

## The Effect of Antenatal Progesterone in the Prevention of Preterm Birth

By

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### ABSTRACT

The current study aimed to evaluate the efficacy of progesterone supplementations to prevent preterm birth in women with a high risk of preterm birth. **Patients and method:** An analytic preventive interventional trial study was conducted in Salahadeen General Hospital, Iraq during the period from the 1st of January to the 30th of June 2023. A convenient sample of 100 pregnant women at 20-28 weeks of gestation with a high risk of preterm birth was enrolled. Those women were submitted into two groups: The intervention group: Included 50 pregnant women who receive progesterone supplementations. Control group: Included 50 pregnant women who received a placebo. The pregnant women were followed until delivery, the outcome including preterm birth <34 weeks, preterm birth <37 weeks, and neonatal outcome including birthweight, birth asphyxia, and neonatal intensive care unit admission. **Results:** The incidence of preterm birth was significantly lower in the intervention than in the control group (P-value=0.044). Among those with a cervical length of <25mm the incidence of preterm birth (<34 weeks and <37 weeks) was significantly lower in the intervention group compared to the control group (P-value=0.497). The percentage of neonates with a birth weight of <2.5 kg was significantly lower in the intervention group compared to the control group (P-value=0.017). **Conclusion:** Progesterone supplementation was significantly effective in reducing the incidence of preterm birth among pregnant women who were at risk of preterm birth. Progesterone supplementation was significantly effective in reducing the incidence of preterm birth among pregnant women with a short cervix. Progesterone supplementation was significantly effective in reducing the percentage of neonates with of birth weight of <2.5kg.

**Keywords:** Preterm birth, Progesterone, Cervical length, Iraq

## Introduction

According to the world health organization, preterm birth is defined as births before 37 completed weeks of gestation or fewer than 259 days from the first date of the last menstrual period<sup>(1)</sup>. It is stratified in three degrees of severity according to gestational age (GA) at birth<sup>(2, 3)</sup>: Extremely preterm (24 weeks+0 days to 27 weeks +6 days), very preterm (GA =28 weeks+0 days to 31 weeks+6 days), and moderate to late preterm (GA = 32 weeks+0 days to 36 weeks+6 days).

The precise mechanism for the cause of preterm birth is still unclear in most cases<sup>(4)</sup>. The physiopathological mechanisms involved in the process of spontaneous preterm birth seem to differ between pregnant women with intact membranes and women who have premature rupture of membranes, particularly if these patients are asymptomatic<sup>(5)</sup>. Clinical and scientific data shows that several pathogenic mechanisms can combine to form a final common route that results in spontaneous preterm labour. Among these mechanisms, the four major pathogenic processes are Premature activation of the fetal hypothalamic-pituitary-adrenal axis in response to maternal and/or fetal stress, severe inflammatory response, infection and/or an alteration in the microbiome of the genital tract, decidual haemorrhage (placental abruption), and pathologic distention of the uterus<sup>(6)</sup>.

Worldwide, preterm birth is a significant contributor to long-term morbidity and mortality in children under the age of five years. Preterm newborns that do survive have a greater chance of neurodevelopmental abnormalities, respiratory and digestive disorders, cognitive problems, motor sensory disorders, and behavioural disorders compared to infants born at term<sup>(7, 8)</sup>.

Additionally, preterm birth places financial and social hardship on the family involved. This is due to the high cost of providing neonatal intensive care, the increased length of hospital stay necessitated by premature infants, and the unexpected mortality rate among very young infants<sup>(9)</sup>. The effects of preterm birth persist far into childhood, adolescence, and adulthood. There is evidence that premature children have a higher risk of neurodevelopmental and sensory disorders, respiratory illnesses with lower achieved lung growth, cardiovascular disease, increased risk of type 2 diabetes mellitus, hypertension, and physical disabilities in addition to other chronic diseases earlier in adulthood than those born at term<sup>(10, 11)</sup>.

The prediction and prevention of preterm births are among the important issues of obstetrics. The most effective method for lowering preterm birth rates would be to predict them by

identifying the risk factors<sup>(12)</sup>. At the same time, women who are not at risk of preterm birth could avoid unnecessary interventions like antenatal tocolysis and corticosteroids<sup>(13)</sup>. Preterm labour can be predicted using risk score systems, digital cervix inspection, biochemical indicators, and ultrasonographic determination of cervical length<sup>(12)</sup>. There are two tests recommended by the American College of Obstetricians and Gynecologists (ACOG) recommends for the prediction of preterm birth: cervical length measurement and the fibronectin test<sup>(5)</sup>. A short cervix is defined as being  $\leq 25$ mm in length when measured by transvaginal ultrasound<sup>(14)</sup>. Fetal fibronectin levels greater than or equal to 50 ng/mL at or after 22 weeks have been associated with an increased risk of spontaneous preterm birth<sup>(15)</sup>.

Progesterone is a female sex hormone, it plays a crucial role in the maintenance of pregnancy. The circulating level of progesterone is elevated during pregnancy; During the first 8 weeks of pregnancy, the corpus luteum is the major source and the placenta thereafter. One of the major mechanisms of progesterone action in maintaining pregnancy is the inhibition of the contractions of the myometrium<sup>(16)</sup>. Progesterone has another role in maintaining pregnancy by suppressing the calcium–calmodulin–myosin light chain kinase system. Additionally, progesterone has documented anti-inflammatory properties that raise a possible association between inflammation, change in progesterone receptor expression, and the onset of preterm birth<sup>(17)</sup>.

The ACOG advises progesterone supplementation (vaginal or intramuscular) for individuals with a history of spontaneous preterm birth and a singleton pregnancy to reduce the risk of a repeat preterm birth. Treatment typically begins between 16 and 20 weeks of pregnancy and lasts for the remaining 36 weeks of pregnancy or until birth<sup>(18)</sup>. The National Institute for Health and Care Excellence preterm birth guidelines currently recommend giving a choice between vaginal progesterone and cervical cerclage for women with a short cervix and a history of spontaneous preterm birth<sup>(19)</sup>.

Aim of the study: To evaluate the efficacy of progesterone supplementations to prevent preterm birth in women with a high risk of preterm birth.

### **Patients and method**

An analytic preventive interventional trial study was conducted in Gynecology and Obstetrics Department at Salahadeen General Hospital, Iraq during the period from the 1st of January to the 30th of June 2023. A convenient sample of 100 pregnant women at 20-28 weeks of gestation with a high risk of preterm birth was enrolled in the current study. The gestational age was

calculated according to the date of the last menstrual period and early pregnancy ultrasound examination. Those women were submitted into two groups: **The intervention group:** Included 50 pregnant women who receive progesterone compounds. **Control group:** Included 50 pregnant women who received a placebo. **Exclusion criteria included** women who had contraindications to progesterone use, recognized structural or chromosomal fetal abnormality, planned cervical sutures, pregnancy loss due to trauma, and women with uterine malformation.

The pregnant women in the intervention groups received either weekly 17  $\alpha$  hydroxyprogesterone caproate injection, daily progesterone suppositories, or oral micronized progesterone (Duphaston®) as oral 10 mg tablets twice a day, according to preference and toleration of the pregnant women. The treatment continued till 34 weeks of gestation or until delivery. While the pregnant women in the control received a placebo.

The participating pregnant women were followed until delivery, the outcome including preterm birth <34 weeks, preterm birth < 37 weeks, and neonatal outcome including birthweight, birth asphyxia, and neonatal intensive care unit (NICU) admission.

Microsoft EXCEL 2019 and Statistical Package for the Social Sciences, version 26 were used for data entry and analysis. The descriptive analysis will focus on frequencies and percentages. Continuous variables were presented as mean  $\pm$  Standard Deviation (SD). The chi-Square test and t-test were used to clarify the significance of the difference between the study groups. A P-value of less than 0.05 was considered statistically significant.

The study was proposed and subsequently approved by the scientific committee of the College of the Medicine/University of Tikrit. Fully informed consent was obtained from the patients verbally after explaining the aim of the study thoroughly and clearly with ensuring the anonymity and confidentiality of responses

## Results

A total of 100 pregnant women were enrolled in the current study, there were no significant differences between the study groups regarding age, occupation, residency, and smoking state (P-values were 0.431, 0.181, 0.410, and 0.461), as shown in table 1.

Table 1: Sociodemographic distribution of the participants

Sociodemographic characteristics		Groups		P-value
		Intervention (N=50) N (%)	Control (N=50) N (%)	
Age group (years)	<20	7 (14.0)	7 (14.0)	0.431
	20-29	17 (34.0)	23 (46.0)	
	≥30	26 (52.0)	20 (40.0)	
Occupation	Housewife	33 (66.0)	39 (78.0)	0.181
	Employer	17 (34.0)	11 (22.0)	
Residency	Urban	29 (58.0)	33 (66.0)	0.410
	Rural	21 (42.0)	17 (34.0)	
Smoking	Yes	5 (10.0)	3 (6.0)	0.461
	No	45 (90.0)	47 (94.0)	

There were no significant differences between the study groups regarding gravida, abortion, preterm birth, and gestational age at enrollment (P-values were 0.885, 0.646, 0.858, and 0.110, as shown in table 2

Table 2: Obstetrical history of the participants

Obstetrical history		Groups		P-value
		Intervention (N=50) N (%)	Control (N=50) N (%)	
Gravida	≤3	21 (42.0)	20 (40.0)	0.885
	4-6	25 (50.0)	27 (54.0)	
	>6	4 (8.0)	3 (6.0)	
Abortion	Yes	2 (4.0)	3 (6.0)	0.646
	No	48 (96.0)	47 (94.0)	
Preterm birth	1 pregnancy	25 (50.0)	24 (48.0)	0.858
	2 pregnancies	22 (44.0)	24 (48.0)	
	3 pregnancies	3 (6.0)	2 (4.0)	
		Mean ±D	Mean ±SD	
Gestational age		23.5 ±1.4	24.0 ±1.5	0.110

No significant differences were obtained between the study groups regarding the medical history and examination including hypertension (P-value=0.402), gestational diabetes (P-value=0.646), and body mass index (P-value=0.402). As shown in table 3.

Table 3: Medical history and examination of the participants

Medical history and examination		Groups		P-value
		Intervention (N=50) N (%)	Control (N=50) N (%)	
Body mass index	≤3	28 (56.0)	33 (66.0)	0.402
	4-6	17 (34.0)	15 (30.0)	
	>6	5 (10.0)	2 (4.0)	
Hypertension	Yes	5 (10.0)	6 (12.0)	0.749
	No	45 (90.0)	44 (88.0)	
Gestational diabetes	Yes	3 (6.0)	2 (4.0)	0.646
	No	47 (94.0)	78 (96.0)	

The incidence of preterm birth was significantly lower in the intervention than in the control group (P-value=0.044), as shown in figure 1.

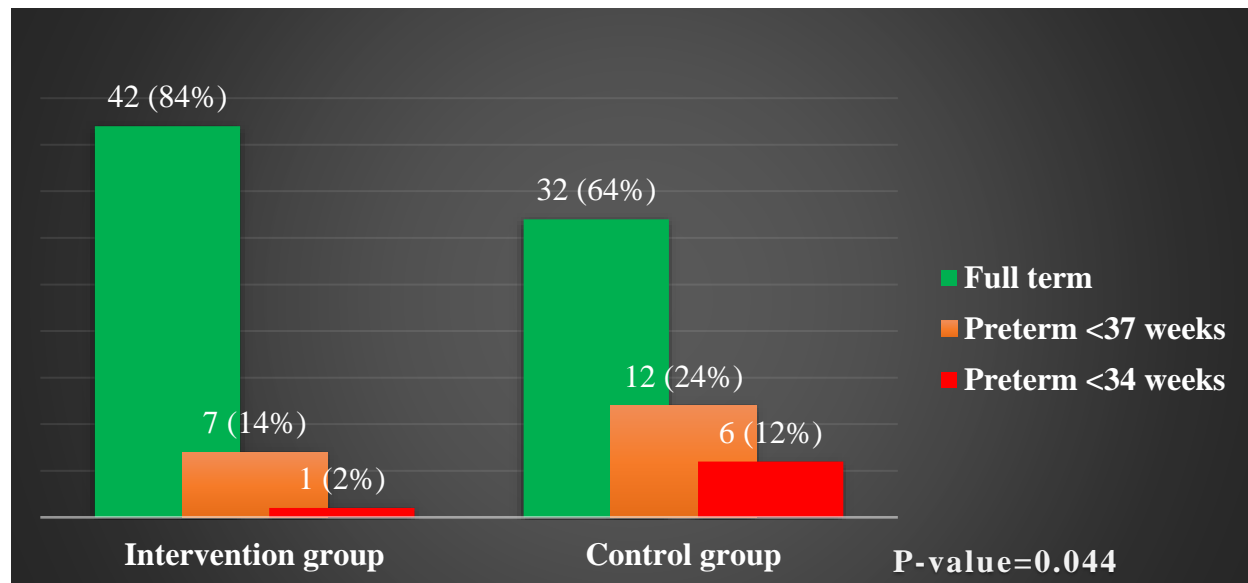


Figure 1: Incidence of the preterm birth

Among pregnant women with twin pregnancies, there was no significant difference between the study groups regarding the incidence of preterm birth (P-value=0.449). Among those with a cervical length of <25mm the incidence of preterm birth (<34 weeks and <37 weeks) was

significantly lower in the intervention group compared to the control group (P-value=0.497). As shown in table 4.

Table 4: Incidence of preterm birth among pregnant women with twin pregnancies and cervical length of <25mm

Pregnancy outcomes	Twin pregnancies		P-value
	Intervention group (N=5) N (%)	Control group (N=3) N (%)	
Preterm <34 weeks	0 (0.0)	1 (33.3)	0.076
Preterm <37 weeks	1 (20.0)	2 (66.7)	
Full term	4 (80.0)	0 (0.0)	
<b>Cervical length &lt;25 mm</b>			
Pregnancy outcomes	Intervention group (N=5) N (%)	Control group (N=3) N (%)	P-value
Preterm <34 weeks	0 (0.0)	2 (33.3)	<b>0.021</b>
Preterm <37 weeks	1 (20.0)	4 (66.7)	
Full term	4 (80.0)	0 (0.0)	

There was 60 live fetus in the intervention group and 56 live fetus in the control group. There was no significant difference between the study groups regarding the number of stillbirths, as shown in figure 2.

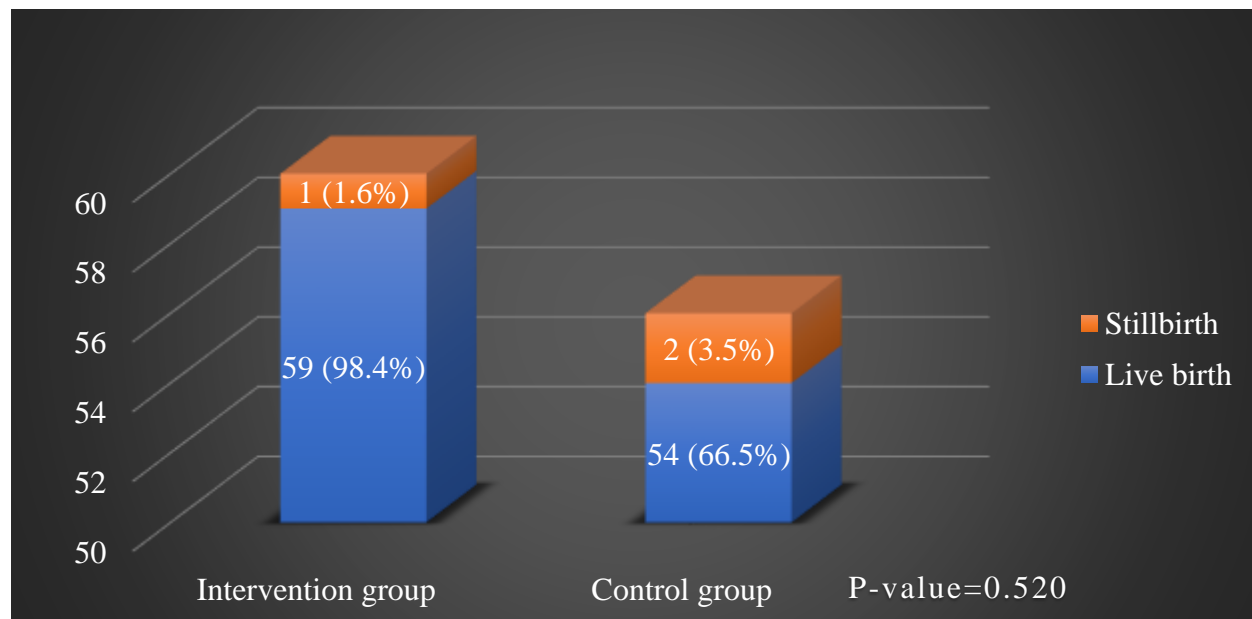


Figure 2: Distribution of the incidence of stillbirth according to the study groups

\ The percentage of neonates with a birth weight of <2.5 kg was significantly lower in the intervention group compared to the control group (P-value=0.017). While no significant difference was obtained regarding the percentage of birth asphyxia and NICU admission. As shown in table 2.

Table 5: Complications of the neonates

Neonatal outcome		Groups		P-value
		Intervention (N=59) N (%)	Control (N=54) N (%)	
Birthweight	≤2.5 kg	11 (18.6)	21 (38.9)	<b>0.017</b>
	>2.5 kg	48 (81.4)	33 (61.1)	
Birth asphyxia	Yes	7 (11.8)	5 (9.3)	0.653
	No	52 (88.2)	49 (90.7)	
NICU admission	Yes	13 (22.0)	20 (37.0)	0.079
	No	46 (78.0)	34 (63.0)	

## Discussion

Prevention of preterm birth is one of the main goals in obstetric care<sup>(20)</sup>. Pregnancy maintenance with progesterone is important in several species<sup>(16)</sup>. This study tried to assess the effect of progesterone in the prevention of preterm birth among a sample of Iraqi pregnant women who were at risk of preterm birth.

The main finding of the current study was that the incidence of preterm birth was significantly lower in the intervention group compared to the control group. In comparison, the same results were obtained in another study that was done by Rashmi et al. in India which concluded that the use of progesterone in pregnant women with a risk of preterm birth significantly reduced the incidence of preterm birth (<34 weeks) and preterm birth (<37 weeks) in current pregnancy<sup>(21)</sup>. This agreed with the results of the meta-analysis study that was done by Angharad et al. and included 17273 pregnant women, it concluded that progesterone significantly decreased the risk of preterm birth<sup>(19)</sup>.

Among those with twin pregnancies, there was no significant difference between the study groups regarding the incidence of preterm birth. The same results were obtained in another study that was done by Stephen et al. in Canada<sup>(22)</sup>. This agreed with the results of another study that was done by Jodie et al.<sup>(23)</sup>. In the same line, Elcin et al. concluded that antenatal progesterone did not affect the incidence of preterm birth among twin pregnant women<sup>(24)</sup>.



In the current study, among those with a cervical length of  $<25$  mm, the incidence of preterm birth was significantly lower in the intervention group compared to the control group. In agreement, Agustin et al. concluded that in women with a singleton pregnancy, a history of spontaneous preterm birth, and a mid-trimester sonographic short cervix, there was equal effectiveness of vaginal progesterone and cerclage to prevent preterm birth and improve perinatal outcomes. The decision depends on the patient's and doctor's preferences in light of potential side effects and the cost-effectiveness of the two interventions<sup>(25)</sup>. The same results were obtained in another study that was done by Hassan et al. in the United States which concluded that The use of vaginal progesterone in pregnant women with a short cervix was associated with a significant (45%) reduction in the incidence of preterm birth  $<34$  weeks of gestation in addition to improved neonatal outcome<sup>(26)</sup>. This agreed with another study that was done by Roberto et al. which concluded that vaginal progesterone reduced the risk of preterm birth perinatal in pregnant women with a mid-trimester sonographic short cervix<sup>(27)</sup>. The same results were obtained in another study that was done by Alfirovic et al. and involved 142 pregnant women, the antenatal progesterone significantly reduced the incidence of preterm birth compared to placebo<sup>(28)</sup>.

In contrast, the results of another study that was done by Cuijpers et al in Australia and included pregnant women with a cervical length of  $<25$ mm revealed no significant difference in the incidence of preterm birth between pregnant women who used antenatal progesterone and those who did not use it<sup>(29)</sup>. In the same line., there is no evidence that antenatal progesterone can decrease the incidence of preterm delivery in women with a short cervix<sup>(30)</sup>. This variation might be related to other factors that could affect the outcome of pregnancy.

The current study revealed an insignificant difference between the study groups regarding the percentage of stillbirths. The same results were obtained in another study that was done by Elcin et al. in Turkey<sup>(24)</sup>.

Regarding neonatal complications, the percentage of neonates with low birth weight was significantly higher in the control group compared to the intervention group, while there was no significant difference between the study groups regarding birth asphyxia and NICU admission. In agreement, Rashmi et al. revealed that the use of antenatal progesterone reduces the percentage of neonates with a birth weight of  $<2.5$  kg among pregnant women who had a risk of preterm birth<sup>(21)</sup>. In another study that was done by Azam et al. in Iraq the percentage of birth

weight of <2.5kg was significantly lower in pregnant women at risk of preterm birth who used antenatal progesterone compared to those who used placebo<sup>(20)</sup>.

In contrast, Angharad et al. revealed that antenatal progesterone for pregnant women with a risk of preterm birth was associated with significantly lower percentages of respiratory distress syndrome and neonatal NICU admission<sup>(19)</sup>. This agreed with another study that was done by Elcin et al. in Turkey and revealed that antenatal progesterone significantly decreases the percentage of NICU admission<sup>(24)</sup>.

**In conclusion**, antenatal progesterone supplementation was significantly effective in reducing the incidence of preterm birth among pregnant women who were at risk of preterm birth. Antenatal progesterone supplementation was significantly effective in reducing the incidence of preterm birth among pregnant women with a short cervix. While it was not significant in those with twin pregnancies. Antenatal progesterone supplementation was significantly effective in reducing the percentage of birth weight of <2.5kg among live birth who belonged to pregnant women with a risk of preterm birth.

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