OBSTETRICS

# Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study

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**BACKGROUND:** Aspirin is offered to pregnant women to prevent preeclampsia, a severe obstetrical complication. Large studies of nonpregnant populations have consistently shown that aspirin prophylaxis increases the risk of hemorrhagic complications. However, there have not been any population-based studies investigating this in a pregnant population.

**OBJECTIVE:** This study aimed to investigate whether aspirin use during pregnancy is associated with an increased risk of bleeding complications.

**STUDY DESIGN:** We performed a register-based cohort study using the Swedish Pregnancy Register wherein we examined 313,624 women giving birth between January 2013 and July 2017. Logistic regression was used to assess the risk of antepartum, intrapartum, and postpartum hemorrhage. A propensity score and inverse probability treatment weighting was used to generate an odds ratio that corrects for differences in baseline characteristics.

**RESULTS:** Aspirin use was registered in 4088 (1.3%) women during pregnancy. Compared with women who did not take aspirin, aspirin use was not associated with bleeding complications during the antepartum period (adjusted odds ratio, 1.22; 95% confidence interval, 0.97−1.54). However, aspirin users had a higher incidence of intrapartum bleeding (2.9% aspirin users vs 1.5% nonusers; adjusted odds ratio, 1.63; 95% confidence interval, 1.30−2.05), postpartum hemorrhage (10.2% vs 7.8%; adjusted odds ratio, 1.23; 95% confidence interval, 1.08−1.39), and postpartum hematoma (0.4% vs 0.1%; adjusted odds ratio, 2.21; 95% confidence interval, 1.13−4.34). The risk of a neonatal intracranial hemorrhage was also increased (0.07% vs 0.01%; adjusted odds ratio, 9.66; 95% confidence interval, 1.88−49.48). After stratifying by mode of birth, a higher incidence of bleeding among aspirin users was present for those who had a vaginal birth but not those who had a cesarean delivery.

**CONCLUSION:** Using aspirin during pregnancy is associated with increased postpartum bleeding and postpartum hematoma. It may also be associated with neonatal intracranial hemorrhage. When offering aspirin during pregnancy, these risks need to be weighed against the potential benefits.

**Key words:** aspirin, bleeding risk, hemorrhage, pregnancy

## Introduction

Preeclampsia is characterized by maternal hypertension and end organ injury and affects 3% to 8% of pregnancies. It is a significant contributor to global maternal and neonatal morbidity and mortality.[1] Aspirin is one of the world's most commonly used drugs.[2] With antiinflammatory and antiplatelet properties, it was first proposed as a treatment to prevent preeclampsia in 1978.[3] Since then, there have been many randomized clinical trials evaluating the effectiveness of aspirin to prevent preeclampsia.[4−8]

Aspirin is now widely offered to women thought to be at an increased risk of developing preeclampsia, a practice that is recommended by most guidelines.[9−13] These generally recommend that pregnant women at high risk or with more than 1 moderate risk factor for preeclampsia take 75 to 150 mg of aspirin daily, from 12 weeks of gestation until 36 to 37 weeks of gestation,[13] or until birth.[10,11,14] Sweden has had a conservative approach with regard to aspirin, and only women considered high risk based on medical and obstetrical history have been offered 75 mg of aspirin from 12 to 36 weeks of gestation. The new 2019 Swedish guidelines are very similar to the National Institute for Health and Care Excellence (NICE) guidelines, where 10% of the pregnant population are expected to be classified as high risk and offered aspirin.[11]

Given the perceived safety of aspirin during pregnancy, there have even been increasing calls to simply administer aspirin universally to all pregnant women.[15−17] A cost-effective analysis published in 2019 theorized that universal administration may prevent 346 cases of preeclampsia and save $8,011,725 compared with the current US Preventative Services Task Force guidelines.[18] Notably, this calculation had an underlying assumption that aspirin is safe, where the authors only considered gastrointestinal bleeding and aspirin-exacerbated respiratory disease as possible adverse effects and did not consider the potential for pregnancy-related bleeding complications.[18]

However, studies of nonpregnant populations have found a consistent association between chronic administration of aspirin and bleeding risk. Recent large randomized trials investigating aspirin for the primary prevention of major cardiovascular events in an older population report an increased risk of bleeding complications.[19−22] A recent meta-analysis of 164,225 participants reported an increased risk for major bleeding complications (hazard ratio [HR], 1.43; 95% confidence interval [CI], 1.30−1.56) and intracranial

**Cite this article as:** Hastie R, Tong S, Wikström AK, et al. Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study. Am J Obstet Gynecol 2020;XX:x.ex−x.ex.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2020.07.023

## AJOG at a Glance

### Why was this study conducted?

Aspirin is widely offered to pregnant women to prevent preeclampsia, one of the most severe obstetrical complications. Large studies of nonpregnant populations taking aspirin to prevent cardiovascular events have decisively shown an increased risk of major hemorrhage. However, there have not been large, adequately powered studies to determine whether there is a risk of bleeding in a pregnant population.

### Key findings

In this population-based register cohort study of 313,624 pregnancies, aspirin use was associated with a clear increased risk of bleeding during labor and the postpartum period.

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

These findings provide clear evidence against more liberal or universal administration of aspirin.

hemorrhage (HR, 1.34; 95% CI, 1.14−1.57) among primary prevention aspirin users,[23] which was confirmed in a second meta-analysis.[24]

To our knowledge, there are no population-based studies addressing whether there is a bleeding risk with aspirin administration during pregnancy (literature search terms presented in Supplemental Table 1). It is a challenging question to examine because aspirin is freely available without a prescription in most countries, but in Sweden, aspirin is a prescribed medication. Sweden also has high-quality national population and quality registers, including the Swedish Pregnancy Register. In the Swedish Pregnancy Register, clinical information is recorded in a uniform manner and medication use is routinely recorded at all trimesters of pregnancy, including aspirin. Therefore, we undertook a population-based register cohort study investigating whether there is an association between aspirin use and bleeding during pregnancy and delivery.

## Methods

### Design and setting

We performed a register-based cohort study using data obtained from the Swedish Pregnancy Register. During 2013, only Stockholm and Gotland regions were included in the register, representing less than one-third of deliveries. However, since 2014, the Swedish Pregnancy Register covers 16 of 20 regions in Sweden (covering 90% of all deliveries) and 98% of all deliveries within the 16 participating regions. The Swedish Pregnancy Register combines prospectively collected data from the Swedish Maternal Health Care Register; the Swedish National Quality Register for Prenatal Diagnosis; and data from electronic standardized prenatal, delivery, and neonatal records, with data collected from the first prenatal visit to the scheduled follow-up 2 to 3 months after delivery.[25]

### Study population

We included women giving birth in Sweden from January 2013 to July 2017. If a woman had given several births during the study period, we only included the last pregnancy and delivery. We excluded 11,254 women with missing maternal prenatal health records and a further 10,735 who had reported use of low-molecular-weight heparin or selective serotonin reuptake inhibitors, owing to the fact that this population might have an increased risk of bleeding. This left a total of 313,624 women for the study.

We extracted maternal demographic variables including age at delivery (categorized into <18 years, 18−34 years, and ≥35 years) and body mass index (BMI) calculated from measured weight and self-reported height registered at first prenatal visit, which was then divided into 2 groups, <30 and ≥30 kg/m$^2$. Country of birth was classified as Sweden, other Nordic countries, other western countries (Europe, North America, Australia, and New Zealand), and nonwestern countries.

We also obtained information on self-reported socioeconomic factors. Years of education were categorized to ≤9 years, 10−12 years, and >12 years. Occupation was defined as employed or government assistance (sick leave, student, or unemployed). Housing situation was defined as living with the father of the child or living in another situation (such as same-sex partner, living alone, or with an extended family). Daily smoking in early pregnancy (yes or no) was recorded at the first prenatal visit, as was the use of alcohol within 3 months before conception, which was determined using the Alcohol Use Disorders Identification Test,[26] where scores ≥6 indicate hazardous use of alcohol or alcohol dependency.

Pregestational and pregnancy variables were extracted from predefined check boxes in the electronic antenatal and birth records and/or from the Swedish version of the International Classification of Diseases, Tenth Revision (ICD-10) (Supplemental Table 2).

### Exposure

Data on aspirin use were obtained from prenatal care records, including the first prenatal visit record (which is a comprehensive record of patient information, sociodemographic data, and medical and obstetrical history) and from each prenatal care visit record, which is typically 8 to 10 visits across pregnancy. Aspirin use during pregnancy was defined as self-reported use of aspirin at any visit during pregnancy.

### Outcomes

The primary outcome was bleeding complications recorded in prenatal or delivery records via the Swedish version of ICD-10, which was categorized into (1) bleeding complications during pregnancy, such as hematemesis (coded

as K92), hematuria (R31), bleeding from the airways (R04), and antepartum hemorrhage (O46) and (2) labor and postpartum complications, such as excessive intrapartum bleeding (O67), postpartum hemorrhage (defined as blood loss >1000 mL recorded in birth records or by ICD-10 code O72), postpartum hematoma (O902 or O717), and neonatal intracranial hemorrhage (P10). Data on whether gastritis occurred were also obtained as assessed through prenatal care records (K92 or K29).

### Additional analyses

Given that the mode of birth may affect the risk of bleeding complications during labor and the postpartum period, we stratified our analyses by vaginal birth or cesarean delivery to examine labor and postpartum outcomes.

To investigate the association between aspirin and bleeding complications without the potential confounding caused by a diagnosis of preeclampsia, we performed sensitivity analyses excluding women who developed preeclampsia.

To investigate the potential of reporting bias, we performed additional analyses investigating a maternal complication unrelated to bleeding (pelvic girdle pain) and associations between paracetamol use and bleeding complications. We selected these 2 variables given that they have no known biological association with bleeding risk.

### Statistical analysis

Characteristics of the population were described according to aspirin use during pregnancy. Aspirin users and nonusers were compared via bivariate analysis using Pearson chi-square test for categorical data and Student *t* test for continuous variables.

Associations between aspirin use and maternal and neonatal complications were estimated by logistic regression and presented as odds ratios (ORs) and 95% CIs.

To adjust for baseline differences in the population by aspirin use, a propensity score and inverse probability treatment weighting (IPTW) was used. The propensity score is the probability of being exposed (aspirin use) given a set of measured covariates, which can be estimated for each individual where the exposure takes the place of the outcome variable and covariates are included as explanatory variables.[27] This methodology attempts to create exchangeability between the exposed and unexposed groups and mimic randomization in observational studies.[27,28] The propensity score was created for each participant using logistic regression, setting aspirin as the outcome and including maternal and socioeconomic factors present at first prenatal visit that included maternal age, BMI, parity, previous cesarean delivery, in vitro fertilization (IVF), country of birth, employment status, smoking status, alcohol risk score, and the presence of pregestational disorders (chronic hypertension, diabetes, endocrine disorders, and inflammatory diseases).

We then used IPTW, whereby the estimated propensity score is used to weight individuals and create a pseudopopulation where the measured covariates are balanced between exposure groups. Exposed individuals were assigned a probability weight of 1/propensity score, whereas the unexposed individuals were assigned a probability weight of 1/(1−propensity score).

The propensity score and IPTW were determined to be successful in balancing covariates and potential confounders in aspirin-exposed and aspirin-unexposed groups by showing that covariates were similarly distributed and not significantly associated with aspirin use after applying IPTW (Supplemental Table 3).

Adjusted analyses were performed using multiple logistic regression including the inverse probability weighting in all models. For the outcomes of gastritis, hematemesis, hematuria, bleeding from the airways, and antepartum hemorrhage, multiple pregnancy was also included as a confounder. Intrapartum and postpartum hemorrhage and postpartum hematoma included multiple pregnancy and preeclampsia as additional confounders. As placenta previa and abruption may mediate maternal prenatal, intrapartum, and postpartum hemorrhage and postpartum hematoma, these were excluded from these analyses. The adjusted analyses of neonatal intracranial hemorrhage included gestational age at delivery and mode of delivery as confounders.

## Results

Of the 313,624 women included in our study, 4088 (1.3%) reported aspirin use during pregnancy. Women using aspirin were older, more obese, and more frequently parous than women who did not take aspirin. In addition, aspirin users were more likely to have a multiple pregnancy, to have conceived through IVF, and to have had a previous cesarean delivery (Table 1). Aspirin users had a higher rate of preexisting medical conditions (including hypertension and diabetes) and pregnancy complications, such as preeclampsia. At the time of birth, women who had used aspirin during pregnancy had higher rates of preterm delivery and induction of labor and were more likely to have a cesarean delivery (Table 1).

### Aspirin use and prenatal complications

The incidence of antepartum hemorrhage among women using aspirin was 2.4% compared with 1.8% among nonusers, which resulted in a crude OR of 1.33 (95% CI, 1.09−1.63). After adjusting via IPTW, the association was no longer significant (adjusted OR [aOR], 1.22; 95% CI, 0.97−1.54). In addition, aspirin use was not associated with gastritis (aOR, 1.33; 95% CI, 0.73−2.40) or the compound outcome of hematemesis, hematuria, or bleeding from the airways (aOR, 1.30; 95% CI, 0.36−4.68) (Table 2).

### Labor and postpartum bleeding complications

Women using aspirin during pregnancy were more likely to experience bleeding during labor and postpartum hemorrhage than those not using aspirin. The incidence of bleeding during labor was 2.9% among aspirin users vs 1.5% in nonusers, with an aOR of 1.63 (95% CI, 1.30−2.05). The incidence of postpartum hemorrhage was 10.2% among aspirin users and 7.8% among nonusers,

TABLE 1
**Maternal characteristics by aspirin use during pregnancy**

| Characteristic | Total births (N=313,624) | Aspirin use | |
|---|---|---|---|
| | | No (n=309,536) | Yes (n=4088) |
| Age (y), mean±SD | 31.1±5.2 | 31.1±5.2 | 33.9±5.4 |
| <35, n (%) | 239,012 (76.2) | 236,625 (76.5) | 1701 (41.6) |
| ≥35, n (%) | 74,503 (23.8) | 72,802 (23.5) | 2387 (58.4) |
| Missing, n (%) | 109 (0.03) | 109 (0.03) | — |
| BMI (kg/m$^2$), mean±SD | 24.8±4.7 | 24.8±4.7 | 26.0±5.4 |
| BMI <30, n (%) | 259,151 (82.6) | 256,032 (82.7) | 3119 (76.3) |
| BMI ≥30, n (%) | 39,724 (12.7) | 38,909 (12.6) | 815 (19.9) |
| Missing, n (%) | 14,749 (4.7) | 14,595 (4.7) | 154 (3.8) |
| Parity, n (%) | | | |
| Nulliparous | 120,770 (38.5) | 119,969 (38.8) | 801 (19.6) |
| 1–3 | 189,269 (60.4) | 186,034 (60.1) | 3235 (79.1) |
| ≥4 | 3585 (1.1) | 3533 (1.1) | 52 (1.3) |
| Multiple pregnancies, n (%) | | | |
| 2–4 fetuses | 4862 (1.6) | 4739 (1.5) | 123 (3.0) |
| Assisted reproduction, n (%) | | | |
| Yes | 16,385 (5.2) | 15,840 (5.1) | 545 (13.3) |
| Missing | 48,797 (15.6) | 48,389 (15.6) | 408 (10.0) |
| Previous cesarean delivery, n (%) | | | |
| Yes | 33,249 (10.6) | 31,828 (10.3) | 1421 (34.8) |
| Country of birth, n (%) | | | |
| Nordic | 204,668 (65.3) | 201,890 (65.2) | 2798 (68.5) |
| Other western | 15,565 (5.0) | 15,378 (5.0) | 187 (4.6) |
| Nonwestern | 58,453 (18.6) | 57,775 (18.7) | 678 (16.6) |
| Missing | 34,918 (11.1) | 34,493 (11.1) | 425 (10.4) |
| Occupation, n (%) | | | |
| Employed | 196,864 (62.8) | 194,208 (62.7) | 2656 (65.0) |
| Government assistance (sick leave, student, unemployed) | 82,063 (26.2) | 81,053 (26.2) | 1010 (25.7) |
| Missing | 34,697 (11.1) | 34,275 (11.1) | 422 (10.3) |
| Smoking at first prenatal visit, n (%) | | | |
| Yes | 14,662 (4.7) | 14,523 (4.7) | 139 (3.4) |
| Missing | 36,567 (11.7) | 36,139 (11.7) | 428 (10.5) |
| Alcohol risk use 3 mo before pregnancy | | | |
| AUDIT >6 | 10,041 (3.2) | 9987 (3.2) | 54 (1.3) |
| Missing | 68,424 (21.8) | 67,569 (21.8) | 855 (20.9) |
| Pregestational disorders, n (%) | | | |
| Hypertension | 1489 (0.5) | 1302 (0.4) | 187 (4.6) |
| Diabetes | 5401 (1.7) | 5271 (1.7) | 130 (3.2) |
| Inflammatory diseases[a] | 2706 (0.9) | 2593 (0.8) | 113 (2.8) |

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**TABLE 1**
**Maternal characteristics by aspirin use during pregnancy** *(continued)*

| Characteristic | Total births (N=313,624) | Aspirin use | |
|---|---|---|---|
| | | No (n=309,536) | Yes (n=4088) |
| Gestational disorders, n (%) | | | |
| Hyperemesis gravidarum | 3317 (1.1) | 3255 (1.1) | 62 (1.5) |
| Preeclampsia—all forms | 9038 (2.9) | 8616 (2.8) | 422 (10.3) |
| Gestational diabetes | 5401 (1.7) | 5271 (1.7) | 130 (3.2) |
| Placenta previa | 1748 (0.6) | 1703 (0.6) | 45 (1.1) |
| Placental abruption | 1164 (0.4) | 1139 (0.4) | 25 (0.6) |
| Gestational age at delivery (wk), mean±SD | 39.3±1.9 | 39.3±1.9 | 38.5±2.3 |
| Induction of labor[b], n (%) | | | |
| Yes | 53,727 (17.1) | 52,591 (17.0) | 1136 (27.8) |
| Missing | 1045 (0.3) | 1032 (0.3) | 13 (0.3) |
| Mode of delivery, n (%) | | | |
| Spontaneous vaginal | 241,459 (76.9) | 239,019 (77.2) | 2440 (56.7) |
| Instrumental vaginal | 16,837 (5.4) | 16,653 (5.4) | 184 (4.5) |
| Cesarean delivery | 55,328 (17.6) | 53,864 (17.4) | 1464 (35.8) |

*AUDIT*, Alcohol Use Disorders Identification Test; *BMI*, body mass index; *SD*, standard deviation.

[a] Inflammatory bowel disease and systemic lupus erythematosus; [b] Exclude elective cesarean delivery.

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with an aOR of 1.23 (95% CI, 1.08−1.39; Table 3). In addition, women using aspirin were more likely to develop a postpartum hematoma, with an incidence of 0.4% among aspirin users vs 0.1% among nonusers (aOR, 2.21; 95% CI, 1.13−4.34).

There was also an association between aspirin use and neonatal intracranial hemorrhage, with an incidence of 0.07% among aspirin users vs 0.01% among nonusers (aOR, 9.66; 95% CI, 1.88−49.48; Table 3).

## Labor and postpartum complications by mode of birth

When the data were stratified for mode of birth, there was no longer an association between aspirin use and bleeding during labor after either a vaginal or cesarean delivery. An increase in postpartum hemorrhage was found among aspirin users who gave birth vaginally (aOR, 1.25; 95% CI, 1.07−1.45) but not among those who gave birth via cesarean delivery (aOR, 0.95; 95% CI, 0.78−1.16). Similarly,

**TABLE 2**
**Prenatal complications by aspirin use during pregnancy**

| Outcome | No aspirin use (N=309,536) | Aspirin use (N=4088) | | |
|---|---|---|---|---|
| | | | OR (95% CI) | |
| | N (%) | N (%) | Crude | Adjusted |
| Bleeding complications during pregnancy | | | | |
| Antepartum hemorrhage[a] | 5585 (1.82) | 97 (2.41) | 1.33 (1.09−1.63) | 1.22 (0.97−1.54) |
| Hematemesis, hematuria, bleeding from the airways | 203 (0.07) | 3 (0.07) | 1.12 (0.36−3.5) | 1.30 (0.36−4.68) |
| Side effects during pregnancy | | | | |
| Gastritis | 724 (0.23) | 13 (0.32) | 1.36 (0.76−2.36) | 1.33 (0.73−2.40) |

Adjusted ORs and 95% CIs were retrieved via logistic regression with inverse probability weighting of treatment and multiple pregnancy included as a covariate for all analyses.

*CI*, confidence interval; *OR*, odds ratio.

[a] Excludes cases with placenta previa or abruption; N=310,759 included in analysis. N=313,624 included in all other analyses.

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**TABLE 3**
**Labor and postpartum complications by aspirin use during pregnancy**

| | No aspirin use (N=309,536) | Aspirin use (N=4088) | | |
|---|---|---|---|---|
| | | | OR (95% CI) | |
| Outcome | N (%) | N (%) | Crude | Adjusted |
| Intrapartum hemorrhage[a] | 4695 (1.53) | 117 (2.91) | 1.93 (1.60–2.32) | 1.63 (1.30–2.05) |
| Postpartum hemorrhage[a] | 24,036 (7.84) | 411 (10.23) | 1.34 (1.21–1.49) | 1.23 (1.08–1.39) |
| Postpartum hematoma | 321 (0.10) | 17 (0.42) | 4.02 (2.47–6.56) | 2.21 (1.13–4.34) |
| Neonatal intracranial hemorrhage[b] | 17 (0.01) | 3 (0.07) | 13.37 (3.92–45.64) | 9.66 (1.88–49.48) |

Adjusted ORs and 95% CIs were retrieved via logistic regression with inverse probability weighting of treatment and multiple pregnancy and preeclampsia included as covariates for analysis of intrapartum and postpartum hemorrhage and postpartum hematoma.

*CI*, confidence interval; *OR*, odds ratio.

[a] Cases of placenta previa and abruption were excluded from analyses; N=310,759 included in analysis; [b] Adjusted via inverse probability weighting of treatment and gestational age at delivery and mode of delivery included as covariates; N=313,581 included in analysis.

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among women giving birth vaginally, those using aspirin were more likely to experience postpartum hematoma (aOR, 20.41; 95% CI, 2.62–158.93) and have an infant with neonatal intracranial hemorrhage (aOR, 17.07; 95% CI, 3.70–78.86) than those not using aspirin. Among women who gave birth via cesarean delivery, no association was found between aspirin use and postpartum hematoma or neonatal intracranial hemorrhage (Table 4).

### Subgroup analyses

In the first sensitivity analysis, women who developed preeclampsia were excluded. Women using aspirin remained more likely to develop bleeding during labor (aOR, 1.69; 95% CI, 1.33–2.14) and postpartum hemorrhage (aOR, 1.27; 95% CI, 1.12–1.45) and experience postpartum hematoma (aOR, 2.67; 95% CI, 1.32–5.41). Neonatal intracranial hemorrhage was no longer associated with aspirin use in this adjusted analysis (aOR, 3.74; 95% CI, 0.80–17.42) (Table 5).

To assess whether reporting bias may be an alternative explanation for our findings, we investigated whether aspirin use was associated with pelvic girdle pain, and no association was found (data not shown). We also investigated the association between paracetamol and bleeding where there was no increased association with bleeding during pregnancy among women who had taken paracetamol compared with nonusers (Supplemental Table 4).

## Discussion

### Principal findings

In this population-based register study, the use of aspirin during pregnancy was associated with increased bleeding complications in the postpartum period among women giving birth vaginally. Of possible concern, there may also be an increased risk of neonatal intracranial hemorrhage and maternal postpartum hematoma, although numbers were low.

### Results

To our knowledge, this is the first population-based register cohort study investigating aspirin use during pregnancy and bleeding complications. Our findings are in agreement with a 2019 Cochrane meta-analysis, which included 19 trials (n=23,769) investigating postpartum hemorrhage and found that antiplatelet agents slightly increased the risk of postpartum hemorrhage (relative risk, 1.06; 95% CI, 1.00–1.12).[29] In addition, most included trials were investigating low-dose aspirin, and most participants received doses below 75 mg, whereas in this study, women were likely to be receiving 75 mg daily. The same investigators initially reported no increased bleeding risk in earlier individual patient data,[30] but those data were included in this recent update.

In support of the plausibility of our findings is the fact that it broadly agrees with large population studies among a nonpregnant population that consistently report an increased risk of bleeding complications with daily aspirin administration. These include an increased risk of major and fatal bleedings, albeit in an older population with extended exposure period.[31,32] Counter to our findings, those studies have also reported an increased risk of gastrointestinal bleeding.[31] This difference may be attributed to the fact that the obstetrical population are younger and are likely to have less underlying gastrointestinal pathology and a shorter exposure. Furthermore, our data are derived solely from the Swedish Pregnancy Register, and there is a risk of nonobstetrical diagnoses being underreported.

We identified a possible association between taking aspirin during pregnancy and neonatal intracranial hemorrhage. There have been previous reports that have observed this association. A prospective study published in 1981 of 108 preterm infants reported an increased risk of intracranial hemorrhage among women using aspirin during pregnancy; however, the dose of aspirin was not described.[33] Similar findings have been reported in other

**TABLE 4**
**Labor and postpartum complications by aspirin use during pregnancy and mode of delivery**

| Outcome | Vaginal deliveries | | | | | Cesarean deliveries | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No aspirin use (N=255,670) | Aspirin use (N=2624) | | | | No aspirin use (N=53,866) | Aspirin use (N=1464) | | | |
| | N (%) | N (%) | OR (95% CI) | | | N (%) | N (%) | OR (95% CI) | | |
| | | | Crude | Adjusted | | | | Crude | Adjusted | |
| Intrapartum hemorrhage[a] | 204 (0.08) | 1 (0.04) | 0.49 (0.07–3.41) | 0.25 (0.03–1.86) | | 4491 (8.70) | 116 (8.27) | 0.95 (0.78–1.15) | 0.96 (0.76–1.21) | |
| Postpartum hemorrhage[a] | 17,572 (6.89) | 244 (9.33) | 1.39 (1.22–1.59) | 1.25 (1.07–1.45) | | 6464 (12.52) | 167 (11.90) | 0.94 (0.80–1.11) | 0.95 (0.78–1.16) | |
| Postpartum hematoma | 11 (0.004) | 1 (0.04) | 8.86 (1.14–68.66) | 20.41 (2.62–158.93) | | 310 (0.58) | 16 (1.09) | 1.91 (1.15–3.16) | 0.99 (0.55–1.76) | |
| Neonatal intracranial hemorrhage[b] | 10 (0.004) | 2 (0.08) | 19.50 (4.27–89.05) | 17.07 (3.70–78.86) | | 7 (0.01) | 1 (0.07) | 5.26 (0.65–42.77) | 4.93 (0.60–40.59) | |

Adjusted ORs and 95% CIs were retrieved via logistic regression with inverse probability weighting of treatment and multiple pregnancy and preeclampsia included as covariates for all analyses.

*CI*, confidence interval; *OR*, odds ratio.

[a] Cases of placenta previa and abruption were excluded from analyses; N=257,736 vaginal delivery and N=53,023 cesarean delivery analyses; [b] Adjusted analysis via inverse probability weighting of treatment and gestational age at delivery included as a covariate; N=258,262 vaginal delivery and N=55,319 cesarean delivery analyses.

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small trials and case reports.[34] Conversely, a 2007 Cochrane meta-analysis of randomized controlled trials found that among 10 trials and 26,184 babies, there was no association between aspirin use and neonatal intraventricular hemorrhage.[35] Given the low number of cases seen within this study, caution is required in interpreting these findings.

Defective placental implantation and poor placental perfusion are thought to be important factors in the pathogenesis of preeclampsia.[36] It has been postulated that aspirin may reduce the risk of preeclampsia by decreasing local thromboses in the maternal vessels supplying the placenta via its antiplatelet properties.[37] This then may improve perfusion to the placenta.[37] If this is the case, then it is plausible that an improved maternal vascular supply to the placenta may also predispose women to an increased bleeding tendency during labor, even if aspirin was ceased at around 36 weeks of gestation. In our data, we had no information about when women stopped taking aspirin. We note Swedish recommendations of cessation of aspirin at 36 weeks of gestation.

Stratifying our analysis by mode of birth revealed aspirin to only be associated with an increased bleeding risk among women who birthed vaginally. The reason for this is not entirely clear, and although it cannot be elucidated within this study, it does warrant further investigation. In addition, it is plausible that the association between aspirin and bleeding may be attributed to an interaction between aspirin and uterotonics. In Sweden, prophylactic oxytocin, at 5 to 10 international units, is routinely offered to all women. Given that all women receive oxytocin, it is difficult to determine whether an interaction with aspirin is an explanation for the differences in postpartum bleeding.

## Strengths and limitations

This study has a number of strengths. It is a population-based study with data from recent years. The exposure was self-reported and not derived from dispensed prescriptions (which might be regarded as both a strength and limitation), increasing the likelihood of actual

**TABLE 5**
**Labor and postpartum bleeding complications among women who did not develop preeclampsia**

| | No aspirin use (N=300,920) | Aspirin use (N=3666) | | |
|---|---|---|---|---|
| | | | OR (95% CI) | |
| Outcome | N (%) | N (%) | Crude | Adjusted |
| Intrapartum hemorrhage[a] | 4446 (1.49) | 102 (2.83) | 1.92 (1.58–2.35) | 1.69 (1.33–2.14) |
| Postpartum hemorrhage[a] | 22,804 (7.65) | 364 (10.10) | 1.36 (1.22–1.51) | 1.27 (1.12–1.45) |
| Postpartum hematoma | 258 (0.09) | 14 (0.38) | 4.47 (2.60–7.66) | 2.67 (1.32–5.41) |
| Neonatal intracranial hemorrhage[b] | 11 (0.003) | 2 (0.05) | 14.93 (3.31–67.39) | 3.74 (0.80–17.42) |

All cases of preeclampsia excluded from analyses. Adjusted ORs and 95% CIs were retrieved via logistic regression with inverse probability weighting of treatment and multiple pregnancy included as covariates.

*CI*, confidence interval; *OR*, odds ratio.

[a] Excludes cases with placenta previa or abruption; N=301,852 included in analysis; [b] Adjusted analysis via logistic regression with inverse probability weighting of treatment and gestational age at delivery and mode of delivery included as covariates; N=304,546 included in analysis.

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intake of aspirin. In our study, 1.3% of women used aspirin, a number that was similar to the reported usage of anticoagulants in previous publications from the Swedish-prescribed drug register.[38] The population was sufficiently large to perform subgroup analyses, which permitted us to explore important mediating factors such as mode of delivery and confounding by indication, in this case women developing preeclampsia. In addition, we performed 2 subanalyses that minimize the possibility of differential misclassification of the exposure by reporting bias. We showed that there was no association between aspirin use and pelvic girdle pain (a pregnancy complication that is not related to bleeding) and no association between reported paracetamol use and bleeding during pregnancy (a drug with no obvious biological association with a tendency to bleed).

There are some limitations to this study. Our data were not derived from randomized clinical trials but from a population register, and consequently, women using aspirin had different baseline covariates. To overcome potential bias arising from unbalanced maternal covariates, we used a propensity score and inverse probability weighting approach. This was found to be effective in improving the balance of maternal covariates between aspirin users and nonusers and therefore reduced the potential for bias. Despite this, there might still be residual confounding. Given that the most common indication for aspirin use during pregnancy is to prevent preeclampsia, a condition that is itself associated with increased bleeding, there is the potential for confounding by indication. To explore this, we performed subgroup analyses excluding women who developed preeclampsia and showed that the positive association between aspirin use and bleeding complications persisted. Another limitation is that although the use of aspirin is recorded, the Swedish Pregnancy Register does not record the specific dose. Swedish guidelines recommend 75 mg of aspirin daily from gestational weeks 12 to 36 for the primary prevention of preeclampsia, which is the main indication for use during pregnancy. Thus, it is likely that most aspirin users will have taken this dose. In addition, nonobstetrical diagnoses may not have been accurately recorded in prenatal records, which may have resulted in underreporting.

## Implications

Commonly regarded as a benign drug, we have discovered an association between aspirin and bleeding during the postpartum period among women with vaginal delivery, where pregnancy and delivery are already times of considerable risk to women. We do not interpret our findings to suggest that aspirin should no longer be used to prevent preeclampsia. In fact, we would strongly advise that women considered at high risk for developing preeclampsia according to guidelines such as NICE (ie, the presence of 1 high risk or 2 moderate risk factors)[11] should still be offered aspirin. However, the benefits of taking aspirin may not outweigh possible dangers for those in whom the absolute risk for developing preeclampsia is relatively low. For instance, it is uncertain whether liberally offering aspirin to women with only 1 moderate risk factor for preeclampsia is overall beneficial, something that may be widely practiced. In our study, women taking aspirin and giving birth vaginally had a 2% absolute risk increase for postpartum hemorrhage, from 7% to 9%. Aspirin is thought to reduce the baseline risk of preeclampsia by approximately 10%.[30] Thus, if a pregnant person had a baseline risk of preeclampsia of 4% (the reported prevalence of preeclampsia in many populations[39]), then taking aspirin might be expected to reduce the absolute risk of preeclampsia by 0.4% but increase the absolute risk of a postpartum hemorrhage by 2%.

Furthermore, there is potential that the bleeding risk may be greater at higher doses of aspirin. This may be quite topical because prescribing aspirin at a dose of 150 mg might become

increasingly common in light of a recent landmark randomized trial that administered aspirin at this dose.[4] Our data caution against calls that aspirin should be universally administered to all pregnant women.[15–18]

## Conclusion

In this population register–based cohort study, the use of aspirin during pregnancy was associated with postpartum hemorrhage among those who had a vaginal birth. It may also be associated with postpartum hematoma and neonatal intracranial hemorrhage. Although the absolute risks of these complications may be low, widespread and liberal use of aspirin during pregnancy might further increase the numbers. Our data argue against universal administration of aspirin to all pregnant women. ■

### Acknowledgments

The authors thank Jonas Söderling and the Swedish Pregnancy Register for data management.

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Received Feb. 2, 2020; revised June 21, 2020; accepted July 14, 2020.

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The authors report no conflict of interest.

This study was approved by the Uppsala Ethics Board on August 15, 2018 (approval number: 2018/287).

The National Health and Medical Research Council of Australia provided salary support to R.H. (#1176922) and S.T. (#1136418). The Center for Clinical Research provided salary support to S.H. (#CKFUU744551) and L.B. (#CKFUU740361).

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## SUPPLEMENTAL TABLE 1
### Search strategy

| | |
|---|---|
| 1 | exp pregnancy/ |
| 2 | aspirin {Including Related Terms} |
| 3 | bleeding {Including Related Terms} |
| 4 | haemorrhage.mp. |
| 5 | bleed {Including Related Terms} |
| 6 | 3 or 4 or 5 |
| 7 | 1 and 2 and 6 |

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## SUPPLEMENTAL TABLE 2
### Mode of data collection for variables with the Swedish Pregnancy Register

| Variable | Checkbox/text | ICD-10 code | Comment |
|---|---|---|---|
| Age | | | Personal identity number |
| Height | x | | Manually entered |
| Weight | x | | Manually entered |
| Parity | x | | |
| Multiple pregnancy | x | | |
| Assisted reproduction | x | | |
| Previous cesarean delivery | x | | |
| Country of birth | | | Manually entered |
| Occupation | | | Manually entered |
| Smoking | x | | |
| AUDIT | | | Manually entered |
| Hypertension | x | I10, O10 | |
| Diabetes | x | O240. O241, E10–14 | |
| Inflammatory disease | x | | |
| Hyperemesis | | O21 | |
| Preeclampsia | | O14–15 | |
| Gestational diabetes | | O244, O249 | |
| Placenta previa | | O44 | |
| Placental abruption | | O45 | |
| Gestational age | x | | |
| Induction of labor | x | O61 | |
| Mode of delivery | x | | |

*AUDIT,* Alcohol Use Disorders Identification Test; ICD-10, International Classification of Diseases, Tenth Revision.
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SUPPLEMENTAL TABLE 3

**Inverse probability weighted and unweighted *P* values of maternal demographics**

| Characteristic | Aspirin users vs nonusers | |
|---|---|---|
| | Unweighted *P* value | Weighted *P* value |
| Maternal age ≥35 y | <.001 | .007 |
| BMI ≥30 kg/m$^2$ | <.001 | .249 |
| Parity | <.001 | .006 |
| Assisted reproduction | <.001 | .352 |
| Previous cesarean delivery | <.001 | <.001 |
| Country of birth | .096 | .575 |
| Occupation | .138 | .614 |
| Smoking at first antenatal visit | .016 | .682 |
| Alcohol risk use 3 mo before pregnancy | .151 | .549 |
| Pregestational disorders | <.001 | .096 |
| Hypertension | | |
| Diabetes | | |
| Inflammatory bowel disease | | |
| Systemic lupus erythematosus | | |

*BMI*, body mass index.

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SUPPLEMENTAL TABLE 4

**Bleeding complications by paracetamol use**

| Outcome | No paracetamol (N=306,874) | Paracetamol (N=6750) | |
|---|---|---|---|
| | N (%) | N (%) | OR (95% CI) |
| Antepartum hemorrhage | 5543 (1.8) | 139 (2.1) | 1.14 (0.96–1.35) |
| Intrapartum hemorrhage | 4695 (1.5) | 117 (1.8) | 1.13 (0.94–1.36) |
| Postpartum hemorrhage | 23,896 (7.9) | 551 (8.2) | 1.05 (0.96–1.15) |
| Postpartum hematoma | 332 (0.11) | 6 (0.0) | 0.82 (0.37–1.84) |
| Neonatal intracranial hemorrhage | 20 (0.01) | 0 (0) | — |

*CI*, confidence interval; *OR*, odds ratio.

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