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Author/s:
Hastie, R;Tong, S;Wikström, AK;Walker, SP;Lindquist, A;Cluver, CA;Kupka, E;Bergman, L;Hesselman, S

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Original Research

Low-Dose Aspirin for Preventing Birth of a Small-For-Gestational Age Neonate in a Subsequent Pregnancy

Roxanne Hastie, MEpi, PhD, Stephen Tong, MBBS, PhD, Anna-Karin Wikström, MD, PhD, Susan P. Walker, MBBS, PhD, Anthea Lindquist, MBBS, DPhil, Catherine A. Cluver, MD, PhD, Ellen Kupka, MD, Lina Bergman, MD, PhD, and Susanne Hesselman, MD, PhD

OBJECTIVE: To estimate whether low-dose aspirin use is associated with an altered risk of delivering a small-for-gestational age (SGA) neonate among women with a history of having an SGA neonate in a prior pregnancy.

METHODS: We performed a Swedish register-based cohort study including women in their second pregnancy who had a history of having an SGA neonate (birth weight less than the 10th percentile). The association between use of low-dose aspirin in subsequent pregnancy and birth of an SGA neonate or a severely SGA neonate (birth weight less than the third percentile) were estimated using inverse propensity-weighted estimation, accounting for potential confounders.

RESULTS: Among 8,416 women who gave birth to an SGA neonate in their first pregnancy, 801 (9.5%) used low-dose aspirin during their second pregnancy. The incidence of SGA neonates was similar among women using low-dose aspirin (21.7%) and those who did not use aspirin (20.7%). Low-dose aspirin use in pregnancy was not associated with an altered risk of having an SGA neonate (adjusted relative risk [aRR] 0.86, 95% CI 0.67–1.10) or a severely SGA neonate (aRR 0.98, 95% CI 0.71–1.34). Given the strong association between preeclampsia and SGA, we performed subgroup analyses based on preeclampsia status. Among women who had an SGA neonate and co-existing preeclampsia in their first pregnancy, low-dose aspirin was not associated with an altered risk of having an SGA (aRR 0.83, 95% CI 0.63–1.10) or severely SGA (aRR 1.02, 95% CI 0.73–1.44) neonate. Additionally, no association was seen among women who developed preeclampsia in their second pregnancy.

CONCLUSION: Among women with a history of having an SGA neonate, low-dose aspirin was not associated with a decreased risk of having an SGA or severely SGA neonate in subsequent pregnancy. These findings suggest that low-dose aspirin should not be used to prevent recurrent SGA.

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From the Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden; Mercy Perinatal, Mercy Hospital for Women, Melbourne, Australia; the Translational Obstetrics Group, Department of Obstetrics and Gynaecology, University of Melbourne, Heidelberg, Australia; the Department of Obstetrics and Gynaecology, Stellenbosch University, Cape Town, South Africa; the Centre for Clinical Research, Dalarna, Sweden; and the Department of Obstetrics and Gynecology, Institute of Clinical Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

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Corresponding author: Roxanne Hastie, MEpi, PhD, Department of Obstetrics and Gynecology, University of Melbourne, Mercy Hospital for Women, Victoria, Australia; email: Hastie.r@unimelb.edu.au.

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Aspirin has been shown to be an effective preventative agent for women at risk of developing preeclampsia.[1] Strong evidence suggests that aspirin use during early pregnancy reduces the relative risk (RR)

of developing preeclampsia by 18% (RR 0.82, 95% CI 0.77–0.82).[2] Preeclampsia and fetal growth restriction often coexist,[3] and, with related placental pathologies, aspirin has been suggested to prevent fetal growth restriction or birth of a small-for-gestational-age (SGA) neonate. However, there is no consensus as to whether women at risk for fetal growth restriction should be prescribed aspirin. The Royal College of Obstetricians and Gynaecologists[4] and the American College of Obstetricians and Gynecologists[5,6] do not recommend aspirin for preventing fetal growth restriction among women without risk factors for preeclampsia, whereas the Society of Obstetricians and Gynaecologists of Canada[7] and the Perinatal Society of Australia and New Zealand support offering aspirin for those at risk of fetal growth restriction, such as women with a history of a growth-restricted neonate.[8]

Using a population-based cohort of more than 8,000 women with a history of having an SGA neonate (birth weight less than the 10th percentile) in their first pregnancy, we examined whether aspirin use was associated with a reduced risk of having an SGA or severely SGA neonate in a subsequent pregnancy.

METHODS

We performed a population-based cohort study using data obtained from the Swedish Pregnancy Register. The Swedish Pregnancy Register currently covers more than 98% of all births among 16 of 20 regions in Sweden and combines prospectively collected data from the Swedish Maternal Health Care Register, the Swedish National Quality Register for Prenatal Diagnosis, and obstetric data from electronic birth records. Data are collected from the first antenatal visit to scheduled follow up two to three months postpartum.[9]

We included women with a first and second singleton birth between 2013 and 2018 recorded in the Swedish Pregnancy Register, who in their first pregnancy gave birth to an SGA neonate. *Small for gestational age* was used as a proxy for fetal growth restriction and was defined as birth weight less than the 10th percentile using the Swedish national reference curve for birth weight according to gestational week and sex.[10] Gestational age was generally determined using ultrasonographic measurements in the late first or early second trimester, which is offered to all pregnant women in Sweden. We excluded 408 women with missing birth weight data and 186 women with missing or uncertain parity data. This left a final study population of 8,416 women with a second birth after the birth of an SGA neonate.

Maternal demographic variables extracted from the second pregnancy data included age (categorized into younger than 35 years or 35 years or older), body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), country of birth, socioeconomic factors and smoking. Body mass index was calculated from measured weight and self-reported height registered at the first antenatal visit, which was then divided into two groups: lower than 30 and 30 or higher. Country of birth was classified as Sweden and the rest of the world. Data on self-reported occupation were classified as employed or government assistance (sick leave, student, or unemployed). Smoking during pregnancy (yes or no) was recorded at the first antenatal visit.

Pregnancy variables were extracted for both the first and second pregnancy and included parity, use of in vitro fertilization, gestational disorders (preeclampsia, gestational hypertension, gestational diabetes, preterm birth, birth weight less than the third percentile and stillbirth), gestational age at delivery, induction of labor and mode of birth (cesarean or vaginal). Information on pregnancy related conditions were extracted from predefined check boxes in the electronic birth records and diagnosis codes recorded by obstetricians per the International Classification of Diseases, Tenth Version (ICD-10): pregestational hypertension (I10, O10), pregestational diabetes (O240, O241, E10-14) and pregnancy disorders; preeclampsia (O14, O15), gestational diabetes (O244, O249).

National Swedish guidelines recommend 75 mg of aspirin daily for the women at high risk of preeclampsia or with several moderate risk factors, based on National Institute for Health and Care Excellence guidelines, from 12 weeks of gestation through 36 weeks. Women with other indications for aspirin use such as systemic lupus erythematosus or other chronic disease may also be treated with aspirin. In Sweden, aspirin is not started after the onset of preeclampsia and in most centers, treatment is stopped when preeclampsia is diagnosed. There are no national guidelines surrounding aspirin for the prevention of SGA or preterm birth, and use for these indications is determined by the treating clinician. Data on aspirin use were obtained from prenatal care records, which include data obtained from the first antenatal visit record and each subsequent care visit record, generally 8–10 visits across a pregnancy. In Sweden, women are typically asked about medication use at each visit. *Aspirin use during pregnancy* was defined as recorded use at any visit during pregnancy.

The primary outcome was having an *SGA neonate*, defined as birth weight less than the 10th percentile based on the Swedish population normal distribution and sex-specific standardized birth weight percentiles,[10] which is similar to the commonly used U.S. population–based curve.[11] The secondary outcome was *severe SGA*, defined as a neonate with birth weight less than the third percentile.

A prespecified statistical analysis plan was generated before data analysis. An a priori power calculation was included with our statistical analysis plan that showed, given a sample size of 8,416 with 801 patients in the exposed group and stipulating an alpha of 0.05 and power of 0.80, the minimum detectable absolute risk difference would be 4.35%.

Characteristics of the population were described for both first and second pregnancy by aspirin use during the second pregnancy. Comparisons were made using bivariate analysis using Pearson's χ^2 test for categorical data and Student's *t* test for continuous variables.

The average treatment effect for aspirin use (average treatment effect on the treated) on delivery of a subsequent SGA neonate (less than the 10th percentile) or severely SGA neonate (less than the third percentile) was estimated using Stata's "teffects" command and presented as RR with 95% CI. Regression models were inverse probability weighted to achieve covariate balance between exposure groups. A propensity score for exposure was calculated for individuals using logistic regression, including variables considered to be confounders. Included covariates were maternal age, BMI, smoking status, country of birth, in vitro fertilization, pregestational disorders (pre-existing hypertension, cardiovascular disease, systemic lupus erythematous, thrombosis), gestational diabetes and first pregnancy outcomes (preeclampsia, birth of a neonate with birth weight less than the third percentile [interacted with preeclampsia], stillbirth, preterm birth). Within the subgroup analyses stratified by whether women developed preeclampsia in their first pregnancy or not, preeclampsia status of the first pregnancy was not included as a covariate. Second, to achieve balance between the exposed and unexposed groups, estimated propensity scores were used to weight each patient, with a score of 1/propensity score assigned to the exposed individuals and 1/(1–propensity score) to the unexposed. Propensity scores were checked for extreme values and overlap between exposure groups. The balance of individual covariates before and after inverse probability weighting was also assessed. Weighted standardized differences of less than 0.1 were indicative of covariate balance (raw and weighted standardized differences for included covariates and each outcome are shown in Appendix 1, available online at http://links.lww.com/AOG/C612). Modelling proceeded only when there was sufficient overlap of propensity scores and covariate balance after weighting was achieved.

This study was approved by the Regional Ethical Board at Uppsala University (Dnr 2018/28, Dnr 2018/287/1, Dnr 2019–04672, Dnr 2020–05731).

RESULTS

Of 8,416 women who delivered an SGA neonate with birth weight less than the 10th percentile in their first pregnancy, 801 (9.5%) used low-dose aspirin during their second pregnancy. The mean maternal age was 31.1 years (SD 4.7), mean BMI was 24.3 (SD 4.7), and most women were born in Sweden (69.0%) (Table 1).

Compared with unexposed women, those using low-dose aspirin were older, more commonly had obesity, were more likely to become pregnant through in vitro fertilization, were more likely to be employed, and were less likely to smoke. Additionally, women using low-dose aspirin were more likely to have pregestational disorders including chronic hypertension, diabetes, chronic kidney disease, thrombosis, or cardiovascular disease. Furthermore, women using low-dose aspirin were also more likely to have experienced complications during their first pregnancy including preeclampsia, gestational hypertension, gestational diabetes, preterm birth and stillbirth. Women using low-dose aspirin were more likely to experience complications in the second pregnancy including gestational diabetes, preeclampsia, stillbirth and preterm birth (Table 1).

The incidence of an SGA neonate (less than the 10th percentile) in the second pregnancy was 21.7% among women using low-dose aspirin and 20.7% among those not using low-dose aspirin (Table 2). This resulted in a crude RR of 1.05 (95% CI 0.91–1.20). After adjustment using inverse probability weighting, there was no association between low-dose aspirin and having an SGA neonate (adjusted relative risk [aRR] 0.86, 95% CI 0.67–1.10). The incidence of delivery of a neonate with severe SGA (less than the third percentile) was higher among women using low-dose aspirin at 9.4%, compared with 6.7% among those not using low-dose aspirin. This resulted in an increased RR of 1.39 (95% CI 1.11–1.79); however, after adjustment using inverse probability weighting, no association remained (aRR 0.98, 95% CI 0.71–1.34).

Given the strong association between preeclampsia and SGA, we stratified analyses by preeclampsia status

Table 1. Maternal Characteristics at Second Pregnancy by Aspirin Use

Characteristic	Total Births (N=8,416)	Aspirin Use in 2nd Pregnancy		
		No (n=7,615)	Yes (n=801)	*P*
Age (y)	31.1±4.7	31.1±4.7	31.7±4.7	<.001
35 or older	1,723 (20.5)	1,528 (20.1)	195 (24.3)	
BMI (kg/m^2)	24.3±4.7	24.2±4.6	25.4±5.3	<.001
30 or higher	946 (11.2)	803 (10.5)	143 (17.5)	
Missing	399 (4.7)	373 (4.9)	26 (3.3)	
Country of birth				
Sweden	5,810 (69.0)	5,210 (68.4)	600 (74.9)	.006
Other Nordic	84 (1.0)	78 (1.0)	6 (0.8)	
Other European	544 (6.5)	500 (6.6)	44 (5.5)	
Rest of the world	1,756 (20.9)	1,620 (21.3)	136 (17.0)	
Missing	222 (2.6)	207 (2.2)	15 (1.9)	
Smoking				
Yes	695 (8.3)	644 (8.5)	51 (6.4)	.11
Missing	147 (1.8)	131 (1.7)	16 (2.0)	
In vitro fertilization				
Yes	269 (3.2)	238 (3.1)	31 (3.9)	.254
Occupation				
Employed	4,825 (57.3)	4,342 (57.0)	483 (60.3)	.057
Government assistance	2,987 (35.5)	2,733 (35.9)	254 (31.7)	
Missing	604 (7.2)	540 (7.1)	64 (7.1)	
Pregestational disorders				
Chronic hypertension	74 (0.9)	42 (0.6)	32 (4.0)	<.001
Diabetes	27 (0.3)	23 (0.3)	4 (0.5)	.347
Chronic kidney disease, thrombosis, or cardiovascular disease	204 (2.4)	141 (1.9)	63 (7.9)	<.001
Systemic lupus erythematosus	19 (0.2)	8 (0.1)	11 (1.4)	<.001
1st pregnancy outcomes				
Preeclampsia	753 (9.0)	390 (5.1)	363 (45.3)	<.001
Gestational hypertension	393 (4.7)	296 (3.9)	97 (12.1)	<.001
Gestational diabetes	96 (1.1)	84 (1.1)	12 (1.5)	.317
Preterm birth (less than 37 wk)	827 (9.8)	440 (5.8)	387 (48.3)	<.001
Cesarean delivery	1,591 (18.9)	1,209 (15.9)	382 (47.7)	<.001
Birth weight less than the 3rd percentile	2,865 (34.0)	2,320 (30.5)	545 (68.0)	<.001
Stillbirth	196 (2.3)	83 (1.1)	113 (14.1)	<.001
Gestational disorders in current pregnancy				
Gestational diabetes	131 (1.6)	110 (1.4)	21 (2.6)	.01
Preeclampsia	193 (2.3)	118 (1.6)	75 (9.4)	<.001
Stillbirth	29 (0.3)	29 (0.4)	0	.08
Gestational age (wk)	39.6±1.7	39.7±1.7	39.0±2.1	<.001
Preterm birth (less than 37 wk)	367 (4.4)	299 (3.9)	68 (8.5)	<.001

BMI, body mass index.
Data are mean±SD or n (%) unless otherwise specified.

in the first pregnancy (Table 3). Among women who did not develop preeclampsia (n=7,663), low-dose aspirin in the subsequent pregnancy was not associated with an altered risk of having an SGA neonate (aRR 0.83, 95% CI 0.63–1.10; 21.0% vs 20.8%) or severely SGA neonate (aRR 1.02, 95% CI 0.73–1.44; 10.1% vs 6.6%). Similarly, among women who developed preeclampsia in their first pregnancy, low-dose aspirin was not associated with an altered risk of having an SGA neonate (aRR 1.15, 95% CI 0.83–1.60; 22.6% vs 18.2%) or severely SGA neonate (aRR 0.78, 95% CI 0.46–1.34; 8.5% vs 9.0%) in their second pregnancy.

We performed subgroup analysis by preeclampsia status in the second pregnancy (Table 4). Among 8,223 women who did not develop preeclampsia in their second pregnancy, low-dose aspirin use (n=726) was not associated with an altered risk of having an SGA (aRR 0.85, 95% CI 0.65–1.11) or severely SGA neonate (aRR 0.99, 95% CI 0.71–1.39). Within our cohort, 193 (2.3%) women developed preeclampsia in their second pregnancy; among these women, low-dose aspirin was not associated with an altered risk of having an SGA neonate (RR 1.01, 95% CI 0.72–1.44) or severely SGA neonate (RR 0.81, 95%

Table 2. Maternal Aspirin Use and Risk of Having a Small-for-Gestational-Age Neonate

		Aspirin Use (n=801)		
Birth Weight Percentile	No Aspirin (n=7,615) [n (%)]	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Less than 10th	1,577 (20.7)	174 (21.7)	1.05 (0.91–1.20)	0.86 (0.67–1.10)
Less than 3rd	510 (6.7)	75 (9.4)	1.39 (1.11–1.76)	0.98 (0.71–1.34)

RR, relative risk.
Adjusted analyses were retrieved using inverse probability weighting, with maternal age, body mass index, employment status, country of birth, smoking, in vitro fertilization, previous pregnancy outcomes (preeclampsia, birth weight less than the third percentile, preterm birth, gestational diabetes, stillbirth), and pregestational disorders (hypertension, diabetes, systemic lupus erythematosus, cardiovascular disease, thrombosis, chronic kidney disease) included as covariates.

CI 0.48–1.38). However, owing to the small numbers of women within this final cohort, adjusted analyses were not performed.

DISCUSSION

In this register-based cohort study, low-dose aspirin use among women with a previous SGA neonate was not associated with a reduced risk of SGA or severe SGA. Stratified by the presence of preeclampsia, there was no association between low-dose aspirin use and SGA regardless of whether women developed preeclampsia in their first or second pregnancy. These findings suggest that, in this population, SGA alone may not be an indication for low-dose aspirin use.

This is a population-based register cohort study aimed at investigating the role of aspirin in preventing SGA among women with a previous SGA neonate. The 2019 Cochrane meta-analysis investigating aspirin for the prevention of preeclampsia reports that aspirin reduced the incidence of SGA from 4.7% to 4.0%, with an RR of 16%.[2] They also reported an 18% RR reduction of preeclampsia.[2] Given similar risk reductions between SGA and preeclampsia it is plausible that the effect of aspirin on SGA may be mediated by reducing the number of women who develop preeclampsia and, thus, those who develop SGA. This is further highlighted by findings of the large multicenter ASPRE trial (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention), which assessed 150 mg of aspirin daily for the prevention of preterm preeclampsia.[12] A secondary analysis of ASPRE data showed that, among women who did not develop preeclampsia, aspirin did not alter the risk of having an SGA neonate regardless of gestational age at birth.[13] However, among women who developed preeclampsia with preterm birth, aspirin was associated with a significant reduction in SGA. Given that the ASPRE trial also found aspirin to reduce preterm preeclampsia by 62%, it is again plausible that the effect of aspirin on SGA may be mediated by reducing preterm preeclampsia rather than by a direct effect on fetal weight.[13] This effect among women who developed preeclampsia was not found in our study. This difference may be attributed to varied risk profiles of our populations. The ASPRE trial included only women deemed high risk for preeclampsia, with

Table 3. Subgroup Analysis by Women With Preeclampsia in the First Pregnancy

	No Preeclampsia in 1st Pregnancy (n=7,663)				Preeclampsia in 1st Pregnancy (n=753)			
		Aspirin Use (n=438)				Aspirin Use (n=363)		
Birth Weight Percentile	No Aspirin (n=7,225) [n (%)]	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	No Aspirin (n=390) [n (%)]	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Less than 10th	1,506 (20.8)	92 (21.0)	1.01 (0.84–1.22)	0.83 (0.63–1.10)	71 (18.2)	82 (22.6)	1.24 (0.93–1.65)	1.15 (0.83–1.60)
Less than 3rd	475 (6.6)	44 (10.1)	1.53 (1.14–2.05)	1.02 (0.73–1.44)	35 (9.0)	31 (8.5)	0.95 (0.60–1.51)	0.78 (0.46–1.34)

RR, relative risk.
Adjusted analyses were retrieved using inverse probability weighting, with maternal age, body mass index, employment status, country of birth, smoking, in vitro fertilization, previous pregnancy outcomes (birth weight less than the third percentile, preterm birth, gestational diabetes, stillbirth), and pregestational disorders (hypertension, diabetes, systemic lupus erythematosus, cardiovascular disease, thrombosis, chronic kidney disease) included as covariates.

Table 4. Subgroup Analysis by Women With Preeclampsia in the Second Pregnancy

	No Preeclampsia in 2nd Pregnancy (n=8,223)				Preeclampsia in 2nd Pregnancy (n=193)		
		Aspirin Use (n=726)				Aspirin Use (n=75)	
Birth Weight Percentile	No Aspirin (n=7,497) [n (%)]	n (%)	Crude RR (95% CI)	Adjusted RR (95% CI)	No Aspirin (n=118) [n (%)]	n (%)	RR (95% CI)
Less than 10th	1,529 (20.3)	143 (19.7)	0.97 (0.83–1.13)	0.85 (0.65–1.11)	48 (40.1)	31 (41.3)	1.01 (0.72–1.44)
Less than 3rd	479 (6.4)	59 (8.1)	1.27 (0.98–1.65)	0.99 (0.71–1.39)	31 (26.3)	16 (21.3)	0.81 (0.48–1.38)

RR, relative risk.

Adjusted analyses were retrieved using inverse probability weighting, with maternal age, body mass index, employment status, country of birth, smoking, in vitro fertilization, previous pregnancy outcomes (preeclampsia, birth weight less than the third percentile, preterm birth, gestational diabetes, stillbirth), and pregestational disorders included as covariates.

9.9% of women developing preeclampsia,[12] compared with 2.3% in our study.

Our findings are further supported by a large randomized controlled trial assessing aspirin (81 mg daily) use for the prevention of preterm birth among unselected nulliparous women.[14] In this trial, aspirin significantly reduced the incidence of preterm birth but did not alter the risk of having an SGA neonate (RR 0.95, 95% CI 0.90–1.01).[14]

Previously, we have reported aspirin to be associated with an increased risk of maternal bleeding, including postpartum hemorrhage and postpartum hematoma.[15] Additionally, a slight increased risk of postpartum hemorrhage was reported in the 2019 Cochrane systematic review of antiplatelet agents for the prevention of preeclampsia.[2] Thus, the use of aspirin for preventing SGA may place women at an increased risk of intrapartum and postpartum bleeding complications.

Our study has several strengths. It is a population-based study with data drawn from recent years. Our cohort included detailed information of both first and second pregnancies. This allowed us to identify women who in their first pregnancy delivered an SGA neonate as well as include details and outcomes of the first pregnancy within our adjusted models. We explored birth of SGA and severely SGA neonates, and the exposure was self-reported and not derived from dispensed prescriptions, which increases the likelihood of actual intake of aspirin.

There are limitations in our study. It is not a randomized controlled trial; thus, there were inherent baseline differences between women using aspirin and those not using aspirin. To overcome this, we used a propensity score inverse probability weighting approach. The success of this approach is demonstrated by the balancing of maternal covariates that differed between aspirin users and nonusers, thus reducing the potential for bias. Given that aspirin is most commonly used in obstetrics, including in Sweden, among women at risk of developing preeclampsia and the strong association between preeclampsia and SGA,[3] there is the potential for confounding by indication. To reduce this potential for bias, we stratified our analyses by preeclampsia status in both the first or the second pregnancy and showed that there was no association between aspirin and SGA regardless of preeclampsia status. Our study was sufficiently powered to detect an absolute difference of 4.35%. Thus, it is plausible that aspirin may have had a smaller protective effect that was not detected in this population. Power within subgroup analyses was substantially reduced, and these findings should be considered exploratory. Additionally, these findings may not be generalizable to non-Swedish populations. Lastly, information on the dosage of aspirin used, indication, and adherence were not captured within our data set, and there is potential for maternal underreporting and ascertainment bias. However, in Sweden, aspirin is routinely prescribed at 75 mg during pregnancy. Further investigations using other populations and higher doses, including 150 mg, are still required, and large randomized clinical trials investigating aspirin for the primary prevention of SGA are warranted.

In this population-based cohort study, the use of aspirin among women who previously had an SGA neonate was not associated with a detectable difference in the risk of having a subsequent SGA neonate. Our data do not support previous SGA alone as an indication for subsequent aspirin use.

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