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PII: S0002-9378(20)30737-7

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

Reference: YMOB 13367

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 2 February 2020

Revised Date: 21 June 2020

Accepted Date: 14 July 2020

Please cite this article as: Hastie R, Tong S, Wikström A-K, Sandström A, Hesselman S, Bergman L, Aspirin use during pregnancy and the risk of bleeding complications: A Swedish population-based cohort study., *American Journal of Obstetrics and Gynecology* (2020), doi: https://doi.org/10.1016/j.ajog.2020.07.023.

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

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Key words: aspirin, hemorrhage, bleeding risk, pregnancy

AJOG at a glance: Aspirin is widely offered to pregnant women to prevent preeclampsia, one of the most severe obstetric complications. Very large studies of non-pregnant populations taking aspirin to prevent cardiovascular events have decisively shown an increase risk of major hemorrhage. However, there have not been large, adequately powered studies to see whether there is a bleeding risk in a pregnant population. In this population-based register cohort study of 313,624 pregnancies, aspirin use was associated with a clear increase risk of bleeding during labor and the postpartum period. These findings provide clear evidence against more liberal, or universal administration of aspirin.

Abstract

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

Objective: 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 where we examined 313,624 women giving birth between January 2013 – 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 4,088 (1.3%) of women during pregnancy. Compared to women who did not take aspirin, aspirin use was not associated with bleeding complications during the antepartum period [adjusted Odds Ratio (aOR) 1.22 (95% confidence interval (CI) 0.97, 1.54)]. However, aspirin users had a higher incidence of intrapartum bleeding (2.9% aspirin users vs 1.5% non-users: aOR 1.63 [95% CI 1.30, 2.05]), postpartum hemorrhage (10.2% vs 7.8%; aOR 1.23 [95% CI 1.08, 1.39]) and postpartum hematoma (0.4% vs 0.1%; aOR 2.21 [95% CI 1.13, 4.34]). The risk of a neonatal intracranial hemorrhage was also increased (0.07% *vs* 0.01%; aOR 9.66 [95% CI 1.88, 49.48]). After stratifying by mode of birth, the higher incidence of bleeding among aspirin users was present for those who had a vaginal birth but not those who had a caesarean section.

Conclusion: Using aspirin during pregnancy is associated with increased postpartum bleeding and postpartum hematoma. It may also be associated with neonatal intracranial

61 hemorrhage. When offering aspirin during pregnancy these risks need to be weighed against
62 the potential benefits.
63

Introduction

Preeclampsia is characterized by maternal hypertension and end organ injury and affects 3-8% 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 anti-inflammatory and anti-platelet 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 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 one moderate risk factor for preeclampsia, take 75 – 150 mg of aspirin daily; from 12 weeks of gestation until 36 - 37 weeks gestation[13], or until birth[10, 11, 14]. Sweden has had a conservative approach with regards to aspirin, and only women considered high risk based on medical and obstetric 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 NICE guidelines, where 10% of the pregnant population are expected to be classed 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 to current U.S 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 side-effects and did not consider the potential for pregnancy related bleeding complications[18].

However, studies of non-pregnant 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% CI 1.30-1.56]) and intracranial 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 supplementary table 1). It is a challenging question to examine because aspirin is freely available without 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. 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 two to three months after delivery[25].

Study population

We included women giving birth in Sweden from January 2013 to July 2017. If a woman had 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 due 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, 18-34 and ≥35 years), body mass index (BMI) calculated from measured weight and self-reported height registered at first prenatal visit which was then divided into two 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 non-western

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 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 three months prior to conception which was determined using the Alcohol Use Disorders Identification Test (AUDIT)[26], where scores ≥6 indicate hazardous use of alcohol or alcohol dependency.

Pre-gestational 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) (Supplementary Table 2).

Exposure

Data on aspirin use was obtained from prenatal care records, including the first prenatal visit record (which is a comprehensive record of patient information, socio-demographic data and past medical and obstetric history) and from each prenatal care visit record, which is typically 8-10 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 i) bleeding complications during

pregnancy; hematemesis (coded as K92), hematuria (R31), bleeding from the airways (R04) and antepartum hemorrhage (O46) ii) labor and postpartum complications; 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, O717) and neonatal intracranial hemorrhage (P10). Data on whether gastritis occurred was also obtained assessed through prenatal care records (K92, K29).

Additional analyses

Given mode of birth may impact the risk of bleeding complications during labor and the postpartum period, we stratified our analyses by vaginal birth or caesarean section birth 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 two variables given 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 non-users were compared via bivariate analysis using Pearson's Chi^2 test for categorical data and Student's t-test for continuous variables.

Associations between aspirin use and maternal and neonatal complications were estimated by logistic regression and presented as odds ratios (OR) and 95% confidence intervals (CI).

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 caesarean section, IVF, country of birth, employment status, smoking status, alcohol risk score and the presence of pre-gestational 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 pseudo-population where the measured covariates are balanced between exposure groups. Exposed individuals were assigned a probability weight of 1/propensity score, whilst 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 unexposed groups by showing that covariates were similarly distributed and not significantly associated with aspirin use after applying IPTW (Supplementary 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.

Ethical approval

This study was approved by the Uppsala Ethics Board on the 15th of August 2018. Approval number: 2018/287.

Results

Of the 313,624 women included in our study, 4,088 (1.3%) reported aspirin use during pregnancy. Women using aspirin were older, more obese and more frequently parous compared to women who did not take aspirin. Additionally, aspirin users were more likely to have a multiple pregnancy, to have conceived through IVF and were more likely to have had a previous caesarean section (Table 1). Aspirin users had a higher rate of pre-existing 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, induction of labor and were more likely to have been delivered by a caesarean section (Table 1).

Aspirin use and prenatal complications

The incidence of antepartum hemorrhage among women using aspirin was 2.4% compared to 1.8% among non-users, which resulted in a crude odds ratio (OR) of 1.33 (95% confidence interval [CI] 1.09, 1.63). After adjusting via inverse probability treatment weighting (IPTW) the association was no longer significant (adjusted OR [aOR] 1.22, [95% CI 0.97, 1.54]). Additionally, 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 compared to those not using aspirin. The incidence of bleeding during labor was 2.9% among aspirin users versus 1.5% in non-users, 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 non-users, an aOR of 1.23 (95% CI 1.08, 1.39; Table 3). Additionally, women using aspirin were more likely to develop a postpartum hematoma; 0.4% among aspirin users vs 0.1% among non-users (aOR of 2.21 [95% CI 1.13, 4.34]).

There was also an association between aspirin use and neonatal intracranial hemorrhage, with a 0.07% incidence among aspirin users *vs* 0.01% among non-users (aOR 9.66 [95% CI 1.88, 49.48]; Table 3).

Labor and postpartum complications by mode of birth

When the data was stratified for mode of birth, there was no longer an association between aspirin use and bleeding during labor after either a vaginal or caesarean section birth. 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 caesarean section (aOR 0.95 [95% CI 0.78, 1.16]). Similarly, among women giving birth vaginally, those using aspirin were more likely to experience postpartum hematoma (aOR 20.41 [2.62, 158.93]) and have an infant with neonatal intracranial hemorrhage (aOR 17.07 [95% CI 3.70, 78.86]) compared to those not using aspirin. Among women who gave birth via caesarean section, 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, postpartum hemorrhage and experience postpartum hematoma (aORs 1.69 [95% CI. 1.33, 2.14], 1.27 [95% CI 1.12, 1.45] and aOR 2.67 [95% CI 1.32, 5.41, respectively). 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 to non-users (Supplementary 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 to 1.12)[29]. Additionally, the majority of included trials were investigating low-dose aspirin and most participants received doses below 75mg, whereas in the present study women were likely to be receiving 75mg daily. The same investigators initially reported no increased bleeding risk in an earlier individual patient data (IPD) [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 non-pregnant population that consistently report an increased risk of bleeding complications with daily aspiring 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 obstetric population are younger and are likely to have less underlying gastrointestinal pathology and a shorter

exposure. Furthermore, our data is derived solely from the Swedish Pregnancy Register and there is a risk of non-obstetrical diagnoses being under-reported.

We identified a possible association between taking aspirin during pregnancy and neonatal intracranial hemorrhage. There have been prior reports that have observed this. 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 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 the present 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 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 the present study it does warrant further investigation. Additionally, 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 – 10 international units, is routinely offered to all women. Given 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 intake of aspirin. In our study, 1.3% of women used aspirin, a number that was similar to reported usage of anticoagulants in prior publications from the Swedish prescribed drug register[39]. 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. Additionally, we performed two sub-analyses that minimize the possibility of differential misclassification of the exposure by reporting bias. We showed there was no association between aspirin use and a 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 within this study. Our data was 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 balance of maternal covariates between aspirin users and non-users and therefore reduced the potential for bias. Though despite this, there might still be residual confounding. Given 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 while 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 – 36 for the primary prevention of preeclampsia, which is the main indication for use during pregnancy. Thus, it is likely the majority of aspirin users will have taken this dose. In addition, non-obstetric 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 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 one high risk, or two moderate risk factors)[11] should still be offered aspirin. However, the benefits of taking aspirin may not outweigh possible dangers for those where the absolute risk for developing preeclampsia is relatively low. For instance, it is uncertain whether liberally offering aspirin to women with

only one moderate risk factor for preeclampsia is overall beneficial, something which 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 around 10%[30]. Thus, if a pregnant person had a baseline risk of preeclampsia of 4% (the reported prevalence of preeclampsia in many populations[40]) 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 since 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 cautions 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 argues against universal administration of aspirin to all pregnant women.

Funding:

National Health and Medical Research Council of Australia (NHMRC) provided salary support to ST (#1136418) and RH (#1176922). Center for Clinical Research provided salary support to SH (#CKFUU744551) and LB (#CKFUU740361).

Acknowledgements:

Jonas Söderling, Swedish Pregnancy Register for data management.

Disclosures: None

Contributions to authorship

RH, SH, LB, AK and ST conceived the study. SH, RH managed the dataset and RH conducted the analyses with intellectual input and technical support of AS. RH wrote the first draft of the manuscript. All authors provided intellectual input and contributed and approved the final manuscript.

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546 **Table 1: Maternal characteristics by aspirin use during pregnancy**

Characteristic	**Total births** N=313,624	**Aspirin use**	
		No (n=309,536)	**Yes** (n=4,088)
Age, (years), mean ±SD	31.1 ± 5.2	31.1 ± 5.2	33.9 ± 5.4
<35	239,012 (76.2)	236,625 (76.5)	1,701 (41.6)
≥35	74,503 (23.8)	72,802 (23.5)	2,387 (58.4)
Missing	109 (0.03)	109 (0.03)	
Body mass index (kg/m2), mean ± SD	24.8 ± 4.7	24.8 ± 4.7	26.0 ± 5.4
BMI<30	259,151 (82.6)	256,032 (82.7)	3,119 (76.3)
BMI≥30	39,724 (12.7)	38,909 (12.6)	815 (19.9)
Missing	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)	3,235 (79.1)
≥4	3,585 (1.1)	3,533 (1.1)	52 (1.3)
Multiple pregnancies, n (%)			
2-4 fetuses	4,862 (1.6)	4,739 (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 caesarean section, n (%)			
	33,249 (10.6)	31,828 (10.3)	1,421 (34.8)
Country of birth, n (%)			
Nordic	204,668 (65.3)	201,890 (65.2)	2,798 (68.5)
Other western	15,565 (5.0)	15,378 (5.0)	187 (4.6)
Non-western	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)	2,656 (65.0)
Government assistance (sick leave, student, unemployed)	82,063 (26.2)	81,053 (26.2)	1,010 (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 three months prior to pregnancy			
AUDIT >6	10,041 (3.2)	9,987 (3.2)	54 (1.3)
Missing	68,424 (21.8)	67,569 (21.8)	855 (20.9)
Pre-gestational disorders, n (%)			
Hypertension	1,489 (0.5)	1,302 (0.4)	187 (4.6)
Diabetes	5,401 (1.7)	5,271 (1.7)	130 (3.2)
Inflammatory diseases [a]	2,706 (0.9)	2,593 (0.8)	113 (2.8)
Gestational disorders, n (%)			
Hyperemesis gravidarum	3,317 (1.1)	3,255 (1.1)	62 (1.5)
Preeclampsia – all forms	9,038 (2.9)	8,616 (2.8)	422 (10.3)
Gestational diabetes	5,401 (1.7)	5,271 (1.7)	130 (3.2)
Placenta previa	1,748 (0.6)	1,703 (0.6)	45 (1.1)
Placental abruption	1,164 (0.4)	1,139 (0.4)	25 (0.6)
Gestational age at delivery, (weeks), mean ±SD	39.3 ± 1.9	39.3 ± 1.9	38.5 ± 2.3
Induction of labour[b]**,** n (%)			
Yes	53,727 (17.1)	52,591 (17.0)	1,136 (27.8)

Missing	1,045 (0.3)	1,032 (0.3)	13 (0.3)
Mode of delivery, n (%)			
Spontaneous vaginal	241,459 (76.9)	239,019 (77.2)	2,440 (56.7)
Instrumental vaginal	16,837 (5.4)	16,653 (5.4)	184 (4.5)
Caesarean section	55,328 (17.6)	53,864 (17.4)	1,464 (35.8)

[a] Inflammatory bowel disease and systemic lupus erythematosus

[b] Exclude elective caesarean section.

554 **Table 2: Prenatal complications by aspirin use during pregnancy.**

	No aspirin use N=309,536		Aspirin use N=4,088	
			Odds ratios (95% confidence interval)	
Outcome	**N (%)**	**N (%)**	**Crude**	**Adjusted**
Bleeding complications during pregnancy				
Antepartum hemorrhage[a]	5,585 (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)

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556 Adjusted ORs and 95% CIs were retrieved via logistic regression with inverse probability
557 weighting of treatment and multiple pregnancy included as a covariate for all analyses. [a]
558 Excludes cases with placenta previa or abruption; N= 310,759 included in analysis.
559 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=4,088		
Outcome	**N (%)**	**N (%)**	**Odds ratio (95% confidence interval)**	
			Crude	**Adjusted**
Intrapartum hemorrhage[a]	4,695 (1.53)	117 (2.91)	1.93 (1.60, 2.32)	1.63 (1.30, 2.05)
Postpartum hemorrhag[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.

[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.

Table 4: Labor and postpartum complications by aspirin use during pregnancy and mode of delivery.

	Vaginal deliveries				Caesarean Section deliveries			
	No aspirin use N=255,670	Aspirin use N=2,624			No aspirin use N=53,866	Aspirin use N=1,464		
Outcome	**N (%)**	**N (%)**	**Odds ratio (95% confidence interval)**		**N (%)**	**N (%)**	**Odds ratio (95% confidence interval)**	
			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)	4,491 (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)	6,464 (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.

[a] Cases of placenta previa and abruption were excluded from analyses; N= 257,736 vaginal delivery and N= 53,023 caesarean section 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 caesarean section analyses.

Table 5: Labor and postpartum bleeding complications among women who did not develop preeclampsia.

	No aspirin use N= 300,920	**Aspirin use** N= 3,666		
Outcome	**N (%)**	**N (%)**	**Odds ratio (95% confidence interval)**	
			Crude	**Adjusted**
Intrapartum hemorrhage [a]	4,446 (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.

[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