspirin recommendation group who had their first prenatal visit at or after 16 week's gestation, the likelihood is that they started aspirin after 16 weeks' gestation which might confer an increased risk of abruption. A further limitation is the potential for unaccounted confounding despite propensity score matching and could include pre-pregnancy health factors and previous pregnancy complications (for example, postpartum hemorrhage) that were not available in the research dataset. Additionally, while pre-pregnancy hypertension and diabetes were accounted for, there was no indication of the severity of these conditions. The high rate of pregnancy complications, including pre-eclampsia, 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 study findings in conjunction with those of previous authors, suggest caution is needed before implementing low dose aspirin 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

Low dose aspirin recommendation in pregnancy was associated with significantly higher risk for placental abruption and for postpartum hemorrhage, even after excluding patients who developed preeclampsia or had chronic hypertension. Our results support the need for more research into aspirin and bleeding complications in pregnancy before recommending low dose aspirin beyond the highest risk pregnancies.

Acknowledgements: The authors thank the members of the Obstetrical Care Outcomes Assessment Program (OB COAP) for contributing the quality improvement data upon which this manuscript is based as well as the OB COAP Management Committee for their leadership of the collaborative. This study was presented as a poster at the Society of Maternal Fetal Medicine Meeting, San Francisco, in February, 2023 and published as an abstract online and in the AJOG supplement accompanying the meeting.

Conflict of Interest: Vivienne Souter is employed as a Medical Director for Natera. The current work was performed independently of her role at Natera.

Funding: This work was supported by Azure sponsorship credits granted by Microsoft's AI for Good Research Lab.

REFERENCES

1 Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Meiri H, Gizurarson S, Maclagan K, Nicolaides KH. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017;377:613-622.

2 Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, McAuliffe F, da Silva Costa F, von Dadelszen P, McIntyre HD, Kihara AB, Di Renzo GC, Romero R, D'Alton M, Berghella V, Nicolaides KH, Hod M. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet. 2019;145 Suppl 1:1-33.

3 Hypertension in pregnancy: diagnosis and management (NG 133). NICE guideline Published: 25 June 2019. www.nice.org.uk/guidance/ng133.

4 LeFevre ML; U.S. Preventive Services Task Force. Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161:819-26.

5 US Preventive Services Task Force; Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, Donahue KE, Doubeni CA, Kubik M, Li L, Ogedegbe G, Pbert L, Silverstein M, Simon MA, Stevermer J, Tseng CW, Wong JB. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: US Preventive Services Task Force Recommendation Statement. JAMA. 2021;326:1186-1191.

6 Wheeler SM, Myers SO, Swamy GK, Myers ER. Estimated Prevalence of Risk Factors for Preeclampsia Among Individuals Giving Birth in the US in 2019. JAMA Network Open. 2022;5:e2142343.

7 Ayala NK, Rouse DJ. A Nudge Toward Universal Aspirin for Preeclampsia Prevention. Obstet Gynecol. 2019;133:725-728.

8 Mallampati D, Grobman W, Rouse DJ, Werner EF. Strategies for Prescribing Aspirin to Prevent Preeclampsia: A Cost-Effectiveness Analysis. Obstet Gynecol. 2019;134:537-544.

9 Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019, Issue 10. Art. No.: CD004659. DOI: 10.1002/14651858.CD004659.pub3. Accessed 07 May 2023.

10 Hastie R, Tong S, Wikström AK, Sandström A, Hesselman S, Bergman L. Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study. Am J Obstet Gynecol. 2021;224:95.e1-95.e12.

11 Mone F, Mulcahy C, McParland P, Breathnach F, Downey P, McCormack D, Culliton M, Stanton A, Cody F, Morrison JJ, Daly S, Higgins J, Cotter A, Hunter A, Tully EC, Dicker P, Alfirevic Z, Malone FD, McAuliffe FM. Trial of feasibility and acceptability of routine low-dose aspirin versus Early Screening Test indicated aspirin for pre-eclampsia prevention (TEST study): a multicentre randomised controlled trial. BMJ Open. 2018;8(7):e022056.

12 Kauffman E, Souter VL, Katon JG, Sitcov K. Cervical Dilation on Admission in Term Spontaneous Labor and Maternal and Newborn Outcomes. Obstet Gynecol. 2016;127(3):481-488.

13 Economic Innovation Group Distressed Communities Index Available at External link https://eig.org/distressed-community. Accessed May 15, 2023.

14 Menard MK, Main EK, Currigan SM. Executive summary of revitalize initiative: standardizing obstetric data definitions. Obstet Gynecol 2014;124:150-3.

15 Postpartum hemorrhage. Practice Bulletin No. 183. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e168-86.

16 R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

17 Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. Am J Obstet Gynecol. 2018;218:287-293.e1.

18 Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. Am J Obstet Gynecol. 2022;226:S1108-S1119.

19 Ren Y, Zhao Y, Yang X, Shen C, Luo H. Application of low dose aspirin in pre-eclampsia. Front Med (Lausanne). 2023;10:1111371.

20 Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, Kenny LC, McCarthy F, Myers J, Poon LC, Rana S, Saito S, Staff AC, Tsigas E, von Dadelszen P. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2022;27:148-169.

21 WHO recommendations on antiplatelet agents for the prevention of pre-eclampsia [Internet]. Geneva: World Health Organization; 2021.

22 Wright D, Poon LC, Rolnik DL, Syngelaki A, Delgado JL, Vojtassakova D, de Alvarado M, Kapeti E, Rehal A, Pazos A, Carbone IF, Dutemeyer V, Plasencia W, Papantoniou N, Nicolaides KH. Aspirin for Evidence-Based Preeclampsia Prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. Am J Obstet Gynecol. 2017;217:685.e1-685.e5.

23 Roberge S, Bujold E, Nicolaides KH. Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage. Am J Obstet Gynecol. 2018;218:483-489.

24 Turner JM, Robertson NT, Hartel G, Kumar S. Impact of low-dose aspirin on adverse perinatal outcome: meta-analysis and meta-regression. Ultrasound Obstet Gynecol. 2020;55:157-169.

25 Henderson JT, Vesco KK, Senger CA, Thomas RG, Redmond N. Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2021;326:1192-1206.

26 Lin L, Huai J, Li B, Zhu Y, Juan J, Zhang M, Cui S, Zhao X, Ma Y, Zhao Y, Mi Y, Ding H, Chen D, Zhang W, Qi H, Li X, Li G, Chen J, Zhang H, Yu M, Sun X, Yang H. A randomized controlled trial of low-dose aspirin for the prevention of preeclampsia in women at high risk in China. Am J Obstet Gynecol. 2022;226:251.e1-251.

27 Society for Maternal-Fetal Medicine (SMFM); Combs CA, Kumar N, Morgan J; SMFM Patient Safety & Quality Committee. Society for Maternal-Fetal Medicine Special Statement: Prophylactic low-dose aspirin for preeclampsia prevention - Quality metric and opportunities for quality improvement. Am J Obstet Gynecol. 2023 May 3:S0002-9378(23)00277-6. doi: 10.1016/j.ajog.2023.04.039. Epub ahead of print.

Table 1. Characteristics of the study population stratified by the presence of a low dose aspirin recommendation in the medical record or not.

	No Aspirin Recommendation (n=64,950)	**Aspirin Recommendation (n=6,677)**	**p-value**
Median maternal age in years (IQR)	30 (26-34)	34 (29-37)	<0.001
Maternal age >=35 years, n (%)	13531 (20.8%)	2954 (44.2%)	<0.001
Median BMI (IQR) in kg/m2	26.3 (22.9–31.2)	29.3 (24.4–35.3)	<0.001
Maternal BMI >=30 kg/m2, n (%)	35958 (55.4%)	4524 (67.8%)	<0.001
Nulliparity, n (%)	27154 (41.8)	2106 (31.5%)	<0.001
Pre-pregnancy hypertension, n (%)	1502 (2.3%)	1361 (20.4%)	<0.001
Pre-pregnancy diabetes, n (%)	812 (1.2%)	452 (6.8%)	<0.001
Previous preterm birth <37 weeks, n (%)	1601 (2.5%)	340 (5.1%)	<0.001
Previous stillbirth, n (%)	696 (1.1%)	167 (2.5%)	<0.001
1st Prenatal visit >16weeks	11630 (17.9%)	833 (12.5%)	<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%)	
Smoking	6053 (9.3%)	672 (10.1%)	0.128
Data not in record	96 (0.1%)	8 (0.1%)	
Race n (%)			<0.001
American Indian/Alaska Native	911 (1.4%)	91 (1.4%)	
Asian	10535 (16.2%)	1119 (16.8%)	
Black	3314 (5.1%)	473 (7.1%)	
Native Hawaiian / Pacific Islander	1148 (1.8%)	120 (1.8%)	
White	(50.5%	(53.2%)	
Multiple Race	968 (1.5%)	85 (1.3%)	
Other Race	8405 (12.9%)	697 (10.4%)	
Data not in record	6873 (10.6%)	542 (8.1%)	
Ethnicity n (%)			<0.001
Hispanic	10342 (15.9%)	892 (13.4%)	
Data not in record	1597 (2.5%)	28 (0.4%)	
Distressed Communities Quintile			<0.001

1 Most affluent	24473 (37.7%)	3078 (46.1%)	
2	17412 (28.8%)	1691 (25.3%)	
3	8891 (13.7%)	820 (12.3%)	
4	9997 (15.4%)	760 (11.4%)	
5 Least affluent	3226 (5.0%)	248 (3.7%)	
Data not in record	951 (1.5%)	80 (1.2%)	
Neonatal level of care at Hospital, n (%)			<0.001
I	7350 (11.3%)	141 (2.1%)	
II	14207 (21.9%)	1347 (20.2%)	
III or IV	43393 (66.8%)	5189 (77.7%)	

Table 2. Pregnancy course stratified by low dose aspirin recommendation during pregnancy.

	No Aspirin Recommendation (n= 64,950)	Aspirin Recommendation (n=6,677)	p-value
Preterm preeclampsia, n (%)	821 (1.3%)	384 (5.8%)	<0.001
Term preeclampsia/ gestational hypertension n (%)	5921 (9.1)	1602 (24.0)	0.001
Preterm birth (<37 weeks) not associated with preeclampsia	2936 (4.5%)	356 (5.3%)	0.003
Placental abruption, n (%)	499 (0.8%)	84 (1.3%)	<0.001
Postpartum hemorrhage	821 (6.5%)	384 (9.6%)	<0.001
Induction of labor, n (%)	21562 (33.2%)	3012 (45.1%)	<0.001
Cesarean birth n (%)	18357 (28.3%)	2815 (42.2%)	<0.001
Scheduled cesarean birth n (%)	10026 (15.4%)	1744 (26.1%)	<0.001
Spontaneous vaginal birth, n (%)	43579 (67.1%)	3649 (54.7%)	<0.001
Forceps or Vacuum delivery, n (%)	3206 (4.9%)	220 (3.3%)	<0.001
Median birthweight in grams (IQR)	3370 (3058-3686)	3280 (2936-3620)	<0.001
Small for gestational age (<10th percentile for gestational age)	5096 (7.8%)	606 (9.1%)	0.002
Stillbirth / neonatal death, n (%)	234 (0.36%)	23 (0.34%)	p=0.915

Table 3. Propensity score analysis by low dose aspirin recommendation during pregnancy.

Postpartum hemorrhage was further stratified by delivery type.

Outcome	No Aspirin Recommendation n (%) (N=64,950)	Aspirin Recommendation n (%) (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	821 (6.5%)	384 (9.6%)	1.54 (1.41, 1.68)	1.21 (1.05, 1.39)
Postpartum hemorrhage stratified by delivery type				
Vaginal birth	2415 (5.2%)	279 (7.2%)	1.42 (1.25, 1.62)	1.22 (0.97, 1.55)
Cesarean	1787 (9.7%)	364 (12.9%)	1.38 (1.22, 1.55)	1.19 (1.00, 1.40)

Table 4. Study outcomes by low dose aspirin recommendation stratified by preeclampsia / gestational hypertension.

Outcome	No Aspirin Recommendation n (%) (N=64,950)	Aspirin Recommendation n (%) (N=6677)	OR (95% CI)	aOR (95% CI)
Placental abruption				
No pre-eclampsia / gestational hypertension	427 (0.7%)	63 (1.3%)	1.84 (1.41, 2.40)	1.51 (1.08, 2.11)
Pre-eclampsia / gestational hypertension	72 (1.1%)	21 (1.1%)	0.99 (0.61, 1.61)	1.12 (0.58, 2.18)
Postpartum hemorrhage				
No pre-eclampsia / gestational hypertension	3562 (6.1%)	427 (9.1%)	1.54 (1.38, 1.71)	1.07 (0.93, 1.24)
Pre-eclampsia / gestational hypertension	640 (9.5%)	216 (10.9%)	1.16 (0.99, 1.37)	1.18 (0.89, 1.55)

Table 5. Study outcomes (placental abruption and postpartum hemorrhage) and cesarean birth by low dose aspirin recommendation, stratified by pre-pregnancy hypertension.

Outcome	No Aspirin n (%) (N=64,950)	Aspirin n (%) (N=6,677)	OR 95% CI	aOR (95% CI)
Placental abruption				
No pre-pregnancy hypertension	481 (0.8%)	67 (1.3%)	1.67 (1.29, 2.16)	1.46 (1.03, 2.07)
Pre-pregnancy hypertension	18 (1.2%)	17 (1.2%)	1.04 (0.54, 2.03)	1.05 (0.51, 2.17)
Postpartum hemorrhage				
No pre-pregnancy hypertension	4059 (6.3%)	506 (9.5%)	1.54 (1.40, 1.70)	1.22 (1.05, 1.42)
Pre-pregnancy hypertension	143 (9.5%)	137 (10.1%)	1.06 (0.83, 1.36)	0.94 (0.71, 1.22)
Cesarean birth				

No pre-pregnancy hypertension	17626 (27.8%)	2116 (39.8%)	1.72 (1.62, 1.82)	1.31 (1.18, 1.46)
Pre-pregnancy hypertension	731 (48.7%)	699 (51.4%)	1.11 (0.96, 1.29)	1.08 (0.89, 1.30)