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Use of Progesterone Supplement Therapy for Prevention of Preterm Birth - Review of Literatures

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KEYWORDS

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ABSTRACT:

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.

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 India [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].

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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, 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.

Table 1: Type, route, dose, and interval progesterone supplement therapy of preterm birth

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.

The 17α-OHPC is a synthetic derivative of 17 hydroxyprogesterone. It is inactivated when orally administered, thus itis 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

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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 supplement 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).

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.

Table 2:

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	≥PTB 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) PTB <35 wk: 20.6% vs. 30.7% (P=0.013) 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	≥PTB 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) PTB <34 wk: 2.8% vs. 18.6% (P=0.002)	↓ mean uterine contraction
Majhi et al. [26]	2009	50 vs 50	≥PTB 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	≥PTB history, uterine anomaly (singleton & twin)[b]	Vaginal suppository	100 mg daily	From 24 until 34	PTB <37 wk[a]: 40% vs. 57.2% (P=0.095) PTB <34 wk: 8.8% vs. 24.3% (P=0.010)	↓ NICU admission, ↓ PTB <37 and 34 wk in PTB history ↓ 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) 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) Neonatal composite outcome[b]: 7% vs. 10% (P=0.072) 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	≥PTB history (singleton)	Vaginal gel	90 mg daily	From 18-24 until 36	PTB <32 wk[a]: 10.0% vs. 11.3% (P>0.050) 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	≥PTB history (singleton)	Oral capsule	200 mg daily	From 18-24 until 36	PTB <37 wk[a]: 39.2% vs. 58.5% (P=0.002) 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	≥PTB 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; ≥PTB, 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.

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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 micronizedprogesterone 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, 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.

Table 3:

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)[a]	Vaginal suppository	200 mg daily	From 24 until 34	sPTB <34 wk[b]: 19.2% vs. 34.4% (P=0.020) 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) PTB <28 wk: 5.1% vs. 10.3% (P=0.036) 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.

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1. 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).

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.

Table 4:

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. 348	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 <32 w, ↓ 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.

1. 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].

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].

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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 thatinjection 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.

Table 5: Continued

Table 5. Continued

Author	Year	No. of patients (progesterone vs. placebo/no treatment)	Inclusion crite-ria	Objective of progesterone treatment	Type of pro-gesterone	Progester-one 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) 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) 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.

1. **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).

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 grouptreated 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

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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].

17OHCP intramuscular injection versus vaginal natural micronized progesterone

A great number of previously mentioned studies, along with the recommendation or guidelines from various societies andassociations, 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 India 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 duringthe 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

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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 ofmembranes, 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.

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