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# Use of progesterone supplement therapy for prevention of preterm birth: review of literatures

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Preterm birth (PTB) is one of the most common complications during pregnancy and it primarily accounts for neonatal mortality and numerous morbidities including long-term sequelae including cerebral palsy and developmental disability. The most effective treatment of PTB is prediction and prevention of its risks. Risk factors of PTB include history of PTB, short cervical length (CL), multiple pregnancies, ethnicity, smoking, uterine anomaly and history of curettage or cervical conization. Among these risk factors, history of PTB, and short CL are the most important predictive factors. Progesterone supplement therapy is one of the few proven effective methods to prevent PTB in women with history of spontaneous PTB and in women with short CL. There are 2 types of progesterone therapy currently used for prevention of PTB: weekly intramuscular injection of 17-alpha hydroxyprogesterone caproate and daily administration of natural micronized progesterone vaginal gel, vaginal suppository, or oral capsule. However, the efficacy of progesterone therapy to prevent PTB may vary depending on the administration route, form, dose of progesterone and indications for the treatment. This review aims to summarize the efficacy and safety of progesterone supplement therapy on prevention of PTB according to different indication, type, route, and dose of progesterone, based on the results of recent randomized trials and meta-analysis.

**Keywords:** Preterm birth; Progesterone; Prevention; 17-alpha-hydroxy-progesterone caproate

## Introduction

Preterm birth (PTB) is one of the most common complications during pregnancy and it occurs 11.1% worldwide [1], and nearly 7% of all births in Korea [2]. It primarily accounts for neonatal mortality and numerous neonatal morbidities, such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia, sepsis, intraventricular hemorrhage (IVH), necrotizing enterocolitis, and retinopathy of prematurity [3]. In addition, PTB incurs certain long-term sequlae including cerebral palsy and developmental disability, which create further social and economic problems [4]. Therefore, an effective prevention and treatment of PTB to reduce maternal and neonatal complications is indeed one of the most crucial realms of research in maternal-fetal medicine.

The risk factors of PTB include history of PTB, short cervical length (CL), multifetal pregnancy, advanced maternal age, infectious diseases, genetic factors, smoking, uterine anomaly, and history of curettage or cervical conization [4]. Among these risk factors, history of PTB and short CL, usually defined as <25 mm, are the most important predictive factors [5].

The most effective treatment of PTB is prediction and prevention of its risks. And the most representative method of prevention of PTB in women with history of PTB and/or short CL nowadays is progesterone supplement therapy [6-8]. Although the exact role and mechanism of progesterone have not yet been elucidated, it is known that the substance creates estrogen antagonism by inhibiting estrogen receptors in uterine myometrial cells, blocks or decomposes oxytocin receptors,

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inhibits prostaglandin synthesis and inflammation [9].

Studies prior to 1990's displayed contradictory results, making it difficult to draw a clear conclusion on the effect of progesterone in prevention of PTB. In 2003, however, 2 randomized, double-blind, placebo-controlled trials demonstrated that progesterone supplement therapy can prevent PTB in women with history of PTB [3,4]. Many following studies were carried out to add evidences about prevention of PTB through progesterone supplement therapy, and now the American Congress of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend the usage of progesterone to prevent PTB in certain pregnant women — those with history of spontaneous PTB, such as preterm labor and premature rupture of membranes, and those with short CL during the midtrimester [10,11].

This review aims to summarize the efficacy and safety of progesterone supplement therapy on prevention of PTB according to different indication, type, route, and dose, based on the results of recent randomized trials and meta-analysis. Published literature on prevention of PTB with progesterone therapy was searched from PubMed and Google Scholar combining the terms "progesterone," "prevention," or "preterm birth." All randomized trials that evaluated the efficacy of progesterone supplement therapy on prevention of PTB since 2003 were reviewed in this article.

## Type, routes, dose, and interval of administration

Progesterone used for prevention of PTB is divided into 2 types: 17-alpha hydroxyprogesterone caproate (17α-OHPC) and natural micronized progesterone. Administration routes, dose and interval of the 2 types of progesterone commonly used in the randomized trials are summarized in Table 1.

The 17α-OHPC is a synthetic derivative of 17 hydroxyprogesterone. It is inactivated when orally administered, thus it is injected intramuscularly. The half-life of 17α-OHPC is 7.8 days [9], and therefore it is usually administered once a week to maintain serum concentration. Weekly intramuscular injection of 250 mg of 17α-OHPC was effective in preventing PTB in pregnant women with history of PTB [12,13]. In the other trials, higher dose or shorter interval was used in women with short CL, twin pregnancy, and after inhibition of preterm labor [14-17]. However, none these studies proved the efficacy of 17α-OHPC in preventing PTB in these subsets of patients.

Micronized progesterone, a natural progesterone, is similar to that produced in corpus luteum and placenta. Micronized progesterone can be utilized as oral capsule, vaginal gel or vaginal suppository, and all of them are self-administered. When it is orally administered, it is metabolized in the liver and loses its potency, entailing irregular blood concentration and more frequent side effects. When administered through vagina, however, it avoids the first-pass effect by the liver, is absorbed quickly, has increased bioavailability, directly affects the uterus, and is maintained in a high concentration in the serum [9,18,19].

Vaginal progesterone gel is administered through a specific applicator and a dose of 90 mg was used in all published studies [20-23]. Vaginal progesterone suppository is inserted in the vagina with clean hands or plastic gloves. The suppository is placed at the vaginal opening first and then pushed approximately 2 inches inside every day before bedtime. A dose of 100 mg was used in trials that targeted pregnant women with history of PTB [24-26], while 200 mg was used in trials of women with short CL [27]. Yet since no study directly compared the efficacy of 100 and 200 mg, there is no explicit evidence on which dosage has greater effect in preventing PTB. Vaginal progesterone suppository was dosed either 200 or 400 mg when used in twin pregnancies [28-31] or as a treatment after inhibition of preterm labor [32-36], but the optimal dose and its efficacy in twin pregnancies and preterm labor requires further evidence.

The beginning time and duration of the progesterone sup-

**Table 1.** Type, route, dose, and interval of progesterone supplement therapy for prevention of preterm birth

| Type | Route | Dose (mg) | Interval |
|---|---|---|---|
| 17α-OHPC | Intramuscular injection | 250 | Weekly |
| Natural micronized progesterone | Vaginal suppository | 100, 200, 400 | Daily |
| | Vaginal gel | 90 | Daily |
| | Oral capsule | 200, 400 | Daily |

17α-OHPC, 17-alpha hydroxyprogesterone caproate.

**Table 2.** Summary of randomized controlled trials of progesterone supplement therapy for prevention of PTB in women with history of PTB

| Author | Year | No. of patients (progesterone vs. placebo/no treatment) | Inclusion criteria | Type of progesterone | Progesterone dose & interval | Treatment period (wk) | Outcomes & results (progesterone vs. placebo/no treatment) | Other outcomes |
|---|---|---|---|---|---|---|---|---|
| Meis et al. [12] | 2003 | 310 vs. 153 | sPTB history (singleton) | IM 17α-OHPC | 250 mg weekly | From 16–20 until 36 | PTB <37 wk[a]: 36.3% vs. 54.9% (*P*<0.001)<br>PTB <35 wk: 20.6% vs. 30.7% (*P*=0.020)<br>PTB <32 wk: 11.4% vs. 19.6% (*P*=0.020) | ↓ LBW, ↓ $O_2$ therapy, ↓ IVH (any grade) |
| Saghafi et al. [13] | 2011 | 50 vs. 50 | PTB history | IM 17α-OHPC | 250 mg weekly | From 16 until 36 | PTB <37 wk[a]: 32% vs. 60% (*P*<0.050) | ↑ mean GAD, ↑ birth weight, ↓ LBW |
| da Fonseca et al. [25] | 2003 | 72 vs. 70 | sPTB history, uterine anomaly, IIOC (singleton) | Vaginal suppository | 100 mg daily | From 24 until 34 | PTB <37 wk[a]: 13.8% vs. 28.5% (*P*=0.030)<br>PTB <34 wk: 2.8% vs. 18.6% (*P*=0.002) | ↓ mean uterine contraction |
| Majhi et al. [26] | 2009 | 50 vs. 50 | sPTB history (singleton) | Vaginal suppository | 100 mg daily | From 20–24 until 36 | PTB <37 wk: 12% vs. 38% (*P*=0.003) | ↑ birth weight |
| Cetingoz et al. [24] | 2011 | 80 vs. 70 | sPTB history, uterine anomaly (singleton & twin)[b] | Vaginal suppository | 100 mg daily | From 24 until 34 | PTB <37 wk[a]: 40% vs. 57.2% (*P*=0.036)<br>PTB <34 wk: 8.8% vs. 24.3% (*P*=0.010) | ↓ NICU admission, ↓ PTB <37 and 34 wk in PTB history<br>↓ PTB <37 wk in twin |
| Azargoon et al. [41] | 2016 | 50 vs. 50 | PTB history, uterine anomaly, intramural myoma ≥7 cm (singleton) | Vaginal suppository | 400 mg daily | From 16–22 until 36 | PTB < 37wk[a]: 36% vs. 68% (*P*=0.001)<br>PTB <34 wk: 18% vs. 42% (*P*=0.009) | ↑ mean GAD, ↑ birth weight, ↓ LBW, ↓ RDS |
| Norman et al. [42] | 2016 | 610 vs. 618 | PTB history, short CL, positive fetal fibronectin with PTB risk factors (singleton) | Vaginal suppository | 200 mg daily | From 22–24 until 34 | PTB or fetal death <34 wk[a]: 16% vs. 18% (*P*=0.670)<br>Neonatal composite outcome[a]: 7% vs. 10% (*P*=0.072)<br>Cognitive composite score at 2 yr[a]: 17.9% vs. 17.5% (*P*=0.680) | No difference in mean GAD and other neonatal and childhood outcome, except for ↓ abnormal brain injury on ultrasound |
| O'Brien et al. [22] | 2007 | 309 vs. 302 | sPTB history (singleton) | Vaginal gel | 90 mg daily | From 18–24 until 36 | PTB <32 wk[a]: 10.0% vs. 11.3% (*P*>0.050)<br>PTB <37 wk: 41.7% vs. 40.7% (*P*>0.050) | No difference in mean GAD and neonatal outcome |
| Rai et al. [44] | 2009 | 74 vs. 74 | sPTB history (singleton) | Oral capsule | 200 mg daily | From 18–24 until 36 | PTB <37 wk[a]: 39.2% vs. 59.5% (*P*=0.002)<br>PTB <28–32 wk: 2.7% vs. 20.3% (*P*=0.001) | ↑ mean GAD, ↓ NICU stay, ↓ low Apgar scores |
| Glover et al. [45] | 2011 | 19 vs. 14 | sPTB history (singleton) | Oral capsule | 400 mg daily | From 16–20 until 33 | PTB <37 wk[a]: 26.3% vs. 57.1% (*P*=0.150) | No difference in neonatal outcome |

PTB, preterm birth; sPTB, spontaneous preterm birth; IM, intramuscular; 17α-OHPC, 17-alpha hydroxyprogesterone caproate; LBW, low birth weight; IVH, intraventricular hemorrhage; GAD, gestational age at delivery; IIOC, incompetent internal os of cervix; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; CL, cervical length.
[a]Primary outcome; [b]A total of 67 twin pregnancies (39 in the progesterone group and 28 in the placebo group) were included.

plement therapy in the published studies varied depending on the indications and the medication type. The therapy usually began at 16 to 24 weeks of gestation for those who had history of PTB, whereas it began at 18 to 24 weeks of gestation for those with short cervixes, as the CL is measured through transvaginal ultrasound conventionally after midtrimester. The therapy usually lasted until 34 or 36 weeks of gestation or rupture of membranes or delivery, whatever comes first. Yet, there is certainly a lack of research on optimal gestational age for beginning and until when medication should be used.

## Summary of previous studies based on the indications

### 1. History of PTB

The incidence rate of PTB among all pregnant women is approximately 7–11%, but the rate among those with history of PTB increases to 20–50% in subsequent pregnancies [37,38]. In addition, the recurrence rate increases with shorter gestational age at previous PTB and increasing number of previous PTBs [37,39]. Therefore, history of PTB was the major indication in randomized trials studying the efficacy of progesterone supplement therapy in preventing PTB (Table 2).

#### 1) 17α-OHPC

In 2003, Meis et al. [12] published a randomized, double-blind trial, in which pregnant women with history of spontaneous PTB were injected with 250 mg of 17α-OHPC or its placebo every week from 16 to 20 weeks to 36 weeks of gestation. The result of this randomized study showed that the 17α-OHPC treatment group had the lower rates of PTB <37, <35, and <32 weeks of gestation than the placebo group. Interestingly, the 17α-OHPC treatment was only effective in preventing recurrent PTB in women whose previous PTB occurred before 34 weeks of gestation [40]. Another randomized trial by Saghafi et al. [13] also showed that the 17α-OHPC treatment from 16 to 20 weeks to 36 weeks of gestation was associated with a significantly lower rate of PTB <37 weeks of gestation, accompanied by longer gestational age at delivery (GAD) and higher birth weight.

#### 2) Vaginal natural micronized progesterone suppository

In 2003, da Fonseca et al. [25], published the result of a randomized, double-blind trial of vaginal natural micronized progesterone suppository therapy in high-risk population in which over 90% of the subjects had history of PTB. The result of this study showed that daily administration of 100 mg of vaginal progesterone suppository resulted in the significantly lower rates of PTB <37 and <35 weeks of gestation than the placebo. The effect of vaginal natural micronized progesterone suppository therapy on prevention of PTB was supported by subsequent randomized trials [24,26,41]. However, a recent multicenter, randomized, double-blind trial of vaginal progesterone therapy (dOes Progesterone Prophylaxis To prevent preterm labour IMprove oUtcoMe [OPPTIMUM] study) showed contradictory results [42]. In this trial, 1,228 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 its placebo daily, from 22 to 24 weeks to 34 weeks of gestation. This study is as far the largest trial of vaginal progesterone treatment for prevention of PTB in women at risk, but it did not show any effect of progesterone treatment on rates of either PTB or neonatal and infant outcome in the whole study group and all subgroup analyses. The authors addressed that although the results showed no overall effect, point estimates of the reduction of the obstetric and neonatal outcome are in the direction of benefit, and further researches are needed to identify specific women who might specifically benefit.

#### 3) Vaginal natural micronized progesterone gel

In a randomized study performed by O'Brien et al. [22], 659 pregnant women with history of spontaneous PTB were administered daily 90 mg of vaginal natural micronized progesterone gel or its placebo. The 2 groups had no significant difference in terms of PTB rate, GAD, and 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 <32 weeks of gestation, a lower rate of admission to neonatal intensive care unit (NICU) and shorter hospital days [43].

#### 4) Oral natural micronized progesterone capsule

In a randomized trial conducted by Rai et al. [44], 100 mg of oral natural micronized progesterone capsule twice a day or placebo was used in women with history of spontaneous PTB. The treatment group had lower rates of PTB <37 weeks of gestation and PTB at 28 to 32 weeks of gestation. Contrarily,

**Table 3.** Summary of randomized controlled trials of progesterone supplement therapy for prevention of PTB in in women with short CL

| Author | Year | No. of patients (progesterone vs. placebo/no treatment) | Inclusion criteria | Type of progesterone | Progesterone dose & interval | Treatment period (wk) | Outcomes & results (progesterone vs. placebo/no treatment) | Other outcomes |
|---|---|---|---|---|---|---|---|---|
| Winer et al. [14] | 2015 | 51 vs. 54 | High risk for PTB[a] and short CL (<25 mm) (singleton) | IM 17α-OHPC | 500 mg weekly | From 20–31 until 36 | Mean (SD) time until delivery[b]: 76±5 vs. 72±5 day ($P$=0.480) | No differences in PTB <37, <34, <32 wk |
| Fonseca et al. [27] | 2007 | 125 vs. 125 | Short CL (<15 mm) (singleton & twin)[c] | Vaginal suppository | 200 mg daily | From 24 until 34 | sPTB <34 wk[b]: 19.2% vs. 34.4% ($P$=0.020)<br>PTB <34 wk: 20.8% vs. 36.0% ($P$=0.020) | No difference in neonatal outcome |
| Hassan et al. [20] | 2011 | 235 vs. 223 | Short CL (10–20 mm) (singleton) | Vaginal gel | 90 mg daily | From 20–24 until 36 | PTB <32 wk[b]: 8.9% vs. 16.1% ($P$=0.020)<br>PTB <28 wk: 5.1% vs. 10.3% ($P$=0.036)<br>PTB <35 wk: 14.5% vs. 23.3% ($P$=0.016) | ↓ RDS, ↓ neonatal composite morbidity |

PTB, preterm birth; CL, cervical length; IM, intramuscular; 17α-OHPC, 17-alpha hydroxyprogesterone caproate; SD, standard deviation; sPTB, spontaneous preterm birth; RDS, respiratory distress syndrome.
[a]History of PTB or cervical surgery or uterine malformation or prenatal diethylstilbestrol exposure; [b]Primary outcome; [c]A total of 24 twin pregnancies (11 in the progesterone group and 13 in the placebo group) were included.

in a randomized trial performed by Glover et al. [45], no difference was noted in the rate of recurrent PTB and neonatal outcome between the 400-mg oral progesterone group and placebo group. However, due to the small number of subjects and various dosages used in the studies, it is difficult to draw a clear conclusion on the effect of oral administration of progesterone therapy on prevention of PTB.

## 2. Short CL

The most useful method to predict the risk of PTB is the measurement of CL by vaginal ultrasound during midtrimester [46,47]. The risk of PTB is substantially high when CL is <25 mm, and the risk increases as the CL decreases [48-50]. Therefore, short CL was another major indication in randomized trials studying the efficacy of progesterone supplement therapy in preventing PTB (Table 3).

### 1) 17α-OHPC

In a randomized trial conducted by Winer et al. [14], pregnant women at high-risk for PTB (history of PTB, cervical surgery, uterine malformation, or prenatal diethylstilbestrol exposure) and CL <25 mm were randomized into weekly intramuscular injection of 500 mg 17α-OHPC or no treatment. However, the 2 groups were similar in terms of GAD and the rates of PTB <37, <34, and <32 weeks of gestation.

### 2) Vaginal natural micronized progesterone suppository

In a study conducted by Fetal Medicine Foundation in United Kingdom, 24,000 low-risk pregnant women were screened for CL during 20 to 25 weeks of gestation, and 413 women were found to have CL <15 mm. Among them, 250 women were randomly assigned into daily administration of 200 mg of vaginal progesterone suppository or its placebo [27]. The progesterone group demonstrated a lower rate of PTB <34 weeks of gestation than the placebo group. This research bears a significance in that it suggested the potential benefit of routine CL screening in low-risk pregnant women in terms of predicting and preventing PTB. A recent meta-analysis, including data from the OPPTIMUM study, showed that vaginal progesterone therapy significantly reduced the risk of PTB and neonatal morbidity and mortality in women with a singleton gestation and a short CL [51]. The authors of this meta-analysis study concluded that universal transvaginal CL screening during midtrimester should be performed in women with a singleton gestation and offer vaginal progesterone

**Table 4.** Summary of randomized controlled trials of progesterone supplement therapy for prevention of PTB in women with twin pregnancy

| Author | Year | No. of patients (progesterone vs. placebo/no treatment) | Inclusion criteria | Type of progesterone | Progesterone dose & interval | Treatment period (wk) | Outcomes & results (progesterone vs. placebo/no treatment) | Other outcomes |
|---|---|---|---|---|---|---|---|---|
| Rouse et al. [59] | 2007 | 325 vs. 330 | Twin | IM 17α-OHPC | 250 mg weekly | From 16–20 until 35 | PTB or fetal death <35 wk[a]: 41.5% vs. 37.3% (*P*>0.050) | No differences in PTB <37, <32, <28 wk |
| Briery et al. [60] | 2009 | 16 vs. 14 | Twin | IM 17α-OHPC | 250 mg weekly | From 20–30 until 34 | PTB <35 wk[a]: 44% vs. 79% (*P*=0.117) | No differences in mean GAD and neonatal outcome |
| Lim et al. [61] | 2012 | 336 vs. 335 | Twin[b] | IM 17α-OHPC | 250 mg weekly | From 16–20 until 36 | Composite adverse neonatal outcome[a]: 16% vs. 12% (*P*>0.050) | No differences in PTB <37, <32, <28 wk |
| Awwad et al. [62] | 2015 | 194 vs. 94 | Twin | IM 17α-OHPC | 250 mg weekly | From 16–20 until 36 | PTB <37 wk[a]: 61.3% vs. 61.7% (*P*=0.950) | ↑ birth weight, ↓ very LBW, ↓ composite neonatal morbidity |
| Senat et al. [15] | 2013 | 82 vs. 83 | Twin & short CL (<25 mm) | IM 17α-OHPC | 500 mg × 2/weekly | From 24–32 until 36 | Median (IQR) time until delivery[a]: 45 (26–62) vs. 51 (36–66) day (*P*>0.050) | No differences in PTB <37, <34 wk, ↑ PTB <32 wk |
| Rode et al. [30] | 2011 | 334 vs. 343 | Twin | Vaginal suppository | 200 mg daily | From 20–24 until 34 | PTB <34 wk[a]: 15.3% vs. 18.5% (*P*>0.050) | No differences in PTB <37, <32, <28 wk |
| Serra et al. [31] | 2013 | 97 vs. 97 vs. 96[c] | Twin | Vaginal suppository | 400 mg, 200 mg daily | From 20 until 34 | PTB <37 wk[a]: 45.4% vs. 49.5% vs. 49.0% (*P*>0.050) | No differences in PTB <34 wk, <32 wk, <28 wk, and neonatal outcome |
| El-Refaie et al. [29] | 2016 | 116 vs. 108 | Twin & short CL (20–25 mm) | Vaginal suppository | 400 mg daily | From 20–24 until 36 | PTB <34 wk[a]: 35.3% vs.52.8% (*P*=0.010) | ↑ mean GAD, ↓ PTB <32w, ↓ very LBW, ↓ RDS, ↓ ventilator, ↓ neonatal death |
| Brizot et al. [28] | 2015 | 189 vs. 191 | Twin | Vaginal suppository | 200 mg daily | From 18–22 until 34 | Mean (SD) GAD[a]: 35.1±3.2 vs. 35.6±2.9 wk (*P*=0.010) | No difference in PTB <37 wk, <34 wk, <32 wk, <28 wk, and neonatal outcome |
| Norman et al. [21] | 2009 | 250 vs. 250 | Twin | Vaginal gel | 90 mg daily | From 24 until 34 | PTB or fetal death <34 wk[a]: 24.7% vs. 19.4% (*P*=0.160) | No difference in maternal and neonatal outcome |
| Wood et al. [23] | 2012 | 42 vs. 42 | Twin | Vaginal gel | 90 mg daily | From 16–21 until 36 | Mean (IQR) GAD[a]: 36+3 (2+6) vs. 36+2 (3+0) wk (*P*=0.585) | No difference in PTB <37 wk, <35 wk, and neonatal outcome |

PTB, preterm birth; IM, intramuscular; 17α-OHPC, 17-alpha hydroxyprogesterone caproate; GAD, gestational age at delivery; LBW, low birth weight; CL, cervical length; IQR, interquartile range; SD, standard deviation; RDS, respiratory distress syndrome.

[a]Primary outcome; [b]Women with history of sPTB were excluded; [c]Progesterone 400 vs. progesterone 200 vs. placebo.



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supplement therapy to those with a short CL. However, routine screening of CL in all low-risk women is still under debate [52-54].

#### 3) Vaginal natural micronized progesterone gel

In the PREGNANT study conducted by Hassan et al. [20], low-risk singleton pregnant women were screened for short CL of 10 to 20 mm and randomized into daily 90 mg of progesterone gel treatment and placebo. The treatment group demonstrated lower rates of PTB <28, <32, and <35 weeks of gestation than the placebo group, as well as the lower rates of neonatal morbidity including RDS, neonate mortality, and very low birth weight (LBW) infants. In a meta-analysis conducted by Romero et al. [55] in 2012, progesterone supplement therapy was found to decrease the rates of PTB <28, <33, and <35 weeks of gestation, along with the improved neonatal outcomes: lower rates of RDS, mortality, very LBW infant, admission to NICU, and use of mechanical ventilator. In terms of maternal and fetal side effects, no significant difference was noted between the progesterone treatment and control groups.

### 3. Twin pregnancy

Twin pregnancy, compared to singleton pregnancy, entails higher risk of PTB and more instances of short CL [49,56,57]. However, most of the studies so far have revealed that progesterone supplement therapy in twin pregnancies did not significantly reduce the risk of PTB (Table 4). The ACOG and the SMFM concluded that the effectiveness of progesterone supplement therapy in multiple pregnancy lacks sufficient evidence [10,11]. A recent meta-analysis also showed that both intramuscular and vaginal progesterone supplement therapy was not effective in improving perinatal outcomes of twin pregnancies [58].

#### 1) 17α-OHPC

A randomized, double-blind trial was conducted to examine the effect of intramuscular 17α-OHPC 250 mg on the risk of PTB in twin pregnancies by National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network [59]. Six hundred fifty-five twin pregnant women were injected with 17α-OHPC 250 mg or its placebo every week. The primary outcome of PTB or fetal death <35 weeks of gestation was similar in the 2 groups. Following randomized trials targeting twin pregnant women also indicated that intramuscular injection of 17α-OHPC did not reduce the PTB rate or improve neonatal outcomes [60-62]. A higher dose of 17α-OHPC (500 mg twice a week) was used in a randomized trial that targeted twin pregnant women with CL <25 mm [15]. However, the period from randomization to delivery and the rates of PTB <37 and <32 weeks of gestation were not significantly reduced by the higher dose of progesterone treatment, while the rate of PTB <32 weeks of gestation was rather higher in the treatment group than the control group.

#### 2) Vaginal natural micronized progesterone suppository

Similar to 17α-OHPC, 200 mg of vaginal natural micronized progesterone suppository was proven ineffective in prevention of PTB in twin pregnancies [28,30]. In the study by Serra et al. [31], subjects were divided into 200 and 400 mg of vaginal progesterone and placebo group. However, the rates of PTB <37, <34, <32, and <28 weeks of gestation was not reduced by either 200 or 400 mg of progesterone therapy. Aboulghar et al. [63] randomized 306 women with singleton and twin pregnancies conceived by in vitro fertilization into 400 mg of vaginal natural micronized progesterone suppository or placebo. However, the rates of PTB <34 and <37 weeks of gestation were not significantly different between the 2 groups. Interestingly, the secondary analysis showed that the progesterone treatment lowered the rate of PTB <37 weeks of gestation in singleton pregnancies, while the treatment did not lower the rates of PTB <34 and <37 weeks of gestation in twin pregnancies. On the other hand, in a randomized trial that enrolled twin pregnant women with CL of 20 to 25 mm, 400 mg of natural micronized progesterone vaginal suppository therapy was associated with lower rates of PTB <34 and <32 weeks of gestation, along with longer GAD and decreased rates of very LBW infant, neonatal RDS, mortality, and use of mechanical ventilators [29].

#### 3) Vaginal natural micronized progesterone gel

According to the Study of Progesterone for the Prevention of Preterm Birth in Twins (STOPPIT) trial in 2009, daily vaginal progesterone gel supplement treatment did not prevent PTB in twin pregnancies [21]. Five hundred twin pregnant women were assigned to either 90 mg vaginal progesterone gel treatment or placebo, but no difference was noted between the 2 groups in terms of occurrence of stillbirth or PTB <34 weeks of gestation. In a randomized trial conducted by Wood et al. [23], daily vaginal progesterone gel supplement therapy did

**Table 5.** Summary of randomized controlled trials of progesterone supplement therapy for prevention of PTB in women with preterm labor or preterm premature rupture of membranes

| Author | Year | No. of patients (progesterone vs. placebo/no treatment) | Inclusion criteria | Objective of progesterone treatment | Type of progesterone | Progesterone dose & interval | Outcomes & results (progesterone vs. placebo/no treatment) | Other outcomes |
|---|---|---|---|---|---|---|---|---|
| Facchinetti et al. [17] | 2007 | 30 vs. 30 | PTL at 25–34 wk (singleton) | Maintenance therapy after acute tocolysis | IM 17α-OHPC | 341 mg biweekly | Mean (SD) shortening of CL[a]: at day 7 (0.83±1.74 vs. 2.37±2.0 mm [*P*=0.002], at day 21 (2.40±2.46 vs. 4.60±2.73 mm [*P*=0.002]) | ↓PTB <37 wk, birth weight |
| Rozenberg et al. [16] | 2012 | 94 vs. 94 | PTL at 24–32 wk (singleton) | Maintenance therapy after acute tocolysis | IM 17α-OHPC | 500 mg semiweekly | Median (IQR) time until delivery[a]: 64 (42–79) and 67 (46–83) day (*P*>0.050) | No differences in PTB <37, <34, <32 wk, and neonatal outcome |
| Briery et al. [67] | 2014 | 22 vs. 23 | PTL at 24–34 wk (singleton) | Maintenance therapy after acute tocolysis | IM 17α-OHPC | 250 mg weekly | PTB <37 wk[a]: 86.4% vs. 95.7% (*P*=0.346) | ↓ PTB <34 wk, ↓ IVH, ↓ sepsis |
| Lotfalizadeh et al. [68] | 2013 | 37 vs. 37 vs. 36[b] | PTL at 26–36 wk (singleton) | Maintenance therapy after acute tocolysis | IM 17α-OHPC<br>Vaginal suppository | 250 mg weekly<br>400 mg daily | LBW: 27% vs. 27% vs. 50% (*P*=0.020) | |
| Briery et al. [70] | 2011 | 33 vs. 36 | PPROM at 20–30 wk (singleton) | Extend latency | IM 17α-OHPC | 250 mg weekly | Mean (SD) time until delivery[a]: 11.2±7.3 vs. 14.5±10.0 wk (*P*=0.146) | No differences in GAD and neonatal outcome |
| Combs et al. [86] | 2015 | 74 vs. 78 | PPROM at 23–31 wk (singleton) | Extend latency | IM 17α-OHPC | 250 mg weekly | Continuation of pregnancy either until 34 wk or until 32–34 wk with documentation of FLM testing[a]: 3% vs. 8% (*P*=0.180) | No differences in GAD and neonatal outcome |
| Arikan et al. [32] | 2011 | 43 vs. 40 | PTL at 24–34 wk (singleton) | Combination with tocolytics | Vaginal suppository | 200 mg daily | Mean (SD) time until delivery[a]: 21.2±16.3 vs. 32.1±17.8 day (*P*<0.050)<br>Mean (SD) GAD[a]: 35.2±2.7 vs. 36.4±2.5 wk (*P*<0.050)<br>PTB <37 wk[a]: 65% vs. 50% (*P*>0.990) | ↑ birth weight, ↓ LBW |
| Borna and Sahabi [33] | 2008 | 37 vs. 33 | PTL at 24–34 wk (singleton) | Maintenance therapy after acute tocolysis | Vaginal suppository | 400 mg, daily | Mean (SD) time until delivery[a]: 24.5±27.2 vs. 36.1±17.9 day (*P*=0.037)<br>Mean (SD) GAD[a]: 34.5±1.2 vs. 36.7±1.5 wk (*P*=0.041)<br>Recurrent PTL[a]: 57.6% vs. 35.1% (*P*=0.092) | ↑ birth weight, ↓ LBW, ↓ RDS |

**Table 5.** Continued

| Author | Year | No. of patients (progesterone vs. placebo/no treatment) | Inclusion criteria | Objective of progesterone treatment | Type of progesterone | Progesterone dose & interval | Outcomes & results (progesterone vs. placebo/no treatment) | Other outcomes |
|---|---|---|---|---|---|---|---|---|
| Saleh Gargari et al. [34] | 2012 | 72 vs. 72 | PTL at 24–34 wk (singleton) | Maintenance therapy after acute tocolysis | Vaginal suppository | 400 mg daily | Mean (SD) GAD: 36.2±1.4 vs. 34.1±1.5 wk ($P$=0.039)<br>Mean (SD) time until delivery: 4.0±1.5 vs. 1.4±0.2 wk ($P$=0.048) | ↑ birth weight, ↓ LBW, ↓ NICU admission |
| Martinez de Tejada et al. [35] | 2015 | 193 vs. 186 | PTL at 24–34 wk (singleton) | Maintenance therapy after acute tocolysis | Vaginal suppository | 200 mg daily | PTB <37 wk[a]: 42.5% vs. 35.5% ($P$>0.050) | No differences in PTB <34 wk, <32 wk, latency and neonatal outcome |
| Palacio et al. [36] | 2016 | 126 vs.132 | PTL at 24–34 wk & short CL (<25 mm) (singleton) | Maintenance therapy after acute tocolysis | Vaginal suppository | 200 mg daily | PTB <34 wk[a]: 7.1% vs.7.6% ($P$=0.910)<br>PTB <37 wk[a]: 28.6% vs. 22.0% ($P$=0.220) | No differences in neonatal outcome |
| Choudhary et al. [72] | 2014 | 45 vs. 45 | PTL at 24–34 wk (singleton) | Maintenance therapy after acute tocolysis | Oral capsule | 200 mg daily | Mean (SD) time until delivery[a]: 33.3±23.2 vs. 23.1±15.4 day ($P$=0.013) | ↓ PTB <37 wk, ↑ birth weight, ↓ LBW |

PTB, preterm birth; PTL, preterm labor; IM, intramuscular; 17α-OHPC, 17-alpha hydroxyprogesterone caproate; SD, standard deviation; CL, cervical length; IQR, interquartile range; IVH, intraventricular hemorrhage; LBW, low birth weight; PPROM, preterm premature rupture of membranes; GAD, gestational age at delivery; FLM, fetal lung maturity; RDS, respiratory distress syndrome; NICU, neonatal intensive care unit.
[a]Primary outcome; [b]IM progesterone vs. vaginal progesterone vs. placebo.

not extend the gestational age, reduce the PTB rate, or improve the neonatal outcome. However, a recent systematic review and meta-analysis of individual patient data from randomized trials comparing vaginal progesterone therapy with placebo/no treatment in women with a twin gestation and a short CL showed that vaginal progesterone therapy was associated with a significant decrease in the rates of PTB <35, <34, <32, and <30 weeks of gestation and neonatal mortality and morbidity [64].

## 4. Preterm labor and premature rupture of membranes

As it is already known that progesterone can prevent the shortening of the cervix and inhibit inflammation [65,66], use of progesterone in women with preterm labor or premature rupture of membranes has been another subject of progesterone research (Table 5).

### 1) 17α-OHPC

In a randomized trial conducted by Facchinetti et al. [17], pregnant women with preterm labor at 25–34 weeks of gestation were treated with tocolytic agents and then randomized into injection of 17α-OHPC twice a week or no treatment. As a result, the treatment group demonstrated less shortening of the cervix, reduction in the PTB <37 weeks of gestation, and larger neonatal birth weight compared to the no treatment group. A randomized study performed by Rozenberg et al. [16], however, demonstrated no difference in interval from randomization until delivery, the rates of PTB <32, <34, and <37 weeks of gestation, and neonatal outcomes between the maintenance 17α-OHPC treatment (500 mg once in 2 weeks) group and no treatment group. In another randomized study done by Briery et al. [67], weekly 250 mg of 17α-OHPC or placebo was injected as maintenance therapy in women with preterm labor at 24–34 weeks of gestation. The rate of PTB <37 weeks of gestation was not significantly different between the 2 groups, while the rates of PTB <34 weeks of gestation, neonatal IVH, and sepsis were significantly lower in the treatment group. In addition, Lotfalizadeh et al. [68] conducted a randomized trial in which the subjects were divided into three groups — a group treated with weekly 250 mg of 17α-OHPC, a group

treated with daily 400 mg of vaginal natural micronized progesterone suppository, and a placebo group. The result of this trial showed that the 17α-OHPC and vaginal progesterone groups had a significantly lower incidence of LBW infant than the placebo group. Furthermore, a meta-analysis performed by Saccone et al. [69] showed that 17α-OHPC maintenance therapy after initial tocolytics therapy did not reduce the PTB rate, but it extended the GAD and increase neonate birth weight. The only randomized study that implemented progesterone supplement therapy in premature rupture of membranes revealed that an injection of 250 mg of 17α-OHPC every week did not extend the interval from randomization until delivery, nor improve neonate outcomes [70].

#### 2) Vaginal natural micronized progesterone suppository

In randomized trials that used daily vaginal natural micronized progesterone suppository, either 200 or 400 mg, resulted in a longer interval from randomization to delivery, an increase in the GAD, an increase in neonate birth weight, and a decrease in the LBW infants [32-34]. In a meta-analysis performed by Suhag et al. [71], vaginal progesterone supplement therapy was associated with a lower rate of PTB, a longer GAD, and a lower rate of neonate sepsis. However, 2 large multicenter, randomized, double-blind, placebo-controlled trial randomized trials [35,36] showed that the maintenance treatment of 200 mg of daily vaginal progesterone suppository in women after an episode of arrested preterm labor did not significantly reduce the rates of PTB <37 and <34 weeks of gestation.

#### 3) Oral natural micronized progesterone capsule

According to a randomized trial that compared the maintenance therapy with daily 200 mg of natural micronized progesterone oral capsule and placebo after inhibition of preterm labor, the treatment group had a longer interval from randomization to delivery, a lower rate of PTB <37 weeks of gestation, a higher neonatal birth weight, and a lower incidence of LBW infants than the placebo group [72].

## 17OHCP intramuscular injection versus vaginal natural micronized progesterone

A great number of previously mentioned studies, along with the recommendation or guidelines from various societies and associations, have validated that progesterone supplement therapy can effectively prevent PTB in women with history of PTB and in women with short CL. However, it has not been fully elucidated whether which progesterone therapy is better with regard to the efficacy of preventing PTB, cost-effectiveness, or side effects. In order to compare the preventative effects of 2 different regimens of progesterone therapy, Maher et al. [73] conducted a randomized 502 singleton pregnant women with history of PTB into weekly intramuscular injection of 250 mg of 17α-OHPC or daily vaginal administration of 90 mg of micronized progesterone gel. The vaginal progesterone group had significantly lower rates of PTB <34 weeks of gestation, PTB at 28 to 32 weeks of gestation, and a lower rate of side effects. However, randomized trials comparing daily vaginal progesterone administration and weekly intramuscular injection of 250 mg of 17α-OHPC in singleton pregnant women with history of PTB or short CL did not show any significant differences in the rate of PTB <37 weeks of gestation, mean GAD, and neonate outcomes between the 2 groups [74-76]. A recent systematic review and meta-analysis showed that women who received vaginal progesterone had significantly lower rates of PTB <34 and <32 weeks of gestation, a lower rate of adverse drug reactions and a lower rate of NICU admission compared with women who received 17α-OHPC [77]. However, only three trials were included in this meta-analysis and different type and dose of vaginal progesterone was used in each trial, therefore the quality of evidence was not sufficient to conclude which type of progesterone is more beneficial.

Currently, the Preterm Birth Committee of Korean Society of Maternal Fetal Medicine is conducting "A multicenter, randomized, open-label, investigator-initiated trial of vaginal compared with intramuscular progesterone for prevention of PTB in high-risk pregnant women: VICTORIA study". In this trial, 360 pregnant women with history of PTB and/or short CL will be recruited in 24 medical centers nationwide. The study will compare the efficacy and safety of 2 regimens of progesterone supplement therapy — weekly intramuscular injection of 250 mg of 17α-OHPC and daily vaginal administration of 200 mg of micronized progesterone.

## Maternal-fetal safety and side effects

It has been reported that the usage of progesterone during

the first trimester of pregnancy can lead to masculinization of a female fetus, congenital heart and brain malformations [78]. Yet, in large-scale studies, a clear relationship between progesterone and fetal anomalies has not been elucidated [79,80]. The Food and Drug Administration (FDA) classified natural micronized progesterone medications as category B for pregnancy [78]. A study from NICHD, which used 17α-OHPC, demonstrated no difference between the progesterone-treated and the control groups in terms of miscarriage and stillbirth [12]. An observational follow up study after 30 to 64 months also reported no significant difference in the long-term infant outcomes [81]. In 2011, FDA approved Makena® (17α-OHPC; Hospira, Inc., McPherson, KS, USA) for reduction of PTB in women with history of PTB [82].

Progesterone may entail various systemic side effects such as mood swings, headache, dyspepsia, abdominal pain, constipation, diarrhea, nausea, vomiting, depression, loss of libido, dyspareunia, drowsiness, breast pain, urinary frequency, fatigue, dizziness, genital itching, back pain, fever, flu-like symptoms, and sleep disorders [9]. The synthetic progesterone, 17α-OHPC, has lower rates of these side effects than the natural micronized progesterone [9]. Yet, vaginal administration of micronized progesterone can help avoiding metabolism by the liver, thereby markedly reducing the risk of these side effects [19,83,84]. The majority of the side effects of 17α-OHPC included pain, edema, redness, itching, and bruise, which were all related to the injection, while some studies noted instances of systemic symptoms such as nausea and vomiting [12]. No systemic side effects appeared in trials that used natural micronized progesterone, with the major side effect being an increase in vaginal secretions [25,26,55]. A recent meta-analysis on the safety of progesterone treatment for the prevention of PTB has revealed that progesterone treatment to women at risk for PTB did not negatively affect neonatal mortality in single or multiple pregnancies regardless of the route of administration [85].

## Summary

Progesterone supplement therapy is effective in prevention of PTB. However, its efficacy varies depending on the indication and type, administration route, and dose of progesterone. For singleton pregnant women with history of spontaneous PTB, including preterm labor and premature rupture of membranes, weekly injection of 250 mg of 17α-OHPC, as well as daily administration of vaginal micronized progesterone suppository (100 or 200 mg) are effective in preventing recurrent PTB, but the preventative effects of vaginal progesterone gel or oral progesterone capsules currently lack evidence. For singleton pregnant women with CL <25 mm during midtrimester, daily administration of vaginal micronized progesterone suppository (100 or 200 mg) or gel (90 mg every day) is effective in preventing PTB, but the preventative effect of 17α-OHPC therapy lack evidence. In women with twin pregnancy, an injection of 17α-OHPC nor an administration of vaginal micronized progesterone suppository or gel could prevent PTB. Yet, for twin pregnant women with short CL, vaginal progesterone supplement therapy may be effective for reducing the rate of PTB and improving the neonatal outcome. As a maintenance therapy after the inhibition of preterm labor, 17α-OHPC cannot prevent PTB but can extend the gestational age and increase the birth weight. Both vaginal and oral micronized progesterone treatment can prevent PTB <37 weeks of gestation, extend the gestational age, and increase the birth weight. Yet the exact role of progesterone as a maintenance therapy after the inhibition of preterm labor remains much to be discovered. In cases of premature rupture of membranes, there lacks evidence on the effect of progesterone supplement therapy in preventing PTB. The progesterone supplement therapy generally begins at 16 to 24 weeks of gestation and ends at 34 to 36 weeks of gestation. No evidence currently exists on which progesterone supplement therapy can maximize the preventative effects while minimizing the side effects. Therefore, further researches are required to uncover the optimal type, dose and duration of progesterone supplement therapy depending on various indications of treatment.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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