GÖTEBORGS UNIVERSITET

Aspirin under graviditet
något för alla?

LINA BERGMAN, SPECIALISTLÄKARE, DOCENT

Intressekonflikter

Medlem i styrgrupp IMPACT-studien; Roche, Perkin Elmer och Thermo Fischer förser IMPACT studien med reagenser för PlGF tester för första trimester prediktion av preeklampsi

Medprövare i APPLE-PIE – studie om metformin för prevention av preeklampsi i Sydafrika, finansierad av Merck

Gravida kvinnor i forskning

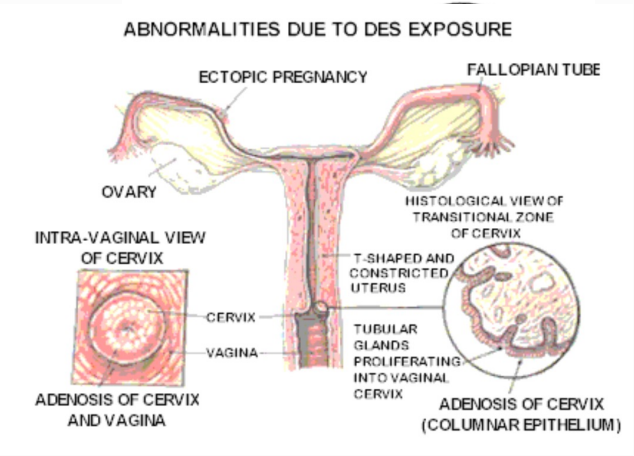
Thalidomid och diethystilbestrol katastroferna (1960 och 1970)

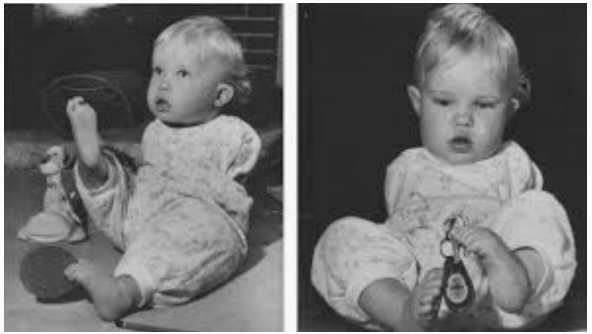
US FDA

Policy för att skydda kvinnor från forskning

Exkluderade gravida kvinnor från kliniska prövningar

Signifikant och potentiellt farlig kunskapslucka





Obstetrisk forskning

"Obstetrics had fewer drugs in development than some single diseases such as Crohn's"

"1636 drugs under development for neurological disease compared to 17 for maternal health"

”Repurposing drugs”

ASPIRIN FOR THE TREATMENT OF RECURRENT TOXÆMIA

In the 15th week of gestation of her third pregnancy, her platelet-count was 59 000/μl and her hæmatocrit was 40%. Bone-marrow and peripheral-blood smear suggested peripheral consumption of platelets. There was no other laboratory suggestion of microangiopathic anæmia or consumption coagulopathy throughout her pregancy. She was treated with heparin 5000 units three times a day for 4 weeks with no appreciable effect on platelet-count. At the 22nd week, aspirin 600 mg three times a day was started, with gradual improvement in platelet-count (figure).

Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis

S. ROBERGE*, K. H. NICOLAIDES†, S. DEMERS‡, P. VILLA§ and E. BUJOLD*‡

Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis

Shireen Meher, MD; Lelia Duley, MD; Kylie Hunter, BA(Hons); Lisa Askie, PhD

Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data

*Lisa M Askie, Lelia Duley, David J Henderson-Smart, Lesley A Stewart, on behalf of the PARIS Collaborative Group**

The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis

Stéphanie Roberge, PhD; Kypros Nicolaides, MD; Suzanne Demers, MD, MSc; Jon Hyett, MD; Nils Chaillet, PhD; Emmanuel Bujold, MD, MSc

?

BAYER ASPIRIN
BAYER
ASPIRIN
FAST RELIEF
HEADACHES
COLDS
The REAL
Wonder Drug!

Ska vi behandla med trombyl?

1) 1-para, preeklampsi med debut i gv 39, nu gravid i gv 17.
2) 0-para med BMI 31, 29 år gammal, syster med graviditetshypertoni, nu gravid i gv 21.
3) 2-para, båda barnen SGA, ingen anamnes på preeklampsi, nu gravid i gv 12.
4) 1-para, spontan förtidsbörd i gv 29, ingen preeklampsi men barnet SGA, nu gravid i gv 13.

Aspirin mot preeklampsi

Reduktion från 9.2% till 7.6% diagnos preeklampsi
12-23% minskad relativ risk, 1.6% minskad absolut risk

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no antiplatelet	Antiplatelet agents				
Proteinuric pre-eclampsia	92 per 1000	**16 fewer per 1000** (22 fewer to 11 fewer)	**RR 0.82** (0.77 to 0.88)	36,716 (60 trials)	⊕⊕⊕⊕ **high**	

Duley et al, Cochrane 2019

Aspirin mot förtidsbörd

Reduktion från 17.5% till 15.9% förtidsbörd
5-13% minskad relativ risk, 1.6% minskad absolut risk

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no antiplatelet	Antiplatelet agents				
Preterm birth (before 37 weeks' gestation)	175 per 1000	**16 fewer per 1000** (23 fewer to 9 fewer)	**RR 0.91** (0.87 to 0.95)	35,212 (47 trials)	⊕⊕⊕⊕ **high**	

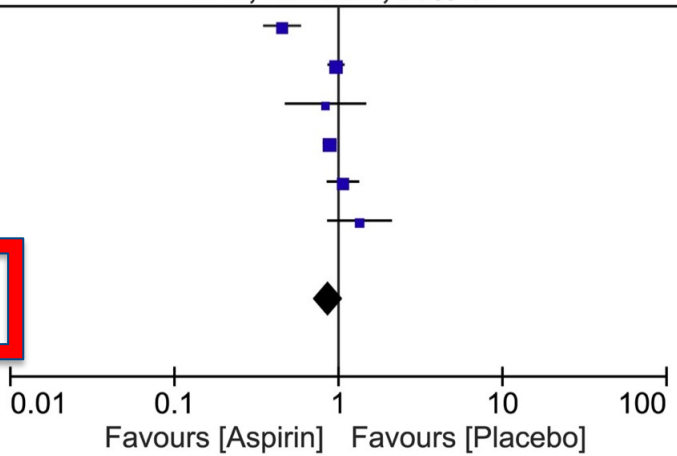
Duley et al, Cochrane 2019

Och de utan hög risk för preeklampsi?

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakhti 2011	34	82	75	82	17.2%	0.45 [0.35, 0.59]
Golding 1998	447	3023	463	3026	21.8%	0.97 [0.86, 1.09]
Hauth 1993	20	302	24	302	8.8%	0.83 [0.47, 1.48]
Hoffman 2020	668	5780	754	5764	22.3%	0.88 [0.80, 0.97]
Sutton 2018	139	1465	132	1482	18.5%	1.07 [0.85, 1.34]
Taherian 2002	39	330	29	330	11.4%	1.34 [0.85, 2.12]
Total (95% CI)		**10982**		**10986**	**100.0%**	**0.87 [0.70, 1.08]**
Total events	1347		1477			

Heterogeneity: Tau² = 0.05; Chi² = 32.61, df = 5 (P < 0.00001); I² = 85%

Test for overall effect: Z = 1.29 (P = 0.20)



Man et al, EJOG 2021

Och hur är det med spontan förtidsbörd?

Meta-analys 2017 Green Journal, lågdos aspirin

17 studier, 28797 kvinnor (data på spontan vs iatrogen förtidsbörd)

Alla kvinnor hade riskfaktorer för preeklampsi, ej specifikt utvalda pga tidigare förtidsbörd

RR för spontan förtidsbörd <37 gv 0.86 (95% KI 0.83-0.996)

Review

Antiplatelet Agents and the Prevention of Spontaneous Preterm Birth

A Systematic Review and Meta-analysis

Elvira O. G. van Vliet, MD, PhD, Lisa A. Askie, PhD, Ben W. J. Mol, MD, PhD, and Martijn A. Oudijk, MD, PhD

OBJECTIVE: Spontaneous preterm birth is an important cause of neonatal mortality and morbidity. An increasing body of evidence suggests that uteroplacental ischemia plays an important role in the etiology of spontaneous preterm birth. We aimed to study whether antiplatelet agents reduce the risk of spontaneous preterm birth.

DATA SOURCES: We included data from an individual participant data meta-analysis of studies that had evaluated the effect of antiplatelet agents to reduce preeclampsia (Perinatal Antiplatelet Review of International Studies Individual Participant Data).

METHODS OF STUDY SELECTION: The meta-analysis included 31 studies that randomized women to low-dose aspirin–dipyridamole or placebo–no treatment as a primary preventive strategy for preeclampsia. For the current study we analyzed data from 17 trials (28,797 women) that supplied data on type of delivery (spontaneous compared with indicated birth).

TABULATION, INTEGRATION, AND RESULTS: Primary endpoints were spontaneous preterm birth at less than 37 weeks, less than 34 weeks, and less than 28 weeks of gestation. We analyzed outcomes for each trial separately using χ^2 statistics and combined in an individual participant data meta-analysis using a binary logistic regression model. Women assigned to antiplatelet treatment compared with placebo or no treatment had a lower risk of spontaneous preterm birth at less than 37 weeks (relative risk [RR] 0.93, 95% confidence interval [CI] 0.86–0.996) and less than 34 weeks of gestation (RR 0.86, 95% CI 0.76–0.99). The RR of having a spontaneous preterm birth at less than 37 weeks of gestation was 0.83 (95% CI 0.73–0.95) for women who have had a previous pregnancy and 0.98 (95% CI 0.89–1.09) for women in their first pregnancy. The treatment effect was stable in all other prespecified subgroups.

CONCLUSION: Antiplatelet agents reduce spontaneous preterm birth in pregnant women at risk for preeclampsia.

(Obstet Gynecol 2017;129:327–36)
DOI: 10.1097/AOG.0000000000001848

Preterm birth is one of the most challenging obstetric problems worldwide and occurs in approximately 5–12% of all deliveries. Preterm birth accounts for 70% of perinatal mortality and 40% of severe neurologic morbidities.[1] Preterm birth can be classified as spontaneous or iatrogenic. Spontaneous preterm birth starts with spontaneous labor with intact membranes or prelabor premature rupture of the membranes (PROM). In iatrogenic preterm birth, pregnancy is prematurely interrupted for maternal or fetal indications, often as a result of preeclampsia or fetal growth restriction.[2] In industrialized high-resourced countries, spontaneous preterm birth accounts for two thirds of all preterm births and is

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Dr. van Vliet was supported by a travel grant of the Dutch Ter Meulen Fund of the Royal Netherlands Academy of Arts and Sciences.

Presented as an abstract at the Society for Reproductive Investigation 62nd Annual Scientific Meeting, March 25–28, 2015, San Francisco, California, and as an oral presentation at the Perinatal Society of Australia and New Zealand 19th Annual Conference, April 19–22, 2015, Melbourne, Australia.

The authors thank the Perinatal Antiplatelet Review of International Studies (PARIS) Steering Committee for their permission to use the data for these analyses.

Each author has indicated that he or she has met the journal's requirements for authorship.

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Financial Disclosure
The authors did not report any potential conflicts of interest.

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ISSN: 0029-7844/17

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Vliet et al, O&G, 2017

Och de med tidigare spontan förtidsbörd?

APRIL study

Kvinnor med tidigare förtidsbörd

Randomiserade till ASA 80 mg fr.o.m gv 8-16 – gv 36 eller förlossning

Huvudutfall: Förtidsbörd <37 gv

Outcome	Aspirin (n=194)	Placebo (n=193)	RR (95% CI)
Preterm birth <37+0	41 (21.2%)	49 (25.4%)	0.83 (0.58-1.20)
Spontaneous	39 (20.1%)	46 (23.8%)	0.84 (0.58-1.23)
Indicated	2 (1.0%)	3 (1.6%)	0.66 (0.11-3.93)
Preterm birth <34+0	18 (9.3%)	17 (8.8%)	1.05 (0.56-1.98)
Preterm birth <28+0	7 (3.6%)	5 (2.6%)	1.39 (0.45-4.31)
Composite poor neonatal outcome	9 (4.6%)	5 (2.6%)	1.79 (0.61-5.25)
Women with ≥80% medication compliance			
Preterm birth <37+0	23/124 (18.5%)	30/121 (24.8%)	0.75 (0.46-1.21)

Landman et al, SMFM abstract 2021

Vad säger guidelines för aspirin mot förtidsbörd?

ACOG och SMFM: Low-dose aspirin prophylaxis is not recommended for the prevention of spontaneous preterm birth, in the absence of risk factors for preeclampsia.

NICE: Ingen rekommendation

RANZCOG: Ingen rekommendation

SFOG: Ingen rekommendation

Aspirin mot liten för tiden

Reduktion från 4.7% till 4.0% diagnos SGA
8-24% minskad relativ risk, 0.7% minskad absolut risk

Cochrane Library

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no antiplatelet	Antiplatelet agents				
Small-for-gestational age	47 per 1000	**7 fewer per 1000** (11 fewer to 3 fewer)	**RR 0.84** (0.76 to 0.92)	35,761 (50 trials)	⊕⊕⊕⊕ **high**	

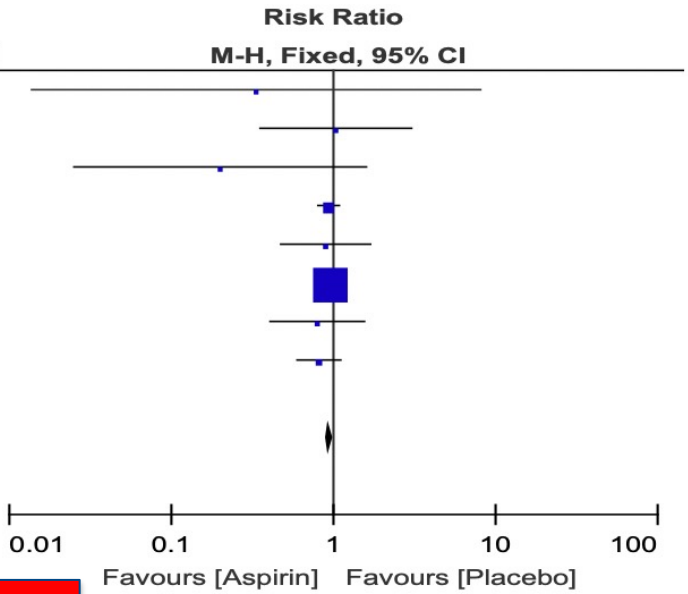
Duley et al, Cochrane 2019

Och de utan hög risk för preeklampsi?

Study or Subgroup	Aspirin Events	Aspirin Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bakhti 2011	0	82	1	82	0.1%	0.33 [0.01, 8.06]
Davies 1995	6	58	6	60	0.3%	1.03 [0.35, 3.02]
Desari 1998	1	25	5	25	0.2%	0.20 [0.03, 1.59]
Golding 1998	303	3023	325	3026	16.0%	0.93 [0.80, 1.08]
Hauth 1993	17	302	19	302	0.9%	0.89 [0.47, 1.69]
Hoffman 2020	1506	5492	1564	5467	77.3%	0.96 [0.90, 1.02]
Mone 2018	14	179	18	183	0.9%	0.80 [0.41, 1.55]
Sutton 2018	70	1465	87	1482	4.3%	0.81 [0.60, 1.11]
Total (95% CI)		**10626**		**10627**	**100.0%**	**0.94 [0.89, 1.00]**
Total events	1917		2025			

Heterogeneity: Chi² = 4.04, df = 7 (P = 0.78); I² = 0%

Test for overall effect: Z = 2.07 (P = 0.04)



0.94 [0.89, 1.00]

Man et al, EJOG 2021

ULTRASOUND
in Obstetrics & Gynecology

Prediction and prevention of small-for-gestational-age neonates: evidence from SPREE and ASPRE

M. Y. Tan, L. C. Poon, D. L. Rolnik, A. Syngelaki, C. de Paco Matallana, R. Akolekar, S. Cicero, D. Janga, M. Singh, F. S. Molina, N. Persico, J. C. Jani, W. Plasencia, E. Greco, G. Papaioannou, D. Wright, K. H. Nicolaides

Table 4 Incidence of small-for-gestational-age neonates in aspirin and placebo groups from ASPRE trial

BW percentile/GA	*Placebo* (n = 807) (n (%))	*Aspirin* (n = 785) (n (%))	*Relative risk* (95% CI)	P
Pre-eclampsia				
BW < 10th percentile				
Any gestation	46 (5.7)	17 (2.2)	0.380 (0.221–0.652)	0.0005
≥ 37 weeks	16 (2.0)	9 (1.1)	0.578 (0.262–1.273)	0.2543
< 37 weeks	30 (3.7)	8 (1.0)	0.274 (0.129–0.583)	0.0008
< 32 weeks	9 (1.1)	1 (0.1)	0.114 (0.019–0.695)	0.0295
No pre-eclampsia				
BW < 10th percentile				
Any gestation	183 (22.7)	154 (19.6)	0.865 (0.715–1.046)	0.1521
≥ 37 weeks	147 (18.2)	123 (15.7)	0.860 (0.691–1.069)	0.1981
< 37 weeks	36 (4.5)	31 (3.9)	0.885 (0.555–1.410)	0.7012
< 32 weeks	14 (1.7)	5 (0.6)	0.367 (0.138–0.974)	0.0741

Men hur är det med indikation tidigare SGA?

Graviditetsregistret
mödrahälsovård • fosterdiagnostik • förlossning

8416 gravida kvinnor med tidigare SGA

Uppdelade i aspirin vs ej aspirin i aktuell graviditet

Data justerade med propensity score

Graviditetsregistret
mödrahälsovård • fosterdiagnostik • förlossning

	No aspirin n= 7,615	Aspirin use n=801	Relative risk (95% confidence interval)	
	n (%)	n (%)	Crude	Adjusted
Birthweight <10th				
Birthweight <3rd				

Hastie et al, Manuskript för submittering UOG

Vad säger guidelines om aspirin mot SGA/IUGR?

ACOG och SMFM: Low-dose aspirin prophylaxis is not recommended for prevention of fetal growth restriction, in the absence of risk factors for preeclampsia.

NICE/RCOG: Aspirin may be protective agains small for gestational age in women with high risk of preeclampsia

RANZCOG: 100-150 mg aspirin in women with previous history of intrauterine growth restriction

SFOG: Ingen rekommendation

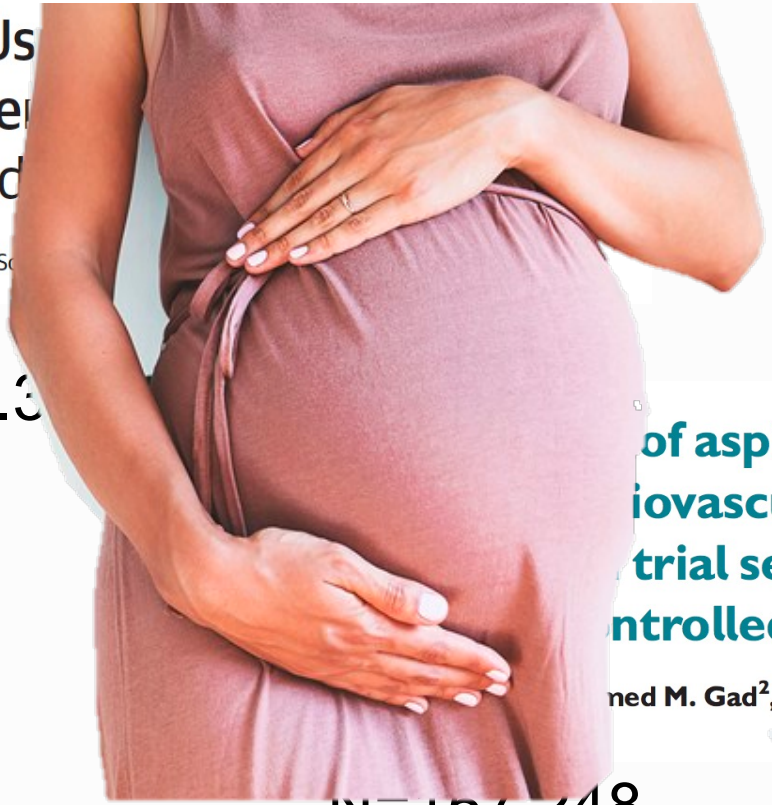
JAMA | Original Investigation

Association of Aspirin Us
With Cardiovascular Eve
A Systematic Review and

Sean L. Zheng, BM, BCh, MA, MRCP; Alistair J. Roddick, BS

N=164,225

HR 1.43 95% CI 1.3



of aspirin for primary
iovascular events: a
trial sequential analysis
ntrolled trials

ned M. Gad[2], Akram Y. Elgendy[1], Islam Y. Elgendy[1†],

N=157,248

RR 1.47 ; 95% CI 1.31 – 1.65

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo/no antiplatelet	Antiplatelet agents				
Postpartum haemorrhage > 500 mL	143 per 1000	**9 more per 1000** (0 fewer to 19 more)	**RR 1.06** (1.00 to 1.12)	23,769 (19 trials)	⊕⊕⊕⊖ **moderate**[a]	
Placental abruption	7 per 1000	**2 more per 1000** (0 fewer to 4 more)	**RR 1.21** (0.95 to 1.54)	30,775 (29 trials)	⊕⊕⊕⊖ **moderate**[b]	

Duley et al, Cochrane 2019

THE LANCET

	Aspirin	Placebo	RR (95% CI)	p value
Hypertensive disorders*	352/5780 (6·1%)	325/5764 (5·6%)	1·08 (0·94–1·25)	0·299
Vaginal bleeding†	214/5933 (3·6%)	246/5940 (4·1%)	0·87 (0·73–1·04)	0·125
Antepartum haemorrhage*	26/5761 (0·5%)	25/5746 (0·4%)	1·03 (0·60–1·79)	0·900
Post-partum haemorrhage‡	54/5928 (0·9%)	43/5907 (0·7%)	1·25 (0·84–1·86)	0·274
Maternal mortality up to 6 weeks post partum† (rate per 100 000 livebirths)	9/5958 (151)	12/5948 (202)	0·75 (0·32–1·78)	0·512
Late abortion† (rate per 1000 pregnancies)	23/5819 (4·0)	30/5808 (5·2)	0·77 (0·45–1·31)	0·331
Early preterm delivery (<34 weeks) and hypertensive disorders*	8/5780 (0·1%)	21/5764 (0·4%)	0·38 (0·17–0·85)	0·015

4,732 gravida med aspirin (1.5%)

Dosering 75mg

Data justerade med propensity score

Original Research ajog.org

OBSTETRICS

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

Roxanne Hastie, PhD, MEpi; Stephen Tong, PhD; Anna-Karin Wikström, MBBS, PhD; Anna Sandström, MD, PhD; Susanne Hesselman, MD, PhD; Lina Bergman, MD, PhD

BACKGROUND: Aspirin is offered to pregnant women to prevent preeclampsia, a severe obstetrical complication. Large studies of nonpregnant populations have consistently shown that aspirin prophylaxis increases the risk of hemorrhagic complications. However, there have not been any population-based studies investigating this in a pregnant population.
OBJECTIVE: This study aimed to investigate whether aspirin use during pregnancy is associated with an increased risk of bleeding complications.
STUDY DESIGN: We performed a register-based cohort study using the Swedish Pregnancy Register wherein we examined 313,624 women giving birth between January 2013 and July 2017. Logistic regression was used to assess the risk of antepartum, intrapartum, and postpartum hemorrhage. A propensity score and inverse probability treatment weighting was used to generate an odds ratio that corrects for differences in baseline characteristics.
RESULTS: Aspirin use was registered in 4088 (1.3%) women during pregnancy. Compared with women who did not take aspirin, aspirin use was not associated with bleeding complications during the antepartum period (adjusted odds ratio, 1.22; 95% confidence interval, 0.97–1.54). However, aspirin users had a higher incidence of intrapartum bleeding (2.9% aspirin users vs 1.5% nonusers; adjusted odds ratio, 1.63; 95% confidence interval, 1.30–2.05), postpartum hemorrhage (10.2% vs 7.8%; adjusted odds ratio, 1.23; 95% confidence interval, 1.08–1.39), and postpartum hematoma (0.4% vs 0.1%; adjusted odds ratio, 2.21; 95% confidence interval, 1.13–4.34). The risk of a neonatal intracranial hemorrhage was also increased (0.07% vs 0.01%; adjusted odds ratio, 9.66; 95% confidence interval, 1.88–49.48). After stratifying by mode of birth, a higher incidence of bleeding among aspirin users was present for those who had a vaginal birth but not those who had a cesarean delivery.
CONCLUSION: Using aspirin during pregnancy is associated with increased postpartum bleeding and postpartum hematoma. It may also be associated with neonatal intracranial hemorrhage. When offering aspirin during pregnancy, these risks need to be weighed against the potential benefits.

Key words: aspirin, bleeding risk, hemorrhage, pregnancy

Introduction

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

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

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

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

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

0002-9378/$36.00
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https://doi.org/10.1016/j.ajog.2020.07.023

Hastie et al, AJOG 2020

Blödningar under och efter förlossning

Graviditetsregistret
mödrahälsovård • fosterdiagnostik • förlossning

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

Ska vi behandla med trombyl?

- 1) 1-para, preeklampsi med debut i gv 39, nu gravid i gv 17.
- 2) 0-para med BMI 31, 29 år gammal, syster med graviditetshypertoni, nu gravid i gv 21.
- 3) 2-para, båda barnen SGA, ingen anamnes på preeklampsi, nu gravid i gv 12.
- ? 4) 1-para, spontan förtidsbörd i gv 29, barnet SGA, nu gravid i gv 13.

Konklusion

- Aspirin sänker risken för preeklampsi med 12-23%. 75 mg/dag, helst start före 20 graviditetsveckor.
- Aspirin sänker risken för SGA men troligen genom effekten på preeklampsi och ingen effekt är visad efter tidigare SGA utan preeklampsi.
- Aspirin har en liten men säkerställd effekt på att sänka risken för förtidsbörd, även spontan. Effekten och storleken är osäker för de utan riskfaktorer för preeklampsi och för de med tidigare förtidsbörd.
- Aspirin kan ha blödningar som bieffekter och bör ges till kvinnor som har hög risk för preeklampsi i minsta möjliga effektiva dos.