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Efficacy and Safety of Low-Dose Aspirin and Vaginal Progesterone in the Prevention of Spontaneous Preterm Birth

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ABSTRACT

Background: The primary cause of newborn morbidity and death is preterm birth (birth before 37 weeks gestation) which carries a substantial economic burden to health care and social services.

Objective: This study aimed to assess the efficacy of low dose of aspirin and vaginal progesterone in prevention of preterm birth.

Patients and Methods: This is randomized controlled clinical trial on 127 pregnant women that was conducted at Obstetrics and Gynecology Department in Samanoud General Hospital at El Gharbia Governorate, which was held from October 2020 to June 2022.

Results: There was a significant difference between aspirin, progesterone and combination groups regarding early preterm birth <34 weeks (P= 0.024). While there were no significant differences among the studied groups regarding preterm birth <37 weeks (P> 0.05).

Conclusion: Vaginal progesterone with low-dose aspirin, starting at 14-16 weeks gestation and continuing until 36 weeks, can considerably lower the incidence of preterm delivery < 34 weeks. Aspirin and vaginal progesterone are safe drugs in pregnancy.

Keywords: Aspirin, Preterm Birth, Prevention, Spontaneous, Vaginal Progesterone.

INTRODUCTION

Preterm birth, defined as delivery prior to 37 weeks of pregnancy, is the primary cause of infant death, is linked to long-term impairment in those who survive, and has a significant financial impact on social services and healthcare [1]. Preterm births (PTB) put surviving children at risk of severe neonatal problems and long-term impairment, and are the leading cause of neonatal mortality globally [2]. PTB is estimated to have cost the UK economy £2.9 billion in a single year, not to mention the significant financial, social, and psychological toll it has on families [3,4].

PTB has been identified as one of the "top ten" research priorities by the WHO until 2025 [5]. The best therapeutic treatment for expectant mothers to prevent or treat PTB is still up for dispute among experts. Women's unique backgrounds and preferences must be taken into account when evaluating the short- and long-term impacts of various treatments [6].

About 15 million PTBs occur annually worldwide, making up 9% to 12% of all live births [7]. Preterm delivery complications are the primary cause of both perinatal and death in children under five [8]. Neonatal survivors are more likely to experience a number of acute and chronic morbidities, including cognitive and neurodevelopmental impairment [9]. About 65 percent of PTB develops spontaneously after contractions or membrane rupture [10]. With a recurrence rate of up to 30% to 35% in singleton pregnancies, a prior spontaneous preterm delivery is the biggest risk factor for spontaneous preterm birth [11].

Many women will deliver preterm again in their following pregnancies, even if progesterone and other prophylactic measures are used. Therefore, the need for further preventative measures is essential [12]. The majority of PTB linked to preeclampsia are caused by preterm C-sections or labor inductions prompted by deteriorating conditions in the mother or fetus [1,13]. Yet, reanalysis of data from aspirin-prevention studies has also demonstrated statistically significant but modest decreases in spontaneous preterm birth [14]. The question of whether aspirin may be used to prevent spontaneous PTB has emerged, as PTB is the primary cause of preterm birth overall [15].

Similar to preeclampsia, there is growing evidence that uteroplacental ischemia contributes significantly to the pathogenesis of spontaneous preterm delivery [15]. Given that aspirin has been shown to lower the incidence of preeclampsia, it is theoretically possible that aspirin's antithrombotic and anti-inflammatory properties might potentially prevent spontaneous preterm birth [16]. Low-dose aspirin has been demonstrated to lower the overall risk of preterm birth and to be beneficial in preventing preeclampsia [15]. Previous research linked a decrease in medically indicated preterm birth associated to preeclampsia to the reduction in preterm birth that occurred after low-dose aspirin treatment [17].

There is a possibility that low-dose aspirin might prevent spontaneous preterm birth since the pathophysiology of uteroplacental ischemia in preeclampsia and spontaneous preterm delivery is somewhat similar [16]. That low-dose aspirin may lessen spontaneous preterm birth has been demonstrated by secondary analyses of randomized controlled trials and a sizable individual patient data meta-analysis of women at risk for preeclampsia [18].

Following the release of the OPPTIMUM trial[19], there has been doubt about the effectiveness of

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vaginal progesterone in avoiding preterm delivery and unfavorable perinatal outcomes in singleton gestations with a short cervix. Without any discernible negative effects on childhood neurodevelopment, vaginal progesterone reduces the chance of preterm delivery and improves perinatal outcomes in singleton gestations with a midtrimester sonographic short cervix [20].

Between <28 weeks of gestation and <35 weeks of gestation, there is a considerable decrease in the risk of preterm delivery when vaginal progesterone is administered [21]. Furthermore, a lower chance of respiratory distress syndrome, hospitalization to the NICU, composite neonatal morbidity and mortality, and birthweight less than 1500 g was linked to vaginal progesterone administration [22].

Vaginal progesterone did not substantially lower the risk of preterm delivery or perinatal morbidity and death in the general population or in the subgroup of women with a cervical length of ≤25 mm, according to the trial's findings [23]. Regarding the clinical effectiveness of vaginal progesterone for avoiding preterm delivery and severe perinatal outcomes in singleton gestations with a short cervix, that report caused uncertainty among doctors and professional/scientific bodies [24].

The aim of the study was to assess the efficacy of low dose of aspirin and vaginal progesterone in prevention of preterm birth.

PATIENTS AND METHODS

This is randomized controlled clinical trial on 127 pregnant women that was conducted at Obstetrics and Gynecology Department in Samanoud General Hospital at El Gharbia Governorate, which was held from October 2020 to June 2022.

Sample size: We started with 154 pregnant women. 13 pregnant women were excluded; 8 were not meeting the inclusion criteria and 5 declined to participate. 141 pregnant women were randomized into three groups.

Inclusion criteria: Age between 17-37 years old, singleton pregnancy, gestational age (GA) between 10-16 weeks, and primigravida or multipara.

Exclusion criteria: multifetal pregnancy, GA <10 weeks, GA >16 weeks, any woman who had to be delivered before term due to medical or obstetric reasons, prior abdominal or vaginal cerclage (current or planned cervical cerclage), history or present medical disease during pregnancy (HTN, cardiac disease, DM), fetal abnormalities, polyhydramnios, low lying placenta, evidence of uterine anomalies, on tocolytic drugs, medical illness contraindicated for aspirin use as hemophilia, vitamin K deficiency, bleeding gastric ulcer and vaginal bleeding during the first trimester of pregnancy.

All 141 pregnant women were randomized in to three Groups:

Method of Randomization:

The included women were randomized into three groups as randomization was done using SPSS program for choosing participants in every group. Group allocation was concealed in sealed, opaque envelopes, a third party (a nurse) was handed 141 opaque envelopes with serial numbers on them, along with the appropriate letter indicating the assigned group. The envelopes were placed in a box and the ladies were given the assignment to study arms. Every lady was asked to take out one envelope. When the envelope was opened, the patient was assigned a number based on the letter inside, and none of the ladies, the doctor, or the nurse knew the medication she would get.

- **Aspirin group:** Included 47 pregnant women who took low dose of aspirin 75 mg one tablet per day from 10 weeks to 36 weeks. 5 women dropped from follow up 42 pregnant women continued till delivery.
- **Progesterone group:** Included 47 pregnant women who took vaginal progesterone 200 mg/day from 10 weeks to 36 weeks. 6 women dropped from follow up 41 pregnant women continued till delivery.
- **Combination group:** Included 47 pregnant women who took low dose of aspirin 75 mg/day and vaginal progesterone 200 mg/day from 10 weeks to 36 weeks. 3 women dropped from follow up 44 pregnant women continued till delivery.

Follow up:

The following data sheet was obtained from each patient as a complete history, with emphasis on high-risk variables.

Personal data: name, age, length of marriage, place of residence, employment, unique habits, phone numbers, husband's name, and line of work.

Previous medical and surgical histories, including hypertensive illnesses, heart issues, and DM, chest issues, renal illness, and a history of laparotomies or other surgeries.

Family history: relatives' prior history of premature birth:

Obstetric history: Including comprehensive information on past pregnancies, such as the date, fetal result, start and manner of delivery, GA at delivery, and any related issues.

History of present pregnancy: Estimated GA as of the first day of life after conception or as determined by an early pregnancy ultrasound, medical and surgical history to identify high risk factors and exclude

specific conditions, labor pains, vaginal bleeding, and the pleasure of feeling the kicks of the fetus.
Physical examination: General exam. as BP, pulse, temperature, BMI, and cardiac and chest examination.

Routine antenatal lab. investigations: including: (blood group (ABO and Rh typing), full blood count and urine analysis):

Abdominal examination (fundal level, lie and presentation of the fetus, monitoring of uterine contractions, auscultation of FHR, presence of scar of previous laparotomy) and **P/V examination** (if indicated): for assessment of presenting part, pelvic capacity, cervical changes, GA at delivery, onset and mode of delivery.

Neonatal outcome as (Apgar score, birth weight, NICU admission, post-partum complications).

Maternal complications during delivery **(**if present**):**
Side effects of the drugs (if present): All of the ladies who consented to participate in the study were properly informed about the nature and objectives of the work. Pregnancy outcome data were collected from the delivery ward filing system and from the patients themselves for those who gave birth at home or in another hospital.

Ultrasound Examination:

All patients were regularly followed up in the outpatient prenatal clinic every two weeks by vaginal and abdominal ultrasound till delivery as **Trans abdominal** ultrasonography was done for assessment of fetal life, number, fetal biometry (BPD-FL-TAD), placental site & maturity. Liquor (quantity and turbidity), cervical measurements every two weeks, **cervical length** was measured using **transvaginal sonography**. Accurate cervical length measures begin from the internal os, go down the endo cervical canal, and conclude at the external os. **Transvaginal sonography** was used to determine the presence or absence of funneling. Funneling of the cervix is defined as the opening of the interior cervical os on ultrasonography. Administration will begin between 10 and 16 weeks of gestation and continue until 36 weeks or birth, whichever comes first.

The three groups were compared according to the outcome:

- **Primary outcomes:** % of preterm birth <37 weeks - % of preterm birth <34 weeks.
- **Secondary outcomes:** Perinatal and maternal outcome: Perinatal outcomes according to: Apgar score, birth weight, admission to NICU, morbidity and mortality and maternal outcomes as (pre-eclampsia, placental abruption and post-partum hge).

Ethical approval:
All adult women as well as the caregivers of women aged below 18 years, gave their informed permission after being fully informed of the hazards and benefits. All women's data were protected by privacy laws, and each woman file contained a code number that identified all investigations. Menoufia Medical Ethics Committee of the Menoufia Faculty of Medicine has approved this study (5/2020 OBSGN14). The Helsinki Declaration was observed throughout the study's operations.

Statistical Analysis

The data were collected, tabulated, and statistically analyzed using a personal computer running SPSS Version 25.0. The following statistics were then employed. In descriptive statistics, the data were described using the mean±SD and range for quantitative data and frequency and percentage for qualitative data. Kruskal-Wallis test (K), One-way ANOVA (F), independent student-t test (t), and Chi-squared (χ^2) were used for analytical statistics. A significant level was defined as $P \leq 0.05$.

RESULTS

There were no significant differences among the studied groups regarding age, body mass index, residence, gravidity, parity and occupation status, abortion, previous PTL and premature rupture of membranes **(Table 1).**

Table (1): Maternal characteristics and maternal history of the studied groups**.**

Variables	Studied groups (n=127)			Sig. test	
	Aspirin group (n=42)	rogesterone group (n=41)	Combination group (n=44)	F	*P value*
Age/ years, no (%)				X^2= 0.10	0.951
< 30 years	32 (76.19%)	33 (80.495)	33 (75.00%)		
≥ 30 years	10 (23.81%)	8 (19.51%)	11 (25.00%)		
Mean ± SD	25.80±4.66	26.20±4.24	25.10±3.95	0.688	0.505
Range	17.00-35	18.00-37.00	19.00-35.00		
BMI (kg/m^2)					
Mean ± SD	29.93±2.45	30.18±2.00	30.05±2.09	0.134	0.875
Range	26.11-35.72	26.57-33.77	26.77-33.77		
Residency, no (%)				X^2= 3.146	0.207
Rural	23 (54.76%)	30 (73.17%)	29 (65.90%)		
Urban	19 (45.24%)	11 (26.83%)	15 (34.09%)		
Gravidity					
Mean ± SD	2.71±1.05	2.59±1.07	2.73±0.81	0.260	0.772
Range	1-5	1-5	1-4		
Parity					
Mean ± SD	1.41±0.92	1.37±0.92	1.39±0.74	0.033	0.968
Range	0-3)	0-3	0-3		
Occupation status, no (%)				X^2= 0.876	0.645
Worker	20 (47.62%)	15 (36.59%)	19 (43.18%)		
Housewife	22 (52.38%)	26 (63.41%)	25 (56.82%)		
Abortion, no (%)				1.518	0.468
No	29 (69.05%)	32 (78.05%)	27 (61.36%)		
Yes	13(30.95%)	9 (21.95%)	17 (38.63%)		
Previous PTL, no (%)					
No	34 (80.95%)	26 (63.42%)	30 (68.18%)	1.29	0.530
Yes	8 (19.05%)	15 (36.58%)	14 (31.82%)		
PROM, no (%)					
Absent	39 (92.86%)	40 (97.56%)	39 (88.63%)	0.417	0.812
Present	3 (7.14%)	1 (2.44%)	5 (11.36%)		

PTL: Preterm labor diagnosis. **PROM:** Premature rupture of membranes. **X^2:** Chi-square test, **BMI:** body mass index**.**
*****Significant. **F:** ANOVA F test.

Also, there were no significant differences among the studied groups regarding heart rate, systolic blood pressure and diastolic blood pressure and hemoglobin **(Table 2).**

Table (2): Maternal vital signs and maternal hemoglobin level among the studied women groups**.**

Variables	Studied groups (n=127)			Sig. test		95%CI	
	Aspirin group (n=42)	Progesterone group (n=41)	Combination group (n=44)	K	P value	Lower	Upper
HR							
Mean ± SD	86.07±7.70	81.02±7.81	82.76±7.62	1.538	0.85	81.87	84.70
Range	65-98	68-95	66-98				
SBP							
Mean ± SD	110.73±9.32	113.90±9.72	115.12±11.86	1.962	0.145	111.39	115.12
Range	90-120	100-150	100-170				
DBP							
Mean ± SD	71.22±8.42	73.66±8.29	73.66±7.99	1.198	0.305	71.37	74.32
Range	60-80	60-90	60-90				
Hb (ng/dl)							
Mean ± SD	11.11±1.05	10.96±0.81	10.79±0.78	t= 1.324	0.270	10.80	11.11

K: Kruskal Wallis test, **t**: independent t-test. *****Significant. **HR:** Heart rate. **SBP:** Systolic blood pressure, **DBP:** Diastolic blood pressure. **CI:** Confidence interval for Mean, **Hb:** Hemoglobin.

There was a significant difference between aspirin, progesterone, and combination groups regarding early preterm birth <34 weeks. While there were no significant differences among the studied groups regarding preterm birth <37 weeks **(Table 3)**. Moreover, there were no significant differences among the studied groups regarding cervical length **(Table 4).**

Table (3): Rate of preterm birth among the studied groups.

Variables	Studied groups (n=127)						Sig. test	
	Aspirin group (n=42)		Progesterone group (n=41)		Combination group (n=44)		X^2	P value
	N	%	N	%	N	%		
Preterm birth <34 weeks							7.47	**0.024***
Yes	5	11.90	1	2.44	0	00.00		
No	37	88.09	40	97.56	44	100.00		
Preterm birth <37 weeks							3.45	0.18
Yes	7	17.07	4	9.76	2	4.56		
No	35	85.37	37	90.24	42	95.45		

Table (4): Cervical length among the studied groups**.**

Variables	Studied groups (n=127)			Sig. test		95%CI	
	Aspirin group (n=42)	Progesterone group (n=41)	Combination group (n=44)	K	P value	Lower	Upper
Cervical Length at 20 weeks/cm Mean ± SD	3.50±0.33	3.40±0.32	3.37±0.29	1.737	0.180	3.37	3.48
Range	(3.00-4.00)	(2.80-4.00)	(2.80-3.80)				

CI: Confidence interval for mean.

Also, there were no significant differences among the studied groups regarding pre-eclampsia, infection, placental and post-partum HGE **(Table 5)**. While, there were no significant differences among the studied groups regarding GA at recruitment, GA at birth, birth weight, Apgar score, admission to NICU, and neonatal mortality. While, there was significant difference among the studied groups regarding Apgar score at 5 min **(Table 6).**

Table (5): Maternal complications during pregnancy and delivery among the studied groups**.**

Variables	Studied groups (n=127)			Sig. test	
	Combination group (n=44)	Progesterone group (n=41)	Aspirin group (n=42)	x^2	P value
Pre-eclampsia, no (%)					
Absent	44 (100%)	40 (97.56%)	41 (97.61%)	1.017	0.602
Present	0 (0%)	1(2.44%)	1(2.38%)		
Infection, no (%)					
Absent	44 (100%)	41 (100%)	42 (100%)	0.00	1.00
Present	0 (0%)	0 (0%)	0 (0%)		
Placental abruption, no (%)					
Absent	44 (100%)	41 (100%)	42 (100%)	0.00	1.00
Present	0 (0%)	0 (0%)	0 (0%)		
Post-partum hge, no (%)					
Absent	42 (95.45%)	41 (100%)	42 (100%)	4.066	0.131
Present	2 (4.54%)	0 (0%)	0 (0%)		

X^2: Chi-square test.

Table (6): Neonatal characteristics among the studied groups**.**

Variables	Studied groups (n=127)			Sig. test		95%CI	
	Aspirin group (n=42)	Progesterone group (n=41)	Combination group (n=44)	K	P value	Lower	Upper
GA at recruitment/ weeks							
Mean ± SD	13.27±1.82	12.88±1.66	13.59±1.84				
Range	10-16	10-16	10-16	1.632	0.200	12.93	13.56
GA at Birth/weeks							
Mean ± SD	37.71±1.07	37.69±1.35	37.69±1.20				
Range	33-39.3	32-40	35-40	0.004	0.996	37.48	37.91
Birth weight/kg Mean± SD Range	3.11±0.225 2.6-3.5	3.63±0.294 2-3.5	3.79±0.312 1.8-3.4	t= 0.324	0.724	3035.30	3134.62
Apgar score at 5 min, no (%)							
<7	9 (21.42%)	8 (19.52%)	8 (18.18%)	X^2=			
>7	33 (78.57%)	33 (80.48%)	36 (81.82%)	0.144	0.930	21.468	0.006
Apgar score							
Mean ± SD	8.78±1.41	8.37±1.07	8.80±1.08				
Range	6-10	6-10	6-10	1.752	0.178	8.44	8.86
Admission to NICU, no (%)							
Absent	33(78.57%)	31 (75.60%)	37 (84.09%)	X^2=			
Present	9 (21.42%)	10 (24.40%)	7 (15.90%)	0.973	0.615	----	----
Neonatal mortality, no (%)							
Absent	42 (100%)	41 (100%)	44 (100%)	X^2=			
Present	0 (0%)	0 (0%)	0 (0%)	0.00	1.00	----	----

Apgar: Appearance, Pulse, Grimace, Activity, and Respiration. **K:** Kruskal Wallis test. **t**: independent t-test. **X^2:** Chi-square test. **CI:** Confidence interval for Mean.

In addition, the results of multiple logistic regression analysis indicated that cervical length, preeclampsia, and PROM were the most significant factors, which affected spontaneous preterm birth. While, age, body mass index, gravidity, parity, heart rate, systolic blood pressure, diastolic blood pressure, hemoglobin, GA at recruitment and previous preterm labor diagnosis didn't show significant association with spontaneous preterm birth **(Table 7).**

Table (7): Multiple regression analysis for the studied variables affected on spontaneous preterm birth**.**

Variables	B	Std. Error	Wald	P value	Exp(B)	95% CI for Exp (B)	
						Lower Bound	Upper Bound
Intercept	21.407	14.711	2.117	**<0.001***	---	---	---
Age	0.027	0.119	0.051	0.820	1.027	0.814	1.296
BMI	-0.141-	0.193	0.535	0.464	0.868	0.595	1.268
Gravidity	-0.385-	0.861	0.200	0.655	0.680	0.126	3.677
Parity	0.823	0.976	0.712	0.399	2.278	0.336	15.422
HR	0.017	0.052	0.102	0.749	1.017	0.918	1.127
SBP	-0.165-	0.186	0.789	0.374	0.848	0.588	1.221
DBP	0.205	0.197	1.077	0.299	1.227	0.834	1.806
Hb	0.577	0.547	1.113	0.291	1.781	0.610	5.205
Cervical length	2.247	1.560	2.075	**0.015***	9.462	0.445	201.35
GA at recruitment	-0.206-	0.252	0.668	0.414	0.814	0.496	1.334
Preeclampsia	1.836	0.202	0.088	**0.047***	6.272	3.301	11917
PROM	-4.107-	1.797	5.224	**0.022***	4.016	0.001	0.557
Previous PTL	0.320	0.917	0.122	0.727	1.378	0.228	8.316

***Significant. **CI:** Confidence interval for Mean.

DISCUSSION

In our study, there were no significant differences between the three study groups regarding all the pre-delivery data. This should nullify any bias skewing the results in favor of one group rather than the other one. The mean age of the included ladies was 25.8, 26.2, and 25.1 years in the aspirin, progesterone, and combined groups respectively, with no significant difference between them (p=0.505). **Allshouse *et al.*** [16] reported that maternal age had mean values of 26.3 and 26.4 years in the aspirin and control groups respectively (p = 0.721)**.** The mean body mass index of the included ladies was 29.93, 30.18, 30.05 with no significant difference between them (p=0.875). **Landman *et al.*** [7] reported much less values for BMI, which had mean values of 23.8 and 23.7 kg/m^2 in the aspirin and placebo groups respectively**. Hoffman *et al.*** [17] also reported similar findings.

According to **Norman *et al.*** [25]**,** 1.228 high-risk women —those with a history of preterm births <34 weeks, a cervical length ≤25 mm, or a positive fetal fibronectin test along with other preterm birth risk factors— were given 200 mg of vaginal micronized progesterone suppository or a placebo every day, starting at 22 to 24 weeks gestation and ending at 34 weeks. This is the biggest trial of vaginal progesterone treatment for preventing preterm delivery in women at risk to date, yet in the total study group and all subgroup analyses, progesterone treatment had no effect on rates of preterm birth or neonatal and infant outcomes.

Another study reported that delivery < 37-week gestation was encountered in 42.5% and 35.5% of women in the progesterone and placebo groups respectively, with no significant difference on statistical analysis [26]. In the study conducted by **Andrikopoulou *et al.*** [18], they found that the risk of spontaneous preterm delivery <34 weeks was 1.03% (n = 13) and 2.34% (n = 30) in the low-dose aspirin and placebo groups, respectively (odds ratio, 0.43, 95% confidence range, 0.26-0.84). The low-dose aspirin group had a rate of spontaneous preterm birth <37 weeks at 6.58% (n = 83) compared to 7.03% (n = 90) in the placebo group (odds ratio, 0.97, 95% confidence interval, 0.71-1.33), while the placebo group had a rate of overall preterm birth <37 weeks at 7.84% (n = 99) and 8.2% (n = 105) (odds ratio, 0.97, 95% confidence interval, 0.72-1.31). The low-dose aspirin group showed a significant decrease in spontaneous preterm birth <34 weeks after controlling for clinically relevant or statistically significant variables such as body mass index, race, tobacco use, marital status, and education level (adjusted odds ratio, 0.46, 95% confidence interval, 0.23-0.89). When low-dose aspirin was taken by healthy nulliparous women without comorbidities, the risk of spontaneous preterm delivery <34 weeks was significantly reduced [18].

The preceding writers explained their results by pointing out that preterm birth is a diverse disease with a variety of potential underlying pathophysiologic processes [27]. It is therefore improbable that all PTB will be prevented by a single preventative intervention.

Regarding early preterm delivery of less than 34 weeks, there was a significant difference (P=0.024) between the Aspirin, progesterone, and combination groups in our research. Regarding preterm births less than 37 weeks, there were no significant differences between the groups under study.

In our research, the mean values of birth weight were 3.11, 3.63, and 3.79 kg in the aspirin, progesterone, and combined groups respectively, with no significant difference between the three groups. In a previous similar study, aspirin intake did not have a significant impact on birth weight, which had mean values of 2437± 808 and 2570± 554 gm in the aspirin and placebo groups respectively [13]. Likewise, the study conducted by **Martinez de Tejada *et al.*** [26] reported that progesterone did not negatively affect birth weight, which had median values of 2880 and 2955 grams in the progesterone and placebo groups respectively.

In the current study, Apgar score had mean values of 8.78, 8.37, and 8.8 in the aspirin, progesterone, and combined groups respectively. These values were comparable in statistical analysis. **Saghafi *et al.*** [28] noted no significant impact of progesterone administration on Apgar score (p > 0.05). One- and five-minute Apgar score had mean values of 7.48 and 8.02 in the progesterone group versus 7.36 and 7.98 in the placebo group respectively. **Silver *et al.*** [13] confirmed the previous findings, as one- and five-minute Apgar scores had median values of 8 and 9 respectively, in both placebo and aspirin groups.

Our findings showed that NICU admission was needed in 21.42%, 24.4, and 15.90% of neonates in the aspirin, progesterone, and combined groups respectively, with no significant difference between the three groups. **Martinez de Tejada *et al.*** [26] reported that 29.8% and 25.4% of neonates in the progesterone and placebo groups needed NICU admission, with no significant difference between the two groups. Another study noted no significant impact of aspirin administration on the need for NICU admission, which was needed in 6.7% and 5.7% of ladies in the aspirin and placebo groups respectively [7].

In the current investigation, neonatal mortality was not seen in any of the three research groups. According to other authors, there was no correlation between the use of aspirin during pregnancy and a higher risk of neonatal death, which occurred in 3.1% and 1% of newborns in the aspirin and placebo groups, respectively [7].

Furthermore, low-dose aspirin started at < 16 weeks of gestation is linked to a higher reduction in

perinatal mortality and other unfavorable perinatal outcomes, according to a prior meta-analysis by **Roberge *et al.*** [29]. All the previous studies agreed with the safety of both tested drugs when administered during pregnancy.

In the current study, preeclampsia occurred in 0, 2.44, and 2.38% of ladies in the aspirin, progesterone, and combined groups respectively. No significant difference was detected between the three groups regarding that parameter. **Hoffman *et al.,*** [17] reported that hypertensive pregnancy disorders were noted in 6.1% and 5.6% of ladies in the aspirin and placebo groups respectively, with no significant group on statistical analysis.

Our study reported that there was no significant difference between the three groups regarding PPH. Other authors also reported that the aspirin and placebo groups showed comparable incidence of PPH and blood loss during delivery. In the low-dose aspirin group, the rate of PPH was 6.8%, while in the placebo group, it was 7.1% [18]. Moreover, **Hoffman *et al.*** [17] noted no significant difference in the rate of post-delivery significant vaginal bleeding, which was noted in 3.6% and 4.1% of ladies in the aspirin and placebo groups respectively.

Our findings showed that short cervix was a risk factor for PTB on multivariate regression analysis. Likewise, **O'Hara *et al.*** [30] reported that one of the most potent markers of PTB in women carrying singletons and twins is a shorter cervix. The probability of spontaneous preterm birth increases with decreased cervical length. Moreover, **Romero *et al.*** [31] came to the conclusion that the probability of spontaneous PTB increased with cervical length. Despite the fact that a direct correlation between PTB and a shorter cervical length has been demonstrated [32].

In the current study, the presence of preeclampsia was strongly associated with PTB. Like the previous findings, **Davies *et al.*** [33] noted a strong correlation (adjusted odds ratio 4.43; 95% confidence range 3.80-5.16) between premature birth and preeclampsia. Pregnancy-related high blood pressure carries the following risks: reduced blood supply to the placenta. The fetus may obtain less oxygen and nutrients if the placenta doesn't get enough blood. This may result in low birth weight, early delivery, or sluggish development (intrauterine growth restriction).

Our findings showed that PROM was a significant risk factor for PTB. Another report stated that about 25 to 30% of ladies who present with PTB are due to PROM [34]. Another study also reported that PROM is linked to an increased risk of PTB [35].

CONCLUSION

Vaginal progesterone with low-dose aspirin, starting at 14-16 weeks gestation and continuing until 36 weeks, can considerably lower the incidence of preterm delivery < 34 weeks. Aspirin and vaginal progesterone are safe drugs in pregnancy.

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