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Association between the duration of progesterone supplementation treatment and premature neonates outcomes: A retrospective cohort study

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Abstract

Background and Aims: Preterm birth (PTB) is the leading cause of perinatal mortality and morbidity, progesterone is one of the main hormones to maintain a normal pregnancy. However, there are still conflicting results regarding using progesterone supplementation to prevent PTB and improve neonatal outcomes. The length of treatment with progesterone supplementation is also one of the challenges ahead, so the present study was conducted to investigate the relationship between the duration of progesterone supplementation treatment and neonatal outcomes.

Methods: This retrospective cohort study was conducted on pregnant women at risk of PTB and who have taken progesterone supplementation. They were asked about the length of treatment with progesterone supplements and finally, the neonatal outcomes of these women were measured.

Results: A total of 265 pregnant women who met the inclusion criteria were included in this study and the subjects were divided into two groups that received progesterone <12 weeks and received progesterone ≥12. In the group of women receiving progesterone with a treatment duration of ≥12 weeks, the rate of preterm labor, respiratory distress syndrome, low birth weight, and the need for hospitalization were significantly lower than in the group receiving progesterone with a treatment duration of ≥12 weeks.

Conclusion: Progesterone administration for longer than 12 weeks in women at risk of PTB can improve neonatal outcomes.

KEYWORDS

neonatal outcome, progesterone supplementation, pregnancy, preterm birth

1 | INTRODUCTION

Preterm birth (PTB, birth before 37 weeks or 259 days of gestation) is the leading cause of perinatal mortality and morbidity worldwide. In recent years, the rate of premature birth has increased. Spontaneous premature birth (SPTB) is one of the most important obstetric complications.[1,2] An estimated 13.4 million neonates were born too early in 2020 and more than one in 10 neonates were born prematurely. Approximately 900,000 children died in 2019 of complications of PTB. Many survived neonates suffer from a lifetime of disability, including learning disabilities and visual and hearing problems.[3] PTB occurs for different reasons. Most PTB happens spontaneously, but some are due to medical reasons such as infections, or other pregnancy complications such as pre-eclampsia, gestational diabetes, or intrauterine growth restriction that require early induction of labor or emergency cesarean birth.[4,5]

Progesterone is necessary to maintain a normal pregnancy. The exact role of progesterone in maintaining pregnancy is not fully understood. However, it has been shown that progesterone deficiency may lead to increased inflammatory mediators. These include cyclooxygenase-2, proinflammatory interleukin-8, and monocyte chemoattractant protein-1, which have been shown to have a role in endometrial destabilization. Therefore, it is thought that the regulation of these inflammatory mediators is necessary to achieve a successful pregnancy, and progesterone plays a role in this.[6] Decrease in the amount of progesterone, in the middle of pregnancy, shortening of the cervix may occur, also any blockage in the function of progesterone can lead to clinical, biochemical, and morphological changes that lead to cervical ripening,[7,8] and this makes the pregnant women prone to PTB.[9] Because treatment of PTB may not be successful, and after years, it is still not well established that the use of approaches that stop uterine contractions can lead to the prevention of PTB. So attention has focused on preventive strategies such as progesterone supplementation. Progesterone supplementation may be effective in some high-risk patients (short cervix), but the results in this field seem contradictory.[10,11] The role of progesterone in the prevention of PTB has been the subject of several randomized controlled trials (RCTs) over the past few years, and various studies have shown the effect of progesterone supplementation on the occurrence of PTB.[12] A study has shown that women who received progesterone therapy before the 34th week of pregnancy had a lower rate of preterm delivery than women who had cervical shortening in the second trimester,[13] and this treatment leads to a decrease in neonatal mortality and low birth weight.[14] Although the most well-known indication for the use of progesterone in pregnancy is the short length of the cervix, other indications of prescribed progesterone are history of miscarriages, bleeding in early pregnancy, or threatened abortion in early pregnancy.[15] However, the duration of progesterone use in these women has not been determined correctly, and it is not known correctly how long treatment with progesterone can be effective in these women.

These trials investigated pregnancies at high risk of SPTB in the setting of previous SPTB or the presence of a short cervix, as confirmed by ultrasound during a routine mid-trimester scan. Also, the importance of progesterone in maintaining pregnancy and preventing adverse premature neonatal outcomes has already been well-proven. But there is no screening program for women at risk of preterm delivery and suitable candidate women for progesterone treatment to reduce neonatal morbidity and mortality. Moreover, it is not yet observed how long progesterone administration can lead to improved neonatal outcomes, and because some guidelines emphasize the continuation of progesterone administration until the 36th–37th week of pregnancy,[16] it is sometimes observed that the use of progesterone is stopped earlier than this time, and it seems necessary to conduct a basic study to demonstrate the effectiveness of progesterone treatment duration. Therefore, the present study was conducted to investigate the relationship between the duration of progesterone supplementation treatment and neonatal outcomes.

Key points

Progesterone treatment with a duration of more than 12 weeks, can reduce the rate of preterm labor, respiratory distress syndrome, low birth weight, and the need for hospitalization.

2 | MATERIALS AND METHODS

2.1 | Setting and patients

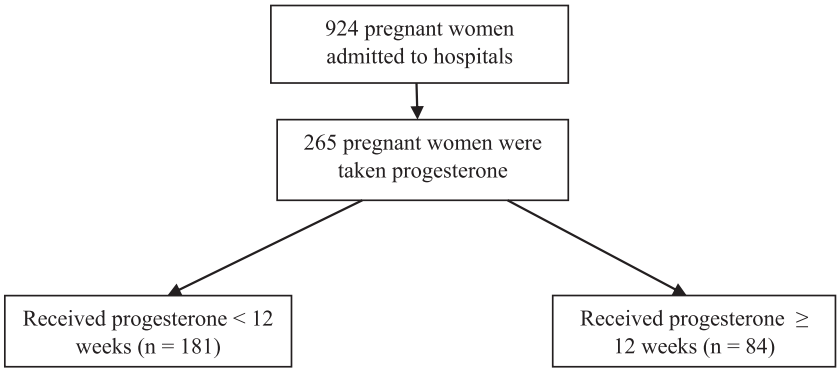
This study is a a part of a large retrospective cohort that was conducted on pregnant women admitted to three hospitals (Rasht, Tehran, Tabriz-Iran) and who gave birth in 2022.

In the initial stage, 924 pregnant women went to each of the mentioned hospitals for delivery and were asked about the use of progesterone supplementation and other common pregnancy supplements and drugs, and, 265 cases of those who had taken progesterone as indicated were included in the study (Figure 1). The inclusion criteria are women with confirmation of fetal viability (based on a sonographic assessment) and singleton pregnancy at risk for PTB owing to previous history or short cervix during the second trimester or threatening abortion in the first trimester of pregnancy. Exclusion criteria include mental retardation, proven fetal disorders, multiple pregnancies, intrauterine fetal death, delivery before 24 or after 37 gestational weeks, and unknown maternal or neonatal outcomes. Women who met the inclusion criteria were included in this study and the subjects were divided into two groups that received progesterone <12 weeks and received progesterone ≥12.

2.2 | Data collection

Detailed maternal demographic and obstetric information (including maternal age, height, and weight (for calculation of body mass index), Pregnancy weight gain, gravidity, parity, education, gestational age at delivery, mode of delivery, and pregnancy complications including

FIGURE 1 Study flowchart.



gestational diabetes mellitus, pre-eclampsia, hypothyroidism, placental disorders, bleeding during pregnancy, infertility) of pregnant mothers who visited predetermined medical centers on the day of delivery and the use of progesterone and the duration of its use were collected by questionnaire.

2.3 | Outcome measures

The newborn outcomes including gestational age (based on the last menstrual period and affirmed by crown-rump length measurement on first-trimester ultrasound scan), birth weight, the need for hospitalization, respiratory distress syndrome (RDS), and perinatal mortality were followed up after delivery.

2.4 | Statistical analysis

Analyses were performed in SPSS V25. The χ^2 and Fisher's exact tests were used to analyze the relationships between nominal scale variables. Factors that were ≤0.5 significant level in the bivariate logistic regression analysis were considered in the multivariable logistic regression analysis. Multivariable analyses were conducted using multiple logistic regression models. We used a 95% confidence interval and defined statistical significance as $p < 0.05$.

2.5 | Ethical approval

This study was approved by Guilan University of Medical Sciences with the ethical code IR.GUMS.REC.1401.75. Also, the authors claim that this study complies with the 1975 Declaration of Helsinki, as revised in 2008 (informed consent).

3 | FINDINGS

A total of 265 pregnant women who met the inclusion criteria were included in this study. The mean age of the participating women was 32.12 ± 5.58, 32.4% of women in the group receiving progesterone <12 weeks and 41% of women in the group receiving progesterone ≥12 weeks were ≥35 years old. Participants' characteristics according to the duration of progesterone received were summarized in Table 1. Compared to the women who received progesterone <12 weeks those who received progesterone ≥12 weeks did not have a university education (51.1% vs. 15.9%) and the difference was statistically significant (<0.001). Also, there was a significant relationship between the two comparison groups regarding primiparous (53.6% vs. 37%) (0.016).

In the group of women receiving progesterone with a treatment duration of ≥12 weeks, the rate of preterm labor, RDS, low birth weight, and the need for hospitalization were significantly lower than in the group receiving progesterone with a treatment duration of <12 weeks (Table 1).

Logistic regression showed that women who received exogenous progesterone for ≥12 weeks were 54% less likely to have PTL than women who received exogenous progesterone for <12 weeks (Table 2).

Logistic regression showed that infants of mothers who received exogenous progesterone for ≥12 weeks were 92% less likely to be hospitalized than infants who received exogenous progesterone <12 weeks (Table 3).

4 | DISCUSSION

In this study, we have shown that administering progesterone for more than 12 weeks to women resulted in improved neonatal outcomes, including reduced incidence of low birth weight, preterm labor, need for hospitalization, and perinatal mortality.

PTB is the leading cause of various neonatal complications.[12,17–19] However, the most well-known indication for taking progesterone supplementation is shortening the length of the cervix, but progesterone supplementation is used to prevent miscarriages in asymptomatic women with a history of miscarriages and in women who have bleeding in early pregnancy,[20] and can prevent neonatal morbidity and mortality.[21] The review of 36 RCTs, involving a total of 8523 women considered to be at increased risk of PTB, and 12,515 infants, found that where progesterone was given, it had beneficial effects, including reducing the risk of neonatal mortality, complications that need

TABLE 1 Participants' characteristics according to the duration of progesterone received.

Variable	Categories	Received progesterone <12 weeks (*n* = 181) *n* (%)	Received progesterone ≥12 weeks (*n* = 84) *n* (%)	*p*-Value*
Age	<35 years	121 (67.6)	49 (59)	0.211
	≥35 years	58 (32.4)	34 (41)	
Education	No university degree	91 (51.1)	13 (15.9)	<0.001
	University degree	87 (48.9)	69 (84.1)	
Parity	Primipara	67 (37)	45 (53.6)	0.016
	Multipara	114 (63)	39 (46.4)	
Abortion	Yes	127 (70.2)	58 (69)	0.886
	No	54 (29.8)	26 (31)	
Infertility	Yes	11 (6.8)	5 (6)	>0.999
	No	150 (93.2)	79 (94)	
Body mass index	<25	77 (42.5)	37 (44)	0.894
	≥25	104 (57.5)	47 (56)	
Pregnancy weight gain	<16 kg	127 (70.2)	49 (58.3)	0.069
	≥16 kg	54 (29.8)	35 (41.7)	
Pre-eclampsia	Yes	5 (2.8)	6 (7.1)	0.183
	No	173 (97.2)	78 (92.9)	
Gestational diabetes	Yes	10 (5.5)	1 (1.2)	0.182
	No	171 (94.5)	83 (98.8)	
Hypothyroid	Yes	41 (22.7)	22 (26.2)	0.538
	No	140 (77.3)	62 (73.8)	
Placental disorders	Yes	23 (12.7)	4 (4.8)	0.051
	No	158 (87.3)	80 (95.2)	
Bleeding during pregnancy	Yes	53 (29.4)	20 (24.1)	0.459
	No	127 (70.6)	63 (75.9)	
Respiratory distress syndrome	Yes	13 (7.2)	0 (0)	0.011
	No	168 (92.8)	84 (100)	
Preterm labor	Yes	65 (36.9)	16 (19.5)	0.006
	No	111 (63.1)	66 (80.5)	
Birth weight	<2500 gr	44 (26)	8 (10.7)	0.007
	≥2500 gr	125 (74)	67 (89.3)	
The neonate need to be hospitalized	Yes	78 (43.1)	10 (11.9)	<0.001
	No	103 (56.9)	74 (88.1)	
Perinatal mortality	Yes	3 (1.7)	1 (1.2)	>0.999
	No	178 (98.3)	83 (98.8)	

*$p < 0.001$.

assisted ventilation, necrotizing enterocolitis or requiring admission to neonatal intensive care unit, by prolonging the pregnancy time.[14] In a clinical trial research has shown that for women with the two risk factors of bleeding in early pregnancy and a history of one or more previous miscarriages vaginal micronized progesterone treatment increases the likelihood of occurrence of a successful live birth. Also, this cost-effective treatment prevents more than 8450 miscarriages a year in the United Kingdom.[10]

TABLE 2 Duration of progesterone use and preterm birth.

Variables	*B*	SE	*p*-Value	OR (95% CI)
Maternal age	0.063	0.028	0.027	1.065 (1.007, 1.126)
Education	−0.434	0.318	0.172	0.648 (0.347, 1.208)
parity	−0.011	0.317	0.971	.989 (0.531, 1.840)
Type of delivery	−0.688	0.411	0.094	0.502 (0.224, 1.125)
Duration of progesterone treatment	−0.762	0.372	0.041	0.467 (0.225, 0.968)

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error.

TABLE 3 The duration of progesterone use on the need for hospitalization.

Variables	*B*	SE	*p*-Value	OR (95% CI)
Maternal age	0.032	0.028	0.246	1.033 (0.978, 1.090)
Education	−0.706	0.309	0.022	0.493 (0.269, 0.904)
parity	0.304	0.317	0.338	1.355 (0.728, 2.523)
Type of delivery	0.214	0.403	0.595	1.239 (0.562, 2.731)
Duration of progesterone treatment	−1.694	0.410	<0.001	0.184 (0.082, 0.410)

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error.

The large multicenter, double-blind, randomized trial by Coomarasamy et al.[22] included 836 women with unexplained recurrent miscarriage or women with bleeding in early pregnancy who were treated with vaginal micronized progesterone or placebo from the time of a positive pregnancy result until the end of 12 weeks of gestation, demonstrated no difference in live births rate in these women and compared to placebo. In the present study, we observed that the use of progesterone with a duration of more than 12 weeks can lead to improved neonatal outcomes, and perhaps these contradictory results can be due to the treatment duration of fewer than 12 weeks in the study of Coomarasamy et al.,[22] and maybe if they continued progesterone treatment, may saw more positive results. In another clinical trial study that prescribed vaginal progesterone from 22 to 24 weeks to 34 weeks of pregnancy in women who were at risk of PTB (history of preterm delivery, cervical length less than 25 mm, positive fetal fibronectin and other factors related to the occurrence of PTB) has been done, it has been concluded that adverse neonatal outcomes do not decrease.[19] In line with the evidence from the present study, it can be concluded again that if the treatment with progesterone was continued, it could have positive effects in reducing PTB and adverse neonatal outcomes.

We observed that in women who received progesterone during pregnancy for more than 12 weeks, neonatal weight was more than 2500 g, and these results are contradictory with a study conducted among women with bleeding in early pregnancy, progesterone administered during the first trimester and not cause in increase the incidence of live births rate compared to placebo.[23] Also in the mentioned study was shown that offspring of mothers with bleeding and progesterone therapy were more likely to be premature, small for gestational age or low birth weight, and progesterone supplementation may have no beneficial effect on improving adverse neonatal outcomes related to early vaginal bleeding.[24] It could be because in their study they only looked at the history of bleeding in pregnancy and the severity of the bleeding was not specified. The presence of mild bleeding in early pregnancy and not threatening bleeding that leads to low birth weight may be a justification for this.

Studies show that factors such as age, parity, diabetes, and gestational blood pressure can cause premature birth and create unfavorable conditions for babies born after low gestational age.[25] In this study, there was no significant difference in the incidence of gestational diabetes and pre-eclampsia between the two groups, so the incidence of these diseases was adjusted as a risk factor underlying PTB in the two groups. Also, a significant relationship was observed between education level and parity with the duration of progesterone treatment. In multiparous women or women whose education level was less than university degrees, the duration of progesterone treatment was less than 12 weeks, and these results were adjusted by regression. This relationship has also been stated in other studies that a lower literacy level and higher parity are related to an increase in the incidence of PTB.[26]

So far, studies have not reported long-term effects on fetuses of women who received progesterone in the first trimester.[27] In the same direction as the studies included in a review, Coomarasamy et al.[22] showed no statistical difference in congenital anomalies between the progesterone group and the placebo group.[28,29] However considering the confounding factors and loss of follow-up evaluation of the long-term effects of progesterone treatment during pregnancy, especially during the first trimester, is difficult.

With these descriptions, there is no accurate evidence of prescribing progesterone to low-risk women, so women who have risk factors are suitable candidates for progesterone administration, and the initiation of progesterone treatment in these women, and continuation of progesterone treatment can partially improve the outcomes of these women's babies. The common use of progesterone supplementation therapy to prevent spontaneous abortion and PTB and the possibility of occurrence of hypersensitivity reactions to progestogens suggested evaluating candidate women to ascertain this individual predisposition in pregnancy.[29] This seems to be the first study to examine the duration of progesterone treatment and neonatal outcomes. Although women at higher risk of PTB indeed use progesterone supplements for a longer period, there is still no study on how long progesterone treatment can provide the best benefits for these women and their neonates. So the strength of this study is to investigate this factor, and one of the limitations of this study is which type of progesterone has the best benefits for women. Among the other limitations of this study, it can be mentioned that this study was conducted retrospectively, and due to the sampling conditions, we could not determine the exact indication of progesterone consumption in these women, and also stressed

condition and not remembering the information, recall bias may occur. Therefore, it is recommended to conduct future studies to evaluate the effectiveness of different types of progesterone and to check the length of treatment with these progesterones under better conditions.

5 | CONCLUSION

Progesterone supplementation appears to be effective in maintaining pregnancy survival and improving neonatal outcomes. Therefore, since prophylactic treatments seem to be more important in preventing PTB in high-risk women, it is reasonable to prescribe progesterone with a duration of more than 12 weeks as an available and cost-effective approach.

AUTHOR CONTRIBUTIONS

Soudabeh Kazemi Aski: Conceptualization; data curation; methodology. **Seyedeh Hajar Sharami**: Conceptualization; data curation; funding acquisition; investigation. **Roya KabodMehri**: Conceptualization; investigation; methodology. **Fatemeh Alsadat Rahnemaei**: Investigation; methodology; writing—original draft. **Forozan Milani**: Methodology. **Shadi Sabetghadam**: Formal analysis; investigation.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

TRANSPARENCY STATEMENT

The lead author Seyedeh Hajar Sharami affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained, and this study was not founded.

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