OBSTETRICS

Low-dose aspirin use in pregnancy and the risk of preterm birth: a Swedish register-based cohort study

Ellen Kupka, MD; Susanne Hesselman, MD, PhD; Roxanne Hastie, PhD; Riccardo Lomartire, PhD; Anna Karin Wikström, MD, PhD; Lina Bergman, MD, PhD

BACKGROUND: Preterm birth is the leading cause of neonatal mortality and morbidity. Women who have had a previous preterm birth are at increased risk for preterm birth in their subsequent pregnancies. Low-dose aspirin use reduces the risk for preterm birth among women at risk of developing preeclampsia, however, it is unclear whether low-dose aspirin may reduce the risk of recurrent preterm birth.

OBJECTIVE: This study aimed to investigate the association between low-dose aspirin use and preterm birth among women with a previous preterm birth.

STUDY DESIGN: We conducted a Swedish register-based cohort study and included women who had a first and second pregnancy between 2006 and 2019, with the first pregnancy ending in preterm birth (medically indicated or with spontaneous onset <37 weeks of gestation). The association between low-dose aspirin use and preterm birth in the second pregnancy was estimated via logistic regression via standardization and expressed as marginal relative risks with the 95% confidence interval.

RESULTS: Among the study cohort (N=22,127), 3057 women (14%) were prescribed low-dose aspirin during their second pregnancy and 3703 women (17%) gave birth prematurely. Low-dose aspirin use was associated with a reduced risk for preterm birth, (marginal relative risk, 0.87; 95% confidence interval, 0.77—0.99). There were no statistically significant associations between low-dose aspirin use and an altered risk for moderate preterm birth, defined as birth between 32 and 36 weeks' gestation (marginal relative risk, 0.90; 95% confidence interval, 0.78—1.03), or very preterm birth, defined as birth <32 weeks' gestation (marginal relative risk, 0.75; 95% confidence interval, 0.54—1.04). Regarding the onset of preterm birth, low-dose aspirin use was associated with a reduced risk for spontaneous preterm birth (marginal relative risk, 0.70; 95% confidence interval, 0.57—0.86) but no reduction in the risk for medically indicated preterm birth (marginal relative risk, 1.09; 95% confidence interval, 0.91—1.30) was observed.

CONCLUSION: Among women with a previous preterm birth, low-dose aspirin use was associated with a reduced risk for preterm birth. When investigating preterm birth by onset in the second pregnancy, low-dose aspirin use was associated with a reduced risk for spontaneous preterm birth. Our results suggest that low-dose aspirin may be an effective prophylaxis for recurrent preterm birth.

Key words: adverse pregnancy outcome, aspirin, preterm birth, prevention

Introduction

Preterm birth, defined as birth before 37 weeks' gestation, claims the lives of approximately 1 million children every year.[1] Women who have had a previous preterm birth (medically indicated or with spontaneous onset) are at increased risk for preterm birth in their subsequent pregnancy.[2–4]

Low-dose aspirin use has been shown to reduce the risk for preeclampsia, a pregnancy condition characterized by hypertension and organ injury. In addition, low-dose aspirin use has been shown to protect against preterm birth among women at risk for developing preeclampsia.[5] There is also a growing body of evidence suggesting that low-dose aspirin use could be associated with a reduced risk for preterm birth and in particular, spontaneous preterm birth among women without major risk factors for preeclampsia.[6–8] Still, there is insufficient evidence regarding the use of low-dose aspirin in pregnant women with a previous preterm birth. The low-dose aspirin in the prevention of recurrent spontaneous preterm labour (APRIL) study, a randomized controlled trial with 406 participants, reported a small but nonsignificant reduction in preterm birth among women with a previous spontaneous preterm birth using low-dose aspirin.[9] However, the study was only powered to detect a difference in preterm birth >35% between groups, and the included population had a lower-than-expected preterm birth rate. A larger study is needed to investigate whether low-dose aspirin use can prevent recurrent preterm birth.[10] Thus, we undertook a population-based study, including >22,000 women with a previous preterm birth, to investigate whether low-dose aspirin use was associated with an altered risk for preterm birth occurring <37 weeks' gestation, moderate preterm birth occurring between 32 and 36 weeks' gestation, and very preterm birth <32 weeks' gestation and to investigate the the association between low-dose aspirin use and the mode of onset of preterm birth.

Material and Methods

Design and participants

We performed a register-based cohort study using the Swedish Medical Birth Register, the Swedish Prescribed Drug Register, and the education register held by Statistics Sweden. The study was

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AJOG at a Glance

Why was this study conducted?

Women who have had a previous preterm birth (medically indicated or spontaneous onset) are at increased risk for preterm birth in their subsequent pregnancies. Low-dose aspirin use reduces the risk of preterm birth among women at risk for developing preeclampsia, but the effect on preterm birth among women with a previous preterm birth is unknown.

Key findings

Low-dose aspirin use was associated with a reduced risk for preterm birth (any onset) and preterm birth with a spontaneous onset.

What does this add to what is known?

Low-dose aspirin could be an effective prophylaxis for recurrent preterm birth.

approved by the ethical review board at Uppsala on January 28, 2020 (Dnr 2019-04925) and on August 26, 2021 (Dnr 8311/2020). The registers were linked using the personal identity number assigned to each Swedish resident at birth or immigration to Sweden.[11] The Swedish Medical Birth Register provides information about pregnancies, labor, and perinatal outcomes from standardized medical records. The data are entered prospectively by healthcare providers during episodes of prenatal, delivery, and neonatal care. The register covers >98% of all births in Sweden, and the information has been validated.[12] The Swedish Prescribed Drug Register started in 2005 and contains patient-level data on all dispensed prescribed drugs in Sweden, using the World Health Organization's Anatomical Therapeutic Chemical Classification (ATC) codes. The register is complete for the entire Swedish population with <0.3% missing data for all dispensed prescriptions.[13] The education register held by Statistics Sweden holds information about the highest level of education obtained. The data are reported by professional and administrative personnel and the data quality is controlled through regular audits.[14]

The study population consisted of all women with a first and second singleton birth recorded in the Medical Birth Register from 2006 to 2019 and who, in their first pregnancy, gave birth prematurely. Preterm birth was defined as a spontaneous or medically indicated birth between 22 weeks+0 days to 36 weeks+6 days.

Covariates

Pregnancy variables from the first and second pregnancy were obtained from the Medical Birth Register and included conception via in vitro fertilization (including intracytoplasmic sperm injection), interpregnancy interval, pregestational disorders (including chronic hypertension, diabetes mellitus, chronic kidney disease, systemic lupus erythematosus), preeclampsia, placental abruption, cesarean delivery, small for gestational age (SGA) birth, and stillbirth. The interpregnancy interval was defined as months from first birth until next conception and categorized into <6 months and 6 months and above.[15] SGA birth was defined as birthweight below 2 standard deviations according to Swedish growth charts.[16] Information on conception via in vitro fertilization, pregestational disorders, and stillbirth was retrieved from predefined checkboxes in the Medical Birth Register and was self-reported by the women.

Information on maternal demographics during the second pregnancy were obtained from the Medical Birth Register and included maternal age at delivery, height, body mass index (BMI), smoking (yes/no), and country of birth. In addition, information on the highest obtained education level (university, upper secondary school degree, or <12 years of school attendance) was retrieved from Statistics Sweden.

Exposure

The primary exposure was low-dose aspirin use during the second pregnancy (regardless of dose and duration) based on data obtained from dispensed prescriptions from the Swedish Prescribed Drug Register. Low-dose aspirin use (ATC code B01AC06) was defined as at least 1 dispensed prescription during pregnancy and included women with a prescription of 75 to 160 mg aspirin from 3 months before conception. During the study period, there was no national guideline on aspirin prescription during pregnancy and different regions had different routines. According to the Swedish Society of Obstetrics and Gynecology, most commonly, only women presenting with major risk factors for preeclampsia were prescribed aspirin at a dosage of 75 mg/day. In a few hospitals in the country, the recommended dosage was 160 mg. Low-dose aspirin is only available by prescription in Sweden, and aspirin at higher doses that are available over the counter are not recommended during pregnancy.

Outcomes

The primary outcome was preterm birth during the second pregnancy. Gestational age was based on a first or early second trimester ultrasound in 93% of the pregnancies. In the remaining pregnancies, gestation age was based on the date of the last menstrual period reported at the first antenatal visit, the date of embryo transfer, or a postnatal assessment (<1%).[12] We further studied preterm birth by severity and onset. Severity was categorized into moderate preterm birth (birth between 32−36 weeks' gestation) and severe preterm birth (birth <32 weeks' gestation). Preterm birth by onset was categorized into spontaneous and medically indicated. The onset of birth was registered in a standardized manner at the delivery ward by midwives using checkboxes in the medical record. Spontaneous onset included preterm labor or preterm premature rupture of the membranes

(identified by the International Classification of Diseases code O42). Medically indicated preterm birth included vaginally induced onset of labor and cesarean delivery before onset of labor unless preterm premature rupture of the membranes were present. Information on the gestational age at delivery and the onset of birth was obtained from the Medical Birth Register. Information on the onset of labor was missing for 174 (0.8%) of the preterm births in the first pregnancy and for 24 (0.1%) of the preterm births in the second pregnancy.

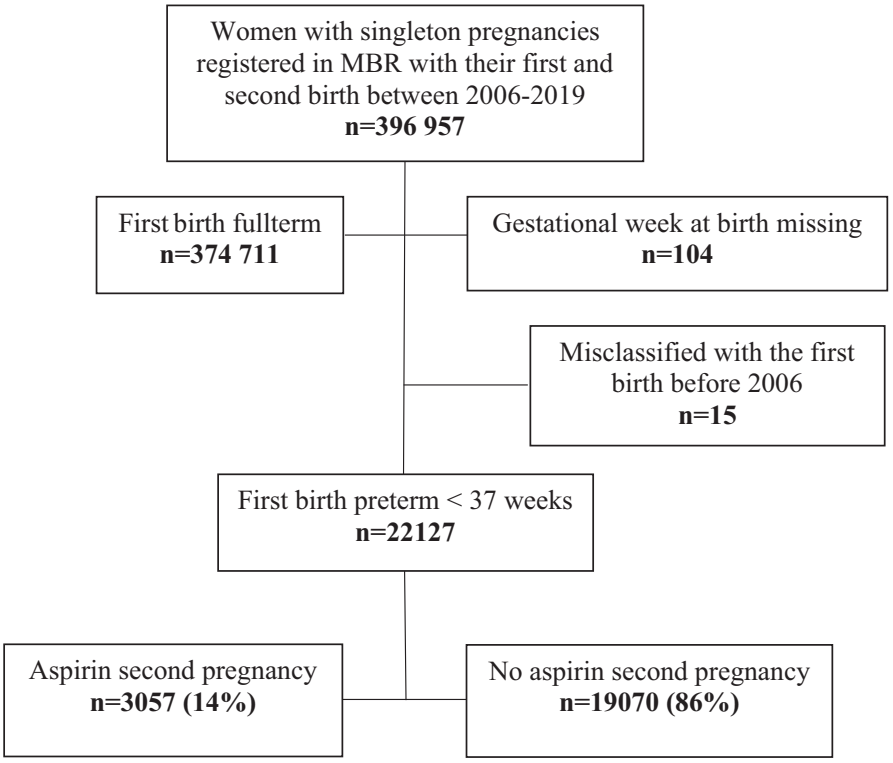
Statistical analysis

An a priori statistical analysis plan was agreed on by all authors. The marginal relative risk (mRR) for preterm birth among women using low-dose aspirin was compared with preterm birth rates among women not using low-dose aspirin and was computed via standardization from logistic regression models,[17] adjusted for confounders, as outlined below. Standard errors were based on the delta method.[17] Continuous variables were modeled with natural cubic splines with 3 degrees of freedom in all models to allow a nonlinear association for the outcome. R, version 4.2.0, (R Core Team, Vienna, Austria) and SPSS Statistics for Windows, version 28.0, (IBM Corp., Armonk, NY) was used for all statistical calculations.

Conceptual model

A theoretical framework and directed acyclic graphs (DAGs) were used to identify covariates. DAGs serve as a visual representation of the hypothesized relationship between variables and can help to identify the presence of confounding and ways to resolve it.[18] We included covariates from the first and second pregnancy that could increase the probability of low-dose aspirin prescription (in other words, risk factors for preeclampsia) and the probability of preterm birth. Based on the DAGs, the covariates maternal age, BMI, country of birth (divided into Nordic or non-Nordic countries), gestational length of first pregnancy, SGA neonate in the first pregnancy, preeclampsia in the first pregnancy, type of onset of preterm birth in the first pregnancy, pregestational disorders, and date of birth were chosen to estimate the association between low-dose aspirin use and preterm birth regardless of mediation (Supplemental Figure).

FIGURE
Flow chart describing participant inclusion



MBR, Medical Birth Register.

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Subgroup analysis

We analyzed rates of preterm birth in the second pregnancy among women with a previous spontaneous preterm birth and a medically indicated preterm birth separately, adjusting for the same covariates as above, except for onset of labor in the first pregnancy.

Results

Sample characteristics

The study population consisted of 22,127 women who experienced a preterm birth in their first pregnancy of which 3057 women (14%) were prescribed low-dose aspirin in their second pregnancy. In total, 3703 women (17 %) had a recurrent preterm birth and 547 of them (15%) used low-dose aspirin during the second pregnancy. The population selection is presented in a flowchart (Figure).

The women who used low-dose aspirin were, on average, 31.5 years old and had a BMI of 25.9 as compared with an average age of 30.6 years and an average BMI of 25.0 for the group of women who did not use aspirin. Pregestational disorders and preeclampsia were common among women using aspirin; 11.1 % of the women had at least 1 pregestational disorder in the second pregnancy, and 16.7 % were diagnosed with preeclampsia in the second pregnancy (Table 1).

Primary outcome

The incidence of preterm birth in the second pregnancy was 17.9% among women using low-dose aspirin and 16.6% among women not using low-dose aspirin. This equates to a crude

TABLE 1
Background characteristics in the second pregnancy for women who had a preterm birth in their first pregnancy with and without low-dose aspirin prescription in the second pregnancy

Characteristic	Missing (n)	Total births n=22,127	Aspirin use	
			No n=19,068	Yes n=3057
Second pregnancy				
Age at delivery (y)	2	30.7±4.8	30.6±4.7	31.5±5.1
≥35		4792 (21.7)	3936 (20.6)	856 (28.0)
Height (cm)	231	165.5±6.4	165.6±6.4	165.4±6.5
BMI (kg/m^2)[a]	1355	25.1±5.0	25.0±4.9	25.9±5.4
BMI ≥30		3232 (15.6)	2648 (14.8)	584 (20.2)
Country of birth	2			
Nordic		18,135 (82.0)	14,656 (82.1)	2479 (81.1)
Non-Nordic European[b]		1017 (4.6)	898 (4.7)	119 (3.9)
Rest of the world[c]		2973 (13.4)	2512 (13.2)	458 (15.0)
Smoking at first antenatal[b] visit	1161	1011 (4.8)	876 (4.8)	135 (4.7)
In vitro fertilization		685 (3.1)	554 (2.9)	131 (4.3)
Education	122			
University		12,886 (58.6)	11,080 (58.4)	1806 (59.4)
Upper secondary school		6148 (27.9)	5340 (28.2)	808 (26.6)
<12 y of school attendance		2971 (13.5)	2543 (13.4)	428 (14.1)
Interpregnancy interval (mo)	7	26.21±18.56	26.19±18.4	26.35±19.8
<6		1216 (5.5)	946 (5.0)	270 (8.8)
≥ 6		20,904 (94.5)	18,117 (95.0)	2787 (91.2)
Pregestational disorders		999 (4.5)	660 (3.5)	339 (11.1)
Chronic hypertension		309 (1.4)	152 (0.8)	157 (5.1)
Diabetes mellitus		528 (2.4)	411 (2.2)	117 (3.8)
Chronic kidney disease		182 (0.8)	118 (0.6)	64 (2.1)
Systemic lupus erythematosus		68 (0.3)	21 (0.1)	47 (1.5)
Pregnancy outcomes				
Preeclampsia		1136 (5.1)	625 (3.3)	511 (16.7)
Placental abruption		146 (0.7)	102 (0.5)	44 (1.4)
Gestational diabetes mellitus		550 (2.5)	444 (2.3)	106 (3.5)
Cesarean delivery	26	4544 (20.6)	3284 (17.2)	1260 (41.2)
Small for gestational age	45	621 (2.8)	394 (2.1)	226 (7.4)
Stillbirth	2	107 (0.5)	87 (0.5)	20 (0.7)
First pregnancy				
Gestational age at delivery (wk)		33.8±3.1	34.1±2.9	31.9±3.7
Moderate preterm birth 32–36 wk		18,584 (84.0)	16,682 (87.5)	1902 (62.2)
Very preterm birth <32 wk		3543 (16.0)	2388 (12.6)	1155 (37.8)
Medically indicated preterm birth	174	5927 (27.0)	3407 (18.0)	2520 (83.5)
Spontaneous preterm birth	174	16,026 (73.0)	15,528 (82.0)	498 (16.5)
Preeclampsia		3212 (14.5)	1362 (7.1)	1850 (60.5)

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(continued)

TABLE 1
Background characteristics in the second pregnancy for women who had a preterm birth in their first pregnancy with and without low-dose aspirin prescription in the second pregnancy *(continued)*

Characteristic	Missing (n)	Total births n=22,127	Aspirin use	
			No n=19,068	Yes n=3057
Placental abruption		614 (2.8)	427 (2.2)	187 (6.1)
Cesarean delivery	95	6880 (31.2)	4752 (25.0)	2131 (70.0)
Small for gestational age	182	2558 (11.7)	1147 (6.1)	1411 (47.0)
Stillbirth		1040 (4.7)	606 (3.2)	434 (14.2)

Data are presented as number (percentage) or mean±standard deviation.

BMI, body mass index.

[a] BMI at first antenatal visit; [b] Combined in the adjusted analysis; [c] Includes Africa, Asia, North America, Oceania and South America.

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relative risk (RR) of 1.08 (95% confidence interval [CI], 1.00−1.17) and an mRR of 0.87 (95% CI, 0.77−0.99) for preterm birth among women using low-dose aspirin as compared with those not using low-dose aspirin (Table 2).

Preterm birth by severity

Compared with women not using low-dose aspirin, women using low-dose aspirin had an increased crude RR of 1.72 (95% CI, 1.30−2.27) for preterm birth occurring before 32 weeks' gestation but not for preterm birth occurring between 32 and 36 weeks' gestation (RR, 0.98; 95% CI, 0.85−1.12). After adjusting for confounders, low-dose aspirin use was not associated with a reduced risk for preterm birth <32 weeks' gestation (mRR, 0.75; 95% CI, 0.54−1.04) or between 32 and 36 weeks' gestation (mRR, 0.90; 95% CI, 0.78−1.03) (Table 2).

Preterm birth by onset

Compared with women not using low-dose aspirin, women using low-dose aspirin had an increased crude RR of 3.46 (95% CI, 2.92−4.10) for medically indicated preterm birth. However, this risk was reduced and no longer statistically significant after adjusting for confounders (mRR, 1.09; 95% CI, 0.91−1.30). Low-dose aspirin use was associated with a reduced crude RR for spontaneous preterm birth of 0.42 (95% CI, 0.34−0.53) that remained after adjusting for confounders (mRR, 0.70; 95% CI, 0.57−0.86) (Table 2).

There was no statistically significant association between low-dose aspirin use and onset of labor among women with a first medically indicated preterm birth (Supplemental Table 1). Among women with a spontaneous preterm birth in their first pregnancy, low-dose aspirin use was associated with an increased risk for medically indicated preterm birth (mRR, 1.93; 95% CI, 1.28−2.91) and a decreased risk for spontaneous preterm birth (mRR, 0.75; 95% CI, 0.57−1.00) (Supplemental table 2) that was not statistically significant.

Comment

Principal findings

In this register-based cohort study of women with a previous preterm birth, we found an association between low-dose aspirin use and preterm birth occurring <37 weeks' gestation, but no statistically significant association between low-dose aspirin use and moderate preterm birth between 32 and 36 weeks' gestation or very preterm birth <32 weeks' gestation. When separating the risk for spontaneous and medically indicated preterm births in the second pregnancy, we found that low-dose aspirin use was associated with a reduced risk for spontaneous preterm birth <37 weeks' gestation.

Results in the context of what is known

The incidence of recurrent preterm birth in our study is lower than generally reported[2] but is in line with the incidence of recurrent preterm birth in other Nordic countries.[3,4]

The low-dose aspirin from the prevention of preterm delivery in nulliparous women with a single pregnancy trial investigated low-dose aspirin treatment for the prevention of preterm birth among healthy nulliparous pregnant women and reported that low-dose aspirin use reduced the risk for preterm birth <37 weeks' gestation (aRR, 0.89; 95% CI, 0.81−0.98) and preterm birth <34 weeks' gestation (aRR, 0.75; 95% CI, 0.61−0.93).[6] Our point estimate for preterm birth <37 weeks' gestation is similar, although our study population had a higher incidence of preterm birth, which may be attributed to our study population comprising women with a previous preterm birth. We did not find a statistically significant association between low-dose aspirin use and moderate or severe preterm birth, but when compared with a randomized controlled trial, it is less certain whether women had an actual aspirin intake in our study.

A secondary analysis of a randomized controlled trial has found a reduction in spontaneous preterm birth <34 weeks' gestation (adjusted odds ratio, 0.46; 95% CI, 0.23−0.89) but not <37 weeks' gestation in healthy nulliparous pregnant women using low-dose aspirin,[7] whereas a meta-analysis reported a reduction in spontaneous preterm birth both at <34 weeks' gestation (RR, 0.86; 95% CI, 0.76−0.99) and <37 weeks'

TABLE 2
Association between low-dose aspirin use and preterm birth in the second pregnancy

	No aspirin use n=19,070	Aspirin use n=3057		
			Relative risk (95% confidence interval)	
Outcome	n (%)	n (%)	Crude	Adjusted
Primary outcome				
Preterm birth <37 wk	3156 (16.6)	547 (17.9)	1.08 (1.00–1.17)	0.87 (0.77–0.99)
Secondary outcomes				
Moderate preterm birth 32–36 wk	2717 (14.2)	426 (13.9)	0.98 (0.85–1.12)	0.90 (0.78–1.03)
Very preterm birth <32 wk	439 (2.4)	121 (4.0)	1.72 (1.30–2.27)	0.75 (0.54–1.04)
Medically indicated preterm birth <37 wk	676 (3.5)	375 (12.3)	3.46 (2.92–4.10)	1.09 (0.91–1.30)
Spontaneous preterm birth <37 wk	2467 (12.9)	168 (5.5)	0.42 (0.34–0.53)	0.70 (0.57–0.86)

Data are presented as frequencies (n) and percentage (%).

Totals of n=22,127 and n=20,464 were included in the crude and adjusted models, respectively. The primary outcome was estimated using a binomial logistic regression and secondary outcomes were estimated using a multinomial logistic regression.

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gestation (RR, 0.93; 95% CI, 0.86–0.996) for low-dose aspirin treatment among women at high risk for developing preeclampsia.[8]

Similar to the APRIL study, which found no statistically significant association between low-dose aspirin use and preterm birth among women with a previous spontaneous preterm birth (RR, 0.83; 95% CI, 0.58–1.20),[9] our subgroup analysis of the risk for recurrent spontaneous preterm birth showed no significant association (mRR, 0.75; 95% CI, 0.57–1.00). However, a small protective effect cannot be ruled out and we believe that our findings could support the hypothesis that low-dose aspirin might decrease the risk for recurrent spontaneous preterm birth, although we did not reach statistical significance. In our primary analysis, including women with a first medically indicated or spontaneous preterm birth, low-dose aspirin use reduced the risk for both preterm birth and spontaneous preterm birth in the second pregnancy, which could be attributed to a larger study population.

Clinical implications

Our data suggest that low-dose aspirin use may be an effective prophylaxis for recurrent preterm birth with an effect size similar to the preventative effect of low-dose aspirin on the development of preeclampsia among women at high risk.[5] However, low-dose aspirin has potential side effects and has been associated with an increased risk fir intrapartum and postpartum hemorrhage.[19] This warrants caution, and treatment of the right target population at high risk for developing the condition at the lowest effective dose is important.[5,20]

Research implications

A larger randomized controlled trial or an individual patient data meta-analysis of smaller randomized controlled trials are warranted to confirm our findings of a protective effect of low-dose aspirin use on the risk for recurrent preterm birth. In Sweden, the recommended low-dose aspirin dose during pregnancy is 75 mg per day and the effect of higher doses, such as 150 mg, needs to be investigated further.

Strengths and limitations

The main strengths of our study are the population-based setting that facilitates generalizability to the target population and the large study sample. We used data from national registers that capture data for >98% of the Swedish population[12,13] and contains information on maternal characteristics, sociodemographic factors, and pregnancy variables prospectively collected relative to the outcome that are available for adjustments in the models.

Our study is limited by the baseline differences between women using low-dose aspirin and those who did not, which we attempted to overcome by adjusting our models for gestational length during first pregnancy and other covariates that affect the risk for preterm birth. Still, there is a risk that our model might have under- or overestimate the preventive effect of low-dose aspirin because of residual confounding. To overcome this, we performed subgroup analyses by spontaneous and medically indicated preterm births in the second pregnancy, which showed an association between low-dose aspirin use and a reduced risk for spontaneous preterm birth. However, the low-dose aspirin group had a higher incidence of preeclampsia in the first pregnancy and therefore a higher risk for preeclampsia and medically indicated preterm birth in the second pregnancy. It is also possible that the women in the low-dose aspirin group were more closely monitored and therefore had a medically indicated preterm birth in cases that otherwise would have ended in a spontaneous

preterm birth. Hence, our model might have overestimated the preventive effect of low-dose aspirin against spontaneous preterm birth. Although our data on low-dose aspirin use is based on dispensed prescriptions because low-dose aspirin is not available over the counter in Sweden, we do not know the compliance and for which time period in the pregnancy low-dose aspirin was used.

Conclusion

In this population register-based cohort study, we found that among women with a previous preterm birth, low-dose aspirin use reduced the risk for recurrent preterm birth (any onset) and specifically spontaneous onset. The use of low-dose aspirin by pregnant women with a previous preterm birth could reduce the global burden of preterm birth, but further research is needed to confirm our findings and investigate the optimal low-dose aspirin dosage and timing of use. ■

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Author and article information

From the Department of Obstetrics and Gynecology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden (Drs Kupka and Bergman); Department of Research and Higher Education, Center for Clinical Research, Dalarna, Uppsala University, Falun, Sweden (Drs Kupka, Hesselman, and Lomartire); Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden (Drs Hesselman, Hastie, Wikström, and Bergman); Mercy Perinatal, Mercy Hospital for Women, Melbourne, Australia (Dr Hastie); Department of Obstetrics and Gynaecology, University of Melbourne, Heidelberg, Australia (Dr Hastie); and Department of Obstetrics and Gynaecology, Stellenbosch University, Cape Town, South Africa (Dr Bergman).

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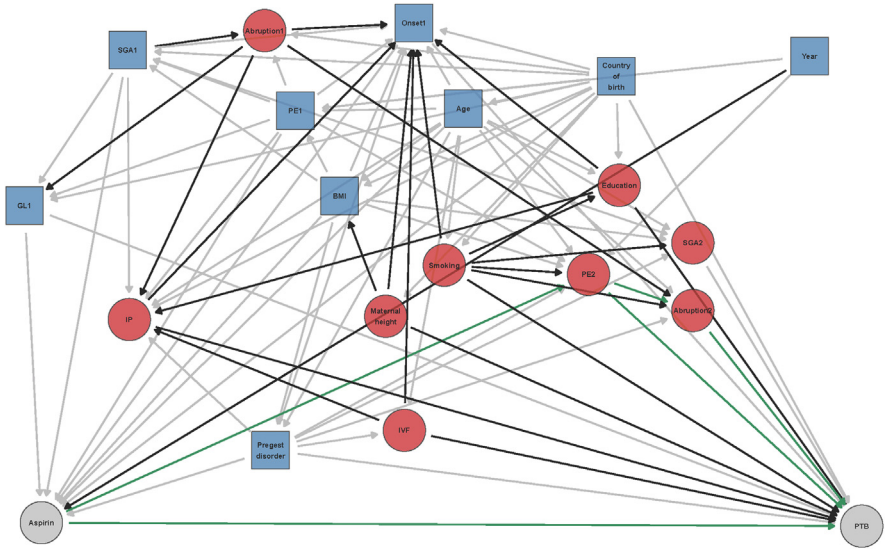
Corresponding author: Ellen Kupka, MD. ellen.kupka@gu.se

SUPPLEMENTAL FIGURE

Directed acyclic graph



Adjustment sets for estimating the total effect, referring to the set of covariates that closes all biasing paths and leaves all causal paths open, of low-dose aspirin use on preterm birth: age, BMI, country of birth, gestational length first pregnancy, small for gestational length first pregnancy, preeclampsia first pregnancy, pregestational disorder second pregnancy, date of birth and medically indicated first birth (www.dagitty.net).

Abruption1, placental abruption first pregnancy; *Abruption2*, placental abruption second pregnancy; *BMI*, body mass index second pregnancy; *GL1*, gestational length first pregnancy; *IP*, interpregnancy interval; *IVF*, in vitro fertilization; *Onset1*, medically indicated first birth; *PE1*, preeclampsia first pregnancy; *PE2*, preeclampsia second pregnancy; *pregest disorder*, pregestational disorder first pregnancy; *PTB*, preterm birth; *SGA1*, small for gestational length first pregnancy; *SGA2*, small for gestational length second pregnancy; *year*, date of birth.

Kupka. Low-dose aspirin and recurrent preterm birth. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE 1
Association between low-dose aspirin use and preterm birth among women with a first medically indicated preterm birth

	No aspirin n=3407	Aspirin use n=2520		
			Relative risk (95% confidence interval)	
Outcome	n (%)	n (%)	Crude	Adjusted
Primary outcome				
Preterm birth <37 wk	547 (16.1)	433 (17.2)	1.07 (0.95–1.20)	0.94 (0.80–1.10)
Secondary outcomes				
Moderate preterm birth 32–36 wk	452 (13.7)	341 (14.0)	1.02 (0.85–1.23)	0.98 (0.83–1.17)
Very preterm birth <32 wk	95 (3.2)	92 (4.2)	1.31 (0.88–1.95)	0.74 (0.49–1.11)
Medically indicated preterm birth <37 wk	353 (11.0)	333 (13.8)	1.28 (1.05–1.56)	1.02 (0.85–1.22)
Spontaneous preterm birth <37 wk	192 (6.3)	96 (4.4)	0.68 (0.48–0.95)	0.77 (0.56–1.07)

Data are presented as frequencies (n) and percentages (%).

Totals of n=5925 and n=5474 were included in the crude and adjusted models, respectively. The primary outcome was estimated in a binomial logistic regression and secondary outcomes in multinomial logistic regression.

Kupka. Low-dose aspirin and recurrent preterm birth. Am J Obstet Gynecol 2022.

SUPPLEMENTAL TABLE 2
Association between low-dose aspirin use and preterm birth in women with a first spontaneous preterm birth

	No aspirin n=15,528	Aspirin use n=498		
			Relative risk (95% confidence interval)	
Outcome	n (%)	n (%)	Crude	Adjusted
Primary outcome				
Preterm birth <37 wk	2576 (16.6)	111 (22.3)	1.34 (1.14–1.59)	0.96 (0.77–1.18)
Secondary outcomes				
Moderate preterm birth 32–36 wk	2235 (14.7)	84 (17.8)	1.17 (0.88–1.55)	0.95 (0.75–1.21)
Very preterm birth <32 wk	341 (2.6)	27 (6.5)	2.45 (1.44–4.24)	0.98 (0.56–1.73)
Medically indicated preterm birth <37 wk	312 (2.4)	39 (9.2)	3.90 (2.47–6.13)	1.93 (1.28–2.91)
Spontaneous preterm birth <37 wk	2254 (14.8)	72 (15.7)	1.00 (0.73–1.35)	0.75 (0.57–1.00)

Data are presented as frequencies (n) and percentages (%).

Totals of n=16,022 and n=14,990 were included in the crude and adjusted models, respectively. The primary outcome was estimated using a binomial logistic regression and secondary outcomes were estimated using a multinomial logistic regression.

Kupka. Low-dose aspirin and recurrent preterm birth. Am J Obstet Gynecol 2022.