

Combined Low Dose Aspirin and 17 α Hydroxyl Progesterone versus 17 α Hydroxyl Progesterone Alone Study in Pregnancy: A Randomized Clinical Trial for Prevention of Spontaneous Preterm Birth

Hassan Awwad Bayoumy, Amgad Abou-Gamrah, Mostafa Fouad Gomaa,
Asmaa Ahmed Mohamed Alashwah

Obstetrics and Gynecology Department, Faculty of Medicine - Ain Shams University

ABSTRACT

Background: Preterm birth: defined as any live birth occurring through the end of the last day of the 37th week (259th day) following the onset of the last menstrual period. Low-dose aspirin (LDA) has been noted to reduce the preterm birth (PTB) rate in multiple meta-analyses of the preeclampsia (PreE) prevention trials. It is unclear if this effect of LDA is entirely due to a reduction in indicated PTB versus reductions in preterm premature rupture of membranes (PPROM) or spontaneous PTB. In the Maternal-Fetal Medicine Unit (MFMU) high-risk aspirin (HRA) study, a near significant decrease in PTB was found despite no effect on preeclampsia. The objective of this study was to assess the impact of LDA on indicated PTB, spontaneous PTB, and PPRM PTB in the MFMU HRA study population. **Aim of the work:** This study aim to assess the efficacy of 17 alpha hydroxyl progesterone and low dose aspirin in reducing the rate of preterm birth in pregnant women at this risk. **Patients and Methods: Study type:** A double blinded randomized placebo controlled clinical trial. **Study settings:** This study conducted at outpatient clinic of Ain Shams University Maternity Hospital. **Time of the study:** The study was held from August 2016 to November 2017.

Results: Data was analyzed according to the intention-to-treat principle. In a total 400 women whom recruited in the study, 160 were excluded. So we ended in to 240 women whom randomized and allocated in to 2 groups to intervention. Primary outcome measure was preterm birth. The most important secondary outcome is a composite of poor neonatal outcome (including bronchopulmonary dysplasia (BPD), periventricular leucomalacia, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity (ROP), sepsis and perinatal death). There was no statistically significant difference between both groups as regarding to age, gravidity, parity, body mass index, mean cervical length, and number of previous preterm labor. There was no significant difference between two groups as regard preterm premature rupture of membranes (P.PROM). There was no significant difference between two groups as regard time of delivery there was no significant difference between both groups in Need for NICU admission, neonatal birth weight, APGAR score, fetal complications (RDS, jaundice, BPD, HIE, NEC, bleeding, sepsis or even neonatal death). Long term neurodevelopmental complications was not conducted at this study as it needs more time. In maternal complications there was no significant difference between both groups.

Conclusion: Further randomized controlled trials with larger sample size should be done to demonstrate the efficacy of low dose Aspirin in prevention of preterm labor and its complications.

Keywords: IGF-1, IGF-2, Insulin- like growth factors 1 and 2; **TVUS:** Transvaginal ultrasound.

INTRODUCTION

Preterm birth: defined as any live birth occurring through the end of the last day of the 37th week (259th day) following the onset of the last menstrual period⁽¹⁾.

Preterm deliveries are those that occur at less than 37 weeks' gestational age; however, the low-gestational age cutoff, or that used to distinguish preterm birth from spontaneous abortion, varies by location. In the USA, the preterm delivery rate is 12–13%; in Europe and other developed countries, reported rates are generally 5–9%⁽²⁾.

Preterm birth rate has risen in most industrialized countries, with the USA rate increasing from 9.5% in 1981 to 12.7% in 2005⁽³⁾.

Preterm births account for 75% of perinatal mortality and more than half the long-term

morbidity. Although most preterm babies survive, they are at increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications⁽⁴⁾.

The obstetric precursors leading to preterm birth are: delivery for maternal or fetal indications, in which labor is either induced or the infant is delivered by prelabour caesarean section. Spontaneous preterm labor with intact membranes, preterm premature rupture of the membranes (PPROM), irrespective of whether delivery is vaginal or by caesarean section. Preterm labor is now thought to be a syndrome initiated by multiple mechanisms, including: infection or inflammation, uteroplacentalischaemia or hemorrhage, uterine overdistension, stress and other immunologically mediated processes⁽⁵⁾.

progesterone is a potent inhibitor of the formation of gap junctions between myometrial cells. These intercellular communications are essential for the propagation of coordinated uterine muscle activity leading to labor⁽⁶⁾.

Meis et al. reported the results of a large multicenter trial of 17alpha hydroxyl progesterone. Delivery at less than 37 weeks was reduced from 54.9% in the placebo group to 36.3% in the treatment group. Similar reductions were seen in delivery at less than 35 weeks, from 30.7% to 20.6%, and delivery at less than 32 weeks, from 19.6% to 11.4%⁽⁷⁾.

Low-dose aspirin (LDA) has been noted to reduce the preterm birth (PTB) rate in multiple meta-analyses of the preeclampsia (PreE) prevention trials⁽⁸⁾.

It is unclear if this effect of LDA is entirely due to a reduction in indicated PTB versus reductions in preterm premature rupture of membranes (PPROM) or spontaneous PTB. In the Maternal-Fetal Medicine Unit (MFMU) high-risk Aspirin (HRA) study, a near significant decrease in PTB was found despite no effect on preeclampsia. The objective of this study was to assess the impact of LDA on indicated PTB, spontaneous PTB, and PPROM PTB in the MFMU HRA study population⁽⁹⁾.

PATIENTS AND METHODS

Study type: A double blinded randomized placebo controlled clinical trial.

Study settings: This study conducted at outpatient clinic of Ain Shams University Maternity Hospital.

The study was approved by the Ethics Board of Ain Shams University.

Time of the study: The study was held from August 2016 to November 2017.

Sample size justification:

Sample size:

Sample size was calculated using PASS© version 11 program, setting the type-1 error (α) at 0.05 and the power ($1-\beta$) at 0.8.

Results showed that the incidence of preterm birth in treatment group with 17 α OH progesterone was 36.3%⁽⁷⁾. Assuming a drop of PTL by 12% was occur in patient on low dose aspirin plus 17 α OH progesterone so incidence of preterm birth was drop reaching 24.3% in such group. Calculation according to these values produced **a minimal sample size of 120 cases** in each group.

Inclusion criteria:

- Age between 20-35 years old.

- History of idiopathic preterm labor.
- Singleton.
- Gestational age between 14_24 weeks.

Exclusion criteria:

- Multiple pregnancy.
- <14 weeks of gestation.
- >24 weeks of gestation.
- Previous abdominal or vaginal cerclage (current or planned cervical cerclage).
- History or current medical disease during pregnancy.
- Fetal anomalies.
- Scarred uterus (previous caesarian section or myomectomy).
- Ruptured membrane.
- Symptoms of preterm labor.
- Polyhydraminos.
- Placenta previa.
- +ve screening test for group B streptococcal infection (GBS).
- +ve screening test for bacterial vaginosis (B.V.)
- Evidence of uterine anomalies.
- On tocolytic drugs.
- Any woman who had to be delivered before term for medical or obstetric indications.

METHODS

After approval of the faculty`s committee, all women participating were subjected to the following:

- Complete history taking, complete clinical examination.
- Gestational age and fetal viability confirmed by ultrasonography.
- Routine antenatal laboratory investigations, including: (blood group and Rh typing, full blood count and urine analysis).
- Patients were recruited between 14-24 weeks of gestation.

All 240 pregnant women were distributed randomly into two groups:

A. Randomization:

Was done using computer generated randomization sheet using MedCalc© version 13.

- **Group A (study group):** women received low dose aspirin (75mg acetyl salicylic acid) (*Aspocid 75 mg tablet produced by chemical industries development (CID, Giza, A.R.E)*) once daily from 14 weeks of gestation to 34 weeks of gestation and 17 alpha hydroxyl progesterone in the form of (*Cidolut depot IM 250 mg amp produced by*

chemical industries development (CID, Giza, A.R.E) once weekly from 24w to 34w of gestation.

- **Group B (control group):** women received placebo once daily from 14 weeks of gestation to 34 weeks of gestation and (*Cidolut depot IM 250 mg amp. produced by chemical industries development (CID Giza A.R.E)*) once weekly from 24w to 34w of gestation.

B. Allocation and concealment:

240 opaque envelopes were numbered serially and in each envelope the corresponding letter which denotes the allocated group were put in one box and given to a third party (nurse) who assigned the women to study arms. Each woman will be invited to pull out an envelope.

After the envelope was opened, the patient was allocated according to the letter inside. Once allocated, the treatment was revealed to both the investigator and the patient. A total 240 females were allocated to intervention in to two groups

Group A (study group):

- 120 females received allocated intervention (*Cidolut depot 250 mg amp. Once weekly and Aspocid 75mg tab. Once daily from 14 w to 34 w.*)

Group B (control group):

- 120 females received allocated intervention (*Cidolut depot 250 mg amp. Once weekly and placebo tab. Once daily from 14 w to 34 w.*)

C. Follow up:

The following data sheet was taken from every patient:

Full history taking stressing on high risk factors

Personal data:

Name, age, , residency, occupation, special habits, phone numbers, husband name and occupation.

Past medical and surgical history:

History of DM, hypertensive disorders, cardiac problems. Renal disease, chest troubles and past history of laparotomies or other operations.

Family history.

Contraceptive history.

Obstetric history

Including full details of previous pregnancies (Date, fetal outcome, onset and mode of delivery, gestational age at delivery and any associated complication)

History of present pregnancy

Estimated Gestational age from 1st day of LMP or ultrasound early done in current pregnancy.

Medical and surgical history to define high risk factors and exclusion criteria.

- ROM, labor pains and vaginal bleeding which are all exclusion criteria.
- Satisfaction of fetal kicks as a method to estimate fetal wellbeing.

Physical examination

- General examination: BP, pulse, temperature, BMI every 2 weeks.
- Cardiac and chest examination
- Routine antenatal laboratory investigations, including: (blood group 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).
- P/V examination (if indicated): for assessment of presenting part, pelvic capacity, cervical changes and presence of intact or ruptured membranes.

Gestational age at delivery, Onset and mode of delivery.

Neonatal outcome: (Apgar score, birth weight, ICU admission, postpartum complications).

Maternal complications during delivery (if present)

Side effects of the drugs(if present).

The nature and aims of the work were fully discussed to all women who agreed to participate in the study. The procedure was explained to the patients and prior verbal consent for all the study was taken.

Data on pregnancy outcome were obtained from the filing system in the delivery ward, and for those that delivered at home or in other hospitals, from the patients themselves.

Ultrasound Examination:

All patients were regularly *followed up* in the outpatient antenatal every two weeks by vaginal (14-24) and abdominal ultrasound till delivery.

- **Transabdominal** was done for assessment of fetal viability, number, fetal biometry (BPD-FL-TAD), placental (site and maturity), liquor (amount and turbidity), cervical measurements
- **Cervical length** was measured by *transvaginalsonography* every two weeks from 14-24 week.

Accurate cervical length measurements begin at the internal os, follow the path along the end cervical canal, and end at the external os. If the canal was curved (a deviation of canal >5mm from straight line from the internal os to external os), then the canal could either be traced, or the sum of 2 straight lines that follow the curve of the canal could be used⁽¹⁰⁾.

- Presence or absence of funneling by **transvaginal sonography**. Funneling of the cervix is defined as the opening of the internal cervical os on ultrasound⁽⁹⁾.
 - The equipment used was **SAMSUNG SonoAce R5 ultrasound (Korea)** with transabdominal probe 3.5MHz and transvaginal probe 8MHz.
- d. **Primary outcome measure** was preterm birth, defined as birth at a GA of less than 37 weeks.
- e. **Treatment:** was continued to 34 weeks of gestation.
- Statistical methods:** Analysis of data was done on an intention to treat basis using SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). **Categorical variables** were presented as number and percentage and between-group differences were compared using **Fisher's exact test** (for nominal data) or the **chi-squared test** for trend (for ordinal data). **Normality of numerical data distribution** was examined using the **Shapiro-Wilk test**. Normally distributed numerical variables were presented as **mean ± SD** and inter-group differences were compared using the **unpaired t test**. **Relative risk or risk ratio (RR)** is the ratio of the probability of an event occurring in an exposed group to the probability of the event occurring in comparison, non-exposed group. **Odds ratio (OR)** is a measure of association between an exposure and an outcome. The OR represents the **odds** that

an outcome will occur given a particular exposure, compared to the **odds** of the outcome occurring in the absence of that exposure. Time to event analysis was done using the **Kaplan-Meier method**. **Multivariable binary logistic regression analysis** was done to examine the relation between the use of low dose aspirin plus 17- α -hydroxyprogesterone and the incidence of preterm delivery. Two-sided p-value <0.05 was considered statistically significant.

RESULTS

Table 1: Demographic characteristics of both study group

Variable	Group A (n=120)	Group B (n=120)	P-value*
Age (years)	28 ± 3	28 ± 3	1.000
BMI (kg/m ²)	27.2 ± 2.3	26.8 ± 1.5	0.112

Data are mean ± SD.

*Unpaired Student t test.

This table shows that in, treatment group the mean age was 28 years. The mean BMI was 27.2

In Control group the mean age was 28 years. The mean BMI was 26.8. There was no significant difference (p>0.05) in the mean age or BMI between two groups.

Table 2: Past obstetric history of both study groups

Variable	Group A (n=120)	Group B (n=120)	P-value*
Gravidity			0.712
G2	53 (44.2%)	45 (7.5%)	
G3	33 (27.5%)	38 (31.7%)	
G4	26 (21.7%)	30 (25.0%)	
G5 or higher	8 (6.7%)	7 (5.8%)	
Parity			0.762
P1	67 (55.8%)	64 (53.3%)	
P2	45 (37.5%)	45 (37.5%)	
P3	8 (6.7%)	11 (9.2%)	
Frequency of previous abortions			0.818
Nil	95 (79.2%)	93 (77.5%)	
1 miscarriage	17 (14.2%)	20 (16.7%)	
2 miscarriages	7 (5.8%)	5 (4.2%)	
3 miscarriages	1 (0.8%)	2 (1.7%)	
Frequency of previous PTL			0.691
1 PTD	108 (90.0%)	107 (89.2%)	
2 PTD	12 (10.0%)	12 (10.0%)	
3 PTD	0 (0.0%)	1 (0.8%)	

Data are number (%). *Chi-squared test for trend.

This table shows no significant difference (p>0.05) between 2 groups regarding gravidity, parity, frequency of previous miscarriage or frequency of previous PTL.

Table 3: Hemodynamic and laboratory parameters in both study groups

Variable	Group A (n=120)	Group B (n=120)	P-value*
HR (bpm)	79 ± 5	80 ± 5	0.123
SBP (mmHg)	111 ± 5	113 ± 5	0.002
DBP (mmHg)	70 ± 5	73 ± 5	0.001
MAP (mmHg)	84 ± 5	86 ± 5	0.002
Hemoglobin (g/dl)	11.2 ± 0.8	11.3 ± 0.7	0.304
RBS (mg/dl)	81 ± 7	80 ± 7	0.270

Data are mean ± SD.

*Unpaired Student t test.

This table shows no significant difference ($p>0.05$) between both groups regarding heart rate, (systolic, diastolic and mean arterial blood pressure), hemoglobin and random blood sugar.

Table 4: Results of obstetric assessment of both study groups

Variable	Group A (n=120)	Group B (n=120)	P-value
Cervical length (cm)	3.38 ± 0.29	3.45 ± 0.34	0.088*
PROM	12 (10.0%)	17 (14.2%)	0.322#

Data are mean ± SD or number (%).

*Unpaired Student t test.

#Fisher's exact test

This table shows that in treatment group (A): mean cervical length was 3.38. While in control group (B): mean cervical length was 3.45. And there was no significant difference ($p>0.05$) between both groups regarding mean cervical length and number of cases experienced PROM in this pregnancy.

Table 5: Gestational age at delivery, mode of delivery and birth weight and Apgar score in both study groups

Variable	Group A (n=120)	Group B (n=120)	P-value
Gestational age at delivery (weeks)	37.4 ± 1.7	37.4 ± 1.7	1.000*
Mode of delivery			1.000#
NVD	120 (100.0%)	119 (99.2%)	
CS	0 (0.0%)	1 (0.8%)	
Birth weight (g)	3035 ± 552	2950 ± 538	0.228*
Apgar score	8 ± 1	8 ± 1	1.000*

Data are mean ± SD or number (%).

*Unpaired Student t test.

#Fisher's exact test.

This table shows that mean gestational age at delivery was 37.4 in both groups. All women in both groups delivered normal vaginal delivery except for one woman who delivered by CS due to breech presented baby. Mean birth weight at delivery in treatment group was 3035 gram. While

it was 2950 in control group. Mean Apgar score was 8 in both groups.

There was no statistical significance ($P>0.05$) between both groups regarding gestational age at delivery, mode of delivery, birth weight and Apgar score.

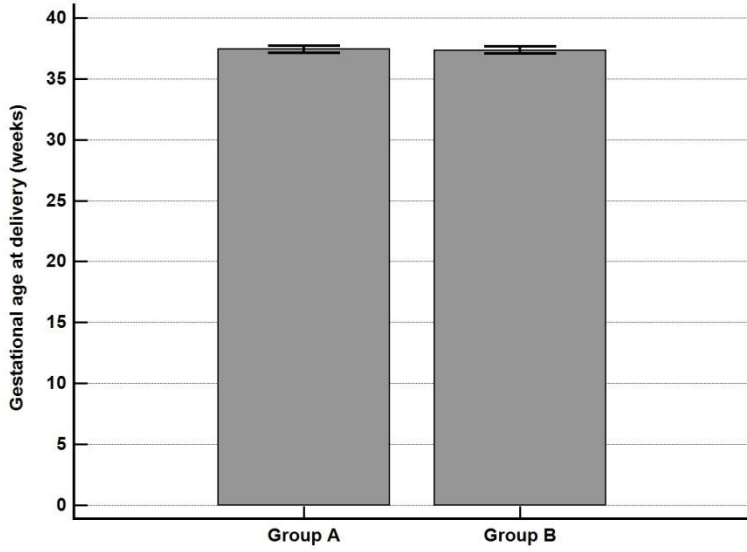


Figure1: Mean gestational age at delivery in both study groups. Error bars represent the 95% confidence interval.

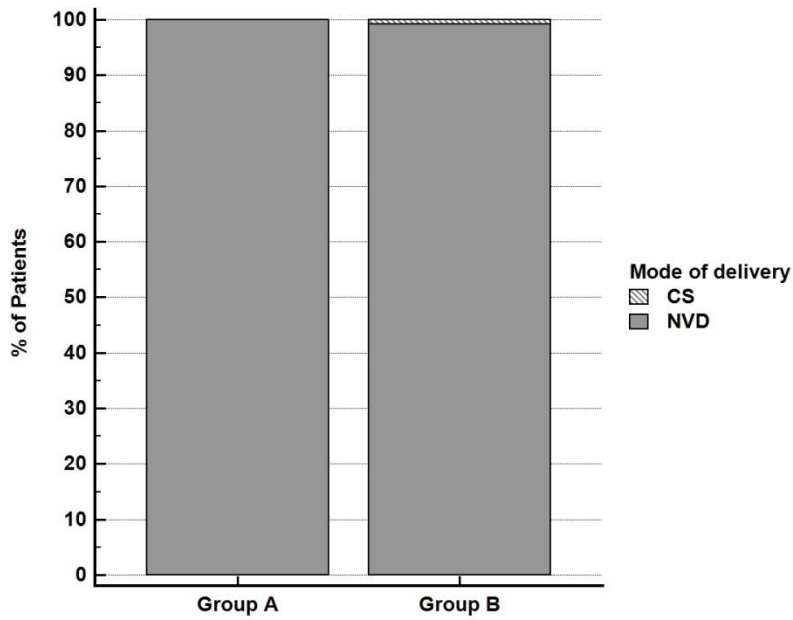


Figure2: Mode of delivery in both study groups.

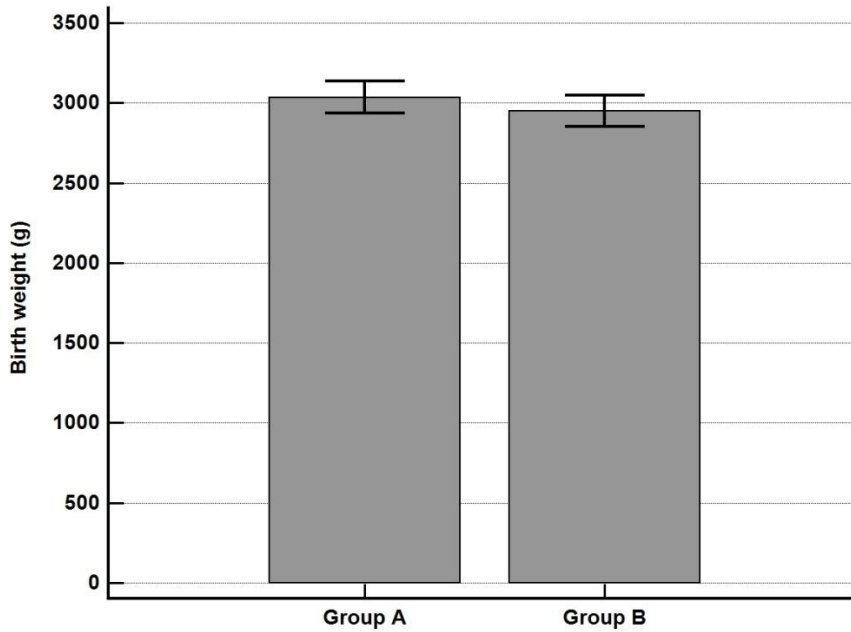


Figure 3: Means birth weight in both study groups. Error bars represent the 95% confidence interval.

Table 6: Incidence of preterm delivery in both study groups

Variable	Group A	Group B	p-value*
PTD	17 (14.2%)	22 (18.3%)	0.484

Risk analysis for PTD

Relative risk	0.77
95% CI	0.43 to 1.38
z statistic	0.871
p-value#	0.384
NNT (Benefit)	24.0
95% CI	19.4 (Harm) to 7.4 (Benefit)

Data are number (%).

NNT = number needed to treat.

* Fisher's exact test.

#Z-test.

This table shows that in treatment group there were 17 women (14.2%) had preterm delivery (gestational age <37w).

While in control group there were 22 women (18.3%) had preterm delivery (gestational age <37w). Making relative risk 0.77 between both groups. Also making number needed to be treated 24 (not being beneficial).

There was no significant difference ($P > 0.05$) between both groups in preterm delivery (gestational age <37w).

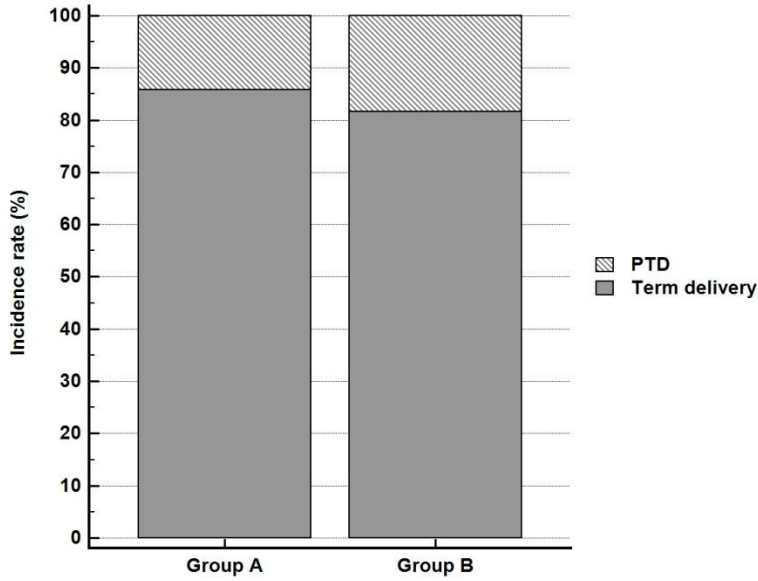


Figure 5: Incidence of preterm delivery in both study groups.

Table 7: Incidence of maternal adverse outcomes in both study groups

Variable	Group A (n=120)	Group B (n=120)	P-value*
PPH	7 (5.8%)	9 (7.5%)	0.797
Perineal tear	9 (7.5%)	8 (6.7%)	1.000
Maternal sepsis	1 (0.8%)	4 (3.3%)	0.370

Data are number (%).

*Fisher's exact test

This table shows no significant difference ($P > 0.05$) between both groups in cases which had postpartum hemorrhage, perineal tear and maternal sepsis.

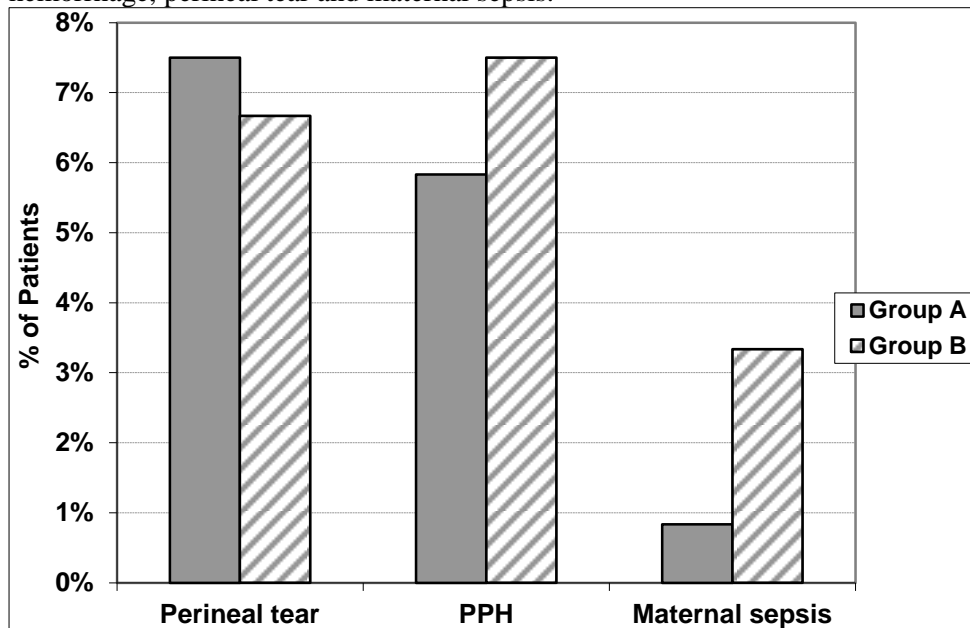


Figure 6: Incidence of maternal adverse outcomes in both study groups.

DISCUSSION

Preterm birth (<37 weeks of gestation) is the most common cause of neonatal morbidity and mortality worldwide. Worldwide in 2010 an estimated 14.9 million neonates were born preterm of whom 1.6 million were born <32 weeks of gestation⁽¹³⁾.

Preterm birth accounts for 70% of all neonatal mortality and for 40% of childhood neurological morbidity⁽¹⁴⁾.

The risk of mortality being inversely proportional to gestational age at birth. Babies who survive have increased rates of disability compared with babies who are not born preterm.⁽¹¹⁾

Rates of disability among survivors have hardly changed over this time period, with rates of bronchopulmonary dysplasia, major cerebral scan abnormality, weight and head circumference (less than 2 standard deviations) being maintained at 68%, 13%, 44% and 23% respectively, although there has been an increase in the proportion treated for retinopathy of prematurity from 13% to 22%⁽¹¹⁾.

The major long term consequence of prematurity is neurodevelopmental disability. This can range from severe motor abnormalities, such as cerebral palsy, through to less severe cognitive abnormalities⁽¹²⁾.

The global burden of neurodevelopmental disabilities is driven by the number of babies born at each of these gestations, and is therefore greatest for babies born between 32 and 36 weeks, less for those born between 28 and 31 weeks, and least for those born at less than 28 weeks' gestation⁽¹³⁾.

Two studies published in 2003 suggested that vaginal progesterone and/or intramuscular 17 hydroxyprogesterone caproate could prevent preterm birth in women at high risk^(7,8).

Also **Likis et al.** found in their systematic review and meta-analysis that progestogens prevent preterm birth when used in singleton pregnancies for women with a prior preterm birth⁽¹⁵⁾.

A recent publication of a large trial showed that vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes⁽¹⁶⁾.

An increasing body of evidence suggests that utero-placental ischemia plays a major role in the genesis of spontaneous preterm labour. Placental vascular pathology and placental bed pathology are common findings in women with a spontaneous preterm birth⁽¹⁷⁾ and increased resistance at midtrimester Doppler measurement of uterine artery flow provides an increased risk of spontaneous preterm birth⁽¹⁸⁾. In addition, women with a spontaneous preterm birth have an increased

risk of developing cardiovascular disease later in life⁽¹⁹⁾.

These findings suggest an overlap with other ischemic placental diseases such as preeclampsia.

Randomized controlled trials and meta-analysis have demonstrated that low-dose aspirin initiated before 16 weeks' gestation is associated with a significant decrease of preeclampsia and intrauterine growth restriction, and most likely the severe and preterm forms of these diseases⁽²⁰⁾.

As observed by **Tyler et al.** and in agreement with current best evidence, aspirin leads to a decrease of early-onset preeclampsia and therefore a decrease in the rate of very preterm births related to preeclampsia. High-risk women who delivered before 28 weeks despite the appropriate use of aspirin were potentially destined to worse perinatal outcomes without the use of aspirin. Moreover, initiation of aspirin in women with preterm labor or premature rupture of membrane could have led to the prolongation of pregnancy and the further growing of intra amniotic infection and inflammation: a major contributor to cerebral palsy⁽²¹⁾.

Aspirin initiated when deep placentation disorders are irreversible, is not beneficial, and in fact potentially harmful. An increased risk of placenta abruption cannot be excluded when low-dose aspirin is begun after 16 weeks^(20, 22).

Aspirin is a safe intervention in pregnancy as a recent review commissioned by the 'U.S. Preventive Services Task Force' concluded⁽²³⁾.

This study is randomized controlled clinical trial. The objective of this study was to evaluate the prophylactic role of administration a combination of low dose aspirin and 17 hydroxyprogesterone caproate (17 OHPC) in reducing incidence of preterm birth in women with history of previous preterm birth.

In this study we chose 240 pregnant females on basis of being singleton pregnancy with history of previous preterm delivery at 14 weeks gestation, age between 20-35 years old, intact membranes, no effacement and no dilatation, no cerclage, not on tocolytic drugs, not a scarred uterus, no history of medical disease during pregnancy, and no congenital fetal malformations. Gestational age was calculated on the basis of the last normal menstrual period, and ultrasonographic examination.

The pregnant women were randomly assigned in two groups: Study group: include 120 pregnant female received low dose aspirin (Aspidol 75mg tab) once daily initiated from 14 weeks of gestation to 34 weeks of gestation with 17 OHPC (cidolut depot 250mg amp) once weekly from 24w to 34w of gestation.

Control group: include 120 pregnant females received placebo from 14 weeks of gestation to 34 weeks of gestation with 17 OHPC (cidolut depot 250mg amp) once weekly from 24w to 34w of gestation.

The pregnant ladies were showed how to use the medication and schedule of follow up:

- There was no statistically significant difference between both groups as regarding to age, duration of marriage, gravidity, parity, body mass index, and number of previous preterm labor. This agreed with the studies of *Chawanpaiboon and Santawibul*⁽²⁴⁾.
- This result doesn't agree with *Mella et al.*⁽²⁵⁾ which found that higher maternal BMI in the first trimester and a greater change in BMI during pregnancy were associated with longer gestation and an increased risk of postdates pregnancy. Higher maternal BMI during the first trimester was also associated with decreased likelihood of spontaneous onset of labor at term and increased likelihood of complications.
- There was no significant difference between two groups regarding mean cervical length.
- Transvaginal ultrasound (TVU) has become the gold standard for measurement of cervical length and evaluating cervical widening⁽²⁴⁾.

Diagnosis of cervical insufficiency in women with one or two prior second-trimester pregnancy losses or preterm births and cervical length ≤ 25 mm on TVU examination or advanced cervical changes on physical examination before 24 weeks of gestation. The diagnosis of cervical insufficiency is usually limited to singleton gestations because the pathogenesis of second-trimester pregnancy loss/preterm delivery in multiple gestations is usually unrelated to a weakened cervix. In addition, preterm labor, infection, abruptio placenta, and bleeding placenta previa should be excluded, as these disorders could account for biochemically mediated cervical ripening leading to second-trimester pregnancy loss or preterm delivery independent of structural/anatomic cervical weakness⁽²⁶⁾.

- In the comparison between two groups as regard route of delivery knowing that women in both groups delivered normal vaginal in their previous parity, only one female in control group delivered CS due to breech presentation.
- There was no significant difference between two groups as regard preterm premature rupture of membranes (PPROM) as it happened in 12 cases in study group and in 17 cases in control group
- There was no significant difference between two groups as regard time of delivery as in study group

103 women delivered full term comparing to 98 in control group with median 37.71 in study group and 37.86 in control group.

This agree with *Jessel et al.*⁽⁹⁾, study which found no reduction in the rate of PTB in any subgroup treated with LDA as stratified by GA at delivery, type of PTB, or risk-group, with the exception of PPROM <35 weeks, a finding of doubtful significance given multiple comparisons. The attributable risk of PTB was high and LDA started relatively late, possibly limiting the generalizability of these findings.

This also agree with *Mackenzie*⁽²⁷⁾, that progesterone treatment initiated in the second trimester of pregnancy among women at increased risk of spontaneous preterm birth had decreased its occurrence by 43% prior to 32 weeks and not agree with studies on low-dose aspirin initiated before 16 weeks gestation is associated with a significant decrease of preeclampsia and intrauterine growth restriction, and most likely the severe and preterm forms of these diseases⁽¹⁹⁾.

And this also agreed with *Meis et al.*⁽⁷⁾ study in which 250 mg of 17 alpha-hydroxyprogesterone caproate (17OHPC) weekly injections were used in women with history of spontaneous preterm labor from 20 to 36 weeks of gestation and reported that the success rate of inhibition of contraction of preterm labor birth was 70.6% (90/306) in progesterone group compared with 54.9% (69/153) in placebo group and the difference was statistically significant, and concluded that 17 alpha-hydroxyprogesterone caproate could be effective in prevention of preterm Labor.

Also in a double-blind, placebo controlled trial of 17OHPC for prevention of recurrent PTB. 195 women delivering at less than 37 weeks of gestation were included in the analysis; 111 received 17P and 84 received placebo. Baseline demographic characteristics including maternal age, parity, and body mass index (BMI) were presented; only BMI differed between groups. The mean interval between the final injection and delivery, and the gestational age at delivery were also similar between groups. When analyzing labor characteristics, there was no significant difference in duration of labor, duration of ruptured membranes, or need for labor induction between those receiving 17P and those receiving placebo. In this cohort of women with a history of PTB, weekly antenatal 17P was not associated with differences in labor characteristics among women delivering prior to term⁽²⁸⁾.

- According to neonatal outcome:

- Need for NICU admission: there was no significant difference between both groups as in study group 21 admitted in comparison to 22 neonate needed to be admitted to NICU.
- Median Days of admission in NICU were 11 days in study group compared to 13 days in control group. This is in agreement with *DEfranco et al.*⁽²⁹⁾ who found that progesterone administration to patient with a history of previous preterm birth decrease the rate of preterm birth and lower the frequency of newborn admission to the intensive care unit and a shorter length of neonatal stay⁽²⁹⁾.

There was no significant difference between neonatal birth weight as median was 3035gram;SD (\pm 552)in study compared to 2950 gram; SD (\pm 538) in control group P value (0.226).These doesn't agreed with *Meis et al.*⁽⁷⁾ study who reported that the incidence of LBW (<2500g) in progesterone group was (27.2%) compared to (41.1%) in placebo group and the difference is statistically significant.

- In Apgar score there also was no significant difference between both groups as it was 8 in study group and control group. These results also agreed with results of *Chawanpaiboon and Sutantawibul (2012)* study⁽²⁴⁾.
- There was no significant difference between both groups in fetal complications on comparing the occurrenceof (RDS, jaundice, BPD, HIE, NEC, bleeding, sepsis or even neonatal death). Overall fetal complications in study group 19 and 20 in control group. This is in agreement with *Rouse et al.* who found that no statistically significant difference identified between progesterone and placebo group in perinatal death⁽³⁰⁾.

Dodd et al. found that considering a women to be at increased risk of preterm birth, progesterone was associated with no significant difference in perinatal death⁽³¹⁾.

- Long term neurodevelopmental complications was not conducted by this study as it would need more time than the limited one for this study.
- In maternal complications there was no significant difference between both groups as:
 - Bleeding occurred in 7 women in study group 6 of them were moderate, only 1 case of severe bleeding comparing to bleeding happened in 9 cases in control with also 1 case of severe bleeding.
 - Sepsis occurred only in one case in study group compared to occurrencein4 cases in control group.
 - No maternal death occurred in both groups.

This agrees with safety of 17P administration in pregnancy is well documented by animal and clinical studies. Reviews of this topic

by knowledgeable authors have uniformly concluded that no evidence exists that administration of 17P in pregnancy represents a significant risk to mother, fetus, or newborn.

Sibai et al.⁽²²⁾ found no increase in the frequency of adverse effects among the women in the aspirin group, as was reported in previous studies in this study, aspirin had a greater benefit among women with higher initial systolic blood pressure, which agrees with our study.

REFERENCES

1. **American College of Obstetricians and Gynecologists (2003):**ACOG Practice Bulletin No. 48. Cervical insufficiency *ObstetGynecol.*,102: 1091-1099.
2. **Berghella V and Saccone G(2016):**Fetal fibronectin testing for prevention of preterm birth in singleton pregnancies with threatened preterm labor: a systematic review and meta analysis of randomized controlled trials. *Am J ObstetGynecol.*, 215: 431-8.
3. **Hamilton BE, Martin JA and Ventura SJ (2006): Births:** preliminary data for 2005. Health E-Stats. <http://www.cdc.gov/>.
4. **Saigal S and Doyle LW (2008):** Preterm births: An overview of mortality and sequelae of preterm birth from infancy to childhood. *Lancet*, 371: 261.
5. **Goldenberg RL, Culhane JF and Iams JD (2008):**Epidemiology and causes of preterm birth, the lancet, 371 (9606): 75-84.
6. **Garfield RE, bytautiene E, Vedernikov YP et al. (2000):** Modulation of rat uterine contractility by mast cells and the in mediators. *Am. J. Obstet. Gynecol.*, 183: 118–125
7. **Meis PJ, Klebanoff M, Thom E and Mitchell P (2003):** Prevention of recurrent preterm delivery by 17-alpha hydroxyl progesterone caproate. *N Engl J Med.*, 348: 2379–2385.
8. **Hauth JC, Cliver S, Hodgkins P et al. (2001):**Mid-trimester metronidazole and azithromycin did not prevent preterm birth in women at increased risk: A double-blind trial. *Am J ObstetGynecol.*, 185: S86.
9. **Owen J, Yost N, Berghella V et al. (2001):** Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *JAMA.*, 286: 1340.
10. **Jessel R, Allshouse A and Heyborne K(2015):** does low dose Aspirin prevent preterm birth published in *American Journal of Obstetrics and Gynecology*, 212 (1): S342.
11. **Costeloe KL, Hennessy EM, Haider S et al. (2012):** Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ.*, 345: e7976.
12. **MacKay DF, Smith GC, Dobbie R and Pell J (2010):** Gestational age at delivery and special educational need: retrospective cohort study of 407,503 schoolchildren. *PLoS medicine*,7(6):e1000289.
13. **Blencowe H, Lee AC, Cousens S et al. (2013):**Preterm birth-associated neurodevelopmental impairment

- estimates at regional and global levels for 2010. *Pediatric research*, 74 (1):17–34.
14. **Hack M and Fanaroff A (1999):** Outcomes of children of extremely low birth weight and gestational age in the 1990's. *Early Hum Dev.*, 53 (3): 193–218.
 15. **Likis FE, Edwards DR, Andrews JC et al. (2012):** Progestogens for preterm birth prevention: a systematic review and meta-analysis. *Obstet Gynecol.*, 120(4):897-907.
 16. **Norman JE, Marlow N, Messow CM et al. (2016):** Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. *Lancet*, 387 (10033): 2106–16.
 17. **Kelly R, Holzman C, Senagore P et al. (2009):** Placental vascular pathology findings and pathways to preterm delivery. *Am J Epidemiol.*, 170 (2): 148–58.
 18. **Misra VK, Hobel CJ and Sing CF (2009):** Placental blood flow and the risk of preterm delivery. *Placenta*, 30 (7): 619–24.
 19. **Heida KY, Velthuis BK, Oudijk M, et al. (2016):** Cardiovascular disease risk in women with a history of spontaneous preterm delivery: A systematic review and meta-analysis. *Eur J PrevCardiol.*, 23 (3): 253–63.
 20. **Bujold E, Roberge S, Lacasse Y, Bureau , et al . (2010):** Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis. *ObstetGynecol.*, 116 (2 Pt 1): 402–14.
 21. **Tyler CP, Paneth N, Allred EN et al. (2012):** Brain damage in preterm newborns and maternal medication: the ELGAN Study. *Am J ObstetGynecol.*, 207: 192.e1-9.
 22. **Sibai BM, Caritis SN, Thom E et al. (1993):** Prevention of preeclampsia with low-dose aspirin in healthy, nulliparous pregnant women. The National Institute of Child Health and Human Development Network of Maternal Fetal Medicine Units. *N Engl J Med.*, 329: 1213-8.
 23. **Henderson JT, Whitlock EP, O'Connor E et al. (2014):** Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: a systematic evidence review for the U.S. Preventive services task force. *Ann Intern Med.*, 160 (10): 695–703.
 24. **Chawanpaiboon S and Sutantawibul . (2012):** Effect of Cervical Length to The Efficacy of Nifedipine and Bed Rest for Inhibiting Threatened Preterm Labor *J Med Assoc Thai.*, 95 (5): 636-43.
 25. **Mella MT and Berghella V (2009):** Prediction of Preterm Birth: Cervical Sonography, 33(5): 317–324.
 26. **Romero R (2007):** Prevention of spontaneous preterm birth: the role of sonographic cervical length in identifying patients who may benefit from progesterone treatment. *Ultrasound ObstetGynecol.*, 30 (5): 675–86.
 27. **Mackenzie R, Walker M, Armson A and Hannah ME (2006):** Progesterone for the prevention of preterm birth among women at increased risk: a systematic review and meta-analysis of randomized controlled trials. *Am J ObstetGynecol.*, 194: 1234–1242.
 28. **Judy AE, Yasser Y, Yair J (2016):** Effect of 17-alpha hydroxyl progesterone caproate on labor at preterm gestations *American Journal of Obstetrics &Gynecology*, 2016: S294
 29. **DeFranco EA, O'Brien JM, Adair CD et al.(2007):** Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo controlled trial. *Ultrasound Obstet Gynecol.*, 30(5):697–705
 30. **Rouse DJ, Caritis SN, Peaceman AM et al. (2007):** A trial of 17 Alpha-hydroxy progesterone caproate to prevent prematurity in twins. *N Engl J Med.*, 357: 454–461.
 31. **Dodd JM, Flenady VJ, Cincotta R and Crowther CA (2008):** Progesterone for the prevention of preterm birth: A systematic review. *Obstet. Gynecol.*, 112:127–134.