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Low Dose Aspirin In Prevention Of Spontaneous Preterm Birth In Nulliparous Women

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ABSTRACT: This research paper is about the reduction of spontaneous preterm births in nulliparous women.Strategy to prevent preterm birth is by prediction and prevention of its risk factors.Progestogen compounds were commonly used in its prevention but still one third of them had spontaneous preterm birth.One of the underlying mechanism involved in preterm birth is ischemic placental diseaseas.Low dose aspirin via cyclooxygnase enzyme inhibition reduces inflammation and uterine contractility and reduces preterm birth.In this study low dose aspirin was given in nulliparous women and number of them delivered preterm and term were observed.

I. INTRODUCTION

1)Across the world, preterm birth is a significant public health problem because of its associated neonatal (first 28 days of life) mortality and short and long-term morbidity and disability in later life. According to WHO, around 15 million babies are born preterm annually, and this number is increasing. World wide, the rate of preterm birth ranges from 5% to 18%. Africa and South Asia account for more than 60% of preterm births. In developing countries, on average, 12% of babies are born too early compared with 9% in developed countries. Within countries, poorer families are at higher risk[1]. Among the top ten countries, India is one among them with the most significant number of preterm births[1].

It accounts for 70% of all neonatal mortality and 40% of childhood neurological Morbidity[2].

2)Children born preterm often suffer from short-term morbidities such as respiratory difficulties (infant respiratory distress syndrome), periventricular leukomalacia, intracranial hemorrhage, bronchopulmonary dysplasia, patent ductus arteriosus, necrotizing enterocolitis, retinopathy of prematurity, and infection and long term morbidity from neurological and developmental disabilities. The morbidity associated with pretermobirth extends to later life, resulting in physical, psychological, and economic burden to the individual and the family[1].

3)DEFINITION: In 1976, the World Health Organization (WHO) and the International Federation of Gynaecology and Obstetrics(FOGSI)defined preterm birth as babies born alive before 37 completed weeks of gestation or fewer than 259 days of gestation since the first day of a woman's last menstrual period (LMP)[1,3].
Preterm birth is a multifactorial syndrome with a wide variety of causes that can be classified into two broad subtypes[1]:
(1) Spontaneous preterm birth: may occur after spontaneous onset of labor or following pre-labor premature rupture of membranes (PPROM). The cause of spontaneous preterm labor in up to half of all cases is unknown
(2) Provider-initiated preterm birth is defined as the induction of labor or elective cesarean birth before 37 completed weeks of gestation for maternal or fetal indications (both "urgent" and "discretionary"), or other non-medical reasons.
Most preterm births occur spontaneously, but some are due to early induction of labor or cesarean birth, whether for medical or non-medical reasons[1].

Of all preterm births, 30 to 35 percent are indicated, 40 to 45 percent are due to spontaneous preterm labor, and 30 to 35 percent follow preterm rupture of membranes[3].
4)Risk factors for preterm birth [1]-
A precise mechanism cannot be established in most cases; Multiple risk factors are
associated with an increase in preterm births.

Risk factors include:
1)Age at pregnancy: adolescent pregnancy and advanced maternal age
2)Previous preterm birth
3)Multiple pregnancies (such as twins, triplets)
4)Infections and chronic conditions such as diabetes and high blood pressure

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5)Genetic influences
6)Nutritional: undernutrition, obesity, micronutrient deficiencies
7)Life style-Women who smoke cigarettes, consume alcohol, and use drugs are at a higher risk of having preterm babies. Stress from any cause, excessive physical work, or long hours spent standing are also known to increase a woman's risk of preterm birth.
However, often no cause is identified[1].

II. STRATEGIES TO PREVENT PRETERM BIRTH

The most effective treatment of preterm birth is the prediction and prevention of its risks.The commonly used strategy for prevention of recurrent spontaneous pretermbirth is the administration of progesterone, either natural progesterone or 17 Alpha-hydroxyprogesterone [10,11].Despite the use of progesterone, at least one-third of the women will have a spontaneous preterm birth, suggesting that multiple underlying mechanisms contribute to its pathogenesis[10,12].

Because of the similar underlying mechanism in ischemic placental diseases and preterm births, preventive measures for the ischemic placental disease might help prevent spontaneous preterm birth. In the prevention of recurrent pre-eclampsia, the most successful intervention is low dose acetylsalicylic acid (aspirin or ASA). Low-dose aspirin is a potential prophylactic agent against preterm birth since it is inexpensive, widely available, and can be given safely during pregnancy [10].

'U.S. Preventive Services Task Force conducted a review and concluded that the use of aspirin is safe in pregnancy. The clinical data prove aspirin's effect in the prevention of spontaneous preterm birth, suggesting that the use of low-dose aspirin may decrease the rate of preterm birth[10,22].

By reducing the risk of pre-eclampsia, small for gestational age, and placental insufficiency low dose aspirin has the potential to reduce medically indicated preterm birth and spontaneous preterm birth by decreasing uterine contractility and inflammation via cyclooxygenase inhibition[11].

Approximately 2 to 8 percent of pregnancies are affected by pre-eclampsia, which is the second leading cause of maternal mortality worldwide[6,7]. In addition to risks to the mother, pre-eclampsia also dramatically increases risks to the fetus and a leading cause of iatrogenic preterm birth.

ASPIRIN : Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID), acts as a platelet aggregation inhibitor, and reduces prostaglandin synthesis by inhibiting cyclooxygenase enzyme, thereby having an anti-inflammatory effect[10].

MECHANISM OF ACTION:
Its mechanism of action primarily involves the inhibition of two cyclooxygenase isoenzymes (COX-1 and COX-2) necessary for prostaglandin synthesis. The COX-1 isoenzyme is present in the vascular endothelium and regulates the production of prostacyclin and thromboxane A2.

Prostacyclin is a potent vasodilator and inhibits platelet aggregation, whereas thromboxane A2(TXA2) is a potent vasoconstrictor and promotes platelet aggregation.
The COX-2 isoenzyme is inducible, and it is expressed following exposure to cytokines or other inflammatory mediators. Aspirin's effect on COX-isoenzymes
is dose-dependent. At lower dosages (60–150 mg/day), it irreversibly acetylates COX-1, resulting in decreased platelet synthesis of TXA2 without affecting prostacyclin production. At higher doses, aspirin inhibits both isoforms of COX-1 and COX-2, thereby inhibiting all prostaglandin production[23,24].

Evidence suggests that at lower doses, aspirin inhibits TXA2, this prompted the studies on low dose aspirin on prevention of pre-eclampsia.

Among the top ten countries, India is among them with the most significant number of preterm births[1]. As it accounts for 40% of neonatal mortality, it is imperative to study the use of low-dose aspirin in the prevention of spontaneous preterm birth and its impact in our hospital.
OBJECTIVES OF THE STUDY: To assess the role of low dose(75mg) aspirin in reducing spontaneous preterm birth rate in nulliparous women in PES institute of medical sciences and research,kuppam,so that the incidence of preterm births can be reduced.

III. METHODS:

SOURCE OF DATA: Pregnant women attending PESIMSR
STUDY PERIOD: 18 months (January 2019-June 2020)
INCLUSION CRITERIA:
All nulliparous pregnant women with any of the moderate risk factors for preeclampsia as per ACOG CRITERIA:
a)Obesity(BMI:>30kg/m2)
b)Sociodemographic characteristics(low socioeconomic status)

c)Age 35yrs or older
d)personal history factors(eg,low birthweight or small for gestational age,previous pregnancy outcome)
e)Pregnant women with singleton non anamolous gestation

EXCLUSION CRITERIA:
• Current pregnancies that resulted in a loss or termination less than 20 weeks.
• Those with co-morbidities like hypertension, renal diseases, diabetes, seizures, heart diseases, collagen vascular diseases, other endocrine diseases.
• Those with ante-partum stillbirth.

Sample size:
The number of pregnant women included in the study was 136.

DATA COLLECTION: Each patient fulfilling the inclusion criteria was included in the study. The following data was collected: A structured interviewer-administered questionnaire was filled for all the participants.
After obtaining written informed consent, data was recorded by using a separate proforma for every study subject. Details regarding age, weight, height, socioeconomic status, parity, occupation, gestational age when aspirin was given, intake of aspirin, they were followed up till the woman delivered and the details was collected regarding pregnancy outcome regarding mode of delivery, delivered at term or preterm was collected.
All results was recorded,tabulated and analyzed using appropriate stastical methods.

StatisticalAnalysis :
Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test of Fischer's exact test was used as test of significance for qualitative data.Continuous data was represented as mean and standard deviation. Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively.

Statistical Software:
MS Excel, SPSS version 21 was used to analyze data. EPI Info was used to estimate sample size, odds ratio and reference management in the study. Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots. p-value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.
Pearson correlation or Spearman's correlation was done to find the correlation between two quantitative variables and qualitative variables respectively

IV. RESULTS:

Table 1 : Demographic data of study population:

AGE(in years)	Frequency	Percent	Cumulative
<25years	110	80.88	80.88
26-30years	21	15.44	96.32
>31years	5	3.68	100.00

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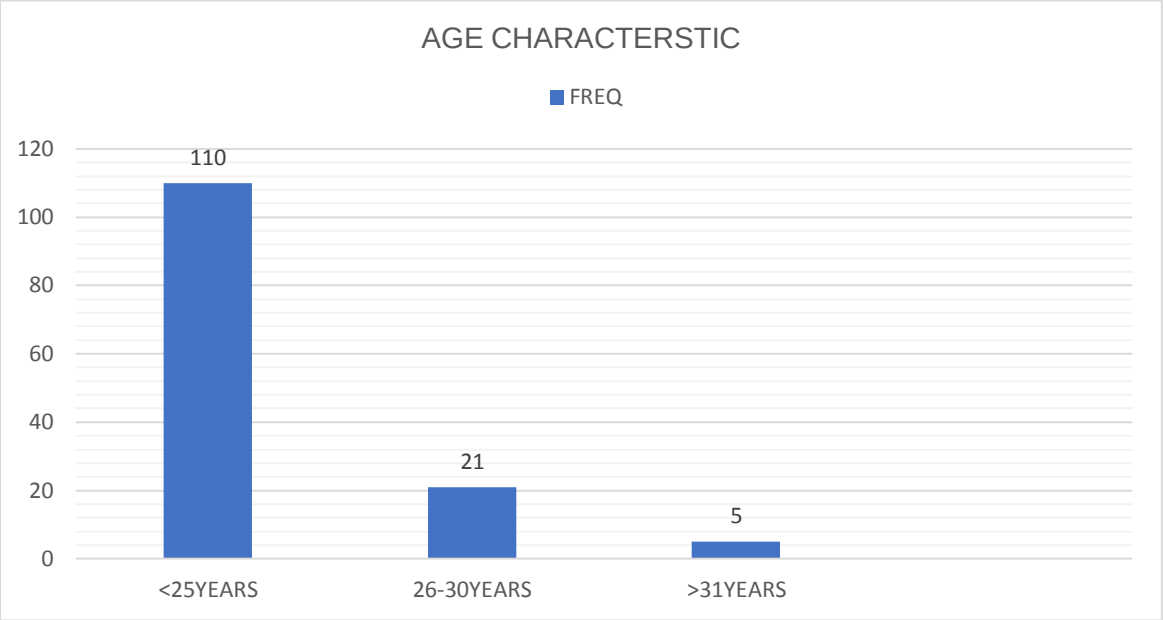
FIGURE1:BAR CHART OF AGE GROUP DISTRIBUTION(N=136)



The above bar chart showing age distribution in study,110 women were <25years ,21 women were between 26-30years,and 5 women were >31 years.

TABLE 2 : SOCIO ECONOMIC STATUS OF STUDY GROUP:

SOCIOECONOMICSTATUS	FREQ	PERCENT	CUM
LOWER	13	9.56	9.56
MIDDLE	104	76.47	86.03
UPPER MIDDLE	19	13.97	100.00
TOTAL	136	100.00	100.00

Table 2 shows socioeconomic status of study population,13 participants belong to lower socioeconomic status,104 belong to middle class and 19 women belong to upper class according to modified kuppuswamy classification.

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FIGURE2:PIE DIAGRAM SHOWING SOCIOECONOMIC STATUS OF STUDY POPULATION:

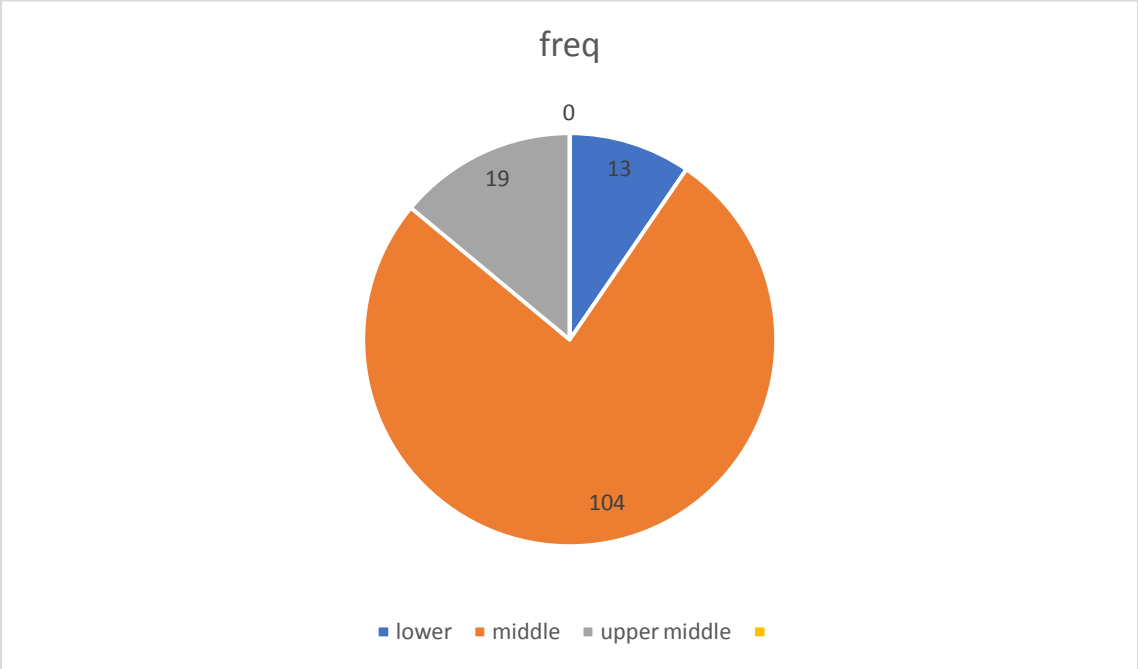

TABLE 3: GESTATIONAL AGE AT WHICH ASPIRIN WAS STARTED

GESTATIONAL AGE	FREQUENCY	PERCENT
<16WEEKS	130	95.59
>16WEEKS	6	4.41
TOTAL	**136**	**100**.00

FIGURE 3:BAR CHART SHOWING GESTATIONAL AGE AT WHICH ASPIRIN WAS STARTED

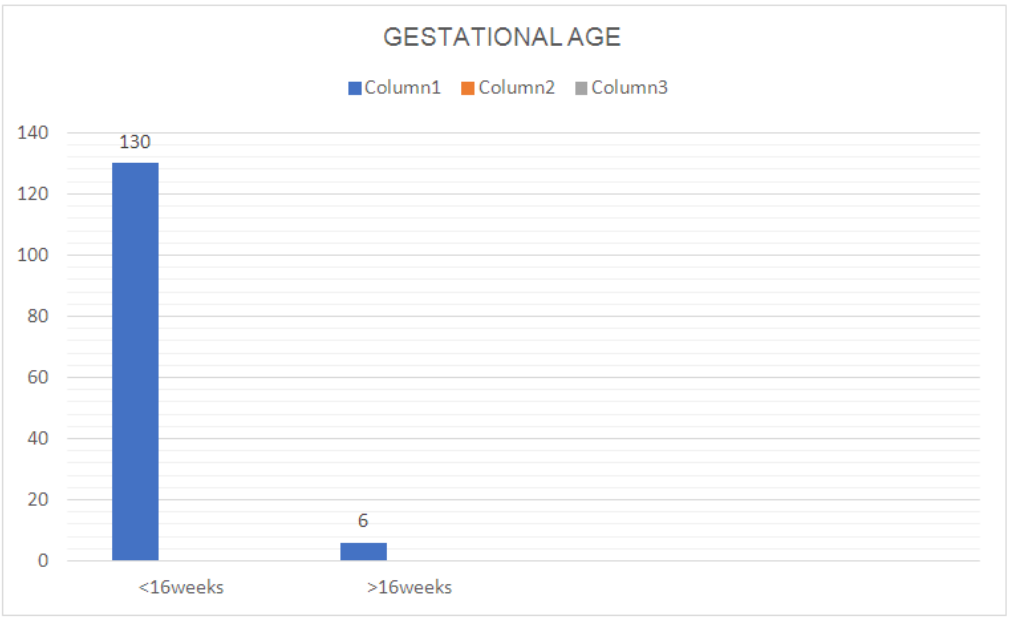

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Table 3 and figure 3 shows gestational age at which aspirin was started.130 women were started at <16weeks and 6 were given >16weeks of gestational age.

Table 4: PREVIOUS PREGNANCY DETAILS

PREVIOUS PREGNANCY DETAILS	Freq	Percent	Cum
Obstetric primi	85	62.50	62.50
PRIMIGRAVIDA	51	37.50	100.00
Total	**136**	100.00	**100**.00

Among 136 participants,85 women were obstetric primis and 51 women were primigravidas.

FIGURE 4:BAR CHART SHOWING PREVIOUS PREGNANCY DETAILS

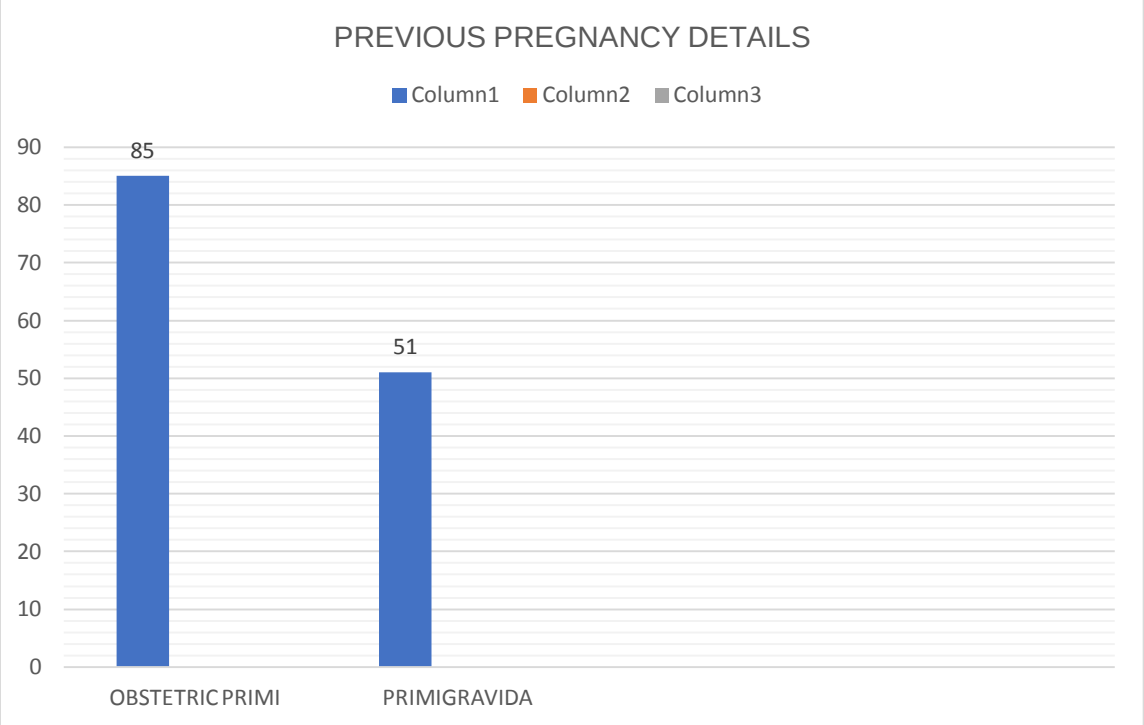

TABLE 5: WEIGHT IN KGS

WEIGHT IN KG	Frequency	Percent	Cumulative
<50kg	62	45.59	45.59
51-75kg	71	52.21	97.79
>75kg	3	2.21	100.00
Total	**136**	**100.00**	**100.00**

The above table showing weight (in kgs)of participants ,62 were 50kgs,71 were 51-75kgs and 3 were> 75kgs.

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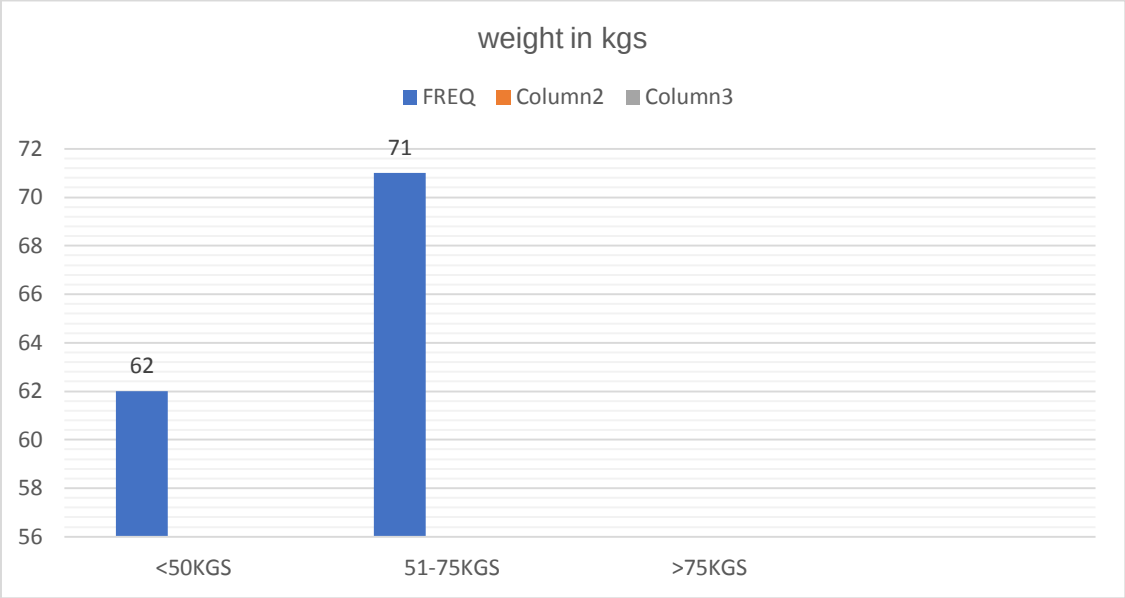
FIGURE5:BAR CHART SHOWING WEIGHT OF STUDY PARTICIPANTS:



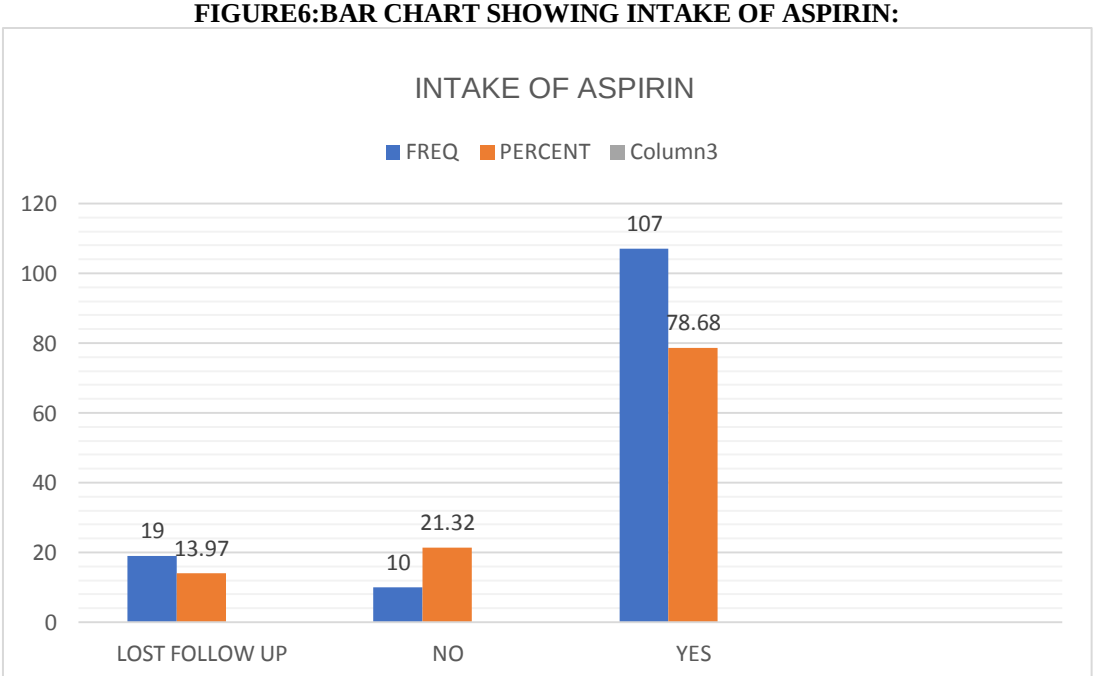
The above bar chart shows weight(in kgs)of participants.
Out of 136 women,71 of them were between 51-75kgs

TABLE 6: INTAKE OF ASPIRIN

INTAKEOF ASPIRIN	Freq	Percent	Cum
LOSTFOLLOW UP	19	13.97	13.97
NO	10	7.35	21.32
YES	107	78.68	100.00
Total	**136**	**100.00**	**100.0**

Among 136 women,19 were lost for follow up,10 women did not take aspirin,107 took aspirin.

FIGURE6:BAR CHART SHOWING INTAKE OF ASPIRIN:



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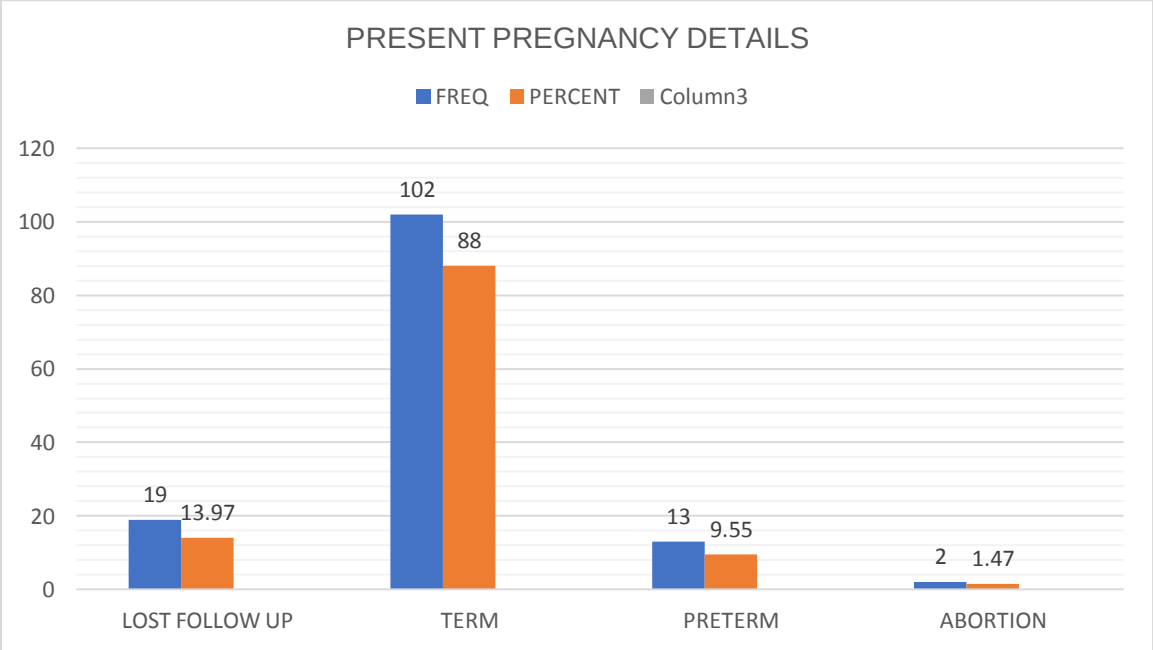
The above bar chart showing intake of aspirin by participants,among 136 women,107(78.68%)women took aspirin,19(13.97%) were lost for follow up,10(21.32%) did not take aspirin.

Table 7: PRESENT PREGNANCY DETAILS

PREGNANCY DETAILS	Freq	Percent	Cum
LOST FOLLOW UP	19	13.97	13.97
TERM BIRTHS	102	75	88.97
PRETREM BIRTHS	13	9.55	98.53
Abortion	2	1.47	100.00
Total	**136**	**100**.00	**100**.00

FIGURE 7:BAR CHART SHOWING PRESENT PREGNANCY DETAILS



The above bar chart shows present pregnancy outcome. 19 were lost for follow up accounts for13.97%,2 of them had pregnancy loss,102 delivered at term accounts for 88%,13 delivered preterm acconts for 9.55%.

TABLE 8 : MODE OF DELIVERY

MODE OF DELIVERY	Frequency	Percent	Cumulative
FTVD	71	52.21	52.21
LOST FOLLOW UP	19	13.97	66.18
PTVD	9	6.62	72.79

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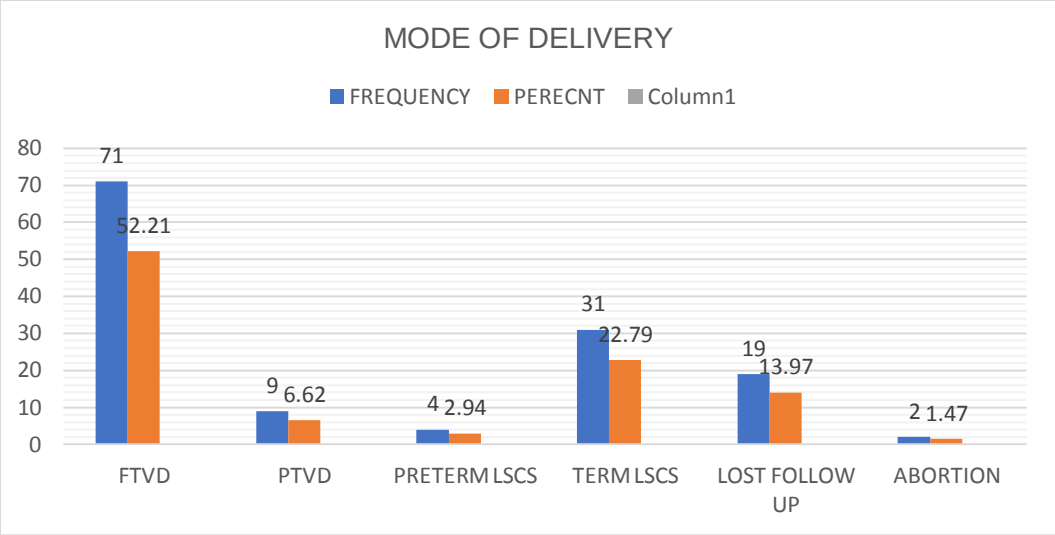
Preterm LSCS	4	2.94	75.74
Term LSCS	31	22.79	98.53
Abortion	2	1.47	100.00
Total	**136**	**100**.00	**100**.00

FIGURE 8:BAR CHART SHOWING MODE OF DELIVERY



Out of 136 women,13 were delivered <37weeks,(9.56%) ,19 lost follow up(13.97%),2 had pregnancy losses,102 women delivered at term, in that 71 delivered vaginally and 31 by lscs accounts for 75.18%.

Table 9: AGE AND PRESENT PREGNANCY DETAILS

AGE	LOST FOLLOW UP	LSCS	VAGINAL	ABORTION
<25YEARS	14	27	67	2
26-30YEARS	3	7	11	0
>31YEARS	2	1	1	0
TOTAL	**19**	**35**	**79**	**2**

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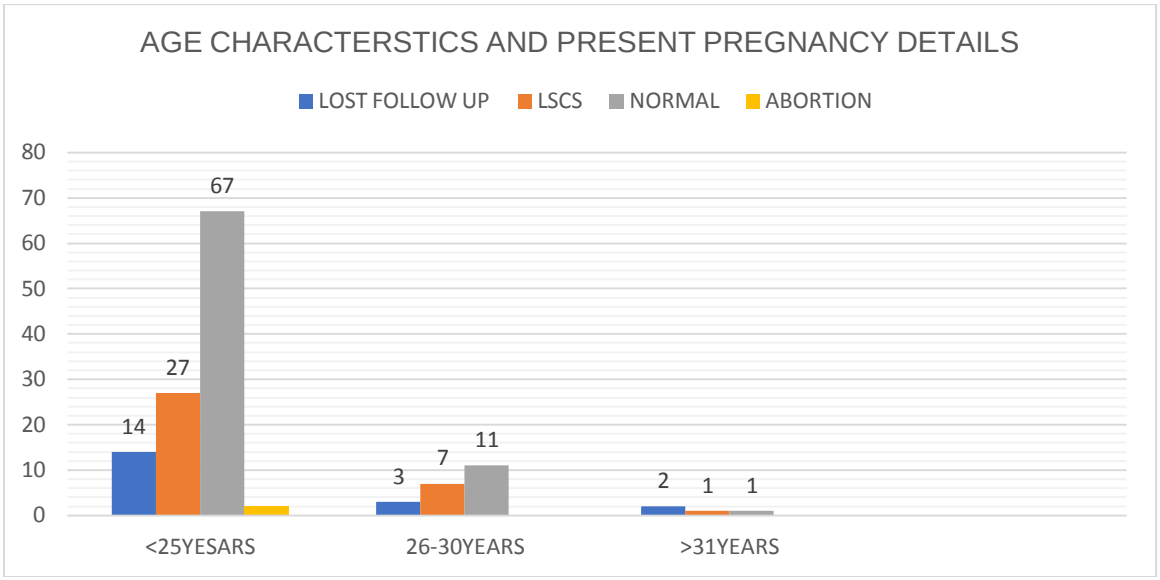
FIGURE 9:BAR CHART SHOWING AGE OF PARTICIPANTS AND PRESENT PREGNANCY DETAILS

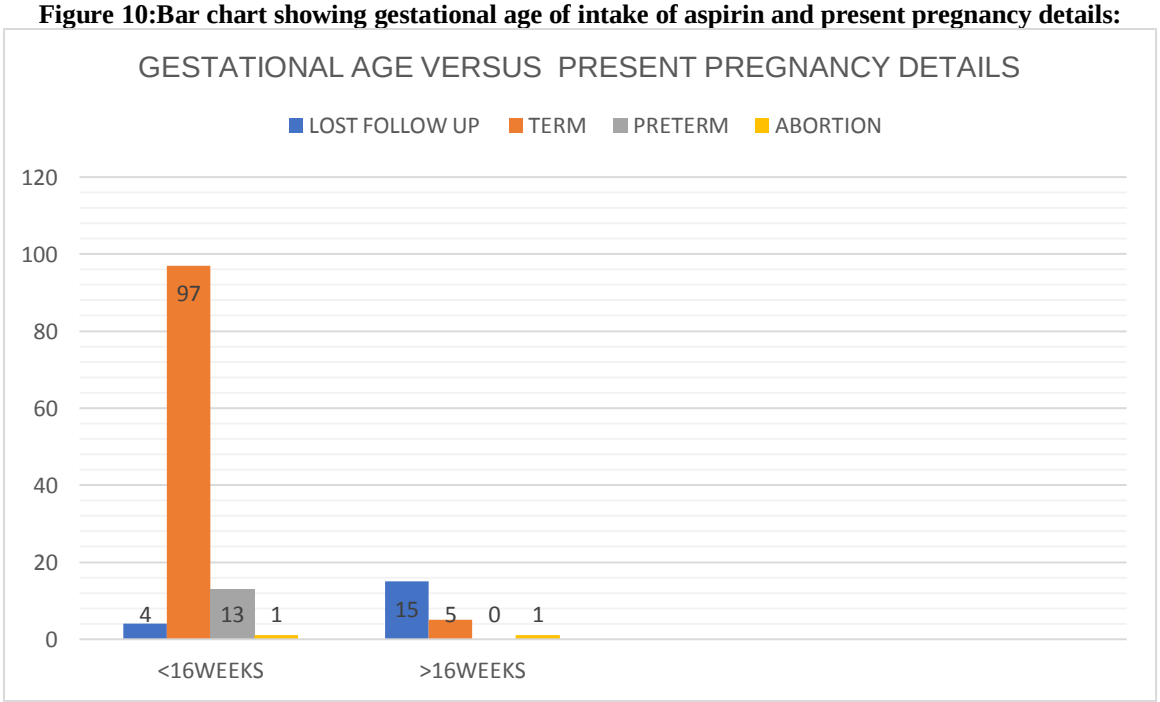


The above bar chart shows age of women participated in study and present pregnancy details.Majority of them women belong to <25 years had live birth and P value statistically not significant.

Table 10: GESTATIONAL AGE OF INTAKE OF ASPIRIN VERSUS PRESENT PREGNANCY DETAILS

GESTATIONAL AGE	LOST FOLLOW UP	TERM	PRETERM	ABORTION
<16WEEKS	4	97	2	1
>16WEEKS	15	5	11	1
TOTAL	**19**	**102**	**13**	**2**

Figure 10:Bar chart showing gestational age of intake of aspirin and present pregnancy details:



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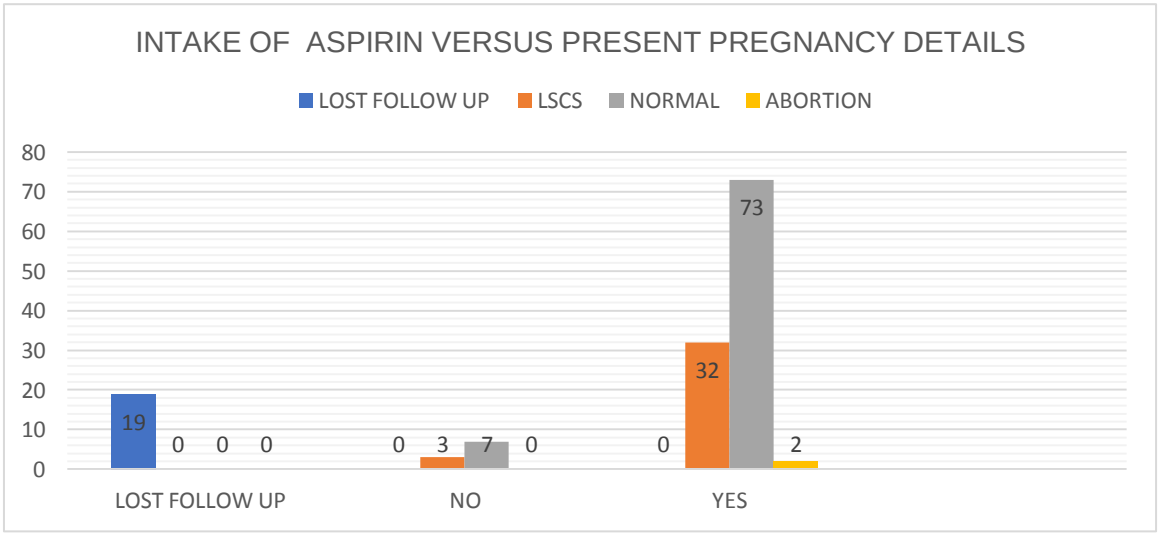
In this study,among 115 women,110 took aspirin <16weeks and 5 took >16weeks.In 110 women who took aspirin <16weeks,97 delivered at term and 13 were delivered preterm.P value is <0.005 and it is statistically significant.

Table 11: INTAKE OF ASPIRIN VERSUS MODE OF DELIVERY

INTAKEOF ASPIRIN	LOST FOLLOW UP	LSCS	NORMAL	ABORTION
LOST FOLLOW UP	19	0	0	0
NO	0	3	7	0
YES	0	32	73	2
TOTAL	**19**	**35**	**80**	**2**



In this study,among 136 women,80 delivered vaginally,in that 7 did not take aspirin and 35 delivered by caesarean section,3 did not take aspirin.The analysis showed p value is statistically significant(0.000)

Table13 : INTAKE OF ASPIRIN VERSUS PREGNANCYOUTCOME

PREGNANCY OUTCOME	LOST FOLLOW UP	NO	YES
LOST FOLLOW UP	19	0	0
TERM	0	6	96
PRETERM	0	4	9
ABORTION	0	0	2

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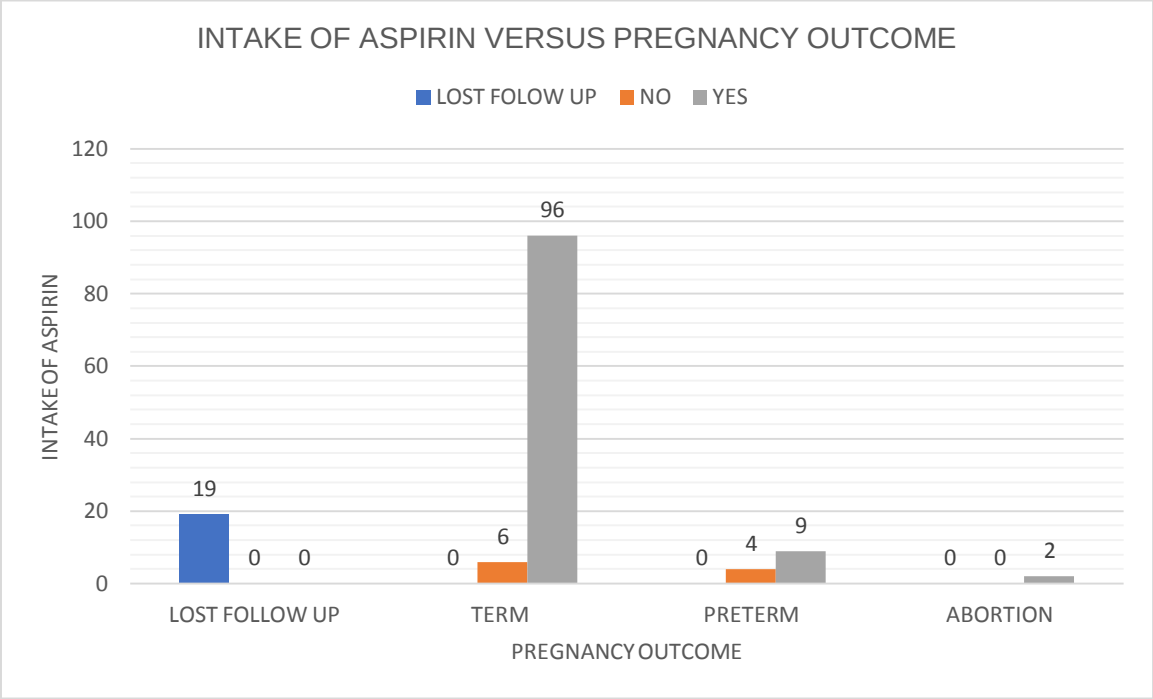
FIGURE13:INTAKE OF ASPIRIN AND PREGNANCY OUTCOME



In this study, 107 women taken aspirin,out of 107 women ,96 women delivered at term accounts for 89.7% ,9 women delivered preterm, accounts for 8.41%,and 2 of them had pregnancy loss,accounts for 1.86%.P value is statistically significant(0.000)

V. DISCUSSION

This longitudinal study provided an opportunity to study the role of low dose aspirin in the prevention of spontaneous preterm birth in nulliparous women.

Preterm birth is one of the major significant public health problem in the world.Its incidence is more in developing countries like India compared to developed countries. Not only it causes neonatal mortality, but also it carries a risk of long term morbidity in children. It also causes economic burden to the society. It was known that preterm birth is a multifactorial syndrome, known to be caused by a variety of factors like infection, spontaneous onset of labor with pre-labor premature rupture of membrane, preeclampsia, multiple gestation etc. Among various strategies in the prevention of preterm birth, currently the preferred method of prevention is by use of antiplatelet agents like acetylsalicylic acid(aspirin) at low doses as studies showed that pathophysiological mechanism involved in preterm birth could be placental ischemia similar to pre-eclampsia. Aspirin is a nonsteroidal anti-inflammatory ,studies showed that at low doses it irreversibly inhibits COX1, resulting in decreased synthesis of thromboxane A2, which is a vasoconstrictor and platelet aggregator. In 2013 ACOG recommended the use of a low dose of aspirin in women with a history of early-onset preeclampsia and preterm delivery or women with more than one prior pregnancy complicated by pre-eclampsia.In 2014 ,the U.S. Preventive Services Task Force(USPSTF) issued guidelines that low dose aspirin should be considered in women with moderate risk factors for pre-eclampsia. Studies showed that aspirin started before 16weeks of gestation was associated with reduction in preterm birth .

PERCENTAGE OF PRETERM BIRTH AMONG OTHER STUDIES:

S.NO	YEAR	STUDY	PERCENTAGE %
1	2007	ASKIE AND DULEY ET AL[26]	8
2	2010	KANDORP ET AL[28]	1.6

3	2014	SILVER ET AL(EAGeR TRIAL)[32]	1.1
4	2014	HENDERSON ET AL[22]	14
5	2018	ANDRIKOUPOULU ET AL[47]	7.84
6	2019	PRESENT STUDY	11.3

With regard to reduction of preterm births reported in other studies, Andrikoupoulu et al[47] 7.84%, Askie and Duley et al 8% were reported slightly higher values but less than present study and contrast to present study, Silver et al 1.1%,Kandorp et al 1.6%, were reported lower values and contrast to the present study.

In this study the percentage of reduction of preterm birth is highly significant comparing to other studies with a p value<0.01.
According to this study, the frequency of preterm birth was 11.3% (total number of preterm births -13 among 115 of total pregnant women studied from Jan 2019 -June 2020).
In 2011,WHO issued recommendations for prevention and treatment of pre-eclampsia and eclampsia, use of low dose aspirin(75mg/day) to high risk women. In 2014 ,U.S.
Preventive Services Task Force suggested the use of low -dose aspirin daily in women with moderate risk factors for pre-eclampsia like nulliparity, age 35years or older, previous
pregnancy outcome, low socioeconomic status, obesity(BMI>30).

Age >35years is one of the risk factor for preterm birth . In present study, majority of the women were between 25 -30years(97.49%),and women >31years(2.61%).
Floret et al 2018[48] showed rate of preterm birth is highest in age group >40year 7.8% and lowest in 30-34years 5.7%.
Yu-jin koo[49] et al studies showed there is increased strength of association between preterm birth and advancing age.

Khalil et al[50] 2013 study showed that there is no significant association between advancing maternal age and preterm birth.In this study as nulliparous women with
advanced age were less,it was not sufficient to compare association of maternal age and preterm birth .

In this study majority of women who took aspirin at gestational age <16weeks .This is in support to studies done by vliet et al ,Henderson et al 14%, and vliet and Askie et al. In our study P-value is not statistically significant.

Studies by Sailhu et al[51] 2010 and Yu-Kang chang52 et al 2020,showed nulliparity carries positive association with preterm birth. In our study, 136 nulliparous women were included,115 women were delivered,102 women delivered at term accounts for 88.7%,13 women delivered preterm accounts for 11.3% and it showed that low dose aspirin given in nulliparous women showed a significant reduction in preterm birth. This is in agreement with USPTF recommendations and EAGeR trial 2014.

In this study there is no incidence of hemorrhagic complications, abruption placenta in women who took aspirin. This is in agreement with studies by Duley et al 2007,Henderson et al,USPSTF 2014.

Out of 115 deliveries, it was observed that there is no incidence of congenital anomalies of the baby,haemorrhagic complications or intracranial bleeding in the fetus and
premature ductal arteriosus closure. This is in support to studies done by Askie et al 2007,Duley and Henderson et al 2007,Wyatt -Ashmead 2011,Henderson et al 2014,Silver et al 2016,Duley and Meher et al 2019.

To conclude this study showed that use of low dose aspirin is safe in pregnancy and its useful as a preventive strategy in reduction in preterm birth.

VI. CONCLUSION

1.Incidence of preterm birth in this study was 11.3%,our study concluded that preterm birth incidence was low.

2.Use of low dose aspirin in nulliparous women before 16weeks of gestation showed significant reduction in incidence of preterm birth

3.Low dose aspirin use is safe in pregnancy

4.Low dose aspirin is not associated with fetal and maternal complications.

5.In this study sample size was low, which is not sufficient to comment about reduction of preterm birth.

6.It requires large sample size and need further studies to evaluate about the use of low dose aspirin in reduction of preterm birth.

Study findings:

OUTCOMES	P VALUE
Age	Not significant
Reduction of Preterm birth	Significant
Nulliparity	Significant
Intake of aspirin	Significant
Gestational age	Significant
Mode of delivery	Significant

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