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ROLE OF PROGESTERONE FOR MAINTENANCE TOCOLYTIC THERAPY AFTER THREATENED PRETERM LABOR

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ABSTRACT

Background: The rate of preterm labor is higher in the developing countries and it is the main cause of neonatal mortality and morbidity. The prevention of preterm labor has become one of the major objectives of perinatal medicine. The causes of P.T.L in most cases remains unclear. Additionally, despite the identification of P.T.L risk factors; to date, no intervention has been associated with decrease in P.T.L rates ,thus early detection women at high risk of P.T.L , and prophylactic treatment could be one of the best ways to prevent P.T.L.

AIM of the Study: The aim of this study was to verify if vagianl progesterone maintenance therapy after a successfully treated episode of preterm labor could increase latency period.

Patients and Methods: This prospective randomized trial was conducted in the Department of Obstetrics and Gynecology, Zagazig University Hospitals during the period from March 2021 to October 2021. It included 72 pregnant women at high risk for preterm labor. All patients received a single course of dexamethasone, consisting of two injections of 12mg dexamethasone during the first 24 hours after admission. After stoppage uterine contraction the women were divided into 2 groups: The first group (study group) comprised 36 patients. Women were given natural progesterone (prontogest) 200 mg vaginal suppository daily. The second group (control group) comprised 36 patients. Women were not given any drugs and follow up and instructed to limit their physical activity.

Results: We found that progestional agents, reduce the risk of delivery less than 37 weeks of gestation for women at increased risk of spontaneous preterm labour, but their effect in spontaneous abortion or perinatal mortality, or measures of neonatal morbidity is uncertain.

Conclusion: prophylactic administration of 200 mg vaginal progesterone suppositories is associated with a longer latency to delivery and better fetal outcome.

Keywords: Progesterone; Tocolytic Therapy; Preterm Labor

1. INTRODUCTION

Preterm birth is defined as the presence of uterine contractions of sufficient frequency and intensity to produce a progressive effacement and dilatation of the cervix prior to term gestation (between 20 and 37 weeks). preterm birth occurs in approximately 12% of pregnancies and is the leading cause of neonatal mortality and morbidity **[1]**.

In Europe and many developed countries, the preterm birth rate is generally 5-9% and in the USA it has even risen to 12-13% in the last decades. Three obstetric events precede preterm birth: spontaneous preterm births (40-45%), preterm births after premature rupture of membranes (25-30%) and preterm births that are induced for obstetrical reasons (30-35%). By gestational age, 5% of preterm births occur at less than 28 weeks (extreme prematurity), 15% at 28-31 weeks (severe prematurity), 20% at 32-33 weeks (moderate prematurity), and 60-70% at 34-36 weeks (late preterm) **[2]**.

the cause of labor remains elusive, the exact cause of preterm birth is also unsolved. Labor is a complex process involving many factors. Four different pathways have been identified that can result in preterm birth and have considerable evidence, fetal endocrine activation, uterine overdistension, decidual bleeding, and intrauterine inflammation/infection **[3]**.

Activation of one or more of these pathways may happen gradually over weeks, even months. From a practical point a number of factors have been identified that are associated with preterm birth; however, an association does not establish causality **[3].**

Preterm birth is prevented by learning the symptoms of preterm labor and following some simple instructions as getting medical care both before and during pregnancy. Medications sometimes slow or stop labor if they are given early enough. The effectiveness of the progesterone on reducing preterm birth have been confirmed **[4]**.

Progesterone and its receptor are the key mediators for the initiation of labor. It is required for implantation and pregnancy development, and its deficiency lead to decrease in the thickness of endometrium of uterus and abortion **[5]**.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

(Crane et al., [6]) stated that progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a history of spontaneous preterm birth. Progesterone supplementation for asymptomatic women with an identified very short cervical length (< 15 mm) may be considered.

progesterone may help to prevent premature birth in some women who have already had a premature baby **[7]**.

2. PATIENTS AND METHODS

Technical design:

Site of Study:

This prospective randomized trial was conducted in the Department of Obstetrics and Gynaecology, Zagazig University Hospitals during the period from Marsh 2021 to october 2021. It included 72 pregnant women at high risk for occurrence of preterm delivery after cessation of previous episode of preterm regular uterine contraction.

Sample size:

Assuming the mean latency period until delivery was 24.5±17.2 vs 36.1±17.9 among control vs intervention group. At 80% power and 95%CI. the estimated sample will be 72 subject, 36 subjects in each group. Open epi

Inclusion criteria:

individuals with the following criteria were included:

Singleton pregnancy, Gestational age 28-36 weeks calculated from 1 st day of LMP regular menstred cycle and/ or by ultrasongraghy during 1 st trimester, Intact membranes, no cervical cerclage, Woman nearly has the same living and social conditions, no history of smoking.

Diagnosis of preterm labor was according to criteria of **(Goffinet et al. (2007) [8]):**

Regular uterine contraction occurring 4 times in 20 minutes plus progressive change in cervix, Cervical effacement ≥ (50) %, and Cervical dilatation ≥ (2cm).

Exclusion criteria:

Individuals with the following criteria were excluded:

Clinical evidence of intrauterine infection, vaginal bleeding and pre-eclampsia, Urinary tract infection, Fetal growth restriction as judged by ultrasonography, Fetal distress or fetal congenital anomalies, Lack of access to patients for follow up, and PROM (Premature rupture of membrane).

Methodology*:*

Objectives of the study was explained to the women before inclusion in the study. An informed consent was obtained prior to inclusion to the study.

All women were subjected to the following:

Full history taking, Including obstetric history (gravidity, parity, previous preterm labor, history of gush of fluid, number of living children, history of cervicel operation).

Examination including, *General examination* including blood pressure, temperature, pulse and body mass index, *Abdominal examination, Local examination* including inspection of urethra, vulva and perineum for detection of any fluid leakage or blood, *Obstetric ultrasonography to* Determine Amniotic Fluid Index (AFI), Confirms gestational age, Exclude multiple pregnancy, Exclude congenital anomalies in the fetus and the uterus, Detect fetal presentation, and Measure cervical length, And doing aprgr to the fetous

Steps:

At admission, all patients were given:

(a) Intravenous fluids: All patients were given 500 ml ringer solution.

(b) Tocolytic therapy: Patients were given intravenous magnesium sulphate, with an initial bolus of 4-6 gm followed by continuous infusion at a rate of 2-4 gm per hour.

(c) Antibiotics: All patients received antibiotic prophylaxis consisting of intravenous ampicillin (2-gm every 12 hours) for 48 hours.

(d) Corticosteroids: All patients received a single course of corticosteroid, consisting of two injection of 12mg dexamethazone during the first 24 hours after admission to reduce the incidence of neonatal respiratory distress syndrome, intraventricular hemorrhage and perinatal death.

If labor pain still present patients were still admitted and if the patients were stable, they were discharged. Patients were instructed to return every 2 weeks for follow up.

After stoppage of uterine contraction, the women were divided into 2 groups:

First group (study group)

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Women were given natural progesterone (prontogest) 200 mg vaginal suppository daily. The women were instructed to limit their physical activity and continue progesterone vaginal suppository until 36 weeks of gestation.
In cases with recurrent uterine contraction, patients were instructed to return to the hospital.

Second group (control group)

Women were not given any drugs and follow up and instructed to limit their physical activity. In cases with recurrent uterine contraction, patients were instructed to return to the hospital and manage according to the fetal and maternal situations.

Outcome:

Delivery details including the period of gestations, mode of delivery and perinatal outcome were noted. Preterm delivery was defined as delivery at < 37 completed weeks of gestation. It was subclassified into early preterm birth (< 34 weeks), and late preterm birth (34 to < 37 weeks).
Primary outcome:
Primary outcome measures of this study included the time from admission until delivery (latency time) and PTB before 34 or 37 completed weeks of gestation (early and late preterm birth).
Secondary outcome:
Secondary outcome measures were birth weight and perinatal morbidity [respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and the admission to Neonatal Intensive Care Unit (NICU)].

Statistical Methods

Data were entered checked and analyzed using Epi-Info version 6 and SPP for Windows version 8. Data were summarized using the arithmetic mean, the standard deviation, student t test, X^2 (chi-squared) (test of significance).
The threshold of significance is fixed at 5% level (p-value). The results was considered:
Significant when the probability of error is less than 5% ($p < 0.05$).
Non-significant when the probability of error is more than 5% ($p > 0.05$).
Highly significant when the probability of error is less than 0.1% ($p < 0.001$).
The smaller the p-value obtained, the more significant are the results (Dean, 2006).

3. RESULTS

Table (1): Mean age of the studied groups

	Study group (n = 36)	**Control group (n = 36)**	**t**	**p**
Mean ± SD	26.7 ± 4.9	26.2 ± 4.5	0.63	**0.57 (NS)**
Range	**18-35**	**18-34**		

This table show age of studied population mean age of study patients was 26.7 ±4.9 ranging from 18 to 35 years and mean age of control was 26.2±4.5 ranging from 18 to 34 years.
NS: Non-significant when the probability of error is more than 5% ($p > 0.05$).

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Table (2): Maternal demographic and clinical characteristics at randomization

	Study group N=36	Control group N=36)	X^2	p
Nullipara	**20 (55.5%)**	**18 (50%)**	**2.78**	**0.09 (NS)**
Multipara	**16 (44.5%)**	**18 (50%)**	**1.8**	**0.17 (NS)**
Positive history of preterm labor	**12 (33.3%)**	**15 (41.6%)**	**1.8**	**0.17 (NS)**
polyhydramnios	**1(3%)**	**0(0%)**	**0**	**0.13 (NS)**
Previous cervical surgery	**0(0%)**	**1(3%)**	**0**	**0.13 (NS)**
Mean ± SD of GA at admission	**32 ± 1.5**	**32 ± 2**	**0.28**	**0.77 (NS)**

NS: Non-significant when the probability of error is more than 5% ($p > 0.05$).

This table show 20 of patient and 18 of control were nulliparous, 41.6% of the patient from control group and 33.3% from study group had previous preterm labor. And show the mean gestational age of the study group was 32 ±1.5 weeks ranging from 28 to 36 weeks and the mean gestation age of the control group 32 ±2 weeks ranging from 28 to 36 weeks.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Table (3) mean gestational age at delivery and latency period

	Study group N =36	Control group N=36	t	p
Mean ± SD of GA at delivery	37.5* ± 2.8	33.6 ± 4.7	4.96	**< 0.001 (HS)**
Range	32-38	28-36		
Mean ± SD of latency period	7.4 ±4.1*	3.3 ±4.4	MW = 24.3	**< 0.001 (HS)**
Range	**1-6**	**0-5**		

MW = Mann-Whitney

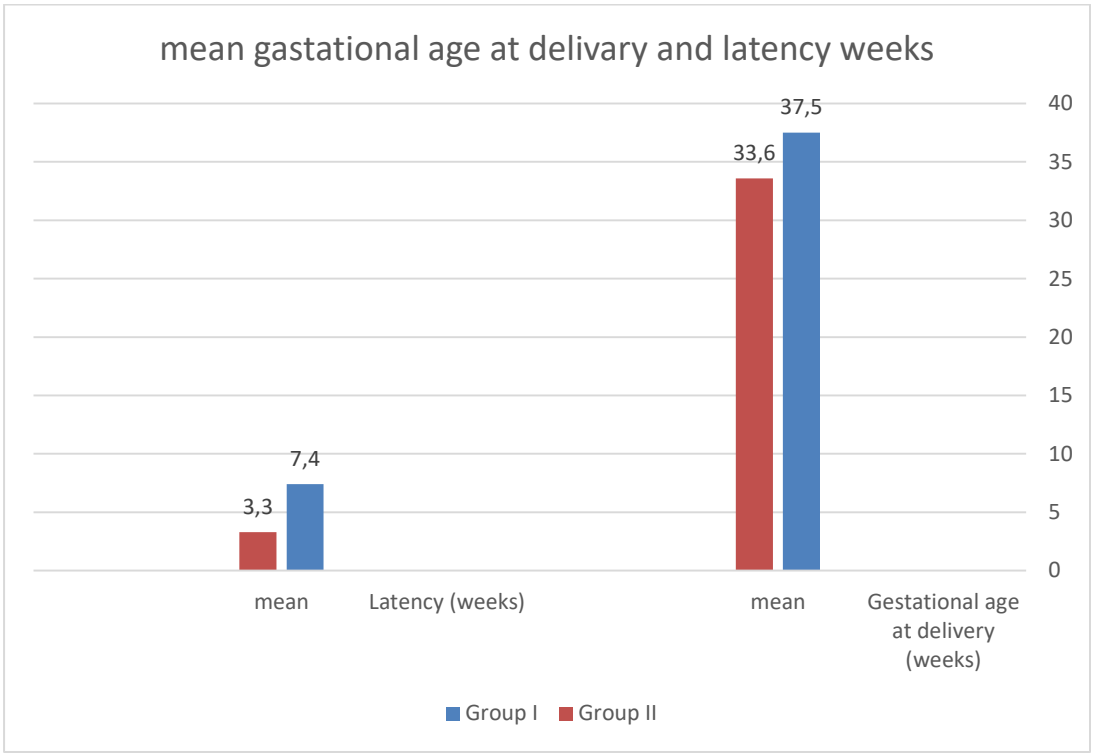

Figure 1: Mean Gestational Age at Delivery and Latency Weeks

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Table (4): Primary outcome results among studied groups

Time of delivery	(Study group) (n = 36)	(Control group) (n = 36)	X^2	p
< 34 weeks	10	16	1.385	0.239 NS
From 34 to 37 weeks	11	8	0.474	0.491 NS
>37weak	15	2	9.941	0.002 sig

There were statistically significant differences at (0.01) level between the study and control group (>37week)

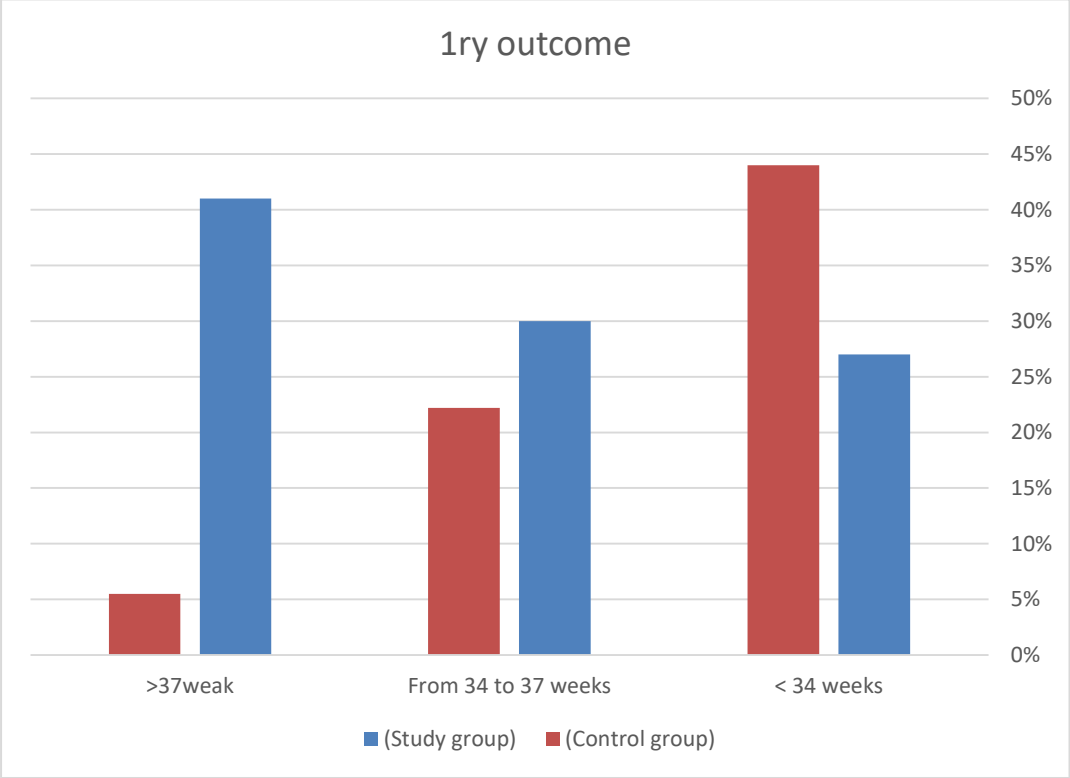

Figure 2: Primary Outcome

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

Table (5): Neonatal outcome

	Group I (Study group) (n = 36)	Group II (Control group) (n = 36)	p
Birth weight (kg)	3.18 ± 0.5	2.60 ± 0.5	**0.48**
Apgar < 7	2 (5.5%)	3 (8.3%)	**0.5**
Admission to NICU	4 (11.1%)	6 (16.6%)	**1**
RDS	5 (13.8%)	8 (22.2%)	**0.27**
Sepsis	2 (5.5%)	4(11.1%)	**0.11**
Neonatal death	**1 (2.7%)**	**6 (16.6%)**	**0.03**

This table show Secondary outcome.

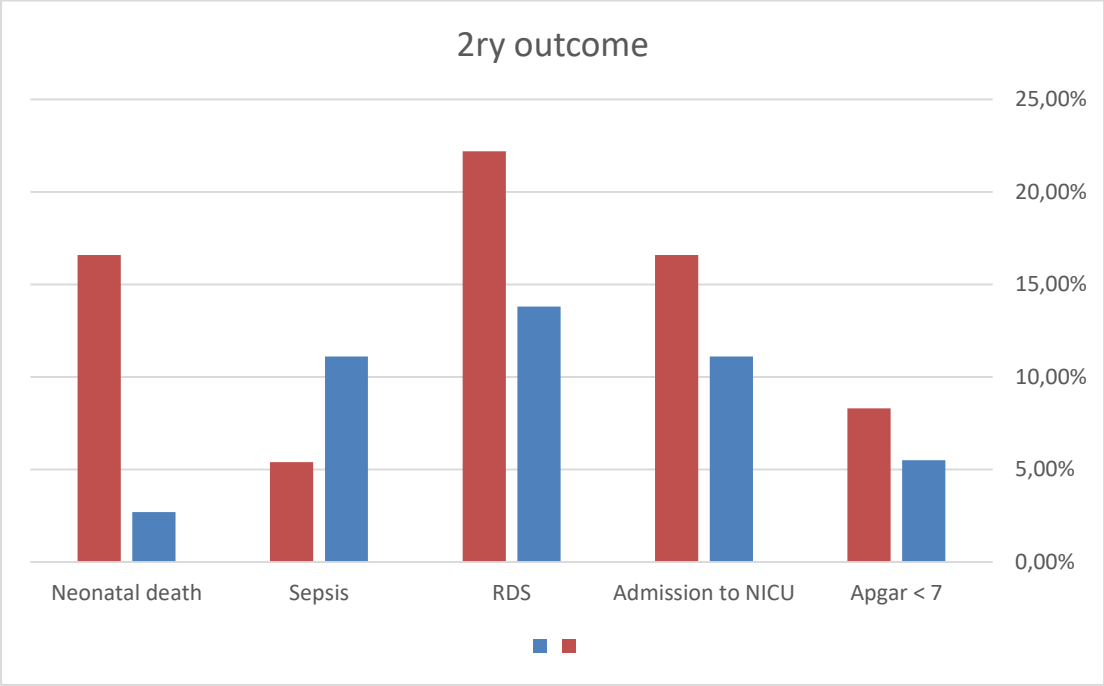

Figure 3: Secondary Outcome

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

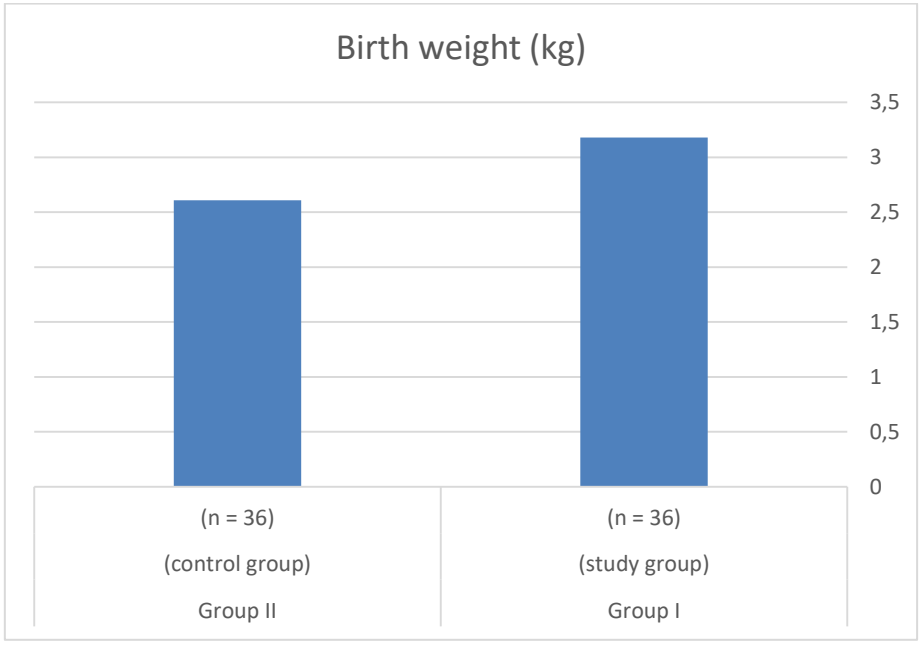

Figure 4: Birth W

DISCUSSION

Preterm delivery is the major cause of neonatal morbidity and mortality, and prevention of preterm delivery due to PTL is a primary goal of obstetricians **[9].** The incidence rate of preterm birth is rising over the last 20 years and continues to rise primarily because of the increased multiple pregnancies resulting from assisted reproduction **[10].**

Despite scientific advance, efforts to prevent preterm birth can be disappointing. The major goal is to delay preterm birth long enough to allow the transfer of the women about to deliver preterm to a facility with a neonatal intensive care unit and to administer corticosteroid to enhance fetal lung maturation.

Prerequisite for the success of this strategy is the reliable identification of women who will give birth preterm.

However, these symptoms of preterm labor strongly suggest preterm birth contraction even if combined with cervical effacement and dilatation don't reliably predict preterm birth**.**

Treatment of the patient with even the slightest signs premature contraction is a well-recognized issue, such treatment results in unnecessary hospitalization and waste provider time and medication **[6]**.

Administration of tocolytic drug in itself is a risk from fluid overload to pulmonary edema, the fetus and the mother are also exposed potent drugs that have significant side effects. It is suggested that 8 to 10 patients admitted to the hospital, with diagnosis of suspected preterm labor probably don't require treatment in the hospital at all **[6].**

The effectiveness of progesterone on reducing PTB in high risk groups of women has been confirmed**.** Two double blind trails: one with daily vaginal progesterone suppositories **[11]** and the other that utilized weekly intramuscular injection of 17 α- hydroxyl progesterone **[12]** claimed that the treatments effectively reduced the incidence of PTB in women at risk for spontaneous PTL.

Progesterone has an important role in maintaining uterine quiescence and its thought to act by suppressing smooth muscle activity in the uterus **[13].** Progesterone administration was considered to be effective in the prevention of PTL at risk women, especially women with history of previous PTL**,** and women with short cervix diagnosed with mid trimester transvaginally ultrasonography **[12].**

In this study, 72 women diagnosed as threated PTL were included in which 36 women were included in study group in which 200 mg vaginal progesterone was given to prevent PTL and 36 cases were considered as a control group.

In this study, the result of preterm birth before 34 weeks in study group was 27.7% and in control group was 44% and preterm from34 to 37 weeks in study group was 30.5% and control group 77.7%. Similar result of the study carried by **[11].** in which 142 women included in which 100mg vaginal progesterone was used nightly from 24 – 34 weeks, and they found that there was significant reduction

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 03, 2021

of preterm labor < 34 (17% in study group 46% in control group and preterm from34 to 37 week 26% in the study group and 69% in the control group)

In additional, there was other study carried by **(Hassan and Romero et al., [14])** in which 458 women with singleton gestations at 19- 23 weeks with 84% of included women had no prior PTB, in which 90 mg vaginal progesterone 90 mg gel was used daily started to 20 – 24 weeks until 36 weeks was associated with 45% significant reduction in PTB < 33 weeks 9% versus 16% in placebo group.

Another study performed 71 singleton gestation with prior of PTB, with vaginal progesterone 100mg. suppositories daily between (24 – 34) weeks was associated with significant reduction in the incidences of PTB < 37 weeks (24% versus 50%) and < 34 weeks 5,4% versus 26.5% in the placebo group **[15]**.

In this study, the latency period until delivery is longer in study group (7.4 ± 4.1 weeks) than in control group (3.3 ± 4.4 weeks) with P of 0.001. In the other study carried by **(Borna et al., [16])** on 70 women, 400 mg vaginal progesterone was used daily, he found that the latency period is longer (7.3 ± 4.2) than the control group (3.2 ± 4.3).

In this study, the using of 200mg vaginally progesterone is effective and that give the same results as vaginally progesterone 400mg. so decreasing the cost and the dose of the drug and decreasing the side effect of the drugs.

On the other hand, **(Facchinettei et al., [17])** reported that treatment by 17 α hydroxyl progesterone associated with reduction of PTl and longer latency period, in which their study included 75 women dividing into study and control groups and they found that the latency period was (35.3 ± 19 day) in the study group and (25.5 ± 15.1) days in the control group.

(Grobaman et al., [18]) suggested that the patient who were treated with 250 Mg I.M 17 α hydroxyl progesterone gives better results than vaginal progesterone, his study performed on 657 singlet gestation with CL ≤ 30 mm at 16- 24 week with using 250mg I.M weekly the incidence of PTL < 35 week was 13.5 versus 16.1% and p value, 0.3 and the incidence of PTL < 37 week was 15 versus 24.2% with P value 0.8. for study and control group respectively.

In other study carried by **(Fonesca et al., [19])** in which 250 women with singletone gestation at 20 -25 week was given vaginal progesterone 200 mg started at 24 weeks until 34 week was associated with decrease incidence of PTL < 19% versus 34% in control group.

Other study which performed by **(Durnwald et al., [20])** in which included the effect of progesterone on the cervical length. In a singleton gestation with PTL, they found that 17 α hydroxy progesterone has not been associated with an effect on the development of the short cervix.

On the other hand, there is a study which performed by **(O'Brien and Defranco et al., [21])** in which they describe that vaginal progesterone was associated with significant reduction in the incidence of short cervical length in women with singleton gestations and prior PTL.

4. CONCLUSION

This study concluded that prophylactic administration of 200 mg vaginal progesterone suppositories after successful tocolysis in patients with threatened idiopathic PTL is associated with a longer latency to delivery and better fetal outcome.

Funding: No funding was received for this study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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