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ROLE OF LOW DOSE ASPIRIN THERAPY IN RECURRENT PREGNANCY LOSS

Dr. Veena Gupta	MS, FICMCH, PGDMLS, Professor, Department of Obstetrics and Gynaecology, M. L. N. Medical College, Prayagraj
Dr. Tanvi Singh	Junior resident, Department of Obstetrics and Gynaecology, M. L. N. Medical College, Prayagraj
Dr. Shakti Jain	MS, Assistant professor, Department of Obstetrics and Gynaecology, M. L. N. Medical College, Prayagraj
Dr. Somya Saxena	MS, Assistant professor, Department of Obstetrics and Gynaecology, M. L. N. Medical College, Prayagraj

ABSTRACT **Background:** Recurrent pregnancy losses are a big concern for women's health. Aspirin at a low dose is an antiplatelet drug that irreversibly inhibits platelet cyclooxygenase and lowers thromboxane A2 synthesis. Understanding the role of low-dose aspirin in preventing recurrent pregnancy loss and prescription at early gestation, is necessary. **Objectives:** This study was aimed to evaluate the role of low dose aspirin in prevention of recurrent pregnancy loss and to evaluate maternal and fetal outcomes in patients with low dose aspirin therapy for management of recurrent pregnancy loss. **Material and Methods:** This observational prospective study was carried out in the Department of Obstetrics and Gynaecology, Swaroop Rani Nehru Hospital, Moti Lal Nehru Medical College & Kamla Nehru Memorial Hospital, Prayagraj from 2021 to 2022 after obtaining ethical clearance and informed consent from patients presenting to antenatal OPD with history of two or more recurrent pregnancy loss. A total of 100 patients were enrolled as per inclusion and exclusion criteria. **Results:** Out of 100 women, in A1 group which took aspirin out of 50 patients, 44 (88%) were live births and on the other hand in patients which didn't take aspirin B1 group only 24(48%) live births took place.The incremental benefit in outcome of pregnancy can be attained through the use of aspirin as the women who took low dose aspirin live births rate was almost double as compared to the women who didn't take aspirin and this was true regardless of the number of miscarriages they had experienced in the past. **Conclusion:** The findings of this study assisted us in determining the current standard of care, which continues to suggest that aspirin should be prescribed and taken by women who have history of recurrent pregnancy loss.

KEYWORDS : Low dose aspirin, Recurrent pregnancy loss

INTRODUCTION

Pregnancy is a state of hypercoagulability. A pregnancy of high risk endangers the health or life of the mother or fetus. It frequently requires specialist care from physicians with specialised training. Some pregnancies become high-risk as they continue, while for a number of reasons, some women are at increased risk for difficulties even before they get pregnant. There is evidence that some cases of repeated miscarriages and subsequent pregnancy difficulties are attributable to an excessive haemostatic response during pregnancy, which results in placental thrombosis and infarction.

Recurrent pregnancy loss (RPL) is defined as the spontaneous loss of 2 or more pregnancies before period of viability. According to **Berek's and Novak**, Recurrent pregnancy loss is the occurrence of three or more clinically documented (ultrasound or histological evidence) pregnancy losses prior to 20 weeks after the last menstrual period [1-3]. Recurrent pregnancy losses are a big concern for women's health. It affects around 1 in 300 pregnancies [4] and less than 1 percent of women. Also, it is an important reproductive health issue, because it affects 2%–5% of couples [5,6]. The probability of repeat pregnancy loss is estimated to be 24% after two clinically recognised pregnancy losses, 30% after three losses, and 40% to 50% after four losses in patients with a history of recurrent pregnancy loss [7,8].

Recurrent pregnancy loss (RPL) may be caused by genetic, endocrine, antiphospholipid antibody syndrome, immunologic, and environmental causes [9]. Mutations in FOXD1 has crucial role in RPL [10,11]. By regulating endometrial and placental genes, FOXD1 has been identified as key molecule in embryo implantation.

Anti-phospholipid syndrome (APS) is currently recognised as the leading cause of recurrent pregnancy loss. Approximately fifty percent of women with recurrent miscarriage have thrombophilia, which includes Anti-phospholipid syndrome. Anti-phospholipid antibody is present in 15 to 20 percent of women with recurrent pregnancy loss [12,13] . Without pharmacological intervention, the spontaneous abortion rate for women with anti-phospholipid syndrome is as high as 90% [14].

Anti-phospholipid antibodies (APLA), an acquired thrombophilia deficiency, and other autoimmune disorders are frequently treated with aspirin in pregnant women with recurrent miscarriages. According to a study by **Roy G. Farquharson et al.**, [15] antiphospholipid syndrome in pregnancy can be effectively treated with low-dose aspirin.

Low dose aspirin (acetylsalicylic acid) is a non-steroidal anti-inflammatory drug (NSAIDS) that functions primarily by inhibiting two cyclooxygenase isoenzymes (COX-1 & COX-2) required for prostaglandin biosynthesis [16]. The vascular endothelium contains the COX-1 isoform, which controls the generation of prostacyclin and thromboxane A2, two prostaglandins with conflicting effects on vascular homeostasis and platelet function [17]. Prostacyclin is a strong vasodilator and platelet aggregation inhibitor. The COX-2 isoform is inducible and nearly exclusively expressed in response to exposure to cytokines or other inflammatory mediators.

Aspirin at a low dose is an antiplatelet drug that irreversibly inhibits platelet cyclooxygenase and lowers thromboxane A2 synthesis [18]. Daily low-dose aspirin use during pregnancy is regarded as safe and is associated with a minimal risk of significant maternal, foetal, or both problems. Understanding the role of low-dose aspirin in preventing recurrent pregnancy losses and APLA-associated pregnancy, is necessary.

AIMS AND OBJECTIVES

This study was aimed to evaluate the role of low dose aspirin in prevention of recurrent pregnancy losses, APLA associated pregnancy and to evaluate maternal and fetal outcomes in patients with low dose aspirin therapy for management of recurrent pregnancy loss.

MATERIAL AND METHODS

This observational prospective study was carried out in Department of Obstetrics and Gynaecology, Swaroop Rani Nehru Hospital, Moti Lal Nehru Medical College & Kamla Nehru Memorial Hospital, Prayagraj from 2021 to 2022 after obtaining ethical clearance and informed consent from patients presenting to antenatal OPD with history of two or more recurrent pregnancy loss. A total of 100 patients were enrolled as per inclusion and exclusion criteria.

Inclusion Criteria

- Pregnant women who are willing to participate in the study.
- Pregnant women with two or more recurrent pregnancy losses.

- Pregnant women who are elderly primigravida.

Exclusion Criteria

- Patients who are not willing to participate in the study.
- Patients with a history of aspirin allergy (e.g., urticaria) or hypersensitivity to other salicylates are at risk for anaphylaxis.
- Patients with nasal polyps may result in life-threatening bronchoconstriction and should not be given
- Patients with gastronomic bleeding, active peptic ulcer disease and severe hepatic dysfunction.The total of 100 patients were divided two groups A1 and B1 (50 in each group) in which group A1 was given low dose aspirin (150 mg) and group B1 was not given low dose aspirin i.e., Group-A1 (n=50; History of abortion + aspirin), Group-B1 (n=50: History of abortion + no aspirin). A detailed clinical history regarding age, occupation, socioeconomic status, and risk factors for recurrent pregnancy losses was taken.

Aspirin was started in patients with a history of 2 or more spontaneous abortions as soon as she visited for the first antenatal visit for recurrent pregnancy loss. Patients were assessed on the basis of the effect of low-dose aspirin (150 mg) therapy with the viability of the fetus in patients with a history of recurrent abortions in previous pregnancies.

RESULTS:

This was a observational prospective study that was performed in the Department of Obstetrics and Gynaecology, Swaroop Rani Nehru Hospital, Moti Lal Nehru Medical College & Kamla Nehru Memorial hospital, Prayagraj in which a total of 100 patients were enrolled as per inclusion and exclusion criteria. All the patients were divided into two groups, i.e., Group-A1 (n=50; History of abortion + aspirin), Group-B1 (n=50: History of abortion + no aspirin)

Table 1: Distribution of study groups based on age, gravida, parity

	HISTORY OF ABORTION [N=100]		P-value
	GROUP-A^1[n=50]	GROUP-B^1[n=50]	
Age in years			
20-24	12 (24.00%)	13 (26.00%)	X=0.1632
25-29	15 (30.00%)	16 (32.00%)	p=0.9217
30-35	23 (46.00%)	21 (42.00%)	
MEAN±SD	25.64±4.40	26.12±4.43	t=0.5436
Gravida			p=0.5880
G2	NA	NA	
G3 and above	50	50	
Parity			
NULLIPAROUS	29	27	X=0.8905
P1	13	17	p=0.6407
P2	8	6	

All the patients in group A1 are G3 and above. G2 was nil in Group A_1 and Group B_1. G3 and above was comparable in Group A_1 and Group B_1. Statistically, a non-significant difference was observed in gravida among the groups [p=0.1925]. Nulliparous and P2 was observed higher in Group A_1 (29) and (8) as compared to Group B_1 (27) and (6) respectively while the P1 was higher in Group B_1 (17). Statistically, a non-significant difference was observed in parity among the groups [p=0.5465]. **[TABLE-1]**

Table 2- Distribution of study groups based on number of spontaneous abortions

Number Of Spontaneous Abortions	History Of Abortion				P-Value
	Group-A^1 [N=50]		Group-B^1 [N=50]		
	No.	%	No.	%	
2	29	58.00%	26	52.00%	X=0.3636
3 And Above	21	42.00%	24	48.00%	P=0.5465

Patients taken with 2 spontaneous abortions was found to be higher in Group A_1 [29(58.00%)] as compared to Group B_1 [26(52.00%)]. 3 and greater than 3 spontaneous abortions were found to be higher in Group B_1 [24(48.00%)] as compared to Group A_1 [21(42.00%)]. Statistically, a non-significant difference was observed in patients taken in view of no. of spontaneous abortion among the groups [p=0.5465]. **[TABLE-2]**

Table 3- Distribution of study groups based on residence and Body Mass Index

Residence	History Of Abortion				P-Value
	Group-A^1[N=50]		Group-B^1[N=50]		
	No.	%	No.	%	
Rural	28	56.00%	24	48.00%	X=0.6410
Urban	22	44.00%	26	52.00%	P=0.4233
Body Mass Index					
Underweight (<18.5)	2	4.00%	4	8.00%	X=0.7696
Normal (18.5-24.9)	42	84.00%	41	82.00%	P=0.6806
Overweight (25.0-29.9)	6	12.00%	5	10.00%	

History of abortion in rural area was observed to be higher in Group A_1 [28(56.00%)] as compared to Group B_1 [24(48.00%)] while the history of abortion in urban area was observed to be higher in Group B_1 [26(52.00%)]. Normal BMI was observed higher in Group A_1 [42(84.00%)] as compared to Group B_1 [41(82.00%)]. Overweight (25.0-29.9) women with history of abortion was observed higher in Group A_1[6(12.00%)]

Table 4- Distribution of study groups based on Gestational age (trimester)

Gestational Age At Which Aspirin Was Started

Gestational Age	Group-A^1 [N=50]	
	No.	%
1st trimester Upto 13 Weeks	33	66.00%
2nd Trimester 14 – 24 Weeks	17	34.00%

Number of women in which aspirin was given in 1ST Trimester upto 13 weeks were higher[33(66.00%)] as compared to number of women in which aspirin was given in 2nd Trimester 14-24 weeks [17(34.00%)]. Statistically, a non-significant difference was observed in Gestational age among the groups. **[TABLE-4]**

Table 5- Distribution of study groups based on Oral glucose tolerance test and S.TSH on first visit

Oral Glucose Tolerance Test [2hr 75 Gm Glucose]	History Of Abortion			
	Group-A^1 [N=50]		Group-B^1 [N=50]	
	Mean	Sd	Mean	Sd
	104.40	15.33	105.14	16.21

S.Tsh [Miu/L]	History Of Abortion				P-Value
	Group-A^1 [N=50]		Group-B^1 [N=50]		
	< 3 Miu/L	45	< 3 Miu/L	43	
	>3 Miu/L	5	>3 Miu/L	7	

The mean of oral glucose tolerance test was higher in Group B_1 [105.14±16.21] as compared to A_1 [104.40±15.33]. In 45 women of group A_1 and 43 women of group B_1 have serum TSH < 3 mIU/L while 5 women of group A_1 and 7 women of group B_1 have serum TSH > 3 mIU/L.

Table 6– Distribution of study groups based on outcome of pregnancy in patients with history of recurrent spontaneous abortions

Outcome Of Pregnancy	History Of Abortion				P-Value
	Group-A^1 [N=50]		Group-B^1 [N=50]		
	No.	%	No.	%	
Abortion	3	6.00%	15	30.00%	X=18.46
Intrauterine Fetal Demise	2	4.00%	7	14.00%	P=0.0004*
Still Birth	1	2.00%	4	8.00%	
Live Birth	44	88.00%	24	48.00%	

Group B_1 had higher abortion [15(30.00%)] than group A_1 [3(6.00%)]. Intrauterine fetal demise was higher in group B_1 [7(14.00%)] as compared to group A_1 [2(4.00%)]. Still Birth were higher in group B_1 [4(8.00%)] as compared to group A_1 [1(2.00%)] while live birth were higher in group A_1 [44(88.00%)] as compared to group B_1 [24(48.00%)]. Statistically, a significant difference was observed in outcome among the groups [**p=0.0004***]. **[TABLE-6]**

DISCUSSION

The study was aimed to investigate the role of low-dose aspirin in the prevention of recurrent pregnancy losses and to investigate the maternal-fetal outcome in patients who were treated with low-dose aspirin therapy for the management of recurrent pregnancy loss.

A total of 100 patient were enrolled as per inclusion and exclusion criteria, out of which mean age of most of the cases was 25-30 years in groups A1 and B1 as the mean child bearing age in India lies between 20-35 years. All the patients were Gravida 3 and above with history of

2 or more spontaneous abortions.

Majority of patients were with 2 spontaneous abortions as compared to 3 or more spontaneous abortions as women usually seek medical opinion after 2 abortions than 3 and above. Most of the studied cases who attended the hospital were from rural areas in recurrent abortion group i.e 28 (56%). This reflected the increased awareness among women in rural areas also.

In present study, it is observed that cases with recurrent abortions belonged to underweight, normal and overweight groups with majority of patients with normal BMI i.e 42(84%) on contrary to the study done by **Utami T.W. et al,** [19] in which they concluded that a high BMI in pregnant women is strongly associated with an increased risk of recurrent pregnancy loss. aspirin was started before 24 weeks of gestation i.e in 1st and 2nd trimester in both the groups. Majority of patients that were taken have been prescribed aspirin in 1st trimester i.e upto 13 weeks of gestation [33(66%)] %)].

In this study, OGTT was done in patients with recurrent abortions on the first antenatal visit of the patient and the mean blood glucose was observed to be 104.4 mg% (SD 15.33) which was in normal range because diabetic patients were already excluded from the study as there is severe risk of recurrent abortions in uncontrolled diabetics.

In this study, serum TSH values were done in patients with recurrent abortions on first antenatal visit and patients were excluded that had serum TSH values more than 5 mIU/L as there are increased risk of recurrent pregnancy losses in hypothyroid patients similar to the study done by **D. Sarkar et al**, [20] in which it had been concluded that even minimal hypothyroidism can increase rates of miscarriages.

Therefore, most patients that were taken belong to serum TSH value <3 mIU/L i.e 45(90%) in group A1 and 43(86%) in group B1.

In present study, in A1 group which took aspirin out of 50 patients, 44 (88%) were live births, 3(6%) had abortion, 2 (4%) were intrauterine fetal demise and 1(2%) was still birth on the other hand in patients which didn't take aspirin B1 group only 24(48%) live births took place,15(30%) patients aborted, 7(14%) were intrauterine fetal demise and 4(%) were still birth.

There had been a very significant difference in number of live births which were higher in group with aspirin similar to the study conducted by **Roy G Farquharson et al.**[15]

There was no such preference with the mode of delivery rather it was a spontaneous decision according to previous mode of delivery, maternal pelvimetry, maternal and fetal well being during labor.

My study was much similar to the study of **Raj Rai et al** [21] as both studies were prospective, divided and compared the cases on basis of aspirin taken or not in early pregnancy. The results were similar but according to the study by **Raj Rai et al**, [21] low dose aspirin significantly improved the livebirth rate amongst women with a previous late miscarriage. It is, however, of no benefit to those women with unexplained recurrent early miscarriages.

But in my study, low dose aspirin significantly improved the outcome of pregnancy irrespective of previous early or late miscarriages. This could be explained as women with a history of recurrent early miscarriage in weeks 4–7 of gestation has an excess of TXA2 production and between weeks 8–11 they are relatively PGI2 deficient, compared with women with no previous history of pregnancy loss **(Tulpalla *et al*., 1991)** [22] **.** In this small study of women with previous miscarriages it was reported that aspirin corrected these biochemical abnormalities and improved the pregnancy outcome.

CONCLUSION

Based on the findings of this study, we may conclude that the incremental benefit in outcome of pregnancy can be attained through the use of aspirin as the women who took low dose aspirin live births rate was almost double as compared to the women who didn't take aspirin and this was true regardless of the number of miscarriages they had experienced in the past.

In addition, the findings of this study assisted us in determining the current standard of care, which continues to suggest that aspirin should be prescribed and taken by women who have history of recurrent pregnancy loss.

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