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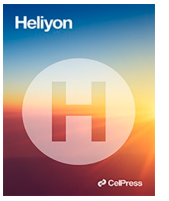

Evaluation of impacts of aspirin therapy versus placebo on preeclampsia: An observational study☆

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ABSTRACT

Background: Gestational hypertension and pre-eclampsia often increase maternal and neonatal mortality. The illness usually appears after the 20th week of pregnancy due to malnutrition or obesity. Untreated, it can lead to neonatal and maternal mortality. Low-dose Aspirin can prevent preeclampsia if started between 11 and 28 weeks. Several studies support this technique, although others have shown limited effectiveness and negative side effects.
Objective: This study aims to assess the effectiveness of aspirin treatment for the prevention of preeclampsia, taking into account any possible adverse reactions.
Methods: This observational research comprised 600 singleton pregnant women at high risk of pregnancy-induced hypertension. The aspirin group had 301 individuals and the placebo group 299. From 11 to 36 weeks of pregnancy, they received 150 mg of aspirin and 150 mg of placebo. Gestational hypertension was assessed at 25 weeks, 36 weeks, and 37 weeks. If any, aspirin and placebo-related adverse pregnancy and neonatal outcomes were reported.
Results: With aspirin therapy, 4 females and 14 females with placebo developed gestational hypertension before 25 weeks of pregnancy with an odds ratio of 0.283 (0.092–0.87); before 36 weeks, 5 females and 15 females with placebo developed GHD with an odds ratio of 0.331 (0.118–0.922); and after 37 weeks, 17 females and 35 females with placebo developed GHD. Preeclampsia occurred in 5 females in the aspirin group and 17 in the placebo group at <25 weeks (odds ratio 0.292 (0.106–0.802), 7 females in the aspirin arm and 25 females in the placebo arm at <36 weeks (odds ratio 0.278 (0.118–0.652), and 21 females in the aspirin arm and 39 females in the placebo arm at >37 weeks (odds ratio 0.5349 (0.307–0.930).
Conclusion: In pregnant women at high risk of prenatal hypertension and preeclampsia, aspirin therapy is very effective with minimal side effects.

1. Introduction

Preeclampsia, alternatively referred to as toxaemia, is a pregnancy-related complication distinguished by elevated blood pressure, the presence of oedema, proteinuria, and the occurrence of damage to multiple organs, particularly the kidneys and liver. Preeclampsia

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typically manifests after the 20th week of pregnancy, resulting from inadequate maternal nourishment or excessive body fat. If left untreated, it can lead to perinatal and maternal mortality. There is a positive correlation between the timing of disease onset and the likelihood of experiencing complications. The occurrence of pre-term birth is considered a negative consequence of gestational hypertension, as supported by multiple studies [1–3]. One of the primary obstacles in the domain of obstetrics pertains to the timely detection of pregnancy-induced hypertension and pre-term eclampsia. Moreover, given the gravity of the ailment, it is imperative to promptly intervene in the therapeutic approaches in order to mitigate the incidence of the condition. Anomalies in the placenta have been found to be associated with pregnancy-induced hypertension [4]. Placental cells experience autophagy as a result of hypertension, which subsequently results in anoxia and ischemia. The release of various inflammatory factors initiates the sequential process of inflammation. The vascular endothelial cells undergo damage, leading to the initiation of an endogenous extrinsic clotting mechanism [5]. The release of Thromboxane A2 (TXA2) from the placenta is elevated, resulting in alterations in hemodynamics and the development of hypertension.

Several randomized controlled trials (RCTs) [6–10] have consistently demonstrated that aspirin therapy is more effective than placebo in reducing the incidence of pre-eclampsia. The observation has been made that aspirin disrupts the synthesis of TXA2, resulting in reduced platelet aggregation and a decreased likelihood of thrombosis. Consequently, the incidence of pregnancy-induced hypertension is diminished.

According to the NICE (National Institute for Health and Care Excellence) guidelines in 2010, it was recommended that pregnant women at moderate or high risk of hypertension or preeclampsia should regularly take 75 mg of aspirin from 12 weeks of pregnancy until labor [11]. To date, no definitive assertions have been made regarding the efficacy of aspirin in preventing the occurrence of pregnancy-induced hypertension in high-risk individuals. Consequently, this observational study was conducted to assess the effects of regular administration of aspirin or placebo on the pregnancy outcomes of individuals with high-risk pregnancy induced hypertension. The investigators give the hypothesis that aspirin therapy is more effective and better than placebo in terms of onset of preeclampsia and pregnancy outcomes of high-risk pregnancy-induced hypertension with minimal adverse effects.

2. Methodology

2.1. Study design and population

With the goal to achieve the research objective, an observational study was carried out within the Department of Obstetrics between August 2017 and August 2020. The study aimed to compare the efficacy of aspirin and a placebo in reducing the occurrence of pregnancy-induced hypertension among patients at high risk. During the period from 11 to 14 weeks of pregnancy until 36 weeks, individuals identified as having a high risk of pregnancy were administered either 150 mg of aspirin in the aspirin group or a placebo at the same dosage in the placebo group.

The study was conducted on a sample of female participants who sought medical care at the Department of Obstetrics. The female participants underwent evaluation between the 11th and 14th weeks of gestation in order to identify those at a heightened risk for pregnancy-induced hypertension and pre-eclampsia. The diagnosis of pregnancy-induced hypertension syndrome was made in accordance with the "2010 NICE guidelines." The algorithm, as outlined in the New England Journal of Medicine (NEJM), was employed to evaluate the elevated risk of developing preeclampsia. Furthermore, the assessment of gestational age was conducted by measuring the length of the fetal crown-rump ratio.

The present study incorporates the following inclusion criteria: Individuals who are 18 years of age or older, solitary pregnancy occurring during the gestational period of 11–14 weeks. There is a significant likelihood of developing pregnancy-induced hypertension and pre-eclampsia. The classification of inclusion criteria for high-risk pregnancies was based on the presence of any of the following factors in the patients. The risk factors for adverse pregnancy outcomes include maternal age of 40 years or older, a pre-pregnancy body mass index (BMI) of 40 kg/m2 or higher, chronic hypertension before pregnancy, and diabetes (either pregestational or gestational). The study's exclusion criteria encompass severely ill patients, individuals with mental illness, and cases of fetal abnormalities at the time of scanning. Bleeding disorders refer to a group of medical conditions characterized by abnormal bleeding tendencies. The utilization of aspirin within a one-month timeframe prior to screening, or the presence of an allergic reaction to aspirin. The utilization of Nonsteroidal anti-inflammatory drugs (NSAIDs) over an extended period of time.

2.2. Ethical clearance and consent

The ethical committee of the Zhengzhou University approved the institute's study (protocol ZU # RC/IRB/2017/1055) and according to the Helsinki Declaration. Each of the study participants was informed to sign a written consent.

2.3. Implementation of the study

The demographic attributes of the female participants were documented and organized into a tabular format. The measurement of mean arterial pressure was conducted utilizing an automated device in accordance with a standardized protocol [12]. The evaluation of the arterial pulsating index was conducted in accordance with established standardized protocols [13]. A serum concentration measurement of pregnancy-associated plasma protein-A and placental growth factors was conducted using an automated device. The study assessed the risk factors associated with pregnancy-induced hypertension, including advanced maternal age (above 40 years), high body mass index (BMI) exceeding 35 kg/m2, familial history of pre-eclampsia, previous multiple pregnancies, history of

hypertension, chronic nephrosis, and Type I or Type II Diabetes mellitus.

2.4. Patients allocation

The female participants deemed suitable for inclusion in the research were randomly assigned to either the treatment or control group using an online platform. The group allocation information was concealed within sealed envelopes, indicating whether each participant would receive aspirin therapy or placebo therapy. The participants were instructed to consume a single tablet each evening in both the aspirin and placebo cohorts. In both cohorts, participants were instructed to orally consume tablets throughout the duration of their pregnancy, either until reaching 36 weeks gestation or in the event of premature delivery coinciding with the onset of labor.

2.5. Outcomes

The primary objectives of this study are to analyze the occurrence rates of pregnancy-induced hypertension and pre-eclampsia in the respective groups prior to reaching 25 weeks of gestation. The secondary objectives of the study were to ascertain the occurrence of adverse outcomes occurring prior to 25 weeks of gestation, between 26 and 36 weeks of gestation, and after 37 weeks of gestation. The frequency of neonatal mortality was analyzed in conjunction with the presence of any complications occurring in the neonatal period.

2.6. Protocol observance data recording

The assessment of adherence to the protocol was based on the recorded tablet intake, with adherence being deemed satisfactory if the tablets taken exceeded 85%. The tablets were enumerated upon the investigator's receipt of the remaining tablets. Moderate adherence was defined as medication administration falling within the range of 50–84.9%.

2.7. Statistical analysis

The N master software was utilized to conduct a Two Proportion - Hypothesis Testing analysis based on the results obtained from a pilot study involving a sample of 60 patients. With a desired marginal error of 5% and a power level of 90%, it was determined that a minimum sample size of 240 was necessary for each group. However, in order to account for a potential 20% loss during the follow-up period, a sample size of 300 participants was determined for each group in the current study. The data that exhibited a continuous nature were analyzed in terms of their median values, while the variables that possessed a categorical nature were analyzed in terms of their frequency distributions. Ultimately, the odds ratio was computed in order to ascertain the level of correlation between the occurrence of pregnancy-induced hypertension, pre-eclampsia, and other associated negative outcomes when administering aspirin and placebo to patients at high risk.

3. Results

Fig. 1 depicts the process of patient recruitment and selection. Table 1 presents the demographic distribution of the study population, specifically classifying the sample size in both the aspirin group and the placebo group. The distribution of categorical variables in both groups was assessed based on gestational age during randomization, patient age, BMI, patient medical history, presence of pre-eclampsia or pregnancy-induced hypertension, obstetric history, and gestational age during the patient's last delivery. Table 2 presents

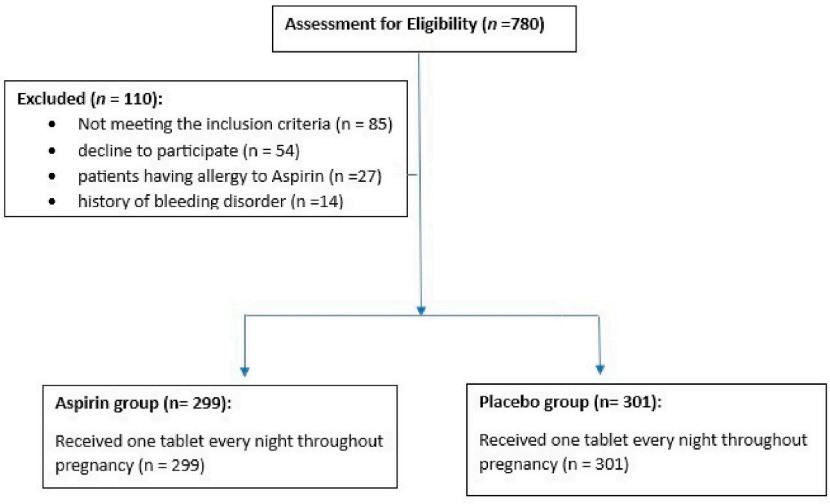

Fig. 1. Study flow diagram.

the distribution of the study population according to the associated risk factors. A total of 281 patients in the placebo group and 175 patients in the aspirin group exhibited postpartum haemorrhage, with a statistically significant p-value of 0.0001. The study population demonstrated good adherence in 54% of participants, while 42% of participants exhibited moderate adherence levels, and the remaining 4% displayed poor adherence. Fig. 2 displays the comparative distribution of the study population between the placebo and aspirin groups, 2 A) represents risk factor recruitment and 2 B) post-partum haemorrhage.

Table 3 shows the adverse effects of aspirin and placebo groups before 25 weeks of pregnancy, under 36 weeks of pregnancy and after 37 weeks of pregnancy.

3.1. Before 25 weeks of pregnancy

Table 1 displays a notable disparity between the group administered with aspirin and the group given a placebo at the initial stage. Prior to reaching the 25-week mark of pregnancy, a total of four individuals in the aspirin group and fourteen individuals in the placebo group were identified as having gestational hypertension. The statistical analysis yielded a p-value of 0.02, indicating a significant finding. Additionally, the odds ratio was calculated to be 0.283 (with a 95% confidence interval of 0.092–0.87). A total of 5 patients in the group receiving aspirin were diagnosed with pre-eclampsia, while 17 patients in the placebo group were found to have pre-eclampsia. The statistical analysis yielded a significant p-value of 0.02, indicating a notable difference between the two groups. Furthermore, the odds ratio was calculated to be 0.292 (with a 95% confidence interval of 0.106–0.802), suggesting a decreased likelihood of developing pre-eclampsia in the aspirin group compared to the placebo group. Within the aspirin group, a total of three miscarriages were observed, while in the placebo group, the number of miscarriages amounted to nine. The calculated odds ratio for this comparison was found to be 0.331, with a corresponding 95% confidence interval ranging from 0.088 to 1.235. One patient in the aspirin group and three patients in the placebo group exhibited abruption without pregnancy-induced hypertension. The odds ratio for this occurrence was calculated to be 0.331 (95% CI: 0.034–3.20). Two patients in the aspirin group and five patients in the placebo group exhibited spontaneous delivery without pregnancy-induced hypertension. The odds ratio for this outcome was calculated to be 0.397 (95% confidence interval: 0.076–2.06).

3.2. Under 36 weeks of pregnancy

A total of 5 females in the aspirin group and 15 females in the placebo group were found to have gestational hypertension. The statistical analysis revealed a significant p-value of 0.03 and an odds ratio of 0.331 (95% confidence interval: 0.118–0.922) for this outcome. A total of 7 patients from the group receiving aspirin were diagnosed with pre-eclampsia, while 25 patients from the placebo group were found to have pre-eclampsia. The statistical analysis yielded a p-value of 0.003, indicating a significant difference between the two groups. Furthermore, the odds ratio was calculated to be 0.278 (with a 95% confidence interval of 0.118–0.652). There was a total of four instances of miscarriage observed in the group administered with aspirin, while the placebo group experienced nine cases. The calculated odds ratio for miscarriage between the two groups was determined to be 0.441, with a corresponding 95% confidence interval ranging from 0.134 to 1.45. Three patients in the aspirin group and six patients in the placebo group exhibited abruption without pregnancy-induced hypertension. The odds ratio for this occurrence was calculated to be 0.496 (95% confidence interval: 0.123–2.004). A total of 15 patients in the aspirin group and 32 patients in the placebo group exhibited spontaneous delivery without pregnancy-induced hypertension. The calculated odds ratio for this outcome was 0.465 (95% confidence interval: 0.247–0.877).

Table 1
Demographic characteristic of the study population (N = 600).

Variables	Placebo Group (N = 299)	Aspirin Group (N = 301)	p value
Gestational age (weeks)	13.1	13.2	0.01
Median range	12.1–13.7	12.3–13.9	
Age (years)	29.7	29.4	0.14
Median	21–35	21–37	
Range			
BMI	25.3	26.1	0.13
Median	22.4–32.1	21.3–31.8	
Range:			
Medical history	24	27	0.005
Chronic hypertension	1	0	0.04
Systemic lupus erythematosus	3	4	0.012
DM type I	5	5	0.001
DM type II			
Mother had preeclampsia	17	14	0.005
Mother had pregnancy induced hypertension	31	33	0.004
Obstetric history	142	149	0.03
Nulliparous	113	109	0.02
Multiparous without pregnancy induced hypertension	35	32	0.001
Multiparous with pregnancy induced hypertension			
Gestational age at delivery of last pregnancy	39 (37–40)	39 (37–40)	0.01

Table 2
Distribution of study population according to risk factor recruitment.

	Placebo group ($n = 299$)		Aspirin group ($n = 301$)		p value
	Number	%	Number	%	
Maternal age greater than or equal to 40 years	34	11.38	31	10.30	0.04
Pre-pregnancy body mass index (BMI) greater than or equal to 40 kg/m^2	46	15.38	49	16.28	0.02
Chronic (pre-pregnancy) hypertension	53	17.73	52	17.28	0.03
Diabetes (pregestational or gestational).	28	9.36	27	8.97	0.01

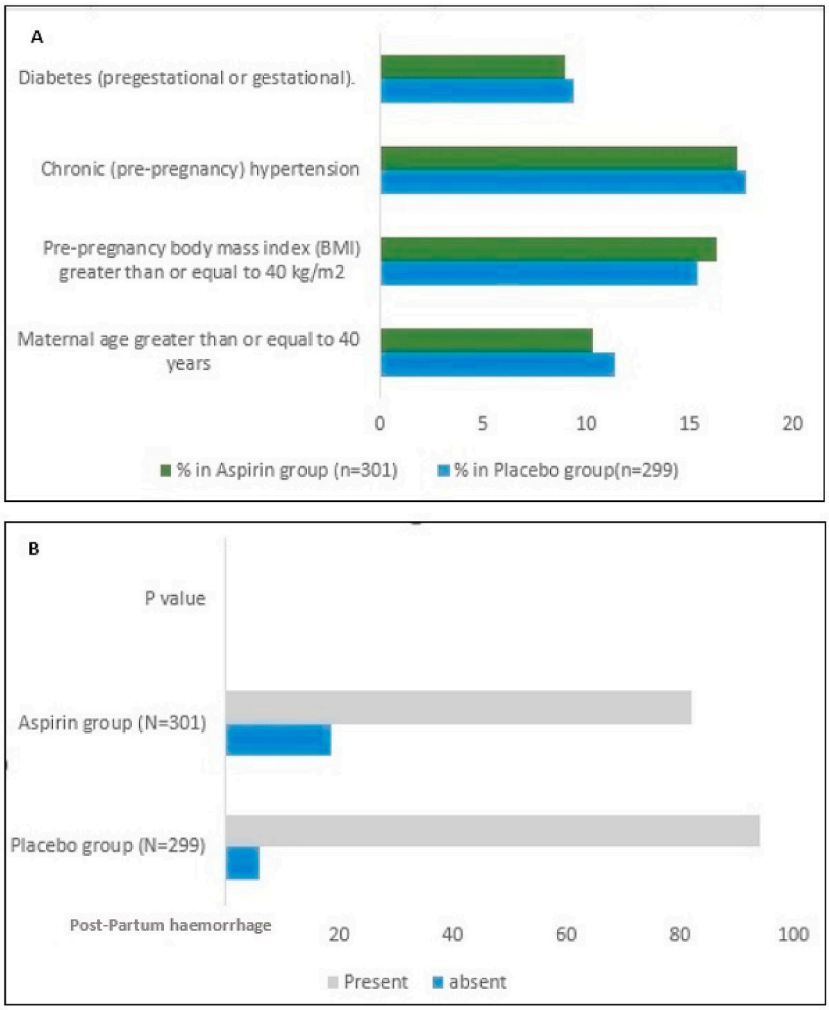

Fig. 2. Comparison of Study population.

3.3. After 37 weeks of pregnancy

A total of 17 individuals in the aspirin group and 35 individuals in the placebo group were found to have gestational hypertension. The statistical analysis revealed a significant p-value of 0.01 and an odds ratio of 0.482 (95% confidence interval: 0.264–0.880) for this outcome. A total of 21 patients in the group receiving aspirin were diagnosed with pre-eclampsia, while 39 patients in the placebo group were found to have pre-eclampsia. The statistical analysis revealed a significant p-value of 0.02, along with an odds ratio of 0.5349 (95% confidence interval: 0.307–0.930). One patient in the aspirin group and five patients in the placebo group exhibited abruption without pregnancy-induced hypertension. The observed p-value was significant, indicating a notable difference between the two groups. The odds ratio for this outcome was calculated to be 0.1987 (95% confidence interval: 0.023–1.71). One patient in the aspirin group and three patients in the placebo group experienced stillbirth without pregnancy-induced hypertension. The p-value was found to be significant, and the odds ratio was calculated to be 0.331 (95% CI: 0.034–3.20).

Table 3
Adverse outcomes in the study population.

Outcomes	Placebo group (N = 299)	Aspirin group (N = 301)	Odds ratio with 95% CI	Z-statistics	P value
Adverse outcomes at <25weeks of pregnancy	14	4	0.283 (0.092–0.87)	2.199	0.02
Gestational Hypertension	17	5	0.292 (0.106–0.802)	2.388	0.02
Preeclampsia	9	3	0.331 (0.088–1.235)	1.646	0.09
Miscarriage without pregnancy induced hypertension	3	1	0.331 (0.034–3.20)	0.955	0.33
Abruption without pregnancy induced hypertension	5	2	0.397 (0.076–2.06)	1.098	0.27
Spontaneous delivery without pregnancy induced hypertension					
Adverse outcomes at <36 weeks of pregnancy	15	5	0.331 (0.118–0.922)	2.114	0.03
Gestational Hypertension	25	7	0.278 (0.118–0.652)	2.939	0.003
Preeclampsia	9	4	0.441 (0.134–1.45)	1.348	0.17
Miscarriage without pregnancy induced hypertension	6	3	0.496 (0.123–2.004)	0.983	0.32
Abruption without pregnancy induced hypertension	32	15	0.465 (0.247–0.877)	2.364	0.01
Spontaneous delivery without pregnancy induced hypertension					
Adverse outcomes at ≥37 weeks of pregnancy	35	17	0.482 (0.264–0.880)	2.376	0.01
Gestational Hypertension	39	21	0.5349 (0.307–0.930)	2.213	0.02
Preeclampsia	5	1	0.1987 (0.023–1.71)	1.47	0.1
Abruption without pregnancy induced hypertension	3	1	0.331 (0.034–3.20)	0.955	0.33
Still birth without pregnancy induced hypertension					

Level of significance set at $p < 0.05$.

This information is depicted in Fig. 3, which displays pie charts representing the different weeks of gestation (A) < 25 weeks, B) < 36 weeks, and C) > 37 weeks). The forest plot in Fig. 4 presents the comparative odds ratio of various adverse effects in pregnant women between the aspirin and placebo groups. Fig. 4A represents the forest plot before 25 weeks, Fig. 4B before 36 weeks and Fig. 4C after 37 weeks. The presence of gestational hypertension was observed to have a significant correlation with the placebo group, in contrast to the Aspirin group, across all three distinct gestational weeks of pregnancy.

3.4. Adverse outcomes in the neonate

Table 4 displays the adverse outcomes observed in the neonatal population. The incidence of stillbirth or fetal death, complications, the necessity for therapy, and inadequate fetal growth were found to be higher in the placebo group compared to the Aspirin group. The statistical analysis revealed that the overall p-value for each variable was less than 0.05, indicating statistical significance. Furthermore, it was observed that the placebo group exhibited a greater prevalence of necrotizing enterocolitis in neonates, as indicated by an odds ratio of 0.198 (0.023–1.71) and a p-value of 0.14. The forest plot in Fig. 5 presents the comparative odds ratio of neonatal outcomes between the aspirin and placebo groups. The observed association exhibited a high level of strength, as indicated by the statistically significant p-value, which was less than 0.05. The Forest plot for odds ratio of neonatal outcomes here in Fig. 5 A) showed the case of Still birth or death B) Complications C) Therapy provided and D) Poor Foetal growth.

Table 5 shows distribution of study population according to post-partum haemorrhage.

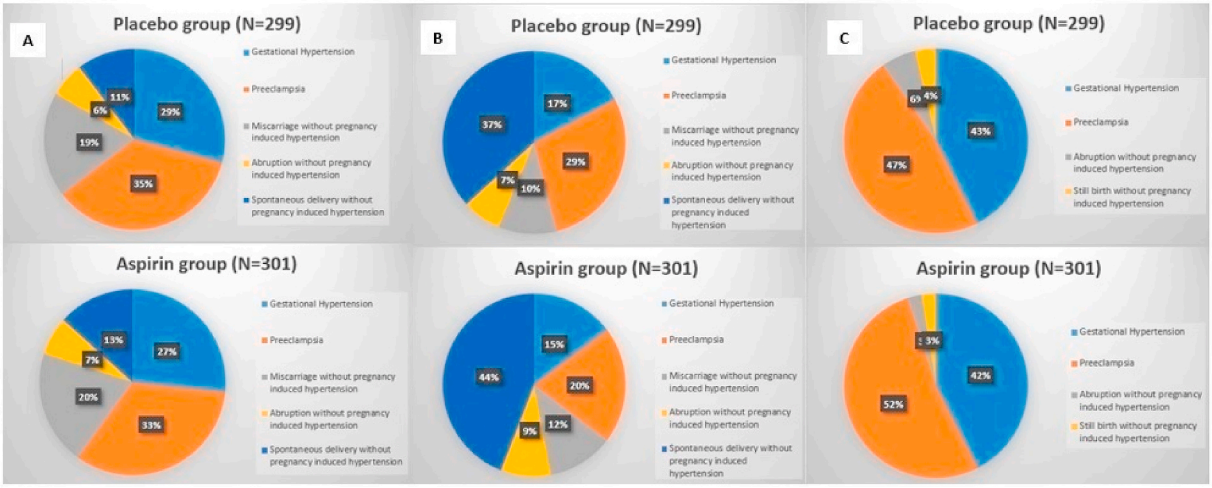

Fig. 3. Adverse outcomes in Females during Pregnancy.

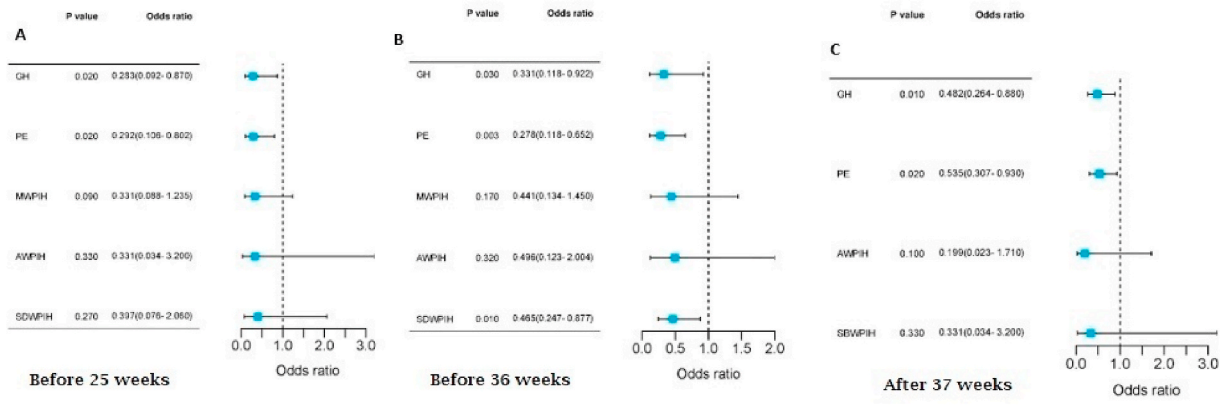

Fig. 4. Forest plot for odds ratio of Adverse outcomes in females during pregnancy A) Still birth or death B) Complications C) Therapy provided D) Poor Foetal growth.

Table 4
Neonatal outcomes in the study population (N = 600).

Outcomes	Placebo group (*n = 299*)	Aspirin group (*n = 301*)	Odds ratio (95% CI)	p value
Stillbirth or death	7	3	0.42 (0.11–1.64)	0.21
All still birth	3	2	0.66 (0.11–3.98)	0.65
Small for gestational age with hypertension	3	1	0.33 (0.03–3.18)	0.34
Small for gestational age without hypertension	1	0	–	–
Without placental abruption or bleeding	0	0	–	–
With placental abruption or bleeding				
Complications	0	0	–	–
Intraventricular haemorrhage of grade > II	2	1	0.49 (0.04–5.49)	0.57
Sepsis with known culture	3	1	0.33 (0.03–3.18)	0.34
Anaemia needing blood transfusion	6	2	0.33 (0.07–1.63)	0.17
Respiratory distress treated with surfactant and ventilation	5	1	0.198 (0.023–1.71)	0.14
Necrotizing enterocolitis needing surgery				
Therapy	21	16	0.74 (0.38–1.45)	0.39
Admission to NICU	18	12	0.65 (0.31–1.37)	0.26
Intubation				
Poor foetal growth	24	32	1.36 (0.78–2.38)	0.27
Birth weight less than 3 percentile	30	40	1.37 (0.83–2.27)	0.22
Birth weight less than 5 percentile	62	71	1.18 (0.80–1.74)	0.40
Birth weight less than 10 percentile				

Based on the obtained results, it is apparent that individuals who use aspirin experience fewer adverse effects and neonatal complications compared to the placebo group. This conclusion is supported by the comparative box and whisker plots for Aspirin vs. Placebo group presented in Figs. 6 and 7, which depict box and whisker plots.

4. Discussion

In the current observational trial, which included only pregnancies with a single baby, it was discovered that the aspirin group had a decreased incidence of gestational hypertension compared to the placebo group. In light of these findings, the hypothesis that the aspirin group would be superior than the placebo group in terms of the incidence of gestational hypertension is shown to be correct. It was discovered that there was a large and strong connection between the evidence of a decreased incidence of gestational hypertension. In addition to other unfavourable outcomes, abruption without pregnancy-induced hypertension and stillbirth without pregnancy-induced hypertension both demonstrated a robust connection with the aspirin group in addition to a lower occurrence. Necrotizing enterocolitis was dramatically decreased in the neonates who were given the medicine aspirin, which was one of the outcomes. Postpartum haemorrhage is an important secondary outcome that was greatly improved by the use of the aspirin medication.

Previous studies focused on lowering the risk of prenatal hypertension in high-risk women, but the current study explicitly chose women with a high risk of gestational hypertension by examining the demographic features and standard recommendations [14–17]. In contrast, the previous studies concentrated on reducing the risk of gestational hypertension in low-risk women. The medication was started between 11 and 14 weeks of pregnancy based on the findings of a meta-analysis that showed that aspirin provides more remarkable effects when taken before 16 weeks of pregnancy in reducing the incidence of pre-eclampsia [18,19]. This led to the decision to start the treatment between 11 and 14 weeks of pregnancy. As a result of the findings [20,21] about the dose-dependent

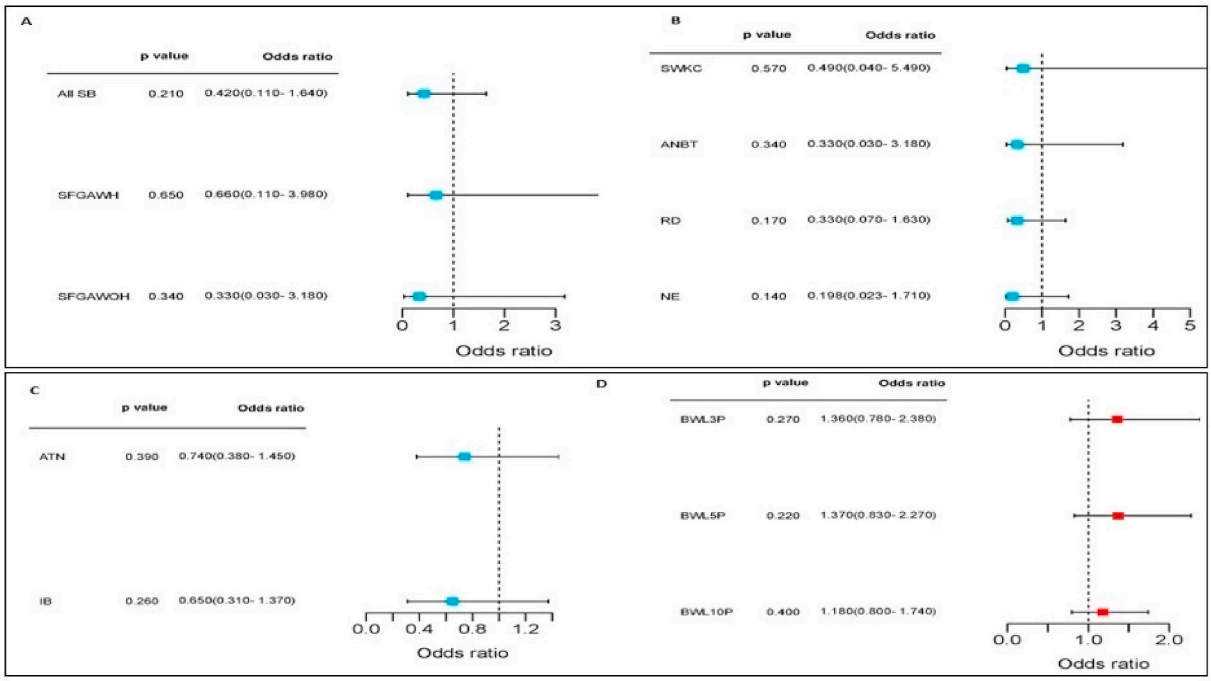

Fig. 5. Forest Plot for Odds ratio of neonatal outcomes A) Before 25 weeks B) Before 36 weeks C) After 37 weeks.

Table 5
Distribution of study population according to post-partum haemorrhage.

	Placebo group (N = 299)		Aspirin group (N = 301)			
Post partum haemorrhage	Number of females (N)	%	Number of females (N)	%	Chi-square statistic[#]	P value
Absent	18	6.02	56	18.73	21.971	0.00001
Present	281	93.98	245	81.94	20.822	0.00001

Chi Square Test, level of significance set at $p \leq 0.05$.

benefit of aspirin, we propose that the aspirin group take 150 mg of aspirin in order to cure preeclampsia. A randomized controlled experiment claimed that the consumption of medications during the night would render it more successful in reducing the incidence of preeclampsia [22], thus the patients were given the instruction to take their medication during the night. In addition, the patients were given the instruction to take their medication during the night. According to the findings of Wang et al. (2022) [23], it is advised to initiate the administration of Aspirin during the gestational period of 12–16 weeks in pregnant women who are deemed to be at a heightened risk for developing preeclampsia (PE). The recommended dosage of aspirin for optimal use is 75 mg per day. According to the US Preventive Services Task Force Recommendation Statement (USPSTF), individuals who are at a high risk for preeclampsia should consider taking low-dose aspirin (81 mg/d) as a preventive measure after 12 weeks of gestation [24]. Based on the available evidence, it is recommended that the course of action be classified as a B recommendation. Similarly, Rolnik et al., 2020 [25] mentioned that the impact magnitude of aspirin was more prominent in females who exhibit high adherence to the prescribed treatment regimen. In their article on the role of serum potassium and sodium levels in the development of postpartum haemorrhage (PPH), Privitera et al., 2020 [26] discussed the significance of voltage-gated ion channels, specifically potassium channels, in regulating uterine contractility. They observed a statistically significant decrease in serum potassium levels and the product of sodium and potassium levels (Na*K) among cases of primary PPH. Likewise, Miranda et al. (2019) [27] discussed in their article about the potential of soluble endoglin (sEng) as a diagnostic marker for preeclampsia. They found that the levels of sEng in circulation exhibit promise as an indicator for assessing the severity of preeclampsia and are correlated with an elevated risk of unfavourable outcomes.

One potential limitation of the study is its reliance on data from a single center. To establish a more definitive conclusion, it would be necessary to conduct a multicenter trial.

5. Conclusion

Based on the constraints of the study, it can be inferred that administering aspirin therapy to pregnant women at a heightened risk of developing gestational hypertension yielded more favourable outcomes compared to administering a placebo, resulting in a

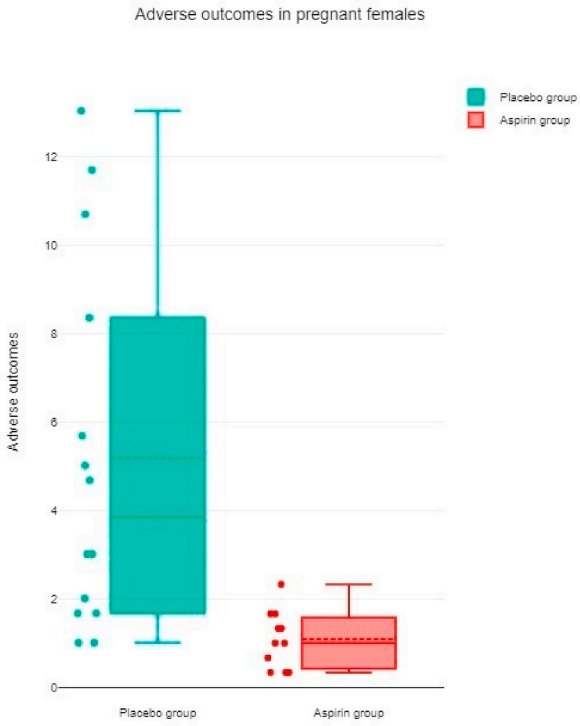

Fig. 6. Comparative Box and whisker plot for Adverse outcomes in pregnant females in Placebo vs. Aspirin group: Red one represents Aspirin group and Green one represents the Placebo group.

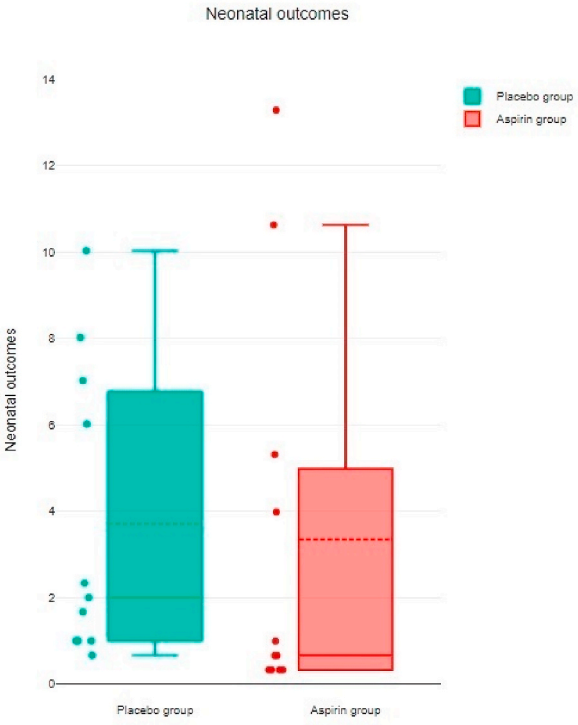

Fig. 7. Comparative Box and whisker plot for Neonatal outcomes in Placebo vs. Aspirin group: Red one represents Aspirin group and Green one represents the Placebo group.

decrease in the occurrence of gestational hypertension. Nevertheless, it is imperative to conduct additional validation as this current study serves as the initial phase of the intervention.

Compliance with ethical standards.

Funding

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Ethical approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee of the Zhengzhou University (protocol ZU # RC/IRB/2017/1055) with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: It was obtained from all individual participants included in the study.

Consent for publication: Not Applicable.

Author contribution statement

Liping Zhou: Conceived and designed the experiments.

Zhenzhen Wang: Performed the experiments; Analyzed and interpreted the data.

Li Wang: Analyzed and interpreted the data.

Sanjay Rastogi: Contributed reagents, materials, analysis tools or data; wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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