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Role Of Low Dose Aspirin In Preventing Preterm Birth In Patients With Previous History Of Preterm Delivery

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Abstract

Objective: Preterm birth (PTB) occurs between 24-37 weeks of gestation. The important risk factor for PTB is a previous PTB and currently progesterone is used for the management of recurrent spontaneous PTB. Some studies have shown good outcomes but recent studies revealed that the use of vaginal progesterone was not related to a decreased likelihood of PTB or neonatal adverse effects. Thus, the controversy in the literature suggests multiple underlying pathological mechanisms involved in the progression of PTB. This study aims to determine the role of low-dose aspirin in the prevention of preterm birth in patients with a previous history of preterm delivery.

Methodology: In this randomized controlled trial, a total of 172 patients fulfilling the inclusion criteria were selected from the inpatient and outpatient departments. Patients were divided randomly into two groups (group A and group B), using random number tables. In Group A, low-dose aspirin (75mg) was given while group B was taken as a control group. Patients were called every 8 weeks in the outpatient department for the assessment of compliance and side effects of the drug. The data were entered and analyzed by using SPSS v25.0. Chi-square was used to compare the two groups for incidence of preterm birth. Relative risk (along with a 95% confidence interval) for the decrease in the incidence of preterm birth with the use of aspirin was calculated.

Results: The age of participants included in the study was 18 to 40 years. The mean age of patients in group A was 33.85±5.210 years and in group B was 32.86±4.139 years. The mean fetal birth weight in group A was 2281.1962±363.125 grams and in group B was 2271.4344±374.797 grams. In the low-dose aspirin group, 10(11.6%) had preterm birth and 31(36.0%) in the control group with a p-value of 0.001, which is statistically significant. The risk of having preterm birth with low-dose aspirin was 1.801 times less than controls.

Conclusion: aspirin in low dose given before 14 weeks of gestation decrease spontaneous preterm birth as compared to the control group in a woman with a history of previous preterm birth which was spontaneous

Keywords: Preterm Birth, Low Dose Aspirin, Low Birth-weight.

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1. Introduction

Preterm birth (PTB) will be labelled between 24-37 weeks of gestation and in underdeveloped countries incidence of PTB is 25%. In Asia, the preterm birth rate is 9.1 per cent, while in Pakistan it is 15.7 per cent and our nation is fourth in pre-term birth rates.[1] Prematurity is a reason for 70% of all neonatal mortality and 40% of total later-life neurological deficits. Increased health costs due to these problems, result in a substantial economic strain on society. These unfavourable neonatal outcomes decrease from 77% at 24-27 weeks to less than 2% when the fetus is delivered after 34 weeks of gestation.[2] Spontaneous preterm birth begins with spontaneous labour with intact membranes or preterm rupture of the membranes (PROM) before labour and accounts for two-thirds of all preterm births. The major risk factor for PTB is previous history of PTB and currently, progesterone is used for the management of recurrent spontaneous PTB. Various studies have shown good outcomes with progesterone but some recent studies revealed that the use of vaginal progesterone was not related to a decreased likelihood of PTB or neonatal adverse effects.[4] Preterm labour is considered a heterogeneous condition in which labour is prematurely triggered by various pathological processes such as infection, inflammation, uterine overdistention, and endocrine or immunological disorders. Some studies have suggested that uteroplacental ischemia and placental vascular disorders also play a part in the pathogenesis of PTB suggesting a connection with other diseases of the ischemic placenta such as preeclampsia.[5]

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For the prevention of recurrent preeclampsia, the most successful therapy used is aspirin (low dose). Preventive measures for diseases of placental ischemia may also be advantageous in avoiding recurrent PTB given the overlapping underlying mechanisms. A recent meta-analysis showed that women with anti-platelet therapy compared with placebo had a decreased risk of spontaneous PTB at less than 34-37 weeks of gestation. But was not known whether this reduction was due to decreased iatrogenic PTB (e.g., through reducing the incidence of pre-eclampsia) or spontaneous PTB was also reduced due to this intervention.[3]

To analyze this hypothesis that there is a low-dose aspirin is helpful in the prevention of spontaneous PTB, 11,976 women from 6 countries were assigned to a placebo (5,986 women) or aspirin (5,990 women) group randomly in a large randomized controlled trial (RCT). 11.6% of aspirin-treated females have preterm birth and 13.1% of placebo-treated females. It was also less likely for women who took aspirin to deliver before 34 weeks of gestation (3.3% vs. 4.0%) or experience perinatal mortality. Thus, this trial demonstrated that the ratio of preterm birth among women with a singleton pregnancy was substantially lower if low-dose aspirin between 6 to 14 weeks through 36 weeks of gestation was administered.[6]

In another study, the incidence of pre-term delivery in the control group was 38% and in the low-dose aspirin group was 13.6%.[7] In light of the possible common underlying aetiology related to the diseases of placental ischemia and promising spontaneous PTB prevention findings in a recent RCT, we hypothesized that low-dose aspirin used between 6-14 weeks up to 36 weeks of gestation will lessen recurrent spontaneous PTB in our local population as well. If proven that aspirin is associated with the reduction of spontaneous PTB then it may be used as a cost-effective and easy-to-use drug with minimal side effects to prevent the complications of prematurity. By establishing its use in routine practice in preventing preterm labour, recurrent hospital admissions, NICU admissions and perinatal mortality can be reduced and better feto-maternal outcomes can be achieved thus, reducing health costs and economic strain on the society.

2. Materials & Methods

This randomized controlled trial was conducted at the Department of Obstetrics and Gynecology, Holy Family Hospital, Rawalpindi from February 2021 to April 2022. The sample size was calculated using the WHO sample size calculator and a total of 172 pregnant women (86 in each group) were recruited for the study. All pregnant women of the age range between 18-40 years having gestational age of 06 weeks onward with a singleton pregnancy and having a history of spontaneous preterm birth (between 22–37 weeks of gestation) in a previous singleton pregnancy were included in the study. The women with absent fetal cardiac activity, presence of multiple gestations or fetal anomaly on ultrasound, history of cervical incompetence, having allergy to aspirin, with severe GI diseases like ulcers were excluded from the study. After the approval from the Hospital Ethical Committee, written informed consent from Seach patients fulfilling the inclusion criteria was taken. A detailed history was taken including demographic data like age, height, weight and previous history of preterm delivery. Patients were divided randomly into two groups (group A and group B) by using random number tables. In Group A, low-dose aspirin (75mg) was given from 06 weeks of gestation while Group B was taken as a control group. Patients were called every 8 weeks in the Outpatient Department for the assessment of compliance and side effects of the drug. All the data were collected through a pre-designed proforma. The data was entered and analyzed by using SPSS v25.0. Quantitative variables like age, gestational age, weight and fetal birth weight were expressed as mean and standard deviation and qualitative variable like preterm delivery was expressed as frequency and percentages. The chi-square test was used to compare the two groups for incidence of preterm birth. Relative risk (along with a 95% confidence interval) for the decrease in the incidence of preterm birth with the use of aspirin was calculated. A p-value of <0.05 was considered statistically significant.

3. Results

172 pregnant patients with a history of spontaneous PTB were included in the study and were divided into two groups i.e. Group A (Low-dose aspirin) and Group B (Controls).

The age of participants in the study was from 18 to 40 years with an average age of 33.5±10.5 years. The average age of patients in group A was 33.85±5.210 years and in group B 32.86±4.139 years. In group A, 26(30.2%) patients were in the 18-30 years age group, while 60(69.8%) were in the 31-40 years age group, while in group B, 23(26.7%) women were in 18-30 years age group, while 63(73.3%) were in 31-45 years age group **(Table-1)**.

Table 1 Comparison of age group distribution between groups

Age Groups			Total (n=172)	P value
	Group-A (Low-dose aspirin) n=86	Group-B (Controls) n=86		
18-30 years	26	23	49	P=0.001
	30.2%	26.7%	28.5%	
31-40 years	60	63	123	
	69.8%	73.3%	71.5%	
Mean	33.9	33	32	
Standard Deviation	±5.21	±4.14	±4.70	

In group A, 25(29.1%) patients had a gestational age between 6-10 weeks and 61(70.9%) had between 11-14 weeks, while in group B, 23(26.7%) patients fell in gestational age between 6-10 weeks and 63(73.3%) had between 11-14 weeks (Table-2).

The average birth weight of babies in group A was 2281.1962±363.125 grams and in group B was 2271.4344±374.797 grams. In group-A, 58(67.4%) women had birth weight of babies ≤2500 grams and 28(32.6%) had >2500 grams, while in group-B, 57(66.3%) patients had babies birth weight ≤2500 grams and 29(33.7%) had >2500 grams (Table-3).

10(11.6%) of patients in group A (low dose aspirin group) had preterm birth while 31(36.0%) women in group B (control group) had preterm delivery with a p-value of 0.001, which is significant statically. The risk of having preterm birth in group A was 1.801 times less than in group B (Table 4).

Table 2 Comparison of gestational age distribution between groups

Gestational age	Groups		Total (n=172)	P value
	Group-A (Low-dose aspirin) n=86	Group-B (Controls) n=86		
6-10 weeks	25	23	48	P=0.001
	29.1%	26.7%	27.9%	
11-14 weeks	61	63	124	
	70.9%	73.3%	72.1%	
Mean	10.5 weeks	9.9 weeks	10 weeks	
Standard Deviation	±1.80	±1.23	±1.70	

Table 3: Comparison of Fetal Birth Weight Distribution between Groups

Fetal birth weight	Groups		Total (n=172)	P-value
	Group-A (Low-dose aspirin) n=86	Group-B (Controls) n=86		
≤2500 gram	58	57	115	P=0.001
	67.4%	66.3%	66.9%	
>2500 gram	28	29	57	
	32.6%	33.7%	33.1%	
Mean	2281.20 grams	2271.48 grams	2275.0 grams	
Standard Deviation	±363.13	±374.78	±366.89	

5. Discussion

Preterm birth is defined as delivery or birth before 37 completed weeks of gestation. Preterm delivery is one of the main reasons which leads to neonatal mortality and morbidity. The lives of approximately 01 million children are affected by it every year, causing a significant burden on the health care and economic structure of a country. [8,9,10]

The woman has an increased risk of preterm birth following pregnancy if has previous delivery which ended in preterm. [11,12]

The role of low-dose aspirin has been established in reducing the risk of pre-eclampsia. Some studies have also proved that aspirin given in low dose assist in protection against preterm labour in women at increased risk of developing pre-eclampsia [13], but still, there is conflicting data regarding its use as a prophylaxis for preterm delivery in women with increased risk of preterm birth.

Meta-analysis of data reveals that the use of low-dose aspirin from early pregnancy is effective in reducing the incidence of pre-eclampsia and its associated complications like preterm delivery. [14]

The present study showed that 11.6% of patients were given low-dose aspirin in early pregnancy at preterm birth as compared to 36% of women in the control group. These results were statistically significant. A randomized, double-blind, placebo-controlled trial (ASPIRIN) published in 2020 also concluded that low-dose aspirin started between 06 weeks and 0 days and 13 weeks and 06 days of gestation in nulliparous women with singleton pregnancy showed a reduction in the incidence of preterm delivery 37 weeks, early preterm birth at less than 34 weeks and perinatal mortality [6]. These findings are similar to our study.

Another secondary analysis of a randomized placebo-controlled trial published in June 2018 also suggested that the use of aspirin in low doses in nulliparous women is linked with a decrease in the incidence of preterm delivery at less than 34 weeks of gestation. [5]

Many other researchers also studied the chance of spontaneous preterm birth in women taking aspirin, but their studies were either restricted to a high-risk population or did not demonstrate any significant advantage [15,16]. Van Vliet et al showed a decrease in spontaneous preterm birth (PTB) with aspirin but its finding was restricted to women at risk for pre-eclampsia [3]. Silver et al found a major but non-significant decrease in spontaneous PTB in women with a previous history of preterm delivery or pregnancy loss [7]. Allshouse et al reported fewer PTB and PPROM in women who received low-dose aspirin compared with placebo, but these findings were not statistically significant [15]. Similarly, a multi-center, trial of aspirin given in 150mg vs. placebo in pregnancies at high risk for pre-eclampsia, found no change in spontaneous PTB at less than 34 weeks or less than 37 weeks gestation [16]. These results are in contradiction to the findings of our study.

The use of low-dose aspirin in the prevention of recurrent spontaneous preterm birth was also studied in another randomized control published in 2022 (APRIL) study [2]. This trial included 406 participants and showed up small reduction in the incidence of PTB among women with a previous history of spontaneous PTB using low-dose aspirin but this result was not statistically significant. The findings of this study are inconsistent with our study.

Table 4 Comparison of preterm birth between groups

Preterm birth	Groups		Total (n=172)	p-value
	Group-A (Low-dose aspirin) n=86	Group-B (Controls) n=86		
Yes	10	31	41	0.001
	11.6%	36.0%	23.8%	
No	76	55	131	
	88.4%	64.0%	76.2%	

The data for the study suggests that low-dose aspirin may be used as an effective prophylaxis for recurrent preterm birth. However, different studies also show that low-dose aspirin use is associated with an increased risk of antepartum and postpartum haemorrhage [17]. Due to these contradictory findings, a larger study is needed to prove the role of low-dose aspirin in the prevention of recurrent preterm birth [9]. Further, research is also required to explore the best optimal dosage of low-dose aspirin for the prevention of recurrent spontaneous PTB [18].

5. Conclusion

Low-dose aspirin given before 14 weeks of gestation reduces spontaneous preterm birth as compared to the control group in women with a history of previous spontaneous preterm birth. Further research is much

needed to determine the short as well as long-term outcomes and to evaluate treatment effect and safety.

CONFLICTS OF INTEREST- None

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Contributions:

M.S, A.S, S.A - Conception of study AAAAAAAAAAAAAA
A.S. A.I - Experimentation/Study Conduction
M.S, A.S, T.F, K.I, A.I - Analysis/Interpretation/Discussion
M.S, T.F, K.I, S.A - Manuscript Writing
M.S, T.F, K.I. S.A- Critical Review
A.S, T.F, K.I, - Facilitation and Material analysis

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