Pregnancy Hypertension 17 (2019) 241–248

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Aspirin use during pregnancy and hypertensive disorders in women with various risks

Jing Zhu[a,b,1], Chang Chen[a,c,1], Danni Lu[a,c], Jinwen Zhang[a,c], Shiwen Jing[a,c], Hehui Xie[d], Jun Zhang[a,c,*]

[a] MOE-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Department of Obstetrics and Gynecology, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[c] Shanghai Jiao Tong University School of Public Health, Shanghai, China
[d] School of Public Health, Hongqiao International Institute of Medicine, Shanghai Jiao Tong University School of Medicine, Shanghai, China

ARTICLE INFO

Keywords:
Aspirin
Preeclampsia
Gestational hypertension
Risk factors

ABSTRACT

Background: It is still unclear how well aspirin performs in women with different risks and how the timing of aspirin use influences its efficacy. This study was to evaluate the association between timing of aspirin exposure and hypertensive disorders in pregnant women with various risks in a prospective cohort.

Methods: We used data from the Collaborative Perinatal Project, U.S., 1959–1976. Women were grouped into high, moderate and low risks based on medical history. We classified the timing of aspirin exposure into 4 weeks before the last menstrual period, the first, second and third trimesters.

Results: A total of 50,579 pregnant women were included in our analysis with 6453, 18,552 and 25,574 women at high, moderate and low risks, respectively. In high-risk women, aspirin use for more than 7 days in the first trimester reduced the risks of preterm and term preeclampsia/eclampsia by 42% (adjusted OR 0.58; 95% CI 0.36–0.94) and 24% (adjusted OR 0.76; 95% CI 0.59–0.97), respectively; in moderate-risk women, aspirin use for more than 7 days during the third trimester reduced the risks of term preeclampsia/eclampsia and gestational hypertension by 37% (adjusted OR 0.63; 95% CI 0.50–0.79) and 27% (adjusted OR 0.73; 95% CI 0.62–0.86), respectively.

Conclusion: Aspirin use in pregnancy reduces the risks of maternal hypertensive disorders. Early initiation of aspirin in high-risk women was associated with lower incidence of preeclampsia/eclampsia. Meanwhile, the protective effect of aspirin on term preeclampsia/eclampsia and gestational hypertension may continue till late pregnancy.

1. Introduction

Since the first case report of using aspirin to treat "recurrent toxemia" was published in 1978 [1], numerous clinical trials have been conducted to test whether low-dose aspirin can prevent preeclampsia. Meta-analyses from individual patient data [2] and aggregate data [3,4] suggested that low-dose aspirin can reduce the risk of preeclampsia. However, previous studies usually included women with various risks and different levels of risks. It is still unclear how well aspirin performs in pregnant women with different risks. Results from meta-analyses [5,6] were also inconsistent as to whether aspirin would be beneficial even commenced after 16 gestational weeks. There is no trial directly comparing an early *vs.* late initiation. Therefore, we evaluate the associations between timing of maternal aspirin exposure and hypertensive disorders of pregnancy in women with various risks in a prospective cohort study.

2. Methods

2.1. Study population

We used data from the Collaborative Perinatal Project (CPP), a cohort study conducted at 12 medical centers in the United States (U.S.). Pregnant women were enrolled at their first prenatal visits from 1959 to 1965. Detailed information on women's medical history, physical examinations, laboratory tests and delivery outcomes were collected. The

* Corresponding author at: MOE-Shanghai Key Laboratory of Children's Environmental Health, Xinhua Hospital, No. 1665 Kongjiang Rd, Shanghai 200092, China.
E-mail address: zhangjun@xinhuamed.com.cn (J. Zhang).
[1] Jing Zhu and Chang Chen contributed equally to the work and should both be considered as first author.

https://doi.org/10.1016/j.preghy.2019.07.005
Received 4 April 2019; Received in revised form 10 July 2019; Accepted 14 July 2019
Available online 15 July 2019
2210-7789/ © 2019 Published by Elsevier B.V. on behalf of International Society for the Study of Hypertension in Pregnancy.

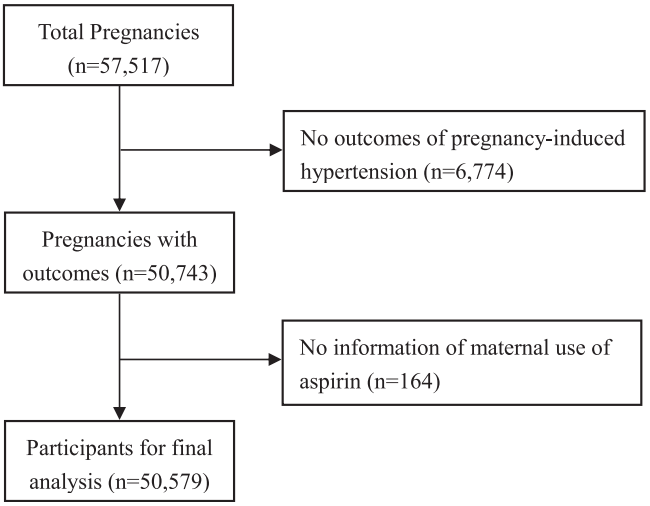

Fig. 1. Flowchart of study population, the Collaborative Perinatal Project, 1959–1976.

offspring were followed until 7 or 8 years of age.

A total of 57,517 pregnant women were registered in the cohort. To evaluate the association between aspirin exposure during pregnancy and hypertensive disorders, we excluded 6774 women with no records on pregnancy outcomes and 164 women with no information on aspirin taken during pregnancy, leaving 50,579 women for our final analysis (Fig. 1).

Based on the clinical risk assessment for preeclampsia recommended by the U.S. Preventative Services Task Force Recommendation Statement [7], we grouped women into high, moderate and low risks based on women's medical history. Chronic hypertension, diabetes mellitus and chronic renal disease were high risk factors for preeclampsia; nulliparity, obesity and older than 35 years of age were moderate risk factors; women without above mentioned risk factors were considered as low risks. Thus, 6453, 18,552 and 25,574 women were classified as high, moderate and low-risk pregnancies. Use of publicly available de-identified data is exempt from our Ethics Committee review.

2.2. Aspirin exposure

The name of medication and timing of exposure were recorded at each prenatal visit. Detailed dosage of medication was not recorded in the CPP. Products containing aspirin alone and active compound containing aspirin were included. Other nonsteroidal anti-inflammatory drugs were excluded. In the CPP, dates of medication taken during pregnancy were recorded and converted to lunar month of pregnancy. We classified the timing of aspirin exposure into 4 weeks before last menstrual period (LMP), first, second and third trimesters. Accumulation of aspirin taken during each exposure period was the sum of days of aspirin used in each month and trimester. The minimal length of aspirin taken during each exposure period was one day.

2.3. Measurement of outcomes

Gestational hypertension was defined as high blood pressure without proteinuria from 24 weeks gestation to 2 weeks postpartum. Preeclampsia/eclampsia was defined as high blood pressure plus any of the following symptoms: mild or severe proteinuria, oliguria, pulmonary edema, or convulsion from 24 weeks of gestation to 2 weeks postpartum. Preterm preeclampsia/eclampsia was defined as preeclampsia/eclampsia leading to delivery < 37 gestational weeks. Term preeclampsia/eclampsia was defined as preeclampsia/eclampsia leading to delivery ≥ 37 gestational weeks. Chronic hypertension was diagnosed based on women's medical history, or hypertension before 24 weeks of gestation, or persistent hypertension 2 weeks postpartum. Gestational age was based on the LMP.

2.4. Statistical analysis

We calculated the frequency and proportion of maternal characteristics in groups with or without aspirin exposure. Stratified analysis and multinomial logistic regression analysis was performed to assess the effects of aspirin exposure on the incidence of preeclampsia/eclampsia and gestational hypertension in high-, moderate- and low-risk women, respectively. We adjusted for maternal age, race, parity, education, social economic status, marriage status, smoking during pregnancy and gestational age at delivery for potential confounders. Results were presented as odds ratios (ORs) and 95% confidence intervals (CIs). We used SAS version 9.4 (Cary, NC) for all the statistical analyses.

3. Results

Among 50,579 women included in the analysis, 4631 women (9.2%) had preeclampsia/eclampsia, including 710 (1.4%) women with preterm preeclampsia/eclampsia and 3921 (7.8%) women with term preeclampsia/eclampsia, and 4527 (9.0%) women had gestational hypertension. Table 1 shows the maternal characteristics by aspirin exposure status during pregnancy. A total of 20,949 (41.4%) women reported using aspirin before or during pregnancy. We observed no substantial difference between aspirin exposed and unexposed groups on maternal age, parity, smoking during pregnancy and maternal pre-pregnant BMI. Aspirin users had a higher proportion of White (50.7% *vs.* 42.7%), marital status (79.0% *vs.* 73.0%) and college education (14.2% *vs.* 10.2%). Meanwhile, the incidence of chronic hypertension and chronic renal disease were higher in aspirin group than in aspirin unexposed group (8.2% *vs.* 6.7% for chronic hypertension; 4.6% *vs.* 3.4% for chronic renal disease).

Table 2 shows the associations between maternal exposure to aspirin before and during pregnancy and hypertensive disorders of pregnancy in high-risk women. Compared with high-risk women without using aspirin, women who used aspirin for more than 7 days in the first trimester had 42% (adjusted OR 0.58; 95% CI 0.36–0.94) lower risks of preterm preeclampsia/eclampsia and 24% (adjusted OR 0.76; 95% CI 0.59–0.97) lower risks of term preeclampsia/eclampsia, respectively. However, we observed no associations of maternal aspirin exposure and gestational hypertension in those women.

We also evaluated the associations between aspirin exposure and hypertensive disorders of pregnancy in moderate- and low-risk pregnant women (Tables 3 and 4). In moderate-risk women, use of aspirin for more than 7 days during the third trimester, but not the first or second trimesters, reduced the risk of term preeclampsia/eclampsia (adjusted OR 0.63; 95% CI 0.50–0.79). Moreover, the protective effect on the risk of gestational hypertension was observed in both groups of women. Compared with women unexposed to aspirin, aspirin use for more than 7 days during the third trimester reduced the risk of gestational hypertension by 27% (adjusted OR 0.73; 95% CI 0.62–0.86) and 18% (adjusted OR 0.82; 95% CI 0.68–0.99) for moderate-risk and low-risk women, respectively.

We further examined the impact of maternal aspirin use for more than 7 days on the risk of hypertensive disorders of pregnancy in women with chronic hypertension, obesity, over 35 years of age and nulliparity, respectively. The results (Table 5) were consistent with our findings in Tables 2 and 3. Hypertensive women using aspirin in the first trimester reduced the risk of preterm preeclampsia/eclampsia by 53%. A trend of lower incidence of term preeclampsia/eclampsia and gestational hypertension was also observed in obese, elder and nulliparous women who had used aspirin for more than 7 days during the third trimester.

Table 1
Maternal characteristics by aspirin using during pregnancy, the Collaborative Perinatal Project, 1959–1976.

Characteristics	Total (n = 50,579) N (%)	Aspirin (n = 20,949) N (%)	Aspirin unexposed (n = 29,630) N (%)	*P* value
Maternal age (year)				< 0.001
< 20	11,897 (23.5)	4463 (21.3)	7434 (25.1)	
20–24	18,478 (36.5)	7604 (36.3)	10,874 (36.7)	
25–29	10,755 (21.3)	4855 (23.2)	5900 (19.9)	
30–34	5709 (11.3)	2482 (11.8)	3227 (10.9)	
≥35	3740 (7.4)	1545 (7.4)	2195 (7.4)	
Race				< 0.001
White	23,270 (46.0)	10,630 (50.7)	12,640 (42.7)	
Black	23,582 (46.6)	9670 (46.2)	13,912 (47.0)	
Other	3727 (7.4)	649 (3.1)	3078 (10.4)	
Parity				< 0.001
0	15,233 (30.1)	6061 (29.0)	9172 (31.0)	
1	11,592 (22.9)	4760 (22.8)	6832 (23.1)	
≥2	23,661 (46.8)	10,094 (48.3)	13,567 (45.9)	
Social economic status				< 0.001
1 (Lowest)	3826 (7.6)	1397 (6.8)	2429 (8.5)	
2	15,449 (30.5)	5782 (28.1)	9667 (33.8)	
3	15,312 (30.3)	6274 (30.5)	9038 (31.6)	
4	9689 (19.2)	4439 (21.6)	5250 (18.3)	
5 (Highest)	4917 (9.7)	2684 (13.0)	2233 (7.8)	
Maternal education levels (year)				< 0.001
Less than high school (≤9)	14,473 (28.6)	5315 (25.6)	9158 (31.7)	
High school (10–12)	29,244 (57.8)	12,471 (60.1)	16,773 (58.1)	
College and above (> 12)	5910 (11.7)	2952 (14.2)	2958 (10.2)	
Married	38,180 (75.5)	16,541 (79.0)	21,639 (73.0)	< 0.001
Smoking during pregnancy	23,398 (46.3)	9916 (47.5)	13,482 (46.0)	0.001
Maternal pre-pregnant BMI (kg/m^2)				< 0.001
< 18.5	7155 (14.1)	2898 (13.9)	4257 (14.4)	
18.5–24.9	31,924 (63.1)	13,406 (64.1)	18,518 (62.8)	
25.0–29.9	7044 (13.9)	2955 (14.1)	4089 (13.9)	
≥30.0	4257 (8.4)	1641 (7.9)	2616 (8.9)	
Chronic hypertension	3696 (7.3)	1720 (8.2)	1976 (6.7)	< 0.001
Diabetes mellitus	1145 (2.3)	438 (2.1)	707 (2.4)	0.028
Chronic renal disease	1990 (3.9)	969 (4.6)	1021 (3.4)	< 0.001

BMI: body mass index.

4. Discussion

In this prospective cohort study, we found that aspirin use during pregnancy was associated with lower risk of hypertensive disorders of pregnancy. In high-risk pregnant women, aspirin exposure during the first trimester reduced the risk of preeclampsia/eclampsia. In moderate-risk women, the protective effect of aspirin on term preeclampsia/eclampsia was notable in the third trimester. In addition, we observed that aspirin exposure in late pregnancy was associated with a lower risk of gestational hypertension.

Our results suggest that aspirin may work in the first trimester in high-risk women; in the third trimester among moderate-risk women. In the CPP, aspirin was used at a dose of more than 300 mg daily. It inhibits prostaglandins synthesis, resulting in analgesic, anti-inflammatory, and antipyretic effects. Inhibition of cyclooxygenase (COX) may inhibit chronically upregulated inflammatory pathways which involves in reproductive process [8,9]. Indeed, preconception low-dose aspirin increased live birth rates in women with elevated high-sensitivity C-reactive protein (CRP) [10]. As defective trophoblast invasion and placental pathology such as infarction are associated with maternal hypertension and hyperglycemia [11–13], an early initiation of aspirin might diminish maternal inflammatory status, improve implantation and placentation and then, reduce the risk of preeclampsia.

Except for poor placentation, enhanced syncytiotrophoblast stress and increased maternal systemic inflammatory responses might mainly contribute to the pathogenesis of late-onset preeclampsia [14,15]. Compared with the early-onset one, late-onset preeclampsia is characteristic with normal intrauterine fetal growth without placental pathology. Obesity and nulliparity are strongly associated with late-onset disease [16,17]. Although a mild but significant inflammatory activity is presented throughout gestation in normal pregnancy, enhanced lipid metabolism-associated inflammation is thought to contribute to maternal high blood pressure in obese women during late pregnancy [18,19]. Meanwhile, oxidative stress biomarkers at 28–32 weeks, e.g., 8-epiprostaglandinF2-α and total antioxidant capacity, also correlated with adverse pregnancy outcomes in women with advanced age and obesity [20,21]. Such increased inflammatory and oxidative stress environment might impair endothelial function even without defective placentation and subsequently result in manifestation of high blood pressure and proteinuria.

Until now, the biological mechanism of aspirin in preventing preeclampsia has not been truly understood. It is noted that COX-derived vasoconstrictor substances might impair nitric oxide availability, resulting in endothelia dysfunction and hypertension [22,23]. Particularly, COX-2 participates in oxidative stress generation, extracellular matrix overdeposition, impaired vascular function and inflammation in hypertension [24,25]. In BPH/5 mouse model for preeclampsia, COX-2 specific inhibitor celecoxib was identified to reduce soluble fms-like tyrosine kinase-1 (sFlt-1) levels and alleviate maternal hypertension [26,27]. Moreover, a higher platelet activation status was also presented in preeclamptic women than in normotensive women [28]. Aspirin is known for antiplatelet effect with a dose-related inhibition of platelet aggregation and P-selectin expression [29]. Therefore, we speculate that use of aspirin during late pregnancy might inhibit platelet activity, reduce inflammatory and oxidative stress levels through inhibiting COX and improve maternal endothelial function. Given that gestational hypertension and preeclampsia have common risk factors such as obesity, nulliparity and diabetes [30], these two diseases may share some potential common pathways (e.g., oxidative stress). As a result, we observed the protective effect of aspirin on gestational hypertension in late pregnancy as well.

5. Strengths and limitations

The CPP is a large prospective cohort study recruited more than 50,000 women and 41.4% women reported using aspirin before or during pregnancy. The CPP dataset preceded any clinical use of aspirin for preventing preeclampsia and detailed information was recorded before clinical onset of disease. Therefore, selection bias and recall bias were unlikely. In addition, the large sample size provided sufficient statistical power to detect a small association. However, several limitations should also be noted. First, we did not have indications for aspirin use in pregnancy. As aspirin was used for a therapeutic purpose of analgesic and antipyretic during 1960s, maternal health conditions such as fever and arthritis might not be associated with hypertensive disorders of pregnancy. Thus, there was less impact of confounding by indication on our results. Second, the dose of aspirin in the CPP is higher than current usage at a dose of 75–150 mg daily. Low-dose aspirin irreversibly acetylates serine 530 of COX-1, inhibits platelet generation of thromboxane-A2, maintains normal prostacyclin production,

Table 2
Relative risks of hypertensive disorders of pregnancy in high-risk pregnant women with aspirin using during pregnancy, the Collaborative Perinatal Project, 1959–1976.

Aspirin exposure	No. of maternal aspirin use, (%)	Preterm Preeclampsia/eclampsia (N = 482)			Term Preeclampsia/eclampsia (N = 2461)			Gestational Hypertension (N = 235)		
		No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)
Total										
No use	3509 (54.4)	283	Ref.	Ref.	1275	Ref.	Ref.	128	Ref.	Ref.
Any use	2944 (45.6)	199	1.13 (0.93, 1.38)	0.95 (0.75, 1.20)	1186	0.86 (0.77, 0.95)	0.94 (0.84, 1.05)	107	0.95 (0.73, 1.24)	0.97 (0.74, 1.28)
> 7 days	1015 (15.7)	78	0.91 (0.70, 1.19)	0.80 (0.59, 1.10)	423	0.85 (0.74, 0.98)	0.95 (0.82, 1.10)	23	1.63 (1.05, 2.53)	1.59 (1.01, 2.50)
4 weeks before LMP										
No use	6287 (97.4)	473	Ref.	Ref.	2396	Ref.	Ref.	230	Ref.	Ref.
Any use	166 (2.6)	9	1.43 (0.72, 2.87)	1.60 (0.67, 3.77)	65	1.01 (0.73, 1.39)	1.11 (0.79, 1.57)	5	1.26 (0.51, 3.12)	1.23 (0.49, 3.09)
> 7 days	65 (1.0)	1	4.75 (0.65, 34.80)	4.52 (0.57, 36.18)	31	0.77 (0.47, 1.27)	0.81 (0.48, 1.35)	1	2.31 (0.31, 16.97)	2.22 (0.30, 16.43)
First trimester										
No use	5631 (87.3)	418	Ref.	Ref.	2101	Ref.	Ref.	204	Ref.	Ref.
Any use	822 (12.7)	64	0.82 (0.62, 1.10)	0.73 (0.52, 1.01)	360	0.74 (0.63, 0.86)	0.80 (0.68, 0.95)	31	0.83 (0.56, 1.23)	0.84 (0.56, 1.26)
> 7 days	313 (4.9)	29	0.67 (0.44, 1.02)	0.58 (0.36, 0.94)	144	0.69 (0.54, 0.88)	0.76 (0.59, 0.97)	5	1.98 (0.80, 4.88)	2.19 (0.80, 6.00)
Second trimester										
No use	4544 (70.4)	340	Ref.	Ref.	1685	Ref.	Ref.	163	Ref.	Ref.
Any use	1909 (29.6)	142	0.93 (0.76, 1.15)	0.85 (0.66, 1.10)	776	0.85 (0.76, 0.95)	0.91 (0.81, 1.03)	72	0.88 (0.66, 1.18)	0.88 (0.66, 1.19)
> 7 days	599 (9.3)	52	0.77 (0.56, 1.05)	0.74 (0.50, 1.08)	255	0.80 (0.67, 0.96)	0.88 (0.73, 1.06)	14	1.46 (0.84, 2.55)	1.41 (0.79, 2.52)
Third trimester										
No use	4618 (71.6)	384	Ref.	Ref.	1681	Ref.	Ref.	174	Ref.	Ref.
Any use	1835 (28.4)	98	1.48 (1.17, 1.87)	1.06 (0.80, 1.40)	780	0.81 (0.92, 0.91)	0.93 (0.82, 1.05)	61	1.07 (0.80, 1.45)	1.09 (0.80, 1.48)
> 7 days	544 (8.4)	33	1.21 (0.83, 1.76)	0.92 (0.59, 1.41)	230	0.86 (0.72, 1.04)	1.00 (0.82, 1.21)	14	1.40 (0.80, 2.44)	1.36 (0.78, 2.37)

Adjusted for maternal age, race, parity, social economic status (SES), maternal education, marriage status, smoking during pregnancy, maternal pre-pregnant body mass index (BMI) and gestational age at delivery.
High-risk pregnant women: women with any of the conditions: chronic hypertension, diabetes mellitus and chronic renal disease.

Table 3
Relative risks of hypertensive disorders of pregnancy in moderate-risk pregnant women with aspirin using during pregnancy, the Collaborative Perinatal Project, 1959–1976.

Aspirin exposure	No. of maternal aspirin use, (%)	Preterm Preeclampsia/eclampsia (N = 157)			Term Preeclampsia/eclampsia (N = 1004)			Gestational Hypertension (N = 2752)		
		No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)
Total										
No use	11,273 (60.8)	113	Ref.	Ref.	592	Ref.	Ref.	1680	Ref.	Ref.
Any use	7279 (39.2)	44	1.66 (1.17, 2.36)	1.16 (0.80, 1.68)	412	0.93 (0.82, 1.06)	0.92 (0.81, 1.05)	1072	1.01 (0.93, 1.10)	1.02 (0.93, 1.11)
> 7 days	2201 (11.9)	15	1.46 (0.85, 2.51)	1.08 (0.62, 1.88)	135	0.85 (0.70, 1.03)	0.83 (0.68, 1.02)	328	0.99 (0.87, 1.13)	0.99 (0.87, 1.13)
4 weeks before LMP										
No use	18,114 (97.6)	156	Ref.	Ref.	979	Ref.	Ref.	2678	Ref.	Ref.
Any use	438 (2.4)	1	3.65 (0.51, 25.95)	2.62 (0.36, 18.94)	25	0.93 (0.61, 1.40)	0.94 (0.62, 1.44)	74	0.86 (0.66, 1.10)	0.87 (0.67, 1.13)
> 7 days	151 (0.8)	1	1.35 (0.19, 9.75)	1.06 (0.14, 7.75)	8	1.08 (0.53, 2.22)	1.10 (0.53, 2.27)	16	1.48 (0.88, 2.50)	1.57 (0.92, 2.69)
First trimester										
No use	16,538 (89.1)	143	Ref.	Ref.	894	Ref.	Ref.	2483	Ref.	Ref.
Any use	2014 (10.9)	14	1.27 (0.73, 2.21)	1.27 (0.71, 2.29)	110	1.01 (0.83, 1.24)	1.00 (0.81, 1.23)	269	1.15 (1.00, 1.32)	1.18 (1.03, 1.35)
> 7 days	778 (4.2)	7	0.99 (0.46, 2.12)	0.98 (0.44, 2.15)	39	1.14 (0.82, 1.59)	1.12 (0.81, 1.57)	85	1.45 (1.15, 1.83)	1.49 (1.18, 1.88)
Second trimester										
No use	14,201 (76.5)	132	Ref.	Ref.	777	Ref.	Ref.	2137	Ref.	Ref.
Any use	4351 (23.5)	25	1.65 (1.07, 2.53)	1.33 (0.85, 2.07)	227	1.07 (0.92, 1.25)	1.01 (0.87, 1.19)	615	1.09 (0.99, 1.20)	1.08 (0.98, 1.19)
> 7 days	1257 (6.8)	8	1.44 (0.70, 2.93)	1.26 (0.61, 2.64)	62	1.17 (0.90, 1.53)	1.14 (0.87, 1.50)	138	1.46 (1.22, 1.75)	1.46 (1.21, 1.76)
Third trimester										
No use	13,792 (74.3)	131	Ref.	Ref.	715	Ref.	Ref.	2042	Ref.	Ref.
Any use	4760 (25.7)	26	1.73 (1.13, 2.63)	1.02 (0.65, 1.58)	289	0.85 (0.74, 0.98)	0.87 (0.75, 1.01)	710	0.99 (0.90, 1.08)	1.00 (0.91, 1.10)
> 7 days	1132 (6.1)	9	0.98 (0.50, 1.93)	0.70 (0.35, 1.42)	88	0.62 (0.49, 0.78)	0.63 (0.50, 0.79)	211	0.72 (0.61, 0.84)	0.73 (0.62, 0.86)

Adjusted for maternal race, social economic status (SES), maternal education, marriage status, smoking during pregnancy and gestational age at delivery.
Moderate-risk pregnant women: women with any of the conditions: over 35 years age, nulliparity, obesity.

Table 4
Relative risks of hypertensive disorders of pregnancy in low-risk pregnant women with aspirin using during pregnancy, the Collaborative Perinatal Project, 1959–1976.

Aspirin exposure	No. of maternal aspirin use, (%)	Preterm Preeclampsia/eclampsia (N = 71)			Term Preeclampsia/eclampsia (N = 456)			Gestational Hypertension (N = 1540)		
		No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)
Total										
No use	14,848 (58.1)	50	Ref.	Ref.	266	Ref.	Ref.	900	Ref.	Ref.
Any use	10,726 (41.9)	21	1.72 (1.03, 2.87)	1.14 (0.67, 1.93)	190	1.01 (0.84, 1.22)	1.01 (0.83, 1.23)	640	1.02 (0.92, 1.13)	1.04 (0.93, 1.16)
> 7 days	3598 (14.1)	7	1.49 (0.68, 3.25)	1.18 (0.53, 2.61)	72	0.87 (0.68, 1.12)	0.93 (0.71, 1.21)	219	0.99 (0.85, 1.14)	0.99 (0.85, 1.15)
4 weeks before LMP										
No use	24,854 (97.2)	69	Ref.	Ref.	439	Ref.	Ref.	1501	Ref.	Ref.
Any use	720 (2.8)	2	1.00 (0.25, 4.09)	0.80 (0.19, 3.36)	17	0.75 (0.46, 1.22)	0.70 (0.43, 1.15)	39	1.12 (0.80, 1.55)	1.10 (0.79, 1.53)
> 7 days	303 (1.2)	1	0.87 (0.12, 6.25)	0.63 (0.08, 4.78)	6	0.93 (0.41, 2.09)	0.90 (0.40, 2.02)	9	2.10 (1.08, 4.09)	2.05 (1.05, 3.99)
First trimester										
No use	22,339 (87.4)	65	Ref.	Ref.	400	Ref.	Ref.	1367	Ref.	Ref.
Any use	3235 (12.6)	6	1.58 (0.69, 3.65)	1.38 (0.59, 3.23)	56	1.05 (0.79, 1.39)	1.05 (0.78, 1.41)	173	1.16 (0.98, 1.36)	1.17 (0.99, 1.38)
> 7 days	1387 (5.4)	2	2.03 (0.50, 8.29)	1.79 (0.43, 7.42)	21	1.22 (0.78, 1.90)	1.36 (0.85, 2.19)	57	1.53 (1.17, 2.01)	1.55 (1.18, 2.04)
Second trimester										
No use	19,202 (75.1)	57	Ref.	Ref.	353	Ref.	Ref.	1174	Ref.	Ref.
Any use	6372 (24.9)	14	1.36 (0.76, 2.44)	1.03 (0.57, 1.88)	103	1.15 (0.92, 1.43)	1.12 (0.89, 1.42)	366	1.07 (0.95, 1.21)	1.06 (0.94, 1.20)
> 7 days	2231 (8.7)	5	1.29 (0.52, 3.19)	1.14 (0.45, 2.87)	34	1.21 (0.85, 1.72)	1.29 (0.89, 1.87)	106	1.32 (1.08, 1.61)	1.31 (1.07, 1.61)
Third trimester										
No use	18,195 (71.1)	55	Ref.	Ref.	318	Ref.	Ref.	1099	Ref.	Ref.
Any use	7379 (28.9)	16	1.39 (0.80, 2.43)	0.80 (0.45, 1.43)	138	0.94 (0.76, 1.14)	0.98 (0.79, 1.20)	441	1.01 (0.90, 1.13)	1.04 (0.92, 1.17)
> 7 days	1879 (7.3)	3	1.77 (0.56, 5.61)	1.22 (0.38, 3.95)	43	0.75 (0.54, 1.03)	0.80 (0.57, 1.12)	135	0.81 (0.68, 0.97)	0.82 (0.68, 0.99)

Adjusted for maternal race, social economic status (SES), maternal education, marriage status, smoking during pregnancy and gestational age at delivery.
Low-risk pregnant women: women without any of the conditions: chronic hypertension, diabetes mellitus, chronic renal disease, over 35 years age, nulliparity and obesity.

Table 5
Relative risks of hypertensive disorders of pregnancy in women with different risks with aspirin use more than 7 days by period of aspirin exposure, the Collaborative Perinatal Project, 1959–1976.

Risks of pregnancies and aspirin exposure	No. of maternal aspirin use, (%)	Preterm Preeclampsia/eclampsia			Term Preeclampsia/eclampsia			Gestational Hypertension		
		No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)	No. of cases	Crude OR (95%CI)	Adjusted OR (95%CI)
Chronic hypertension										
4 weeks before LMP	40 (1.1)	1	3.48 (0.43, 27.98)	5.98 (0.43, 83.21)[a]	31	0.52 (0.24, 1.14)	0.67 (0.29, 1.52)[a]	/	/	/
First trimester	194 (5.2)	26	0.54 (0.31, 0.92)	0.47 (0.23, 0.96)[a]	136	0.48 (0.32, 0.71)	0.50 (0.33, 0.77)[a]	/	/	/
Second trimester	375 (10.1)	50	0.71 (0.48, 1.03)	0.69 (0.41, 1.15)[a]	244	0.67 (0.51, 0.88)	0.75 (0.57, 1.00)[a]	/	/	/
Third trimester	353 (9.6)	27	1.92 (1.23, 2.99)	1.40 (0.76, 2.59)[a]	207	1.16 (0.91, 1.49)	1.42 (1.09, 1.85)[a]	/	/	/
Obesity										
4 weeks before LMP	38 (0.9)	1	0.75 (0.10, 5.61)	1.59 (0.11, 22.95)[b]	8	0.45 (0.21, 1.01)	0.60 (0.21, 1.69)[b]	1	3.91 (0.53, 28.87)	3.24 (0.44, 24.17)[b]
First trimester	193 (4.5)	5	0.79 (0.31, 2.01)	0.62 (0.18, 2.08)[b]	24	0.80 (0.51, 1.26)	0.85 (0.49, 1.48)[b]	16	1.29 (0.76, 2.20)	1.19 (0.69, 2.08)[b]
Second trimester	333 (7.8)	9	0.72 (0.35, 1.48)	0.75 (0.30, 1.88)[b]	49	0.64 (0.46, 0.90)	0.83 (0.55, 1.26)[b]	33	1.03 (0.70, 1.51)	0.90 (0.61, 1.35)[b]
Third trimester	350 (8.2)	6	1.01 (0.43, 2.38)	0.90 (0.33, 2.47)[b]	66	0.45 (0.33, 0.60)	0.70 (0.48, 1.02)[b]	51	0.62 (0.45, 0.86)	0.63 (0.44, 0.89)[b]
Over 35 years age										
4 weeks before LMP	45 (1.2)	1	1.09 (0.15, 8.13)	2.45 (0.17, 36.30)[c]	6	0.83 (0.35, 1.98)	1.09 (0.32, 3.70)[c]	0	/	/
First trimester	192 (5.1)	6	0.78 (0.33, 1.84)	0.59 (0.19, 1.81)[c]	18	1.18 (0.71, 1.96)	1.29 (0.65, 2.53)[c]	6	3.49 (1.53, 7.97)	3.29 (1.43, 7.56)[c]
Second trimester	309 (8.3)	6	1.21 (0.51, 2.86)	1.55 (0.50, 4.78)[c]	32	1.04 (0.70, 1.53)	1.25 (0.73, 2.12)[c]	18	1.82 (1.10, 2.99)	1.66 (1.00, 2.75)[c]
Third trimester	308 (8.2)	3	2.11 (0.65, 6.82)	1.30 (0.36, 4.78)[c]	46	0.63 (0.44, 0.89)	0.78 (0.49, 1.25)[c]	39	0.73 (0.50, 1.05)	0.72 (0.49, 1.05)[c]
Nulliparity										
4 weeks before LMP	113 (0.7)	1	2.24 (0.31, 16.14)	1.13 (0.15, 8.40)[d]	12	0.86 (0.47, 1.57)	0.99 (0.50, 1.96)[d]	16	1.09 (0.64, 1.87)	1.08 (0.62, 1.89)[d]
First trimester	582 (3.8)	5	2.34 (0.96, 5.73)	1.94 (0.76, 4.91)[d]	65	0.83 (0.63, 1.08)	0.86 (0.64, 1.17)[d]	72	1.27 (0.98, 1.64)	1.34 (1.02, 1.75)[d]
Second trimester	970 (6.4)	15	1.32 (0.78, 2.25)	1.42 (0.76, 2.67)[d]	103	0.88 (0.71, 1.10)	0.96 (0.75, 1.23)[d]	108	1.43 (1.16, 1.77)	1.42 (1.14, 1.77)[d]
Third trimester	856 (5.6)	13	1.19 (0.67, 2.10)	0.88 (0.47, 1.65)[d]	106	0.67 (0.54, 0.83)	0.81 (0.63, 1.04)[d]	157	0.77 (0.64, 0.93)	0.76 (0.62, 0.92)[d]

[a] Adjusted for maternal age, race, parity, social economic status (SES), maternal education, marriage status, smoking during pregnancy, maternal pre-pregnant body mass index (BMI), diabetes mellitus, chronic renal disease and gestational age at delivery.

[b] Adjusted for maternal age, race, parity, social economic status (SES), maternal education, marriage status, smoking during pregnancy, chronic hypertension, diabetes mellitus, chronic renal disease and gestational age at delivery.

[c] Adjusted for maternal race, parity, social economic status (SES), maternal education, marriage status, smoking during pregnancy, maternal pre-pregnant body mass index (BMI), chronic hypertension, diabetes mellitus, chronic renal disease and gestational age at delivery.

[d] Adjusted for maternal age, race, social economic status (SES), maternal education, marriage status, smoking during pregnancy, maternal pre-pregnant body mass index (BMI), chronic hypertension, diabetes mellitus, chronic renal disease and gestational age at delivery.

and results in an antithrombotic effect. Whereas a higher dose of aspirin inhibits both COX-1 and COX-2, decreases the production of prostaglandins and thromboxane-A2 [31]. Thus, the reduced risks of preeclampsia and gestational hypertension in late pregnancy might be due to a dose-dependent effect of anti-inflammation and inhibition of platelet activation [29,32]. Nonetheless, we should interpret our findings with caution as the effect of high-dose aspirin (more than 300 mg daily), not the effect of a low-dose one.

6. Conclusions

Maternal aspirin use in pregnancy reduces the risks of preeclampsia and gestational hypertension. Early initiation of aspirin in high-risk women was associated with lower incidence of preeclampsia/eclampsia. Meanwhile, the protective effect of aspirin on the reduction of term preeclampsia/eclampsia and gestational hypertension might continue till late pregnancy. Taken together with findings from other studies [5,33], we support an early prophylactic use of aspirin in women who are considered at high risks for hypertensive disorders in pregnancy [7,34].

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Acknowledgements

We are grateful to all research staff of MOE-Shanghai Key Laboratory of Children's Environmental Health and Department of Obstetrics and Gynecology at Xinhua Hospital for their support during the study.

Contribution to authorship

Jun Zhang conceived the study. Jing Zhu and Chang Chen drafted the manuscript. Danni Lu and Jinwen Zhang analyzed the data. Shiwen Jing and Hehui Xie undertook the literature search. All authors were involved in revising the manuscript and approved the final version before submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.07.005.

References

[1] R.C. Goodlin, H.O. Haesslein, J. Fleming, Aspirin for the treatment of recurrent toxaemia, Lancet 2 (8079) (1978) 51.
[2] L.M. Askie, L. Duley, D.J. Henderson-Smart, L.A. Stewart, PARIS Collaborative Group, Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data, Lancet 369 (9575) (2007) 1791–1798.
[3] L. Duley, D.J. Henderson-Smart, S. Meher, J.F. King, Antiplatelet agents for preventing pre-eclampsia and its complications, Cochrane Database Syst. Rev. 2 (2007) CD004659.
[4] E. Bujold, S. Roberge, Y. Lacasse, M. Bureau, F. Audibert, S. Marcoux, J.C. Forest, Y. Giguère, Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis, Obstet. Gynecol. 116 (2010) 402–414.
[5] S. Roberge, K.H. Nicolaides, S. Demers, P. Villa, E. Bujold, Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis, Ultrasound Obstet. Gynecol. 41 (2013) 491–499.
[6] S. Meher, L. Duley, K. Hunter, L. Askie, Antiplatelet therapy before or after 16 weeks' gestation for preventing preeclampsia: an individual participant data meta-analysis, Am. J. Obstet. Gynecol. 216 (2) (2017) 121–128.e2.
[7] M.L. LeFevre, U.S. Preventive Services Task Force, Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement, Ann. Intern. Med. 161 (2014) 819–826.
[8] H.N. Jabbour, K.J. Sales, R.D. Catalano, J.E. Norman, Inflammatory pathways in female reproductive health and disease, Reproduction 138 (6) (2009) 903–919.
[9] N. Singh, P. Prasad, P. Kumar, L.C. Singh, B. Das, S. Rastogi, Does aberrant expression of cyclooxygenase-2 and prostaglandin-E2 receptor genes lead to abortion in Chlamydia trachomatis-infected women, J. Matern. Fetal Neonatal Med. 29 (6) (2016) 1010–1015.
[10] L.A. Sjaarda, R.G. Radin, R.M. Silver, E. Mitchell, S.L. Mumford, B. Wilcox, et al., Preconception low-dose aspirin restores diminished pregnancy and live birth rates in women with low-grade inflammation: a secondary analysis of a randomized trial, J. Clin. Endocrinol. Metab. 102 (5) (2017) 1495–1504.
[11] B. Groen, G.A. Uuldriks, P. de Vos, J.T. Visser, T.P. Links, M.M. Faas, Impaired trophoblast invasion and increased numbers of immune cells at day 18 of pregnancy in the mesometrial triangle of type 1 diabetic rats, Placenta 36 (2) (2015) 142–149.
[12] G. Barrientos, M. Pussetto, M. Rose, A.C. Staff, S.M. Blois, J.E. Toblli, Defective trophoblast invasion underlies fetal growth restriction and preeclampsia-like symptoms in the stroke-prone spontaneously hypertensive rat, Mol. Hum. Reprod. 23 (7) (2017) 509–519.
[13] J.H. Veerbeek, P.G. Nikkels, H.L. Torrance, J. Gravesteijn, E.D. Post Uiterweer, J.B. Derks, S.V. Koenen, G.H. Visser, B.B. Van Rijn, A. Franx, Placental pathology in early intrauterine growth restriction associated with maternal hypertension, Placenta 35 (9) (2014) 696–701.
[14] E.A. Steegers, P. von Dadelszen, J.J. Duvekot, R. Pijnenborg, Pre-eclampsia, Lancet 376 (9741) (2010) 631–644.
[15] C.W. Redman, I.L. Sargent, A.C. Staff, IFPA senior award lecture: making sense of pre-eclampsia – two placental causes of preeclampsia? Placenta 35 (Suppl) (2014) S20–S25.
[16] J.K. Durst, M.G. Tuuli, M.J. Stout, G.A. Macones, A.G. Cahill, Degree of obesity at delivery and risk of preeclampsia with severe features, Am. J. Obstet. Gynecol. 214 (5) (2016) 651.e1-5.
[17] S. Lisonkova, K.S. Joseph, Incidence of preeclampsia: risk factors and outcomes associated with early- versus late-onset disease, Am. J. Obstet. Gynecol. 209 (6) (2013) 544.e1–544.e12.
[18] M. Palm, O. Axelsson, L. Wernroth, A. Larsson, S. Basu, Involvement of inflammation in normal pregnancy, Acta Obstet. Gynecol. Scand. 92 (5) (2013) 601–605.
[19] R.A. Tinius, A.G. Cahill, E.A. Strand, W.T. Cade, Altered maternal lipid metabolism is associated with higher inflammation in obese women during late pregnancy, Integr. Obestet. Diab. 2 (1) (2015) 168–175.
[20] E. Odame Anto, W.K.B.A. Owiredu, S.A. Sakyi, C.A. Turpin, R.K.D. Ephraim, L.A. Fondjo, et al., Adverse pregnancy outcomes and imbalance in angiogenic growth mediators and oxidative stress biomarkers is associated with advanced maternal age births: a prospective cohort study in Ghana, PLoS One 13 (7) (2018) e0200581.
[21] A.B. Zavalza-Gómez, Obesity and oxidative stress: a direct link to preeclampsia? Arch. Gynecol. Obstet. 283 (3) (2011) 415–422.
[22] S. Taddei, A. Virdis, L. Ghiadoni, A. Salvetti, Vascular effects of endothelin-1 in essential hypertension: relationship with cyclooxygenase-derived endothelium-dependent contracting factors and nitric oxide, J. Cardiovasc. Pharmacol. 35 (4 Suppl. 2) (2000) S37–S40.
[23] D. Tsikas, D.O. Stichtenoth, Endothelial nitric oxide synthase, cyclooxygenase-2, and essential hypertension: is there an interaction? Hypertension 62 (4) (2013) e15.
[24] M.S. Avendaño, S. Martínez-Revelles, A. Aguado, M.R. Simões, M. González-Amor, R. Palacios, et al., Role of COX-2-derived PGE2 on vascular stiffness and function in hypertension, Br. J. Pharmacol. 173 (9) (2016) 1541–1555.
[25] R. Hernanz, A.M. Briones, M. Salaices, M.J. Alonso, New roles for old pathways? A circuitous relationship between reactive oxygen species and cyclo-oxygenase in hypertension, Clin. Sci. (Lond.) 126 (2) (2014) 111–121.
[26] D. Reijnders, C.C. Liu, X. Xu, A.M. Zhao, K.N. Olson, S.D. Butler, et al., Celecoxib restores angiogenic factor expression at the maternal-fetal interface in the BPH/5 mouse model of preeclampsia, Physiol. Genomics 50 (5) (2018) 385–392.
[27] J.L. Sones, J. Cha, A.K. Woods, A. Bartos, C.Y. Heyward, H.E. Lob, Decidual,, et al., Cox2 inhibition improves fetal and maternal outcomes in a preeclampsia-like mouse model, JCI Insight 1 (3) (2016) 75351.
[28] M.R. Holthe, A.C. Staff, L.N. Berge, T. Lyberg, Different levels of platelet activation in preeclamptic, normotensive pregnant, and nonpregnant women, Am. J. Obstet. Gynecol. 190 (4) (2004) 1128–1134.
[29] T. Furuno, F. Yamasaki, T. Yokoyama, K. Sato, T. Sato, Y. Doi, et al., Effects of various doses of aspirin on platelet activity and endothelial function, Heart Vessels 26 (3) (2011) 267–273.
[30] M. Shen, G.N. Smith, M. Rodger, R.R. White, M.C. Walker, S.W. Wen, Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia, PLoS One 12 (4) (2017) e0175914.
[31] A.P. Cadavid, Aspirin: the mechanism of action revisited in the context of pregnancy complications, Front. Immunol. 8 (2017) 261.
[32] E.H. Awtry, J. Loscalzo, Aspirin, Circulation 101 (10) (2000) 1206–1218.
[33] D.L. Rolnik, D. Wright, L.C. Poon, N. O'Gorman, A. Syngelaki, C. de Paco Matallana, et al., Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia, N. Engl. J. Med. 377 (2017) 613–622.
[34] ACOG Committee opinion no. 743: low-dose aspirin use during pregnancy, Obstet. Gynecol. 132(1) (2018) e44–e52.