Progesterone

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Abstract

Progesterone has been widely used for the prevention of preterm births (PTBs). However, progesterone supplement therapy is considered ineffective for women in preterm labor diagnosed strictly with regular uterine contractions and cervical ripening.

Recent studies have shown that the efficacy of progesterone therapy for preventing PTB may depend on the administration route, type of supplementation, and indication.

First, a detailed medical history should be taken regarding the existence of a prior spontaneous singleton PTB. If a prior singleton PTB is noted, weekly intramuscular (IM) injections of 250 mg of 17-alpha-hydroxyprogesterone caproate (17α-OHPC) from 16 to 20 weeks' gestation until 36 weeks' gestation should be recommended.

Universal screening with transvaginal ultrasonography to detect the cervical length (CL) at 18–24 weeks should be offered to all pregnant women without a prior PTB. If the CL is less than 25 mm, the daily administration of a vaginal progesterone suppository (200 mg) until 36 weeks' gestation should be recommended.

In multifetal pregnancies, the administration of progesterone (either IM or vaginal) does not appear to reduce the incidence of PTB or improve neonatal outcomes. However, in twin pregnancies with a short cervix, vaginal progesterone supplement therapy may be effective in reducing the rate of PTB and improving neonatal outcomes.

According to the Japan health insurance system, 17α-OHPC injections can be used weekly to treat threatened abortion or preterm labor, at a maximum dose of

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125 mg, whereas a natural micronized vaginal progesterone suppository can be used to legally treat infertile patients; however, this treatment is not covered by the health insurance for PTB prevention.

Keywords
Preterm birth · Prevention · Progesterone · 17-alpha-hydroxyprogesterone caproate

15.1 Introduction

Every year, an estimated 15 million babies are born preterm, comprising 11.1% of all live births worldwide and ranging from about 5% in several European countries to 18% in some African countries [1]. Preterm births (PTBs) comprise 5.6% of all births in Japan [2]. The time trends for PTB rates were estimated for 65 countries in the developed nations, Latin America, and the Caribbean regions, with more than 10,000 births in the year 2010 [1]. The mean estimated PTB rate in these countries in 1990 was 7.5% compared to 8.6% in 2010 [1]. Despite many trials regarding tocolytic therapy, antibiotic therapy, and other strategies for prevention, no effective and reproducible method for preventing PTB has been demonstrated [3] and, in most of these countries, including Japan, the PTB rate had been increased in 2010 compared to that in 1990 [1, 2].

However, it is believed that the most effective treatment for PTB is prediction and prevention, depending on its risks. The risk factors for PTB include a history of PTB, short cervical length (CL), multifetal pregnancy, maternal age (<19 and >35 years), infectious diseases, genetic factors, smoking, uterine anomaly, and history of dilatation and curettage or cervical conization [4]. Among these risk factors, a history of PTB and a short CL, usually defined as CL <25 mm on transvaginal ultrasound, are the most important [4].

Progesterone was formerly used as a standard medication for threatened abortion or PTB prevention. Because most obstetricians have been interested in tocolytic agents and infection control for the treatment of preterm labor, progesterone therapy is being decreasingly used for PTB. Since progesterone therapy is cheap and convenient for outpatients, it has been recently reconsidered and reviewed. In 2003, two randomized double-blind placebo-controlled trials demonstrated that progesterone therapy can prevent PTB in women with a history of PTB [5, 6]. Thereafter, many studies and meta-analyses were conducted to reevaluate the efficacy or to add new evidence concerning the prevention of PTB with progesterone therapy. The American Congress of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine recommend the use of progesterone therapy for PTB prevention in selected pregnant women who have a history of spontaneous PTB, including cases of premature rupture of the membranes, and a short CL identified on transvaginal ultrasound at the mid-trimester [7, 8].

In this chapter, we introduce evidence regarding the use of progesterone supplement therapy for the prevention of PTB, depending on the administration route, type of supplementation, and indication.

15.2 Progesterone Supplementation

Progesterone has been used in two supplementation types, a naturally produced (natural micronized progesterone) or synthetic hormones [17-alpha-hydroxyprogesterone caproate (17α-OHPC)], and via two routes of administration, intramuscularly or vaginally. The supplement, 17α-OHPC, is a synthetic derivative of 17-hydroxyprogesterone. The half-life of 17α-OHPC is 7.8 days [9]; therefore, it is usually administered intramuscularly once a week to maintain serum concentrations. In the Japan health insurance system, 17α-OHPC injections can be used weekly to treat threatened abortion or preterm labor at a maximum dose of 125 mg. Micronized progesterone, a natural progesterone, can be self-administered, as an oral capsule, vaginal gel, or vaginal suppository. When micronized progesterone is administered orally, it is metabolized quickly in the liver and loses its potency. When micronized progesterone is administered vaginally, avoiding metabolism in the liver, it acts on the uterus directly and maintains in a high serum level [9–11].

The mechanism of action of progesterone for PTB prevention is poorly understood. Several investigators have reported the effects of progesterone on PTB, including a decrease in oxytocin receptivity [12–14], anti-inflammatory action [15], and reduced cervical maturation [16]. As there is little evidence regarding the efficacy of progesterone in reducing uterine contractions [17], progesterone supplement therapy is considered ineffective for women in preterm labor diagnosed strictly with regular uterine contractions and cervical ripening.

Concerning maternal and fetal safety, it has not been proven that progesterone causes fetal anomaly. The Food and Drug Administration (FDA) classified natural micronized progesterone medications as category B for pregnancy [18]. The National Institute of Child Health and Human Development (NICHD) study showed there were no significant increases in the rate of miscarriages and stillbirths in the progesterone group compared with the placebo group [5]. An observational follow-up study also reported no significant difference in long-term infant outcomes between progesterone and placebo groups [19, 20]. Moreover, in 2011, FDA approved 17α-OHPC for the reduction of PTB in women with a history of PTB [21].

15.3 Screening Algorithm for Predictive Risk Factors (Fig. 15.1)

The risk factors for PTB include a history of spontaneous PTB, short CL, multifetal pregnancy, maternal age, infectious diseases, genetic factors, smoking, uterine anomaly, and a history of dilatation and curettage or cervical conization [4]. Among the risk factors, a history of spontaneous PTB and a short CL are the most important.

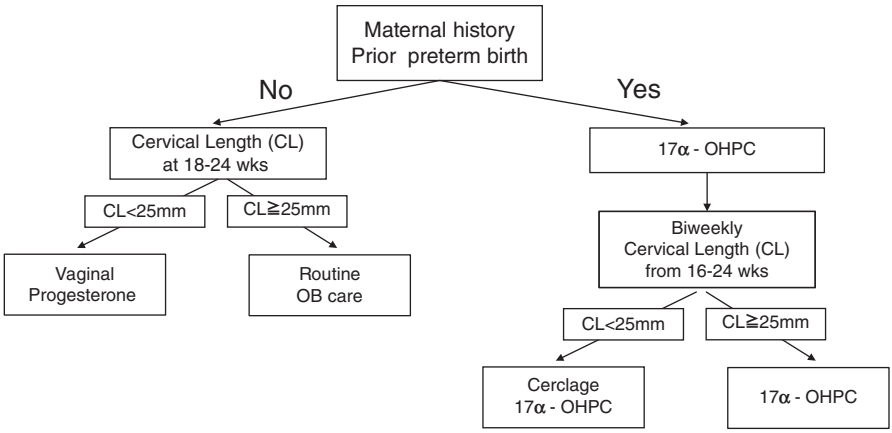

Fig. 15.1 Algorithm for progesterone use in singletons to prevent preterm birth

An accurate history should be taken regarding the risk factors for PTB. A detailed maternal history includes whether the prior PTB was spontaneous or indicated. Spontaneous PTB is defined as PTB prior to 37 weeks caused by preterm labor, premature rupture of the membrane, or cervical insufficiency. The evaluation of women with a prior spontaneous PTB or mid-trimester abortion should include a detailed medical history, comprehensively reviewing all previous pregnancies and the risk factors, and determining their candidacy for prophylactic interventions such as progesterone supplementation, cervical cerclage, or both. A previous spontaneous PTB is commonly reported to confer a 1.5–2-fold increased risk of PTB in subsequent pregnancies [7]. The recurrence rate significantly increases with a shorter gestational age in the previous PTB and an increase in the number of previous PTBs. A previous term delivery confers a lower risk than the aforementioned situations [22, 23].

Another important method for predicting the risk for PTB is the measurement of CL by vaginal ultrasound during the mid-trimester [4, 7, 24, 25]. Transvaginal ultrasonography has been shown to be a reliable and highly reproducible method for assessing the length of the cervix. Screening with transvaginal ultrasound CL at around 18–24 weeks should be offered for all asymptomatic singleton pregnancies. The risk of PTB is substantially high when CL is <25 mm, and the risk increases as CL decreases. Therefore, in randomized trials studying the efficacy of progesterone supplement therapy for preventing PTB, a short CL was another major indication for therapy.

Progesterone supplement therapy is one of the few proven methods that are effective for preventing PTB in women with a history of spontaneous PTB and in women with a short CL.

15.3.1 17α-OHPC for a History of PTB

In a 2003 NICHD report, Meis et al. conducted a randomized double-blind multicenter trial to evaluate the effectiveness of 17α-OHPC in women with a PTB history for the prevention of PTB in subsequent pregnancies [5]. Women who were enrolled at 16–20 weeks of gestation received either weekly intramuscular injections of 250 mg of 17α-OHPC or weekly injections of a placebo; the injections were continued until delivery or 36 weeks of gestation. Treatment with 17α-OHPC significantly reduced the risk of delivery at <37 weeks [relative risk (RR) 0.66, 95% confidence interval (CI) 0.54–0.81], <35 weeks (RR 0.67, 95% CI 0.48–0.93), and <32 weeks (RR 0.58, 95% CI 0.37–0.91) of gestation. Infants of women treated with progesterone had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. They concluded that weekly injections of progesterone resulted in a substantial reduction in the rate of recurrent PTB among women who had a particularly high risk for PTB and reduced the incidence of several complications in their infants. After this study, another randomized trial, reported by Saghafi et al., also showed that 17α-OHPC treatment was associated with a significantly lower rate of PTB at less than 37 weeks of gestation [26].

As shown in Table 15.1, a meta-analysis of four randomized controlled trials (RCTs) also showed the benefit of weekly intramuscular 17α-OHPC in terms of the reduction of PTB at <37 weeks' gestation (RR 0.62, 95% CI 0.52–0.75) and the reduction of perinatal mortality (RR 0.41, 95% CI 0.23–0.73) in women with a previous PTB [27].

Table 15.1 Meta-analysis of progesterone versus placebo/no treatment in singletons with a previous history of spontaneous preterm birth

Outcome	No. of studies	No. of participants	Risk ratio (M-H, fixed, 95% CI)
Preterm birth <37 weeks	10	1750	0.55 [0.42, 0.74]
Intramuscular	4	652	0.62 [0.52, 0.75]
Vaginal	5	1065	0.52 [0.29, 0.92]
Oral	1	33	0.46 [0.19, 1.11]
Preterm birth <34 weeks	5	602	0.31 [0.14, 0.69]
Intramuscular	0	0	0.0 [0.0, 0.0]
Vaginal	4	454	0.21 [0.10, 0.44]
Oral	1	148	0.59 [0.39, 0.90]
Perinatal mortality	6	1453	0.50 [0.33, 0.75]
Intramuscular	3	553	0.41 [0.23, 0.73]
Vaginal	2	752	0.67 [0.34, 1.29]
Oral	1	148	0.43 [0.12, 1.59]

CI confidence interval

In summary, for singleton pregnancies with more than one previous spontaneous PTB, weekly intramuscular injections of 17α-OHPC 250 mg from 16 to 20 weeks' gestation until 36 weeks' gestation should be recommended.

15.3.2 Vaginal Progesterone for a History of PTB

In 2003, at the same time as the Meis et al. report, da Fonseca et al. reported the result of a randomized double-blind trial on vaginal natural micronized progesterone suppository therapy in singleton pregnancies, a majority of whom (>90%) had a previous PTB [6]. Nightly administration of vaginal progesterone (100 mg) from 24 to 34 weeks was associated with a significant reduction in the incidence of PTB (<37 weeks) (RR 0.48, 95% CI 0.25–0.96) [6]. In another randomized study reported by O'Brien et al. in 2007, 659 women with singleton pregnancies who had a previous PTB (20–35 weeks) were administered 90 mg of vaginal natural micronized progesterone gel daily starting at 18–23 weeks' gestation [28]. The vaginal progesterone gel did not reduce the incidence of PTB at <37, <36, <33, and <29 weeks or improve neonatal outcomes. However, in a secondary analysis of women with CL <28 mm, the progesterone gel treatment was associated with a significantly lower rate of PTB at <32 weeks of gestation. Several women screened for this trial were excluded because of a short CL; therefore, there is, at present, stronger evidence of the effectiveness of 17α-OHPC compared to vaginal progesterone.

As shown in Table 15.1, a meta-analysis of five RCTs also showed the benefit of vaginal progesterone in women with a previous PTB for the reduction of PTB<37 weeks (RR 0.52, 95% CI 0.29–0.92) and <34 weeks (RR 0.21, 95% CI 0.10–0.44) and with no reduction of perinatal mortality (RR 0.67 95% CI 0.34–1.29) [27]. Vaginal progesterone, thus, seems to have an equivalent, if not greater, effectiveness as 17α-OHPC.

15.3.3 17α-OHPC for a Short CL

Regarding 17α-OHPC, a multicenter RCT evaluating the effect of 17α-OHPC compared with placebo in women with singleton gestations, no prior PTB, and short CL <30 mm showed no difference in the rate of PTB at <37 weeks (RR 1.03, 95% CI 0.79–1.35) [29].

In another later study, pregnant women at high risk for PTB (prior PTB, cervical surgery, uterine malformation, or prenatal diethylstilbestrol exposure) and CL <25 mm were randomized to weekly intramuscular injections of 500 mg of 17α-OHPC or no treatment. There were no significant differences between the groups [30].

In summary, 17α-OHPC cannot be recommended for the prevention of PTB in singleton pregnancies with a short CL and without prior PTB.

15.3.4 Vaginal Progesterone for a Short CL

Several RCTs have been conducted to evaluate the efficacy of vaginal progesterone on asymptomatic cervical shortening cases. In 2007, the Fetal Medicine Foundation in the UK showed the effects of vaginal progesterone on women with a short cervix [31]. This trial enrolled 250 women mostly (90%) with singleton pregnancies and a very short CL (<15 mm at 20–24 weeks) and demonstrated a lower risk for PTB in those treated with vaginal progesterone suppository, 200 mg nightly, started at 24–34 weeks, compared with those treated with a placebo. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (RR 0.56, 95% CI 0.36–0.86). However, there were no significant effects on composite neonatal adverse outcomes (RR 0.57, 95% CI 0.23–1.31) [31]. In a subsequent randomized trial, the use of vaginal progesterone gel, 90 mg daily, was associated with a decrease in spontaneous PTB at <33 weeks of gestation (RR 0.55, 95% CI 0.33–0.92) and a decrease in neonatal morbidity and mortality (RR 0.57, 95% CI 0.33–0.99) among asymptomatic singleton-pregnant women with a CL of 10–20 mm at 19–24 weeks of gestation [32]. In this study, an analysis of only women without prior PTB confirmed a significant benefit of progesterone in preventing PTB before 33 weeks of gestation. However, a very recent multicenter randomized double-blind trial of vaginal progesterone therapy (OPPTIMUM study) showed contradictory results [33]. In this trial, 1228 high-risk women (history of PTB <34 weeks, CL ≤25 mm, or positive fetal fibronectin test with other risk factors for PTB) received 200 mg of vaginal natural micronized progesterone suppository or placebo daily, from 22–24 weeks to 34 weeks of gestation. To date, this study is the largest trial of vaginal progesterone treatment for the prevention of PTB in women at risk; however, it did not show any effects of progesterone treatment on the rates of either PTB or neonatal and infant outcome in the entire study group and all subgroup analyses. These results are conflicting regarding the clinical efficacy of vaginal progesterone for preventing PTB and concerning adverse perinatal outcomes in singleton pregnancies with a short cervix. Therefore, Romero et al. conducted a meta-analysis of five high-quality RCTs, including the OPPTIMUM study, to clarify whether vaginal progesterone prevents PTB and improves perinatal outcomes in asymptomatic women with a singleton gestation and a mid-trimester sonographic short cervix [20]. This meta-analysis showed the benefit of vaginal progesterone in asymptomatic women with a short cervix detected by vaginal ultrasound (<25 mm) for the reduction of PTB at <33 weeks' gestation (RR 0.62, 95% CI 0.47–0.81) (Fig. 15.2) and for improving neonatal outcomes (RRs from 0.47 to 0.82). Moreover, vaginal progesterone significantly decreased the risk of PTB at <36, <35, <34, <32, <30, and <28 weeks of gestation [20].

In summary, in women with singleton gestations, no prior PTB, and short CL, vaginal progesterone is associated with a reduction in PTB and improved neonatal outcomes. If CL <25 mm is identified at <24 weeks, vaginal progesterone should be offered for PTB prevention. There is insufficient evidence indicating that any type of vaginal progesterone or doses is superior.

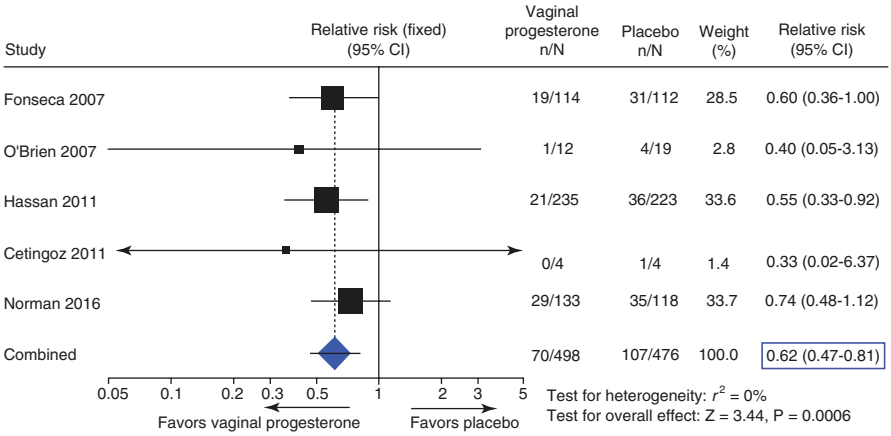

Fig. 15.2 Meta-analysis of the effect of vaginal progesterone on preterm birth at <33 weeks of gestation in singleton pregnancies with a short cervix. *CI* confidence interval

Table 15.2 Meta-analysis of prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy

Outcome	No. of studies	No. of participants	Risk ratio (M-H, fixed, 95% CI)
Intramuscular (IM) progesterone versus no treatment or placebo			
Preterm birth <37 weeks	5	2010	1.05 [0.98, 1.13]
Preterm birth <34 weeks	2	399	1.54 [1.06, 2.26]
Preterm birth <28 weeks	5	1920	1.08 [0.75, 1.55]
Perinatal death	6	3089	1.45 [0.60, 3.51]
Vaginal progesterone versus no treatment or placebo			
Preterm birth <37 weeks	6	1597	0.97 [0.89, 1.06]
Preterm birth <34 weeks	6	1727	0.83 [0.63, 1.09]
Preterm birth <28 weeks	4	1569	1.22 [0.68, 2.21]
Perinatal death	3	2287	1.23 [0.74, 2.06]
Intramuscular (IM) progesterone versus no treatment: multiple (twin) pregnancy with a short cervix			
Preterm birth <37 weeks	1	161	1.06 [0.90, 1.25]
Preterm birth <34 weeks	1	161	1.67 [1.04, 2.68]
Perinatal death	1	330	9.11 [1.17, 71.10]
Vaginal progesterone versus no treatment: Multiple (twin) pregnancy with a short cervix			
Preterm birth <34 weeks	1	224	0.67 [0.49, 0.91]
Preterm birth <28 weeks	1	224	0.37 [0.07, 1.88]
Respiratory distress syndrome	1	439	0.68 [0.55, 0.84]

15.4 Progesterone for Multiple Pregnancy

Multiple pregnancy is a strong risk factor for PTB, and more than 50% of women with a twin pregnancy will give birth prior to 37 weeks' gestation.

As shown in Table 15.2, a recent meta-analysis also showed that both intramuscular 17α-OHPC and vaginal progesterone supplement therapy were ineffective for

the reduction of PTB and for improving perinatal outcomes in unselected women with uncomplicated multiple pregnancies [34]. However, natural micronized vaginal progesterone suppository, but not intramuscular 17α-OHPC [35], may be effective for the reduction of PTB at <34 weeks' gestation and adverse perinatal outcomes in twin-pregnant women with a CL ≤25 mm [36]; nevertheless, there is insufficient evidence to recommend this study. Further studies are needed to evaluate the efficacy of vaginal progesterone in multiple pregnancies with short CL.

In unselected women with multiple pregnancies, the administration of progesterone (either intramuscular or vaginal) does not appear to reduce the incidence of PTB or to improve neonatal outcomes. However, in a case of twin pregnancies and a short cervix, vaginal progesterone supplement therapy may be effective for reducing the rate of PTB and for improving neonatal outcomes.

15.5 Japan Prospective Study (TROPICAL STUDY: Trial of Progesterone Vaginal Tab in the Prevention of Preterm Delivery Evaluated by Cervical Length)

In Japan, 17α-OHPC injections administered weekly at a maximum dose of 125 mg are covered under health insurance. However, a natural micronized vaginal progesterone suppository for infertile patients can legally be used, but is not underwritten by health insurance for PTB prevention and medication for preterm labor.

Currently, in Japan, a multicenter collaborative, double-blind, placebo-controlled, randomized parallel-group comparison trial has been conducted for 3 years since 2014. This RCT aims to evaluate the effect of daily natural micronized progesterone suppository therapy (Cyclogest 200 mg) in women with a short CL in reducing PTB. Women with singleton pregnancies and CL < 30 mm at 16–24 weeks' gestation were enrolled and serial measurements of CL were carried out biweekly. This trial should provide new evidence from Japan regarding the prevention of PTB.

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