

# Effect of progesterone on latent phase prolongation in patients with preterm premature rupture of membranes

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## SUMMARY

**AUTHORS' CONTRIBUTION:** (A) Study Design · (B) Data Collection · (C) Statistical Analysis · (D) Data Interpretation · (E) Manuscript Preparation · (F) Literature Search · (G) No Fund Collection

**Objectives:** To investigate the effect of progesterone given before 32 week gestation to cases of Preterm Premature Rupture of Membranes (PPROM) on prolongation the pregnancy and thereafter reduce neonatal morbidities.

**Methods:** This study was conducted on 112 pregnant women diagnosed with PPRM and admitted to Ain shams university hospital for standard management. They were divided into two groups: the study group was given weekly IM progesterone and the control group which received a placebo therapy to test the effect of progesterone in prolonging the latency period in such cases. The age of recruited cases was between 18-35 years, carrying Singleton pregnancy, at gestational age between 24-34 weeks. The pregnant women were randomly arranged by closed envelop method according to randomization table into two groups, (placebo group and intramuscular progesterone group), 56 women in case (control) group & 56 women in (intramuscular progesterone) group. All patients were followed up until delivery. The primary outcome measure is prolongation of the pregnancy until 34.0 weeks of gestation or documentation of fetal lung maturity at 32.0 to 33.9 weeks.

**Results:** Respiratory distress syndrome (RDS), neonatal intensive care unit (NICU) admission and neonatal death were statistically non-significant but less frequent among intramuscular group. The present study failed to elucidate an evidence that 17OHP-C is beneficial in women with PROM.

**Conclusion:** 17-hydroxyprogesterone caproate when given to cases of preterm prelabor rupture of membranes does not show a significant effect of prolongation of latency period in such cases vs. placebo.

**Keywords:** Preterm premature rupture of membranes; Progesterone

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## INTRODUCTION

Prelabor rupture of membranes (PLROM) is disruption of the chorion and amnion before the onset of active labor. It account for a serious perinatal morbidity and mortality. It occurs in 18-20% of pregnancies. Preterm prelabor rupture of membranes (PPLROM) occurs in 1-5% of all pregnancies. It is the underlying cause for nearly 30-40% of all preterm birth.

Preterm delivery is defined as the delivery before the end of the 37th week of gestation and is possibly the single most important health related issue in pregnancy. Latency period is the period from the occurrence of prelabor ROM till start of preterm delivery. Preterm delivery carries the highest risk of morbidity and mortality on the neonates especially in the developing countries nearly 85% [1].

A prolonged latent period in cases of PPRM is not without a risk and is also linked to maternal, fetal and neonatal morbidities especially if infections occurred [2]. The vital organs may be affected as in pulmonary hypoplasia, the heart, enterocolitis, periventricular leukomalacia and intracranial hemorrhages beside the complications of prolonged oligohydramnios with the development of adhesion bands that may lead to amputations of limbs [3-5].

Now it is possible to screen for patients at a risk of developing preterm labor and PPRM by the serial transvaginal measurement of cervical length and cervicovaginal fetal fibronectin which is the glue that connect the fetal chorion to maternal decidua and rise in the level of it is denoting fetal membranes disruption [6-8]. Unfortunately, uptill now there is no sufficient therapeutic option to suppress or delay birth.

In cases of PPRM, management options include bed rest, oral fluids, no coitus or PV examination, prophylactic antibiotics, corticosteroids to enhance fetal lung maturity [9], tocolytics [10], cervical cerclage [11] and most notably progesterone [12-14].

The mechanism of action of Progesterone includes a strong effect in suppressing premature birth [15]. However there is a dilemma regarding if it is should be used in the clinical practice and if used what is the best route and the effective dose of such medication [1,16].

Progestins as progesterone and 17- hydroxyprogesterone caproate (17P) were used effectively to suppress preterm labor specially in patients with short cervix [17,18], and those who responded well to tocolysis [19,20]. Still, the

role of 17P in PPRM is not well studied. Several actions may be proposed in prolonging the latent phase of prelabor ROM such as inhibiting the inflammatory substrates, depression of the production of gap junction proteins which are the contractions associated proteins and have a major role in the progression of preterm birth [21].

The present study was undertaken to test the hypothesis that 17P given to mothers with PROM before 32 weeks of gestation will prolong the pregnancy and thereby reduce neonatal morbidity.

## PATIENT AND METHODS

### Type of the Study

Randomized controlled interventional prospective study.

### Study Settings

This clinical trial was conducted at Ain-Shams University Maternity Hospital, in the period from January till December 2020.

### Study Population

The patients were recruited from women admitted from obstetric clinic or from emergency room and from patients following up in outpatient clinic 112 patients will be recruited to this study.

### Sample size justification

Depending on Combs, et al. [22] who found that Mean  $\pm$  SD of GA at delivery in IM progesterone and placebo groups  $30.0 \pm 4.0$  and  $28.0 \pm 3.0$  days respectively, and assuming the power= 0.80 and  $\alpha=0.05$ , and by using PASS 11<sup>th</sup> release the minimal sample size for an equal size a controlled clinical trial is 51 in each group.

A drop out of 10% was included to avoid the dropped out patients.

### Inclusion criteria

- Singleton pregnancy.
- Gestational age between 24 and 34 weeks.
- They are admitted for Preterm premature rupture of membranes and received prophylactic antibiotics.

### Exclusion criteria

1. Medical or obstetric conditions that could put them at risk for uterine atony and postpartum hemorrhage and infection, such as:

- Emergency Caesarean section
- Chorioamnionitis
- Placenta previa
- Multiple gestation

- Preeclampsia.
- Macrosomia

2. Non reassuring fetal status or fetal distress
3. Presence of fetal anomalies incompatible with life
4. Woman with antepartum haemorrhage
5. Diagnosis of established preterm labour

The included patients were randomized using sealed opaque envelope method into one of two groups:

**Group I (study group):** In which 17-hydroxyprogesterone caproate (17P) (250 mg in castor oil, 1 mL total volume, intramuscular injection weekly) administered in 56 patients.

**Group II (control group):** In which an identical-appearing placebo (1 mL castor oil only) administered another 56 patients.

### Randomization and Blinding

- Included patients were randomized into one of the study groups. Randomization was performed using a computer-generated randomization system (Microsoft office excel, 2007).
- A plan of management was sealed in closed envelopes, numbered according to the randomization tables. Packing, sealing and numbering were all performed by 2 independent doctors other than the investigator.
- Neither the investigator nor the residents following up the patient were aware which patient had received 17-hydroxyprogesterone caproate (17P) therapy and which hadn't (double-blinding). Randomization coding tables were hidden from the investigator till the end of the study.

**Ethics:** Informed written consent was obtained from all participants before recruitment in the study, and after explaining the purpose and procedures of the study and possible risks.

## METHODOLOGY

After taking informed written consent, the recruited patients were subjected to the following:

1. Detailed history and full Examination of the patients (General and abdominal)
2. Pelvic Examination only by sterile cusco speculum to exclude cord prolapse, bloody liquor and cervical dilatation and effacement
3. Non stress test to ensure reassuring fetal well being
4. Ultrasound examination to:
  - a) Assess fetal viability
  - b) Amniotic fluid index

- c) Determine gestational age
- d) Exclude major anomalies
- e) Placental location
- 5. Baseline laboratory investigations: CBC, PT, PTT, Liver and renal function tests

PPROM was established by vaginal examination using sterile Cusco speculum with trickling of liquor from the cervix, pooling of liquor in the posterior fornix or presence of meconium in the vagina which was performed by a single team of physicians.

Sonography was performed with documentation of the estimated gestational age and assessing the Amniotic fluid index by 4 pocket method.

Women were divided into two groups; the intervention group which received 17P IM weekly injections till completed 36 completed weeks and the control group which received placebo (1ml castor oil). All patients received the standard management of PPRM in the form of hospital admission, prophylactic antibiotics and betamethasone to enhance fetal lung maturity. Tocolytics were not given. Fetal surveillance was performed on regular basis (daily Fetal Non-Stress Test and bi-weekly biophysical profile). Signs of chorioamnionitis were watched.

### Primary outcomes

Prolongation of the pregnancy until a favorable gestational age, which we defined as either 34.0 weeks of gestation or documentation of fetal lung maturity at 32.0 to 33.9 weeks.

The investigators agreed that continuation of pregnancy beyond these time points was not indicated.

### 2ry outcomes

1. Latency (interval from randomization to delivery).
2. Composite neonatal morbidity, which will be defined per Mercer, et al. [23] as one or more

of: stillbirth, neonatal death, infant death before hospital discharge, respiratory distress syndrome (RDS), intracranial hemorrhage (ICH) grade 3 or 4, necrotizing enterocolitis (NEC) stage 2 or 3, culture-proven neonatal sepsis within 72 h of birth. In addition to the components defined by Mercer, et al., [23] our definition of composite neonatal morbidity included periventricular leukomalacia (characteristic lesions in the subcortical white matter seen on cerebral imaging studies within 96 h of birth). The occurrence of chorioamnionitis, and puerperal metritis.

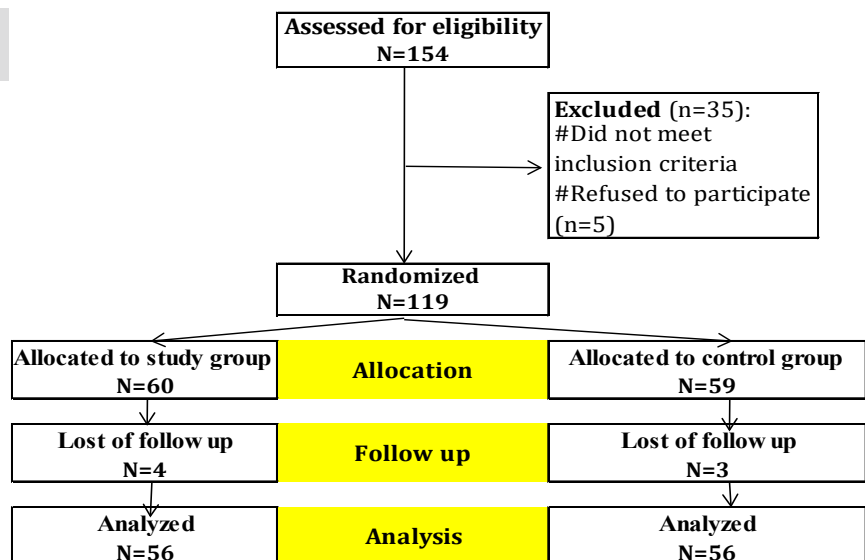
## RESULTS

**Fig. 1.** Presents the flow chart of studied cases and **Tab. 1.** Shows that No significant difference between the studied groups regarding baseline characteristics. **Tab. 2.** And **Fig. 2.** Shows that there is no significant difference between the studied groups regarding causes of termination; contractions, chorioamnionitis and fetal distress. **Tab. 3.** Shows that no significant difference between the studied groups regarding enrollment and gestational age at time of delivery. Latency period was non-significantly higher among study group than among control group. **Fig. 3.** Show that no significant difference between the studied groups regarding rate of delivery. **Tab. 4.** Shows that no significant difference between the studied groups regarding gestational age at delivery. **Tab. 5.** Shows that no significant difference between the studied groups regarding neonatal condition. **Tab. 6.** and **Fig. 4.** Shows that neonatal complications were non-significantly less frequent among study group than among control group. Death was non-significantly less frequent among study group than among control group. **Fig. 5.** Indicates the death among the studied groups

## DISCUSSION

PPROM has many adverse effects on many vital organs of the fetus and neonate. It can cause pulmonary hypoplasia, skeletal deformities due to affection of fetal

**Fig. 1.** Flow chart of the studied cases.



**Tab. 1.** Baseline characteristics among the studied groups.

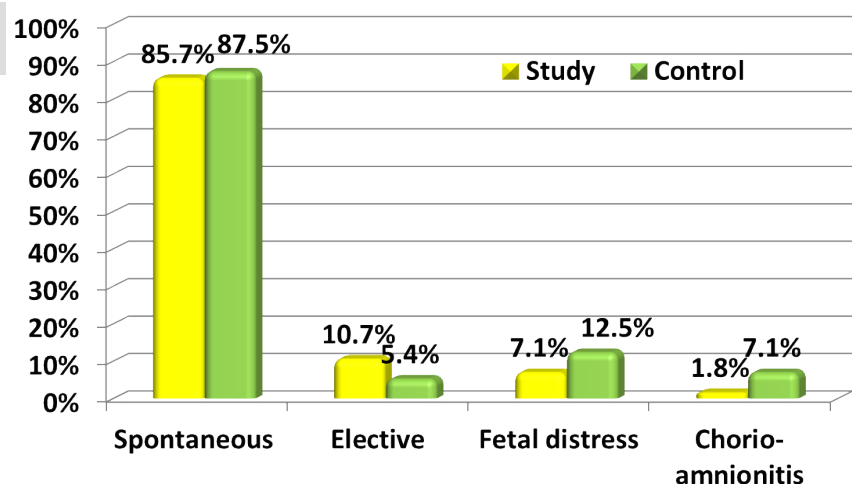
Items	Measure	Study (N=56)	Control (N=56)	P-value
Age (years)	Mean $\pm$ SD	28.2 $\pm$ 4.6	29.3 $\pm$ 3.9	$\wedge$ 0.293
	Range	19.0–35.0	20.0–35.0	
BMI (kg/m <sup>2</sup> )	Mean $\pm$ SD	30.6 $\pm$ 3.2	31.0 $\pm$ 3.3	$\wedge$ 0.448
	Range	24.5–36.0	24.9–36.2	
Parity (n, %)	Primi	17 (30.4%)	15 (26.8%)	#0.676
	Multi	39 (69.6%)	41 (73.2%)	
Hemoglobin (gm/dL)	Mean $\pm$ SD	11.4 $\pm$ 0.9	11.3 $\pm$ 0.8	$\wedge$ 0.876
	Range	9.6–13.8	9.9–13.4	
TLC ( $\times 10^3$ /mL)	Mean $\pm$ SD	7.3 $\pm$ 0.8	7.5 $\pm$ 0.8	$\wedge$ 0.208
	Range	5.9–9.8	5.6–9.2	
CRP	Positive	0 (0.0%)	0 (0.0%)	Not applicable
	Negative (<10 mg/L)	56 (100.0%)	56 (100.0%)	
History of previous abortion		8 (14.3%)	6 (10.7%)	#0.568
History of previous preterm labor		3 (5.4%)	2 (3.6%)	\$0.999

$\wedge$ Independent t-test. #Chi square test. \$Fisher's Exact test

**Tab. 2.** Causes of termination among the studied groups.

Findings	Study (N=56)	Control (N=56)	P-value	RR (95% CI)
Spontaneous	48 (85.7%)	49 (87.5%)	#0.781	0.98 (0.85–1.13)
Elective	6 (10.7%)	3 (5.4%)	\$0.489	2.00 (0.53–7.60)
Fetal distress	4 (7.1%)	7 (12.5%)	#0.341	0.57 (0.18–1.84)
Chorioamnionitis	1 (1.8%)	4 (7.1%)	\$0.364	0.25 (0.03–2.17)
labs	N=1	N=4	-	Mean $\pm$ SE 95% CI
CRP (mg/L)	16.3	16.9 $\pm$ 1.2	$\wedge$ 0.697	-0.6 $\pm$ 1.3 -4.6– 3.5
TLC ( $\times 10^3$ /mL)	24.0	15.0 $\pm$ 6.0	$\wedge$ 0.685	-3.0 $\pm$ 6.7 -24.4–18.3

RR: Relative Rate. CI: Confidence Interval.  $\wedge$ One sample t-test. #Chi square test. \$Fisher's Exact test

**Fig. 2.** Causes of termination among the studied groups.

movements, also, the development of intraamniotic adhesion bands which may lead to amputations of limbs. The cardiovascular and central nervous systems are markedly affected in preterm babies [1,3,5,24]. These complications become more frequent and severe in maternal morbidities as chorioamnionitis and sepsis [25].

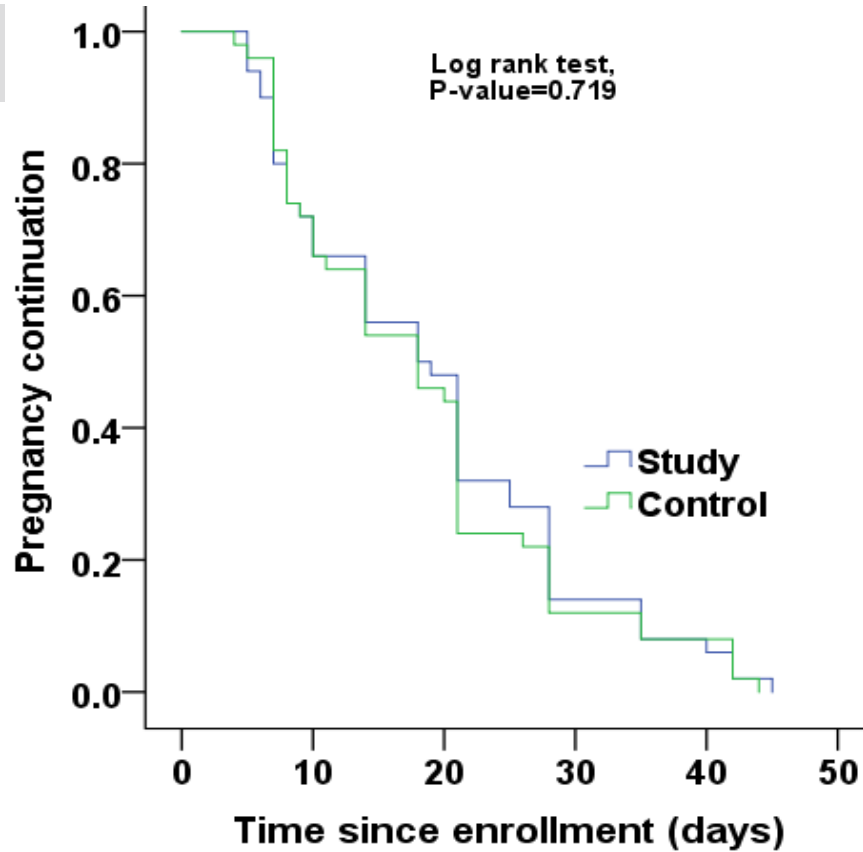
Management of PPRM is usually by expectant management including hospitalization, best rest, fluids, antibiotics, steroids and magnesium sulphate for neuroprotection. The second option is or delivery when the risks of expectant treatment outweigh the benefit [24].

The present study was a prospective, randomized controlled trial to evaluate the effect of intramuscular injection of 17-hydroxyprogesterone corporate (17-OHPC) on latency of pregnancy in patients with PPRM, aiming to prevent the perinatal morbidities and mortality. Eligible 112 patients (according to our inclusion criteria which are patient with PPRM confirmed on clinical examination were randomly allocated to one of two treatment arms in a double blind manner by computer generated system. A total number of 154 patients were recruited and eligible to participate in the study. 30 patient excluded from study not meet inclusion criteria and 5 patient refused to participate.

**Tab. 3.** Enrollment, gestational age at time of delivery and latency period among the studied groups.

Time	Measure	Study (N=56)	Control (N=56)	^ P-value	Mean ± SE 95% CI
Enrolment (week)	Mean ± SD	28.2 ± 2.7	28.4 ± 2.8	0.701	-0.2 ± 0.5
	Range	24.1–34.0	24.3–34.0		-1.2–0.8
Delivery (week)	Mean ± SD	31.2 ± 3.4	31.6 ± 3.6	0.495	-0.4 ± 0.7
	Range	25.1–36.0	25.1–36.0		-1.8–0.9
Latency period (days)	Mean ± SD	20.5 ± 12.0	17.7 ± 11.3	0.215	2.8 ± 2.2
	Range	4.0–44.0	5.0–45.0		-1.6–7.1

**Fig. 3.** Kaplan Meiere curve for time to delivery among the studied groups.



**Tab. 4.** Gestational age at delivery among the studied groups.

Time (weeks)	Study (N=56)	Control (N=56)	^ P-value
<28.0	13 (23.2%)	14 (25.0%)	#0.203
28.0–32	17 (30.4%)	8 (14.3%)	
32.0–34	9 (16.1%)	14 (25.0%)	
≥ 34.0	17 (30.4%)	20 (35.7%)	
#Chi square test			

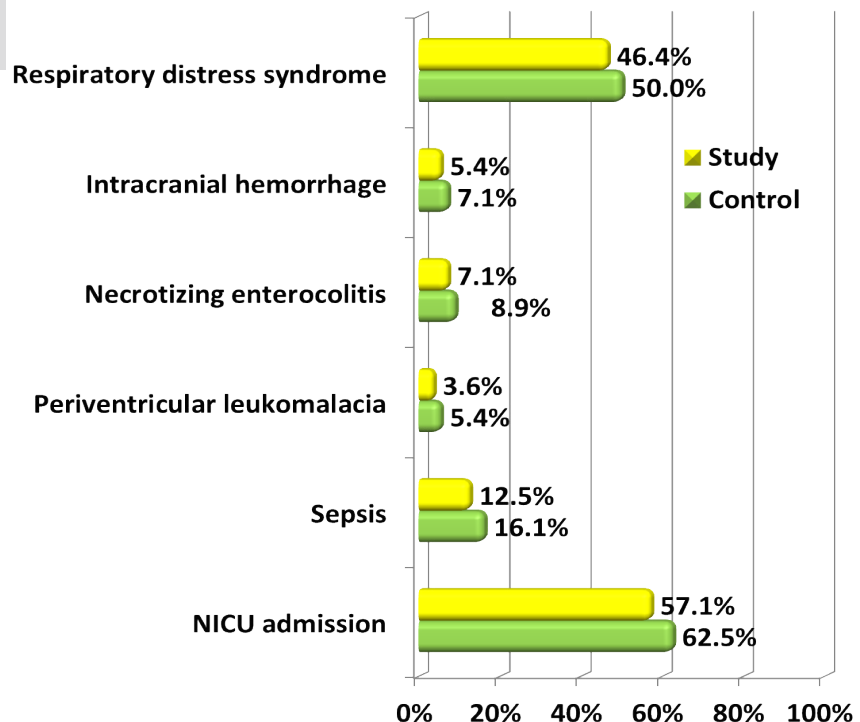
**Tab. 5.** Neonatal condition among the studied groups.

Time	Measure	Study (N=56)	Control (N=56)	^ P-value	Mean ± SE 95% CI
Birth weight (kg)	Mean ± SD	1.9 ± 0.9	1.7 ± 0.9	^	0.2 ± 0.2
	Range	0.5–3.1	0.6–3.0	0.352	-0.2–0.5
APGAR (first minute)	Mean ± SD	5.6 ± 1.3	5.6 ± 1.2	^	0.0 ± 0.2
	Range	4.0–8.0	4.0–8.0	0.879	-0.4–0.5
APGAR (fifth minute)	Mean ± SD	6.4 ± 1.4	6.3 ± 1.2	^	0.1 ± 0.2
	Range	4.0–9.0	4.0–9.0	0.560	-0.3–0.6
Blood PH	Mean ± SD	7.3 ± 0.1	7.3 ± 0.1	^	-0.01 ± 0.02
	Range	7.1–7.5	7.2–7.6	0.516	-0.04–0.02
Labs					RR 95% CI)
WBC (×10 <sup>3</sup> /mL)	≥25.0	7 (12.5%)	9 (16.1%)	#0.589	0.78
	<25.0	49 (87.5%)	47 (83.9%)		(0.31–1.94)
CRP (mg/L)	≥10.0	7 (12.5%)	9 (16.1%)	#0.589	0.78
	<10.0	49 (87.5%)	47 (83.9%)		(0.31–1.94)
RR: Relative Rate. CI: Confidence Interval. #Chi square test					

**Tab. 6.** Neonatal complications and mortality among the studied groups.

Complications	Study (N=56)	Control (N=56)	P-value	RR (95% CI)
<b>Neonatal</b>				
Respiratory distress syndrome	26 (46.4%)	28 (50.0%)	#0.705	0.93 (0.63–1.36)
Intracranial hemorrhage	3 (5.4%)	4 (7.1%)	\$0.999	0.75 (0.18–3.20)
Necrotizing enterocolitis	4 (7.1%)	5 (8.9%)	\$0.999	0.80 (0.23–2.82)
Periventricular leukomalacia	2 (3.6%)	3 (5.4%)	\$0.999	0.67 (0.12–3.84)
Sepsis (culture proven)	7 (12.5%)	9 (16.1%)	#0.589	0.78 (0.31–1.94)
NICU admission	32 (57.1%)	35 (62.5%)	#0.563	0.91 (0.67–1.24)
NICU admission duration (days) N=32,35	3.25 ± 1.19 2.00–5.00	3.09 ± 1.20 1.00–6.00	^ 0.576	0.2 ± 0.3 -0.4–0.7
<b>Mortality</b>				
Stillbirth	0 (0.0%)	0 (0.0%)	-	-
Neonatal death	3 (5.4%)	4 (7.1%)	\$0.999	0.75 (0.18–3.20)
Hospital death	3 (5.4%)	4 (7.1%)	\$0.999	0.75 (0.18–3.20)

RR: Relative Rate. CI: Confidence Interval. ^ Independent t-test. #Chi square test. \$Fisher's Exact test

**Fig. 4.** Neonatal complications among the studied groups.

Among them 119 consented to participate. They were randomized to placebo group and study group. The first group consists of 60 patients with 4 lost in follow up and the second group 59 patient with 3 lost in follow up.

In the study group, progesterone intramuscular (Cidolut depot) (250 mg per week) were administered until delivery or completion of the 36th gestational week and was compared with placebo effect (intramuscular castor oil) in control group. The latent phase and maternal and neonatal outcome variables were compared between the two groups. The two groups were almost identical in the confounding factors, as regards demographic characteristics: Age, parity, BMI (kg/m<sup>2</sup>), Enrollment (weeks) (p values=0.293, 0.676,

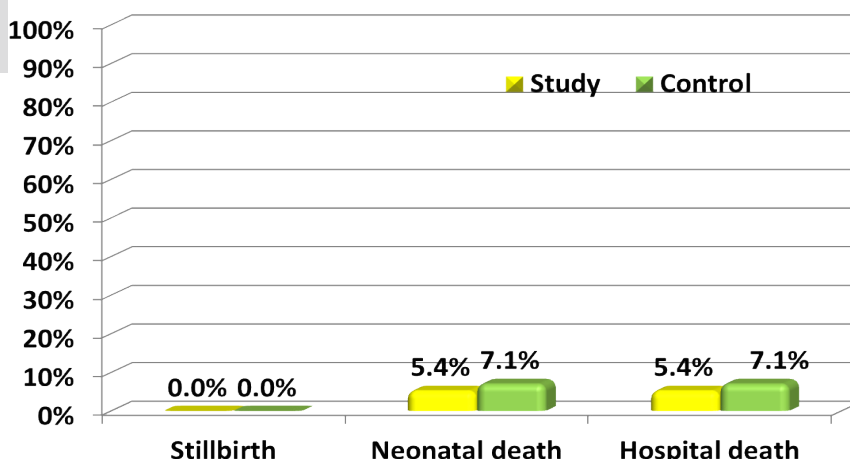
0.448, 0.701) respectively not to affect the study results and interpretation. The mean latent phase was 20.5 ± 12 days in the intervention group *vs.* 17.7 ± 11.3 days in the control group, which was statistically non-significant in the intervention group (P=0.215).

The study results showed that it is no statistically significant difference between the two groups regarding number of neonatal RDS, NICU admission and neonatal death but lower percentage among study group. NICU stay was statistically insignificant between 2 groups.

There is prolongation in the mean GA in (Days) in the study group compared to control group but with non-statistically significance (P value =0.215, CI= -1.6 -7.1).



Fig. 5. Death among the studied groups.



This result is in agreement with [26] who had performed a similar study on 1228 women and also reported that 17P was not effective in prolonging the latency period. Also the drug didn't increase the maternal or neonatal morbidities or mortalities.

Similar results was reported by Combs, et al. [22] and Quist-Nelson, et al. [27] who investigated 17P in singleton gestations with PPRM (n=545 participants). 17-OHPC intake was not associated with a significant increase of the latency period. They also concluded that progesterone did not increase morbidity or mortality in the mother or the child.

Abdali, et al. [28] used progesterone suppositories (400 mg per night) in his study on 120 patients till 34th gestational week and were compared with placebo effect in control group. The latent phase and maternal and neonatal outcome variables were compared between the two groups.

Mirzaei, et al. [29] also performed a clinical study on patients with PPRM. 171 PPRM patients were selected, group 1 (57 patients) using 17OHP 250 mg/week, group

2 (57 patients) using 400 mg progesterone suppositories/day, and group 3 (57 patients) using 17OHP 250 mg/day. 102 patients) did not take the drug. The mean latency from rupture of membranes to delivery was 15/5 days in the first group, 15/2 days in progesterone recipients, and 11/5 days in unmedicated patients. This difference was statistically significant, which contradicts our study.

In a similar study done by Da Fonseca, et al. [30] on 142 women using progesterone (100 mg suppository/day) with placebo. Progesterone significantly reduced the rate of premature birth. This contradicts our studies on the effective role of progesterone in prolonging latency, route of administration, dose, and large sample sizes.

## CONCLUSION AND RECOMMENDATIONS

Weekly intramuscular 17-hydroxyprogesterone caproate does not prolong the latency in PPRM *vs.* placebo. Further studies with larger number of patients are needed to prove or refute our results.

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