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Analysis of the effectiveness of aspirin in preventing preeclampsia in high-risk pregnant women and the influencing factors of preeclampsia

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Abstract: This study explores the effect of aspirin on preeclampsia (PE) and analyzes the influencing factors of PE in high-risk pregnant women. We encompassed 110 high-risk pregnant women receiving prenatal examination at Maternal and Child Health Hospital of Yichang City between January 2022 and December 2023, categorized them into the intervention group(n=58,received aspirin therapy), and the control group(n=52,didn't receive pharmaceutical prophylaxis). Clinical and laboratory parameters were compared between groups, with logistic regression performed.The intervention group demonstrated significantly lower PE incidence (25.00% vs 46.55%, P=0.019, 95% CI:[0.170,0.862]), reduced preterm birth (28.85% vs 60.34%, P<0.001, 95%CI:[0.120,0.592]), and decreased neonatal asphyxia (1.92% vs 17.24%, P=0.008, 95% CI:[0.012,0.763]), longer delivery pregnancy week (P<0.001,95%CI:[-2.100,-0.725]), higher neonatal birth weight(P=0.018,95%CI: [-319.524,-30.332]), and improved 1-minute Apgar scores(P=0.001,95%CI:[-1,0]). Coagulation profiles revealed elevated PT(P<0.001, 95%CI:[-3.423,-2.355]) and APTT(P<0.001, 95%CI:[-6.544,-4.473]), with reduced D-dimer (P<0.001, 95%CI:[0.776,0.887]) and FIB levels (P<0.001,95%CI:[0.389,1.068]). Logistic regression identified that age ≥35 years old and BMI≥28Kg/m^2 were risk factors for PE in high-risk pregnant women(P=0.006,OR=3.701,95% CI:1.445-9.475; P=0.001, OR=4.529, 95% CI:1.818-11.281), aspirin use was a protective factor for PE in high-risk pregnant women (P=0.005, OR=0.260, 95% CI:0.101-0.667). Aspirin demonstrates efficacy in safeguarding against PE in women who are at an increased risk of developing the condition.

Keywords: Aspirin, High-risk pregnant women, preventive effect, influencing factors, preeclampsia.

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INTRODUCTION

Preeclampsia (PE), a prevalent pregnancy-related disorder, typically manifests after the 20th week of gestation and can result in severe outcomes including elevated blood pressure, the presence of protein in urine, swelling and in extreme cases, unconsciousness, seizures, and maternal mortality (Khadivzadeh *et al*., 2023). Research data show that the global incidence of PE is usually about 2%-8% and the number of pregnant women and infants who die due to PE is as high as more than 70,000 and more than 50,000 (Huai *et al*., 2021). Pregnant women with PE, to avoid adverse pregnancy termination of gestation, most have to choose the maternal and child health of pregnant women and fetal life even caused serious influence; Compared with normal, healthy pregnant women, high-risk pregnant women is because of the body, age and so on various aspects, are more likely to happen PE (Lin *et al*., 2022). Therefore, in urgent need of clinical drug used to prevent pregnant women especially in high-risk pregnant women in PE. Currently, aspirin is the prevalent therapeutic approach for managing PE, the reason is that the onset of PE principle is the body vasospasm contraction, lead to reduced blood flow to the body organs, blood, body damage, at the same time caused inflammation, immune regulating function decline, vascular endothelial cell injury and frozen platelet aggregation, etc. (Rolnik *et al*., 2022). In clinic and aspirin can play an anticoagulant, anti-inflammatory, antiplatelet aggregation effect; therefore, aspirin may be considered for PE prevention. However, these treatment schemes have not formed a complete and sound standard system and there are still many effects and standards to be investigated (Hoffman *et al*., 2020). Consequently, the current research delves into the strategy of utilizing aspirin for the prophylaxis of PE in women identified as high risk. It evaluates the efficacy of this preventative approach and concurrently examines the determinants that contribute to the vulnerability of high-risk pregnant women to PE. This investigation aims to offer insights that could inform the formulation of future PE prevention strategies tailored for high-risk expectant mothers, as well as guide the integration of aspirin within these preventative frameworks.

MATERIALS AND METHODS

Research design and patient choice

According to the EPV principle, this study took the occurrence of PE as the outcome index. Based on literature review, this study estimated that there were at least 2 influencing factors contributing to the occurrence of PE among the study's population, within the context of aspirin intervention (Henderson, *et al*., 2021). In the study of China's high-risk pregnancy women believe that under the intervention of aspirin high-risk pregnant women the

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incidence of PE can amount to 16%, compared to placebo effect under no statistical difference and some studies have pointed out that the incidence of PE in high-risk pregnant women in China is still on the rise in the future. Consequently, this research has projected that the prevalence of PE among pregnant women at elevated risk is approximately 26% (Lin *et al*., 2022; Shi *et al*., 2021). According to the principle of EPV sample size calculation formula: n=Y×EPV/P. Where n is the sample size required for the study, EPV is 10 and P is the outcome rate, which is set at 26%. Therefore, this study will be incorporated into n=2×10/27%=77 cases, combining with 10% lost to follow-up, fall off wait for a circumstance, this study finally need to include at least 85 cases were analyzed.

In this research, a cohort of expectant mothers identified as high risk and who received antenatal care at our medical facility between January 2022 and December 2023 was assembled. Utilizing predefined eligibility and exclusion parameters, a total of 110 such women were selected to participate in the study, ensuring that the sample size met the necessary thresholds for the research. Inclusion criteria: (1) natural pregnancy; (2) Individuals who, upon presenting to our facility between the 12th and 20th weeks of gestation, exhibited one or more of the designated high-risk maternal indicators, including (Poon *et al*., 2019): ① age ≥35 years old; ② BMI before pregnancy ≥28kg/m2; ③ A familial predisposition to preeclampsia; ④ Chronic hypertension of pregnancy, previous history of PE; ⑤ Pre-pregnancy diabetes and renal disease; (3) those who did not take aspirin before 12 weeks of pregnancy; (4) single pregnancy; (5) No previous history of aspirin allergy. Exclusion criteria: (1) clinical data is incomplete; (2) In the prevention of PE, in addition to aspirin, other drugs were used to prevent PE; (3) with hemophilia and congenital absence of clotting factor; (4) has a serious disease of heart head blood-vessel, respiratory disease, liver dysfunction; (5) patients with digestive tract diseases, such as peptic ulcer and digestive system tumors.

According to the actual choice and application of PE prevention programs by high-risk pregnant women, we segregated a sample of 110 participants into two distinct groups for the study: One group received aspirin as an intervention (n=58) and the other served as a control, devoid of pharmaceutical prophylaxis (n=52). The intervention group was given oral aspirin 100mg/d from 12 to 20 weeks of gestation until delivery. The general data, coagulation function, liver and kidney function, pregnancy outcome and neonatal outcome of the two groups were compared and the effect of aspirin on the prevention of PE in high-risk pregnant women was analyzed. Finally, based on whether the high-risk pregnant women had PE during the study period as the basis for grouping, we explored whether aspirin could be used as a protective factor for the occurrence of PE in high-risk women and the risk ratio of prevention effect. The International Federation of Gynecology and Obstetrics (FIGO) has established diagnostic standards for PE: The patient developed Maternal systolic pressures of 140 mmHg or higher and diastolic pressures of 90 mmHg or higher, post the 20-week mark of gestation, are indicative of a condition that is also characterized by the excretion of 24-hour urinary protein levels exceeding 0.3 grams (Poon *et al*., 2019).

Data collection

Data on eligible patients were collected, including the following data: (1) General information: age, gravidity, BMI, gestational weeks, family history of PE, Persistent hypertension and diabetes mellitus diagnosed prior to pregnancy, renal function disease, previous history of PE; (2) Coagulation function indexes: Prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, fibrinogen (FIB); (3) Liver and kidney function indexes: albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid, creatinine (Cr), Blood urea nitrogen (BUN).

Outcome index

Primary outcomes: Proportion of PE in the intervention and control groups; Secondary outcomes: (1) Neonatal outcomes: neonatal birth weight, incidence of preterm birth, incidence of neonatal asphyxia, 1min Apgar score. (2) Maternal outcomes: delivery pregnancy week, incidence of cesarean section, postpartum hemorrhage, and HELLP syndrome. (3) Coagulation function, liver and kidney function indicators.

STATISTICAL ANALYSIS

Using SPSS 26.0 statistical software for data analysis, to meet the needs of normal distribution data using mean ± standard deviation (x±S) description, compares the t test; Can not meet the needs of normal distribution data using interquartile range description, comparison with U test. Count data were expressed as n[(%)] and χ^2 test was used for comparison. Using single factor and Logistic regression analysis the influence factors of high risk happened PE. A P-value threshold of less than 0.05 was established as the criterion for statistical significance.

Ethical approval

This study was approved by Maternal and Child Health Hospital of Yichang City, China (YCFY-RLL2024007).

RESULTS

An examination of the overall data was conducted to compare the two cohorts of high-risk expectant mothers at the time of their initial assessment. Results show that the comparison between the two groups of high-risk pregnant women yielded no statistically significant variation in their general data or risk factors associated with PE at enrollment (P>0.05) (table 1).

Table 1: Analysis of general data contrasting two groups

Indicators	Control group (n=58)	Intervention group (n=52)	t/χ^2	*P*
Age (years)	31.81±5.70	32.25±4.38	-0.450	0.654
Number of pregnancies (times)				
≤2	35(60.34)	31(59.62)	0.006	0.938
>2	23(39.66)	21(40.38)		
BMI（kg/m^2）	26.89±3.93	27.94±3.87	-1.414	0.160
Number of Gestational week (weeks)	16.31±1.83	16.23±2.19	0.207	0.836
Family history of preeclampsia			2.270	0.132
No	45(77.59)	46(88.46)		
Yes	13(22.41)	6(11.54)		
Chronic hypertension			0.060	0.807
No	31(53.45)	29(55.77)		
Yes	27(46.55)	23(44.23)		
Pre-pregnancy diabetes			0.387	0.534
No	44(75.86)	42(80.77)		
Yes	14(24.14)	10(19.23)		
Renal function diseases			0.168	0.682
No	45(77.59)	42(80.77)		
Yes	13(22.41)	10(19.23)		
Previous history of PE			0.069	0.793
No	48(82.76)	44(84.62)		
Yes	10(17.24)	8(15.38)		

Table 2: When assessing the profiles of hemostasis alongside hepatic and renal indices, a comparative analysis was performed. (x ± S)

Indicators	Control group (n=58)	Intervention group (n=52)	t	*P*
Coagulation function				
PT (seconds)	10.38±0.88	13.27±1.83	-10.724	<0.001
APTT (seconds)	25.07±1.63	30.57±3.59	-10.541	<0.001
D-dimer (mg/L)	1.41±0.18	0.58±0.11	29.645	<0.001
FIB (g/L)	4.03±0.97	3.30±0.81	4.240	<0.001
Liver function				
Albumin (g/L)	38.00±7.85	39.46±7.26	-1.011	0.314
AST (U/L)	13.51±3.05	13.09±3.69	0.658	0.512
ALT (U/L)	11.88±3.32	11.34±2.58	0.944	0.347
Renal function				
Uric acid (μmol/L)	258.56±41.63	254.88±39.01	0.477	0.634
Cr (μmol/L)	52.62±8.07	50.97±8.38	1.052	0.295
BUN(mmol/L)	2.94±0.51	2.96±0.54	-0.235	0.814

Table 3: Comparison of neonatal outcomes

Indicators	Control group (n=58)	Intervention group (n=52)	$t/Z/\chi^2$	*P*
Neonatal birth weight(g)	2863.38±357.41	3038.31±407.67	-2.398	0.018
Preterm birth [n(%)]			10.972	＜0.001
No	23(39.66)	37(71.15)		
Yes	35(60.34)	15(28.85)		
Neonatal asphyxia [n(%)]			7.149	0.008
Unoccurred	48(82.76)	51(98.08)		
Occurred	10(17.24)	1(1.92)		
1min Apgar score (points)	9(8,10)	9.5(9,10)	-3.29	0.001

Table 4: Univariate analysis of PE in high-risk pregnant women [n(%)]

Factors	Occurrence group (n=40)	Non-occurrence group (n=70)	χ^2	*P*
Age (years)			8.102	0.004
≥35	19(47.50)	15(21.43)		
<35	21(52.50)	55(78.57)		
Number of pregnancies (times)			0.655	0.418
≤2	26(65.00)	40(57.14)		
>2	14(35.00)	30(42.86)		
BMI(kg/m^2)			10.646	0.001
≥28	26(65.00)	23(32.86)		
<28	14(35.00)	47(67.14)		
Number of Gestational week (weeks)			2.31	0.129
≥16.5	22(55.00)	28(40.00)		
<16.5	18(45.00)	42(60.00)		
Family history of preeclampsia			0.227	0.634
No	34(85.00)	57(81.43)		
Yes	6(15.00)	13(18.57)		
Chronic hypertension			0.106	0.745
No	21(52.50)	39(55.71)		
Yes	19(47.50)	31(44.29)		
Pre-pregnancy diabetes			3.200	0.074
No	35(87.50)	51(72.86)		
Yes	5(12.50)	19(27.14)		
Renal function diseases			0.636	0.425
No	30(75.00)	57(81.43)		
Yes	10(25.00)	13(18.57)		
Previous history of PE			1.729	0.189
No	31(77.50)	61(87.14)		
Yes	9(22.50)	9()12.86		
PT (seconds)			0.757	0.384
≥11.00	20(50.00)	41(58.57)		
<11.00	20(50.00)	29(41.42)		
APTT (seconds)			0.096	0.757
≥29.50	12(30.00)	23(32.86)		
<29.50	28(70.00)	47(67.14)		
FIB(g /L)			2.568	0.109
≥4.25	14(35.00)	17(24.29)		
<4.25	26(65.00)	53(75.71)		
D-dimer (mg/L)			2.993	0.084
≥1.37	16(40.00)	17(24.29)		
<1.37	24(60.00)	53(75.71)		
Uric acid (μmol/L			2.771	0.096
≥258.69	14(35.00)	36(51.43)		
<258.69	26(65.00)	34(48.57)		
Cr (μmol/L)			0.701	0.402
≥45.57	32(80.00)	51(72.86)		
<45.57	8(20.00)	19(27.14)		
BUN(mmol/L)			3.315	0.069
≥3.29	15(37.50)	15(21.43)		
<3.29	25(62.50)	55(78.57)		
Albumin (g/L)			3.608	0.057
≥40.78	12(30.00)	34(48.57)		
<40.78	28(70.00)	36(51.43)		
AST (U/L)			2.619	0.106
≥14.51	20(50.00)	24(34.29)		
<14.51	20(50.00)	46(65.71)		
ALT (U/L)			0.735	0.391

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≥12.22	17(42.50)	24(34.29)		
<12.22	23(57.50)	46(65.71)		
Cesarean section			0.815	0.367
Unoccurred	29(82.50)	56(80.00)		
Occurred	11(27.50)	14(20.00)		
Postpartum hemorrhage			0.797	0.372
Unoccurred	33(82.50)	62(88.57)		
Occurred	7(17.50)	8(11.43)		
HELLP syndrome			0.025	0.874
Unoccurred	38(95.00)	66(94.29)		
Occurred	2(5.00)	4(5.71)		
Delivery pregnancy week (weeks)			1.892	0.169
≥36.05	26(65.00)	54(77.14)		
<36.05	14(35.00)	16(22.86)		
Preterm birth			0.106	0.745
Yes	19(47.50)	31(44.29)		
No	21(52.50)	39(55.71)		
Neonatal asphyxia			0.437	0.509
Unoccurred	35(87.50)	64(91.43)		
Occurred	5(12.50)	6(8.57)		
Neonatal birth weight(g)			0.482	0.488
≥3047	15(37.50)	31(44.29)		
<3047	25(62.50)	39(55.71)		
1min Apgar score (points)			1.473	0.225
≥9.5	27(67.50)	39(55.71)		
<9.5	13(32.50)	31(44.29)		
Use of Aspirin			5.503	0.019
Yes	13(32.50)	39(55.71)		
No	27(67.50)	31(44.29)		

Table 5: Assignment of relevant factors

Factors	Assignment of value
Use of Aspirin	1=Yes, 0=No
Age	1=≥35 years, 0=<35 years
BMI	1=≥28 Kg/m^2, 0=<28 Kg/m^2

When evaluating the hemostatic, hepatic and renal profiles of the two study groups, a discernible divergence was noted. The intervention group exhibited a pronounced elevation in PT(95%CI:[-3.423,-2.355]) and APTT (95%CI: [-6.544,-4.473]), coupled with a significant reduction in D-dimer (95%CI:[0.776,0.887]) and FIB (95%CI:[0.389,1.068]) levels, in stark contrast to the control group, with these differences reaching statistical significance (P<0.05). On the other hand, the comparative analysis of hepatic and renal function parameters did not yield any variations that met the threshold for statistical significance across the two cohorts (P>0.05) (table 2).

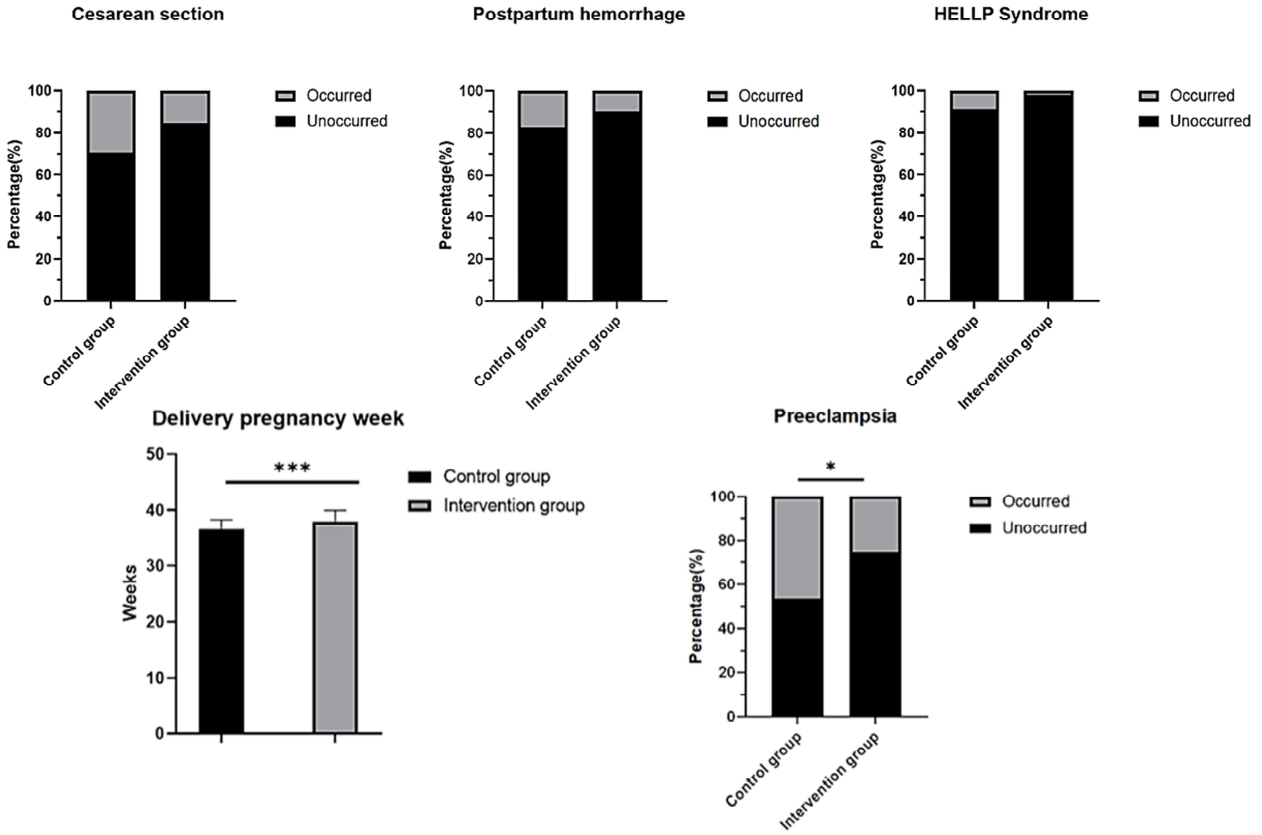
An evaluation of infant outcomes was undertaken to discern differences between the two study cohorts The incidence of PE (25.00%) in the intervention group was was notably lower compared to the control group (46.55%)(95%CI: [0.170,0.862]), with the delivery pregnancy week being longer in the intervention group (95%CI: [-2.100,-0.725]), with statistical significance observed in this difference (P<0.05); Two groups of the incidence of cesarean section, postpartum hemorrhage and HELLP syndrome differences had no statistical significance (P>0.05) (fig. 1).

Comparison of neonatal outcomes between the two groups

The intervention group exhibited a higher neonatal birth weight (95%CI:[-319.524,-30.332]) and 1-minute Apgar score (95%CI:[-1,0]) compared to the control group. The incidence of preterm birth (28.85%) (95%CI: [0.120, 0.592]) and neonatal asphyxia (1.92%) (95%CI: [0.012, 0.763]) in the intervention group were notably lower than the incidence of preterm birth (60.34%) and neonatal asphyxia (17.24%) in the control group, with all these differences being statistically significant (P<0.05) (table 3).

Univariate analysis of PE in high-risk pregnant women

Based on the presence or absence of preeclampsia (PE), a total of 110 high-risk pregnant women were categorized into two distinct groups: a PE occurrence group consisting of 40 cases and a non-occurrence group comprising 70 cases.



Note: A: Cesarean section; B: Postpartum hemorrhage; C: HELLP Syndrome; D: Delivery pregnancy week; E: Preeclampsia.

Fig. 1: Comparison of pregnancy outcomes

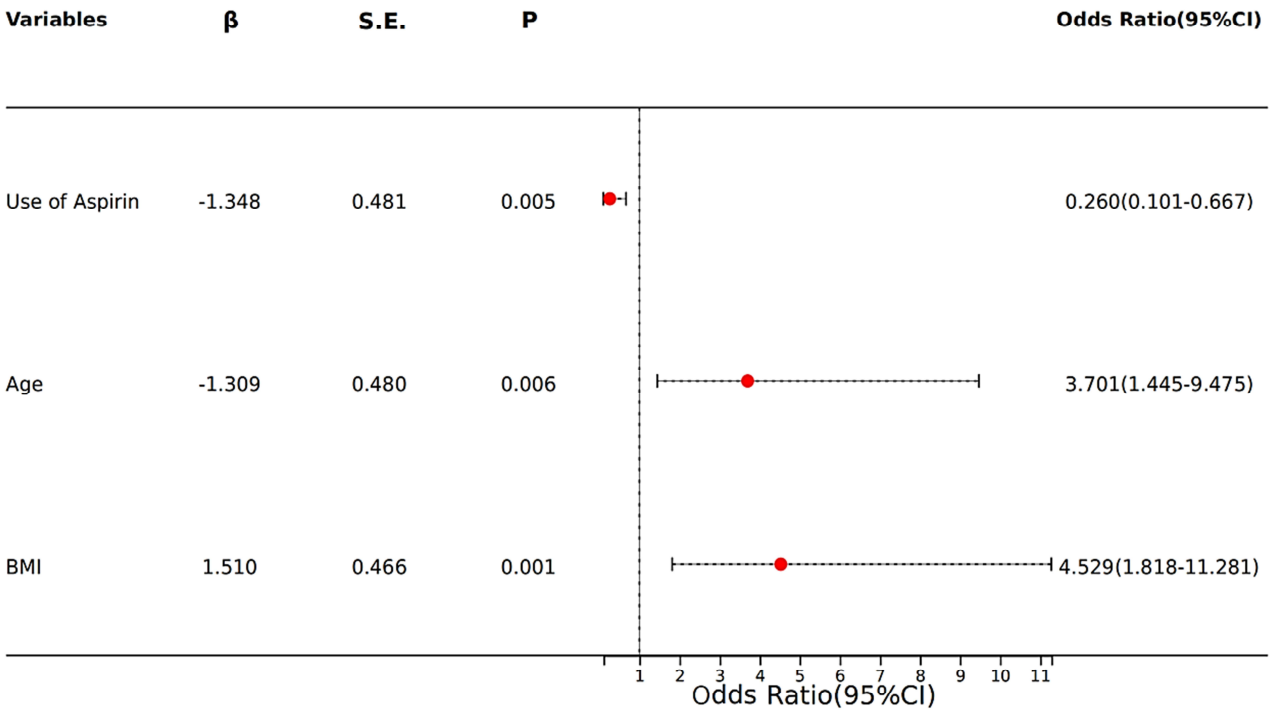


Fig. 2: Logistic regression analysis of PE in high-risk pregnant women

All continuous variables according to the ROC curve best cutoff value is divided into binary classification variables for the single factor analysis. The findings revealed notable disparities in age, BMI and use of aspirin between the occurrence and the non-occurrence groups (P=0.004, 95% CI: [1.428,7.709]; P=0.001, 95% CI: [0.321,1.604]; P=0.019, 95% CI:[0.170,0.862]) (table 4).

Logistic regression analysis of PE in high-risk pregnant women

Whether or not PE occurred in high-risk pregnant women (occurrence =0, non-occurrence =1) was taken as the dependent variable, and statistically significant variables identified in the univariate analysis, including Aspirin usage, age, and BMI, were designated as independent variables, with their respective values assigned were shown in table 5. Logistic regression results showed that age ≥35 years and BMI≥28 Kg/m^2 were risk factors for PE in high-risk pregnant women (P=0.006, OR=3.701, 95%CI: 1.445-9.475; P=0.001, OR=4.529, 95%CI: 1.818-11.281), use of Aspirin was a protective factor for PE in high-risk pregnant women (P=0.005, OR=0.260, 95% CI: 0.101-0.667) (fig. 2). Based on this, the calculation formula of Logistic regression analysis model is as follows:

$$P=\frac{1}{(1+e^{-[-1.152+1.309\times(age\geq 35)+1.510\times(BMI\geq 28kg/m2)-1.348\times(use\ of\ Aspirin)]})}$$

DISCUSSION

PE is a serious pregnancy complication that poses a major threat to the health of both the pregnant woman and the fetus. Therefore, preventing the occurrence of PE is crucial to improve maternal and child health. There is growing evidence that aspirin has the potential to lower the incidence of PE in high-risk women and enhance pregnancy outcomes, and its safety and cost-effectiveness also make it an attractive prevention option (Ninan *et al*., 2023). However, most studies have demonstrated the effectiveness of aspirin in prevention of PE in high-risk pregnant women in the form of comparative incidence, lacking specific risk ratios for aspirin prevention of PE, and the actual risk of PE after combining other independent factors. Therefore, this study explored the mechanism of action based on aspirin, discussed the effectiveness and safety of preventing PE in high-risk pregnant women, and clarified the specific risk ratio of aspirin under the influence of other factors through Logistic regression analysis. Thus, this analysis evaluates the potency of aspirin as a preventive measure against preeclampsia in the at-risk pregnant cohort, furnishing a benchmark for crafting prophylactic protocols for this specific demographic in subsequent endeavors.

Preventive effect of aspirin

This research demonstrated a notable decrease in the prevalence of preeclampsia among pregnant women at high risk who consumed aspirin. Specifically, the rate of PE among participants in the aspirin intervention group stood at 25.00%, markedly lower than the 46.55% observed in the control group, indicating that aspirin had a preventive effect on the occurrence of PE, which was similar to the research results of Huai *et al*. (2021). In addition, this study also found that aspirin prevented PE by altering coagulation function (such as extending PT and APTT, reducing D-dimer and FIB levels) and possibly anti-inflammatory and anti-angiogenic effects in high-risk pregnant women, which is consistent with existing studies on the mechanism of action of aspirin (Ma'ayeh *et al*., 2020). During normal pregnancy, the balance between thromboxane A2 (TXA2) produced by platelets and prostacycline I2 (PGI2) produced by endothelial cells is critical for regulating platelet aggregation and vascular reactivity, which helps maintain blood perfusion of the uterine placenta (Stepan *et al*., 2020). However, in the case of PE, vascular endothelium is damaged, cyclooxygenase is activated and prostacycline synthase is inhibited, resulting in the balance between TXA2 and PGI2 being broken, which aggravates vasospasm and endothelial dysfunction (Feng *et al*., 2021). Among them, TXA2 is a potent vasoconstrictor and platelet aggregation promoter, while PGI2 plays a role in vasodilating and inhibiting platelet aggregation (Mirabito *et al*., 2020; Braune *et al*., 2020). In this study, we noted a marked elevation in the PT and APTT measurements among participants receiving aspirin intervention, in comparison to the control group, indicating that the prolongation of clotting time was consistent with its anti-platelet aggregation properties. Combined with the significantly decreased D-dimer level and fibrinogen, we believe that aspirin reduces TXA2 production by inhibiting COX activity, thereby restoring the balance between PGI2 and TXA2, inhibiting platelet aggregation, improving blood circulation, and reducing thrombosis, and ultimately reducing the risk of PE. In addition, research has identified the anti-angiogenic factor soluble tyrosine kinase-1 (sFlt-1) and the pro-angiogenic factor placental growth factor (PLGF) as pivotal contributors to the development of PE. During PE, endothelial cells and trophoblast release excessive sFlt-1 due to vasospasm and hypoxia, resulting in decreased PLGF concentration and endothelial dysfunction (Stepan, *et al*., 2023; Verlohren, *et al*., 2021). Aspirin can prevent PE by inhibiting the cyclooxygenase-1 and amino-terminal kinase/ transcription factor activating protein-1 (JNK/ATF-1) signaling pathway and reducing the expression of sFlt-1 in trophoblast cells (Lin *et al*., 2021); aspirin may also reduce the production of inflammatory factors by inhibiting the activity of cyclooxygenase, but its specific mechanism needs further study.

In the assessment of secondary endpoints, our findings revealed no discernible disparities in the rates of cesarean delivery or postpartum hemorrhage and HELLP syndrome

between the two groups, indicating that aspirin use did not increase the risk of these pregnancy complications. Meanwhile, neonatal birth weight and 1-minute Apgar scores, which measure the health of newborns immediately after birth, were observed to be more favorable in the group that received the intervention compared to the group that served as the control. The incidence of asphyxia in preterm infants and neonates was lower than in the control group, and these results indicate that aspirin consumption has a beneficial impact on newborn health, without elevating the risk of adverse neonatal outcomes. Therefore, the findings support the positive effect of aspirin use as a preventive measure for PE in high-risk pregnant women in terms of improved neonatal outcomes, and no significant safety concerns were found. The findings aligned with the meta-analysis conducted by Yeo *et al*. whose subgroup analysis further confirmed that aspirin use starting before 20 weeks of gestation was markedly linked to a lower risk of PE, as well as increased birth weight and gestational age (RR=0.76, 95%CI =0.64,0.90, P=0.001) (Choi *et al*., 2021). During pregnancy, the invasion of trophoblast cells is crucial for the development of the placenta and the maintenance of normal pregnancy. Aspirin aids in fostering the proliferation and invasion of trophoblast cells and inhibit their apoptosis, thus promoting the normal development of the placenta and preventing the occurrence of PE (Huppertz *et al*., 2021; Kumar *et al*., 2013). This also explains why, after the intervention of aspirin, the notable increase in neonatal birth weight observed in the intervention group compared to the control group, and the incidence of preterm birth and neonatal asphyxia was lower. In conclusion, this study concluded that aspirin effectively decreased the incidence of PE in high-risk pregnant women and improved neonatal health indicators without increasing the risk of pregnancy complications. Nevertheless, further studies are needed regarding the optimization of dosage and timing of intervention.

Mechanism analysis of influencing factors

The results of multivariate regression analysis confirmed the positive effect of aspirin in preventing PE, but also revealed the influence of age and BMI on the effect of aspirin. According to the calculation formula of the results, we predicted that a high-risk pregnant woman ≥35 years old, BMI≥28 Kg/m2, with aspirin (100mg/ day) intervention, the probability of eventually developing PE could reach 58%. This result may suggest that aspirin has a limited effect on PE prevention in high-risk pregnant women with both advanced age and obesity, a finding similar to some previous studies suggesting that advanced age and obesity may reduce the efficacy of aspirin (Palomo *et al*., 2024; Cercato *et al*., 2019). With the growth of age, women's physiological functions gradually decline, including the functions of the cardiovascular system, endocrine system and immune system may be affected, and they are more prone to chronic diseases such as hypertension and diabetes, which are closely related to the occurrence of PE (Glick *et al*., 2021; Frick *et al*., 2019). It also means that older pregnant women may be treated for more diseases and may need to take other drugs while maintaining the dose of aspirin, which may reduce the effect of aspirin, but further research is needed to confirm this possibility. At the same time, the increase of age also means that coagulation dysfunction is more common. For example, Ivan Palomo *et al*. found that age significantly affects coagulation function through RhoA/Rho kinase signaling pathway, mainly by promoting endothelial cell dysfunction, increasing oxidative stress, reducing NO production and activating platelets. This increases the risk of thrombosi (Palomo *et al*., 2024). Thus, activation of the RhoA/Rho kinase signaling pathway in older pregnant women leads to vascular endothelial dysfunction and platelet overactivation, which, in theory, may increase the need for antiplatelet drugs such as aspirin. As Stephanie *et al* pointed out, higher doses (≥100mg/day) seem to be more likely to reduce the risk of placental abruption or prenatal bleeding than lower doses (<100mg/ day) (Roberge *et al*., 2018). Recent evidence-based medical studies have shown that high-risk pregnant women who start taking 150mg/d of aspirin at night before 16 weeks of pregnancy can significantly reduce the incidence of preterm PE by up to 62%; Aspirin doses of 150 to 162mg per day were associated with a lower risk of preterm PE compared to aspirin doses of 75 to 81 mg per day (Rolnik *et al*., 2022; Ghesquiere *et al*., 2023).Therefore, for pregnant women aged ≥35 years old, aspirin 100mg/d may have limited effect on preventing PE and its dose can be appropriately increased in clinical practice. It should be noted that increasing the dose of aspirin may bring potential bleeding risks, such as placental abruption or prenatal hemorrhage (Roberge *et al*., 2018). When adjusting the dose, the risk of bleeding must also be weighed against the benefit of preventing PE, considering that older women may be taking multiple drugs at the same time, closely monitoring drug interactions, and adjusting the dose of aspirin and the use of other drugs as needed to ensure the best treatment effect.

In terms of BMI, although it does not directly affect the coagulation system, adipose tissue in the body will actively secrete a variety of adipokines and inflammatory mediators under the condition of obesity. These substances exert an influence on the functionality of vascular endothelial cells, promote platelet activation and aggregation, and increase blood viscosity, thus leading to abnormal coagulation function and cardiovascular risk (Cercato *et al*., 2019). The process may also involve an elevation in both the quantity and functionality of platelets, a rise in the concentration of coagulation factors like fibrinogen and a possible decrease in the level of

anticoagulant substances such as antithrombin (Atawia *et al*., 2019), Each of these factors has the potential to attenuate the efficacy of aspirin. For instance, evidence from randomized controlled trials suggests that the preventative impact of low-dose aspirin, in the range of 75-100 mg, against cardiovascular incidents lessens with an increase in body mass. A discernible benefit was noted among individuals with a weight of 50-69 kg, whereas, in those exceeding 70 kg, no significant effect was detected (Rothwell *et al*., 2018). Gestational weight gain and increased Body Mass Index (BMI) are typical occurrences throughout pregnancy; however, they can swiftly become excessive. Over recent decades, there has been a marked escalation in the prevalence of obesity on a global scale. Notably, in the United States, a staggering majority of over 50% of pregnant women are categorized as overweight or obese (Paredes *et al*., 2021). In view of the fertility risk caused by obesity during pregnancy, a review of the guidelines of four countries, namely the United States, Australia, New Zealand and Canada, found that there are differences in the recommendations of low-dose aspirin (Vitner *et al*., 2019). This situation also suggests that for pregnant women with high BMI, it is obvious that aspirin cannot be relied on only for PE prevention, but a more active prevention program should be required, and aspirin prevention programs should be supplemented from diet, exercise and other aspects. Liu *et al*. study pointed out that administering low molecular weight heparin, vitamin D and calcium engaging in regular exercise, can collectively mitigate the risk of PE and hypertension during pregnancy (Liu *et al*., 2023). Therefore, comprehensive preventive measures including lifestyle modification and possibly alternative therapies are recommended in clinical practice to more effectively reduce the risk of preeclampsia and gestational hypertension. In the meantime, decisions to increase aspirin doses should be made cautiously and with adequate information about the risks and benefits.

In summary, aspirin (100mg/d) is of limited benefit in preventing PE in high-risk pregnant women ≥35 years of age and BMI ≥28 Kg/m². Advanced age and obesity increase the risk of chronic diseases and blood clotting disorders, reducing the effectiveness of aspirin. Consequently, the formulation of a holistic prevention strategy necessitates an escalated dosage of aspirin, coupled with lifestyle enhancements and the exploration of alternative therapeutic approaches, to diminish the incidence of preeclampsia among older, obese pregnant women with greater efficacy.

Research limitation

This study provides valuable insights and data to explore the role of aspirin in the prevention of PE in high-risk pregnant women, but there are still some limitations that may affect the general applicability of the findings and conclusions. From the perspective of sample size, although 110 high-risk pregnant women were included in this study, which also met the minimum sample size requirement of the study design, the sample size was still limited compared to the whole pregnant women group. Small sample sizes may limit the ability of results to extrapolate, especially across ethnic groups, geographic regions, and health care systems. Second, the selection of study populations may also bring limitations. This study focuses on women with high-risk pregnancies in China who may differ from pregnant women in other countries or regions in terms of lifestyle, genetic factors, and disease history. Therefore, future studies with larger sample sizes and larger sample collection areas are needed to verify the preventive effect of aspirin in different study populations. This population-specific selection may limit the generality of the findings, and future studies are needed to validate aspirin's preventive effects in a wider population. There may also be selection bias and confounding factors in the study design. For example, the inclusion and exclusion criteria may exclude certain high-risk subgroups that may be critical to assessing the effects of aspirin. In addition, the study did not fully control for all confounding factors that may affect the development of PE, such as the diet, exercise habits of pregnant women, mental stress, etc., which may have affected the study results. In light of these limitations, questions to be addressed in future studies include determining the optimal dose and duration of aspirin use. This research posits that aspirin serves as a viable preventive measure against PE; however, additional studies are warranted to refine the dosage and temporal aspects of its administration. For example, whether increasing the dose or earlier intervention time can further improve the prevention effect needs to be verified by large-scale clinical trials. Furthermore, subsequent investigations ought to contemplate the synergistic impact of aspirin when amalgamated with a spectrum of additional preventative strategies. Given the multifactorial nature of PE, a combination of interventions, such as lifestyle improvements, the use of other drugs or nutrient supplementation, may be required to achieve the best preventive effect. Exploring the effects of these combined intervention strategies may help develop more comprehensive and effective PE prevention programs. Although this study provides evidence of benefit in the prevention of PE with aspirin, limitations of the study suggest the need for more rigorous design, broader sample size, and multifactorial integrated intervention strategies in future studies to further optimize aspirin use and improve the effectiveness of prevention of PE.

CONCLUSION

Aspirin has shown some effectiveness in preventing PE in high-risk women, but its effect is affected by factors such

as the age and BMI of the pregnant woman. Although aspirin can improve pregnancy outcomes and reduce the risk of adverse neonatal outcomes, a dose of 100mg/ day may not be sufficient to provide an adequate preventive effect in high-risk groups of older and obese pregnant women. Therefore, for high-risk pregnant women with advanced age and obesity, further studies are needed to determine better dose regimens, timing of intervention, and strategies for combined use with other preventive measures. However, when increasing the dose of aspirin, the risk of bleeding and the benefits of preventing PE must be carefully weighed to ensure the safety and effectiveness of the treatment. In summary, future research should consider a variety of factors to optimize the use of aspirin strategies to improve the effect of prevention of preeclampsia.

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