

Original Article

Role of Low Dose Aspirin in Prevention of Pre-Term Delivery: A Quasi-Experimental Study

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Abstract

Objective: To assess the role of low-dose aspirin (75 mg) in preventing spontaneous preterm birth among high-risk pregnant women in Pakistan.

Methodology: This quasi-experimental study was conducted at the Department of Obstetrics and Gynecology, Railway General Hospital, Rawalpindi, from August 2023 to August 2024. This study received formal ethical approval from the institutional review committee of Islamic International Medical College Rawalpindi, approval number IRC/23/3087. The study was conducted in strict adherence to the institutionally approved protocol and the ethical standards of the Declaration of Helsinki. A total of 250 pregnant women with a previous history of preterm birth were recruited at 12-15 weeks of gestation through consecutive sampling. Participants were allocated to two parallel groups based on the clinical intervention schedule. Group A received aspirin 75mg daily with folic acid and standard preventive therapies, while Group B received folic acid and routine preventive measures only. Outcomes included incidence of preterm delivery before 34 weeks and neonatal birth weight. Data were analysed using SPSS version 26. Statistical significance was set at $p < 0.05$. The baseline demographic and clinical characteristics of both groups were compared to ensure comparability. The normality of all continuous variables, including maternal age and birth weight, was verified using the Shapiro-Wilk test and visual inspection of Q-Q plots. Data following a normal distribution were summarised as mean(SD). Intergroup comparisons for categorical outcomes were performed using the chi-square test.

Results: Preterm birth before 34 weeks occurred in 5.6% (7/125) of women in the aspirin group compared to 14.4% (18/125) in the control group ($p[P1.1]=0.02$; RD:8.8%, 95% CI:1.6-16.0%). Low birth weight (< 2500 g) was observed in 32% of neonates in the aspirin group versus 48% in the control group ($p=0.014$). Mild adverse effects of aspirin, such as epigastric pain and allergic reactions, were reported in 8.8% (11/125) of participants in the intervention group.

Conclusion: Low-dose aspirin (75 mg) initiated in early pregnancy significantly reduces the risk of spontaneous preterm birth and improves neonatal outcomes in high-risk women. Its use is recommended as an affordable preventive strategy in resource-limited settings.

Keywords: Aspirin; Premature Birth; Chemoprevention; Pregnancy; High-risk; Infant; Premature.

Introduction

In Pakistan, the incidence of preterm birth is disproportionately high at 21.64%, which is almost double the global average of 11%. This high burden of preterm birth, defined as delivery before 37 weeks of gestation, strains limited health resources and contributes significantly to poor neonatal outcomes, including respiratory distress syndrome, low birth weight, neurodevelopmental delays, long-term sensory impairments, longer hospital stays, higher medical costs, and emotional distress for families.¹ Despite various preventive strategies, identifying effective and low-cost interventions remains a priority for reducing neonatal morbidity and mortality in our population.²

Several risk factors contribute to the occurrence of PTB, with maternal conditions such as diabetes, hypertension, pre-existing kidney disease, obesity, placental abnormalities,

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Data Availability Statement: The raw de-identified datasets analysed in the current study and the full institutional trial protocol are not publicly available due to institutional data protection policies and participant confidentiality agreements. However, both the dataset and full protocol are available from the corresponding author upon reasonable request.

Institutional Review Board

Approval

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and a previous history of preterm birth being among the most well-known.³ These risk factors may also interact with each other. Environmental and foetal factors have been associated with the development of spontaneous preterm birth (SPTB). Identifying women at high risk for PTB remains a clinical challenge, especially in low-resource settings, such as Pakistan. While transvaginal cervical length (TVCL) measurement and foetal fibronectin (fFN) testing have shown significant potential in predicting PTB, their routine use in asymptomatic women remains debated due to cost and accessibility limitations.

Despite these challenges, the previous history of preterm birth remains one of the most reliable predictors of subsequent preterm delivery, increasing the risk of recurrence by approximately 2.5-fold. In light of these risks, preventive strategies such as low-dose aspirin (LDA) have gained attention, with several studies supporting their role in reducing the incidence of PTB in high-risk populations.⁴ The 2023 ASPIRIN trial, a large multi-country study, demonstrated that in pregnant women at high risk, low-dose aspirin significantly reduced the incidence of PTB.⁵ Given the high burden of PTB in Pakistan and the resource constraints facing the healthcare system, the search for affordable and scalable interventions, such as low-dose aspirin, is crucial. This quasi-experimental study aimed to evaluate and compare the clinical outcomes and incidence of SPTB among high-risk pregnant women taking 75 mg of aspirin daily.⁶ Most studies have used a daily dose of 81 mg; however, in Pakistan, the available formulation is 75 mg, and its effectiveness has not been well studied. The results may offer valuable insights into the effectiveness of lower doses, providing clinical guidance for the management of aspirin in high-risk pregnancies in Pakistan and similar resource-limited settings. By addressing this critical issue, we can work towards improving maternal and newborn health outcomes in Pakistan and other countries facing high rates of premature births.⁷

Methodology

This study was approved by the Institutional Ethics Committee of the Islamic International Medical College, Rawalpindi. This quasi-experimental study was conducted from August 2023 to August 2024. This study was conducted in the obstetrics and gynaecology outpatient department at Railway General Hospital, Rawalpindi. The study's design, execution, and reporting were structured to ensure transparent reporting in strict accordance with the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) guidelines. This was an open-label, two-arm parallel quasi-experimental study with a 1:1 allocation ratio.

Inclusion criteria: 250 pregnant women aged 18–40 years were enrolled. Those with a history of PTB were chosen at gestational amenorrhoea of 12–15 weeks.

Exclusion criteria: This study excluded pregnant women with multiple pregnancies, gestational diabetes, chronic illnesses (such as diabetes mellitus or high blood pressure), smoking, clotting disorders, heart disease, continuous antiplatelet medication, peptic ulcer disease, abnormal uterine artery Doppler on ultrasound screening, or aspirin allergies.

Using the WHO calculator, a sample size of 250 was determined to compare two independent proportions. The parameters underlying the calculation were explicitly defined based on a baseline incidence of preterm birth ($P_1=0.30$ or 30%) among high-risk women without intervention and an expected clinical reduction to 15% ($P_2=0.15$) with early low-dose aspirin therapy. Setting a two-sided alpha error (type I error) at 5% ($\alpha=0.05$) and a statistical power of 80% ($\beta=0.20$), the minimum required sample size was determined to be 125 participants in each group, yielding a total study population of 250 participants.

Due to the operational nature of prescribing a physical prophylactic medication versus routine care without a matching placebo, this study utilised an open-label design, where both the participants and healthcare providers were aware of treatment allocation. Participants were enrolled via a non-randomized consecutive sampling method. Allocation to either Group A or Group B followed a strict 1:1 parallel schedule based on the odd or even sequence of OPD registration numbers. Participants with odd serial numbers were allocated to Group A, while those with even serial numbers were allocated to Group B, eliminating selection bias by the clinical team. Following informed verbal consent, all study participants underwent baseline investigations, including CBC, urine dipstick, obstetrical ultrasound, and general physical and obstetrical examinations. Low-dose aspirin (75 mg) is an established protocol with a well-documented safety profile in routine clinical practice. The requirement for written informed consent was formally waived by the IRC of Islamic International Medical College during protocol approval. This waiver was primarily granted to accommodate patient literacy variations and avoid potential non-cooperation while ensuring that the study fully maintained the ethical standards of the Declaration of Helsinki. Hence, informed verbal consent was explicitly obtained from all eligible participants before their formal enrolment and baseline clinical evaluation.

Folic acid 5 mg was administered to all pregnant women in both groups along with standard preterm birth therapies (progesterone, cervical cerclage "if needed", tocolytics, and steroids) until 36 weeks or delivery, whichever occurred first. Group A women with a risk of preterm birth received aspirin 75 mg plus folic acid 5 mg daily along with standard

preterm birth strategies. Monitoring of this group was maintained until 37 weeks or delivery. Group B received only folic acid 5 mg along with standard therapies. The two groups were followed up until either delivery or 37 weeks, whichever came first.

PTB assessment was carried out using

1. Uterine monitoring (rate of uterine contractions > 4–6 per hour in <37 weeks).
2. Digital examination: The diagnosis of spontaneous preterm labour was verified by an effaced or dilated cervix 2, 3, and 4 cm with 50% effacement.
3. Transvaginal ultrasonography (TVUS) was used to determine cervical length (cut-off 2.5 cm).

All data were analysed using Microsoft Excel and SPSS version 26.0. The baseline demographic and clinical characteristics of both groups were compared to ensure pre-intervention comparability. Quantitative data are expressed as mean and standard deviation, and qualitative variables are represented as frequencies and percentages. In compliance with the TREND statement for non-randomized designs, potential baseline confounding factors, including maternal age, parity, and gestational age at previous preterm birth, were evaluated. Baseline comparability between the two groups was assessed using independent t-tests for continuous variables and chi-square tests for categorical data to ensure that there were no statistically significant differences before the intervention. Intergroup comparisons for categorical outcomes were performed using the chi-square test. In accordance with the SAMPL guidelines, the magnitude of the clinical effect and precision of the estimates were reported using 95% Confidence Intervals alongside exact p-values. A p-value of less than 0.05 was considered statistically significant for all statistical analyses.

Results

The study included 250 pregnant women with a history of spontaneous preterm birth. Participants were allocated to two parallel groups based on the clinical protocol. Group A (intervention group, n=125) received low-dose aspirin 75 mg, and Group B (control group, n=125) received placebo. All 250 participants were included in the final analysis (Table I). No participants were lost to follow-up.

The overall mean age (SD) of the participants was 31.75 (4.9) years, ranging from 18 to 40 years. In Group A, the mean age (SD) was 30.5(4.5) years. Within this group, 65 (52.0%) women were aged 18-30 and 60 (48.0%) were aged 31-40.

In Group B, the mean age (SD) was 33(5.3) years. In this group, 40(32.0%) were aged 18-30 while 85(68.0%) were in the 31-40 age category. Statistical analysis indicated that the baseline age distribution showed a statistically significant difference between the two study groups ($\chi^2=10.16$, $df = 1$, $p = 0.001$ for categorical age and $t = -4.01$, $df = 248$, $p < 0.001$ for continuous mean age). Participants in Group A were slightly younger on average than those in Group B, which represents a baseline characteristic of the study's quasi-experimental design.

Table 1: Baseline age characteristics of study participants (n=250)

Age Variable	Group A (Aspirin)(n=125)	Group B (Control)(n=125)	Total(n=250)	Statistical Test	p-value
Age Group, n (%)				$\chi^2 = 10.16$ (df = 1)	0.001
18–30 years	65 (52.0%)	40 (32.0%)	105 (42.0%)		
31–40 years	60 (48.0%)	85 (68.0%)	145 (58.0%)		
Mean $\pm$ SD (years)	30.5 $\pm$ 4.5	33.0 $\pm$ 5.3	31.7 $\pm$ 4.9	$t = -4.01$ (df = 248)	< 0.001

Note: SD, Standard Deviation; n, number of participants. Categorical age distribution was compared using the chi-square test, and continuous mean age was compared using the independent samples t-test.

The primary findings revealed a significant reduction in the preterm birth rates and differences in the neonatal outcomes between the groups.

In the intervention Group A (Group A), only seven (5.6%) women experienced PTB before 34 weeks compared to 18(14.4%) women in the control group (Group B) with a risk difference of 8.8% (95% CI: 1.6-16.0%). This difference was statistically significant ($p=0.020$) (Table 3), [Figure 1]. The average birth weight in group A was 2450 (350) g, whereas in group B, it was 2250 (360) g. This difference was statistically significant (independent samples t-test, $p=0.027$; 95% CI: 23.36-376.64). In group A, 40 (32%) neonates weighed less than 2500 g, compared to 60 (48%) in group B ($p=0.014$). (Table 2)

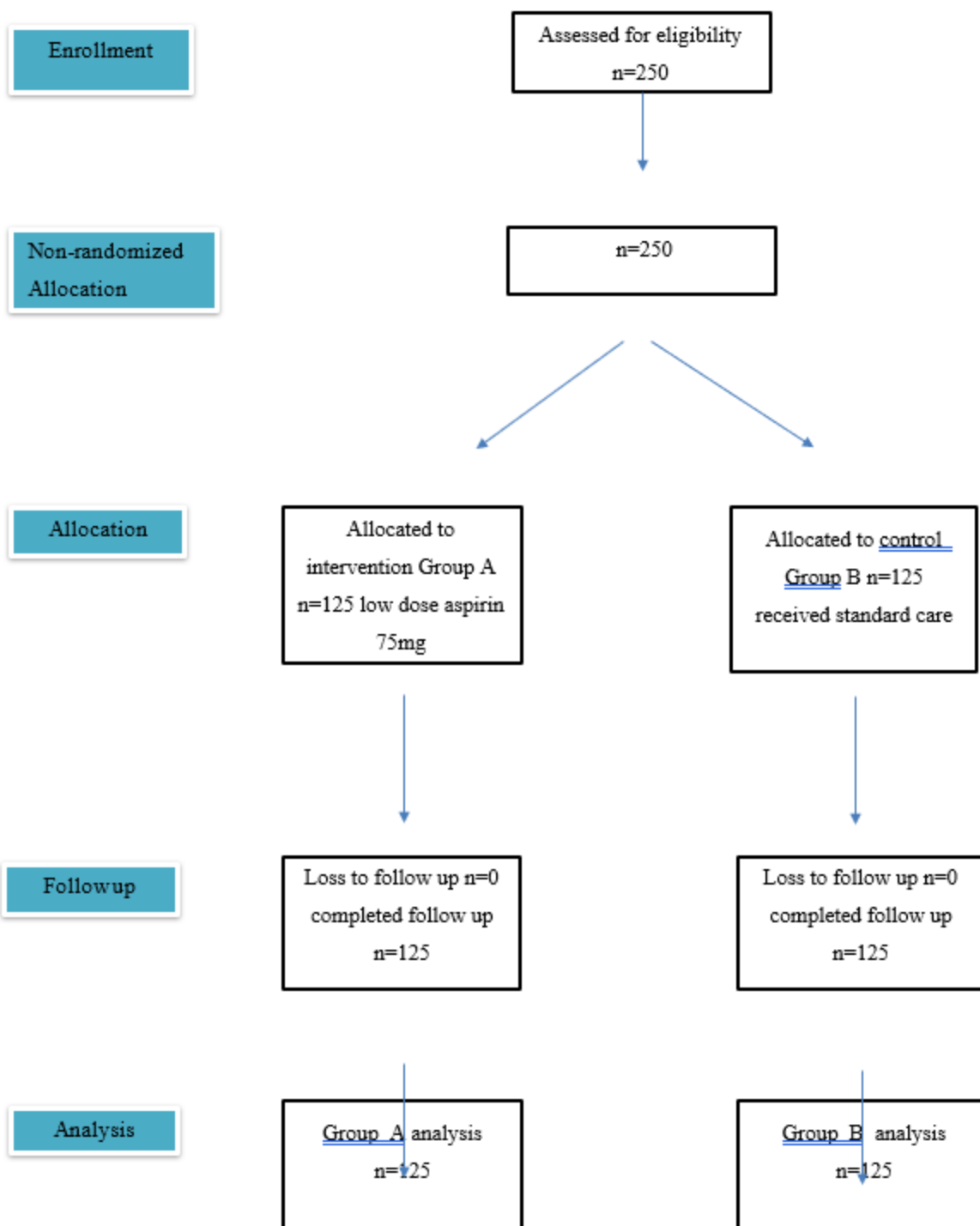


Figure 1: Flow diagram of participant progression through study steps.

Table 2: Fetal birth weight distribution comparison between intervention group A and control group B

Birth Variable	Weight	Group A(n=125)	Group B (n=125)	Total(n=250)	Statistical Test	p-value
Birth Category, n (%)	Weight				$\chi^2 = 6.67$ (df = 1)	0.014
	≤ 2500 g	40 (32.0%)	60 (48.0%)	100 (40.0%)		
	≥ 2500 g*	85 (68.0%)	65 (52.0%)	150 (60.0%)		
	Mean $\pm$ SD (g)	2450 $\pm$ 350	2250 $\pm$ 360	2350 $\pm$ 368	$t = 2.23$ (df = 248)	0.027

*(95% CI: 23.36 to 376.64)

**Comparison between groups was performed using the chi-square test ($P=0.014$). Comparisons were performed using the independent samples t-test for continuous means; 95%CI represents the continuous interval for the difference between the two means. Statistical significance was set at $p < 0.05$.

*** Note: SD, Standard Deviation; g, gram; n, number of participants

Table 3: Preterm birth comparisons between groups

Preterm Birth	Group A (Aspirin)(n=125)	Group B (Control)(n=125)	Total(n=250)	Risk Difference(95% CI)*	p-value**
Yes	7 (5.6%)	18 (14.4%)	25 (10.0%)	8.8% (1.6% to 16.0%)	0.020
No	118 (94.4%)	107 (85.6%)	225 (90.0%)	—	—

*Comparison between groups was performed using the chi-square test ($\chi^2 = 5.41$, df = 1, $p = 0.020$). Statistical significance was set at $p < 0.05$.

Note: CI, Confidence Interval; n= number of participants

A small proportion of the study population (8.8%, 11/125) experienced aspirin-related adverse events in the Intervention Group. Specifically, 2.4% (3/125) of women in the Intervention Group reported a mild allergic reaction, while 6.4% (8/125) experienced epigastric pain following the use of low-dose aspirin 75 mg. No serious adverse events or complications were reported in either group.

Discussion

Preterm birth (PTB) remains a leading cause of newborn morbidity and mortality because of its high incidence and complicated management strategies. It has become a significant economic burden. Premature babies are more likely to experience respiratory and gastrointestinal issues as well as neurodevelopmental impairment, even though the majority of them survive.⁸ Important foetal measures include early ultrasound for accurate gestational age assessment and detection of multiple pregnancies. Antenatal care should begin before 12 weeks of gestation and include at least eight consultations with health care professionals throughout pregnancy. These visits help identify and manage risk factors, such as infections. The WHO antenatal care guidelines also recommend counselling regarding tobacco and substance use, along with advice on adequate nutrition and a healthy diet to help reduce the risk of preterm birth.⁹

A minor but statistically significant decrease in preterm births has been observed in data from aspirin trials for preventing preeclampsia.¹⁰ Pregnant women with a high risk of preterm birth were treated with folic acid 5 mg, and the usual methods were used to prevent it in the control group. In contrast, pregnant women in the intervention group received low-dose aspirin 75 mg plus folic acid 5 mg along with the usual methods for preventing preterm birth, such as progesterone administration and cervical cerclage "if indicated", in accordance with the NICE and ACOG guidelines for the prevention of preterm birth, with ongoing follow-up until 36 weeks of gestation or delivery, whichever occurred first. In contrast to the Control Group, our study revealed a significant decrease in PTB in the Intervention Group. The findings of the 2020 ASPIRIN Trial by Hoffman et al,¹¹ were similar to those of our investigation. In another study, low-dose aspirin (81 mg daily) was administered to nulliparous women with a singleton viable pregnancy and an ultrasound confirming gestational age between 6 weeks and 0 days and 13 weeks and 6 days of pregnancy in a multi-country, randomised, double-masked, placebo-controlled study.¹²

Women with their first and second pregnancies between 2006 and 2019 were included in another Swedish register-based cohort study.¹³ In women who had previously experienced a preterm delivery, low-dose aspirin treatment reduced the risk of subsequent preterm births (of any origin, but particularly spontaneous onset) in both medically indicated and spontaneous onset cases.

In another clinical study by Landman AJ, it was demonstrated that low-dose aspirin significantly decreased the relative risk of preterm birth before 34 weeks of gestation by 50%.¹⁴ According to Van Doorn R, a meta-analysis of participant data from studies examining the impact of antiplatelet agents on lowering pre-eclampsia, women who took antiplatelet agents were much less likely to develop PTL at <37 and <34 weeks of pregnancy than those who received a placebo or no treatment.¹⁵

The results of our study demonstrated a strong correlation between high parity and an elevated probability of SPTB. The results of our investigation indicated that, compared to the control group, the rate of SPTB was considerably reduced when high-risk pregnant women were administered a low dose of 75 mg aspirin for SPTB prevention. Regarding neonatal birth weight, the intervention group exhibited a slightly higher mean weight, which aligned with the lower percentage of low birth weight infants in this group. Given the data and discussion above, our study's primary advantage is that it was a quasi-experimental clinical investigation comparing two study groups to evaluate the effectiveness of low-dose aspirin in reducing the incidence of SPTB among "high risk" pregnant women. The main limitations of this study are its single-centre design, open-label nature, and non-randomized allocation, which are characteristic of quasi-experimental designs. Our study findings demonstrate that this intervention is particularly effective in reducing spontaneous preterm birth. Therefore, it should be implemented in all mother-child healthcare facilities to prevent SPTB.

Conclusions

Early administration of low-dose aspirin (75 mg), initiated between 12-15 weeks and continued until 36 weeks of gestation, was associated with a lower incidence of spontaneous preterm birth (SPTB) in high-risk women. Its routine use in such populations is considered to improve maternal and neonatal outcomes and reduce the associated healthcare costs. Thus, our findings suggest that women with known risk factors may benefit from beginning low-dose aspirin early in pregnancy to prevent SPTB and the financial burden that comes with it. This will help prevent complications and reduce the associated financial burdens.

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Contributions:

TS SA MF - Conception, Design

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TS MS MF - Drafting

SS NA SA - Critical Review

All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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