
REVIEW ARTICLE

Progesterone for Prevention of Preterm Birth

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Preterm birth is a major cause of perinatal mortality and morbidity. It is also the main directed cause of neonatal death globally⁽¹⁾. Preterm birth is responsible for more than 80% of neonatal deaths and 50% of long term morbidity in the surviving infants⁽¹⁻³⁾. Preterm birth rates have been rising over the past 3 decades. The worldwide incidence of preterm birth is 9.6 % with the highest rate occurs in the least developed regions⁽⁴⁾. The increase in assisted reproductive technologies, labor induction or elective cesarean section during preterm period may be responsible for these high rates⁽²⁾. Various risk factors are associated with preterm birth but only half of them can be identified⁽⁵⁾. Although there are many interventions to prevent or treat preterm births, none of them appears to be efficacious⁽⁶⁾. Recent evidences showed that progesterone supplementations are helpful to prevent preterm birth. This article pays attention to the role of progesterone for the prevention of preterm birth.

Role of progesterone and initiation of labor

Progesterone withdrawal leads to cervical ripening and parturition in non-human species. Administration of exogenous progesterone effectively prevents labor and delivery process^(7, 8). However, effects of progesterone in human are still questionable

because the levels of progesterone in maternal circulation, fetal blood and the amniotic fluid are not changed before the onset of labor and delivery^(9,10). There are hypotheses on the functional progesterone withdrawal including loss of progesterone receptors, change in receptor isoforms expression, binding of progesterone to a high affinity protein and reduction in free active form⁽¹¹⁻¹³⁾. Unfortunately, none of them has been proved.

Formulations and pharmacokinetics of progestins

1. Natural progesterone: micronized progesterone, 17-hydroxyprogesterone

Different routes of administration effect plasma concentration, bioavailability and side effects of progesterone. Oral progesterone is not recommended because of its first-pass hepatic metabolism, high side effects and extreme variability in plasma concentrations. Transvaginal administration, avoids first-pass hepatic metabolism, has rapid absorption, high bioavailability, no local pain and less side effects^(14,15).

2. Synthetic progestins: 17 alpha-hydroxyprogesterone caproate (17 OHP-C)

17 OHP-C is a 17-hydroxyprogesterone derivative

which is inactive by oral route, but working as a long-acting progestin when given intramuscularly. Half-life is approximately 7.8 days for intramuscular injection⁽¹⁶⁾.

Progesterone for prevention of preterm birth

Most studies of progesterone in prevention of preterm birth concerned 2 target groups: 1) pregnant women with previous preterm birth and 2) the women with short cervix during mid-trimester. Most studies used either intramuscular or vaginal progesterone for the prevention of preterm birth. Only few studies with small number of cases used oral progesterone. So, we do not include oral progesterone in this review.

Effect of progesterone in the women at risk for preterm birth (Table 1)

da Fonseca (2003) published the first randomized, placebo controlled, double-blind study of progesterone and preterm birth⁽¹⁷⁾ using either transvaginal, 100 mg of natural progesterone or placebo in pregnant women at risk for preterm birth during 24-34 weeks of gestation. The incidence of preterm birth was significantly lower in the progesterone group (28.5% VS 13.8%). Study by Meis (2003) showed that intramuscular 17 OHP-C significantly reduced preterm birth. Infants of women treated with 17 OHP-C had significantly lower rates of necrotizing enterocolitis, intravascular hemorrhage, and need for supplemental oxygen⁽¹⁸⁾. The gestational age at delivery and the reduction of spontaneous preterm birth before 37 weeks were greatest in women with history of previous preterm birth before 34 weeks' gestation⁽¹⁹⁾. In contrast, O'Brien (2007) found that progesterone vaginal gel could not reduce preterm birth rate, neonatal morbidity and mortality⁽²⁰⁾.

Subsequent meta-analysis concluded that progesterone supplementation reduced the rate of preterm birth while the reduction in perinatal or neonatal morbidity and mortality were not consistently demonstrated⁽²¹⁻²⁴⁾.

Effect of progesterone in the women who had short cervical length during mid-trimester (Table 2)

Short cervical length detected during mid-trimester ultrasound screening is an important risk factor for preterm birth⁽²⁵⁾. Cervical length measurement of less than 15 mm is the highest risk factor⁽²⁵⁻²⁷⁾. Randomized, placebo controlled, double-blind studies showed the efficacy of daily, vaginal, micronized progesterone for the prevention of preterm birth, but did not significantly decrease neonatal morbidity and mortality^(25,28,29). Recent meta-analysis concluded that vaginal progesterone supplementation reduced preterm birth rate, neonatal respiratory distress syndrome, composite neonatal morbidity and mortality and birth weight less than 1,500 grams⁽³⁰⁾.

Effect of progesterone in twin pregnancy (Table 3)

Randomized, placebo controlled, double-blind studies showed that progesterone supplementation in twin pregnancy, either micronized progesterone or 17 OHP-C, did not reduce preterm birth rate or improve perinatal outcome⁽³¹⁻³⁵⁾. Mechanisms of preterm birth in twin pregnancy may be different from those in singleton pregnancy.

Table 1. Effect of progesterone in the women at risk for preterm birth

Study (year)/ Study type	Progesterone/ Dosage	Treatment GA/ Inclusion criteria	Cases/ Controls	Result		p / RR / OR (95% CI)	
				Cases	Controls		
da Fonseca ⁽¹⁷⁾ (2003)/ RCT	Micronized progesterone 100 mg vagina daily	GA 24 to 34 wk/ - Previous preterm birth - Cervical cerclage - Uterine malformation	72 / 70	Delivery GA < 37 wk: 13.8%	Delivery GA < 37 wk: 28.5%	p = 0.03	
				Delivery GA < 34 wk: 2.8%	Delivery GA < 34 wk: 18.6%		p = 0.002
Meis ⁽¹⁸⁾ (2003)/ MC-RCT	17 OHP-C 250 mg IM weekly	GA 16-20 to 36 wk/ - Previous preterm birth	306 / 153	Delivery GA < 37 wk: 36.3%	Delivery GA < 37 wk: 54.9%	RR = 0.66 (0.54, 0.81)	
				Delivery GA < 35 wk: 20.6%	Delivery GA < 35 wk: 30.7%		RR = 0.67 (0.48, 0.93)
				Delivery GA < 32 wk: 11.4%	Delivery GA < 32 wk: 19.6%		
Spong ⁽¹⁹⁾ (2005)/ MC-RCT	Secondary analysis of Meis's study			Previous preterm birth at 20-27.9 wk		RR = 0.43 (0.19, 0.98) p = 0.44	
				Previous preterm birth at 28-33.9 wk		RR = 0.44 (0.23, 0.85) p = 0.14	
				Previous preterm birth at 34-36.9 wk		RR = 0.62 (0.29, 1.32) p = 0.215	
O'Brien ⁽²⁰⁾ (2007)/ MC- RCT	Micronized progesterone gel 90 mg vagina daily	GA 16-22 to 37 wk/ - Previous preterm birth	309 / 302	Delivery GA < 37 wk: 41.7%	Delivery GA < 37 wk: 40.7%	OR = 1.08 (0.76, 1.52)	
				Delivery GA ≤ 35 wk: 22.7%	Delivery GA ≤ 35 wk: 26.5%		OR = 0.9 (0.61, 1.34)
				Delivery GA ≤ 32 wk: 10.0%	Delivery GA ≤ 32 wk: 11.3%		
				Delivery GA ≤ 28 wk: 3.2%	Delivery GA ≤ 28 wk: 3.0%		OR = 1.07 (0.38, 2.96)

RCT: Randomized, placebo-controlled, double-blind study, MC-RCT: Multi-center, randomized, placebo-controlled, double-blind study, 17 OHP-C: 17 alpha-hydroxyprogesterone caproate, GA: Gestational age

Table 2. Effect of progesterone in the women with short cervical length during mid-trimester

Study (year) / Study type	Progesterone / Dosage	Treatment GA / Inclusion criteria	Cases / Controls	Result		p / RR / OR (95% CI)
				Cases	Controls	
Fonseca ⁽²⁵⁾ (2007) / RCT	Micronized progesterone 200 mg vagina daily	GA 24 to 34 wk / - Cervical length \leq 15 mm at 20 – 25 wk	250 / 163	Delivery GA < 34 wk: 19.2%	Delivery GA < 34 wk: 34.4%	RR = 0.56 (0.36, 0.86)
DeFranco ⁽²⁸⁾ (2007) / RCT	Micronized progesterone gel 90 mg vagina daily	GA 16-22 to 37 wk / - Previous preterm birth - Cervical length < 28 mm in the mid-trimester	19 / 27	Delivery GA < 32 wk: 0%	Delivery GA \leq 32 wk: 29.6%	p = 0.014
Hassan ⁽²⁹⁾ (2011) / MC-RCT	Micronized progesterone gel 90 mg vagina daily	GA 20-24 to 37 wk / - Cervical length 10-20 mm at 19+0 - 23+6 wk	235 / 223	Delivery GA < 28 wk: 5.1%	Delivery GA < 28 wk: 10.3%	RR = 0.50 (0.25, 0.97) p = 0.04
				Delivery GA < 33 wk: 8.9%	Delivery GA < 33 wk: 16.1%	RR = 0.52 (0.31, 0.91) p = 0.02
				Delivery GA < 35 wk: 14.5%	Delivery GA < 35 wk: 23.3%	RR = 0.62 (0.42, 0.92) p = 0.02
Romero ⁽³⁰⁾ (2012) / Meta-analysis	Progesterone vagina daily	- Cervical length < 25 mm in the mid-trimester	388 / 387	Delivery GA < 28 wk		RR = 0.50 (0.30, 0.81)
				Delivery GA < 33 wk		RR = 0.58 (0.42, 0.80)
				Delivery GA < 35 wk		RR = 0.69 (0.55, 0.88)
				Respiratory distress syndrome		RR = 0.48 (0.30, 0.76)
				Neonatal morbidity and mortality		RR = 0.57 (0.40, 0.81)
Birthweight < 1,500 gm		RR = 0.55 (0.38, 0.80)				

RCT: Randomized, placebo-controlled, double-blind study, MC-RCT: Multi-center, randomized, placebo-controlled, double-blind study, GA: Gestational age

Table 3. Effect of progesterone in twin pregnancy

Study (year) / Study type	Progesterone / Dosage	Treatment GA / Inclusion criteria	Cases / Controls	Result		p / RR / OR (95% CI)
				Cases	Controls	
Rouse ⁽⁶⁴⁾ (2007) / MC-RCT	17 OHP-C 250 mg IM weekly	GA 16-20 to 35 wk / - Twin pregnancy	325 / 330	Delivery or death GA < 35 wk: 41.5%	Delivery or death GA < 35 wk: 37.3%	RR = 1.1 (0.9, 1.3)
Norman ⁽³²⁾ (2009) / MC-RCT	Micronized progesterone gel 90 mg vagina daily	GA 24 to 34 wk / - Twin pregnancy	247 / 247	Delivery or death GA < 34 wk: 24.7%	Delivery or death GA < 34 wk: 19.4%	OR = 1.36 (0.89, 2.09) p = 0.16
Comb ⁽⁶¹⁾ (2011) / MC-RCT	17 OHP-C 250 mg IM weekly	GA 16-24 to 34 wk / - Dichorionic-diamniotic twins	160 / 80	Composite neonatal morbidity: 14%	Composite neonatal morbidity: 12%	p = 0.62
Rode ⁽⁶³⁾ (2011) / MC-RCT	Micronized progesterone 200 mg pessaries vagina daily	GA 20-24 to 34 wk / - Twin pregnancy	334 / 341	Delivery GA < 28 wk: 2.7%	Delivery GA < 28 wk: 2.1%	OR = 1.3 (0.5, 3.6)
				Delivery GA < 32 wk: 7.2%	Delivery GA < 32 wk: 9.1%	OR = 0.8 (0.4, 1.3)
				Delivery GA < 34 wk: 15.3%	Delivery GA < 34 wk: 18.5%	OR = 0.8 (0.5, 1.2)
Klein ⁽⁶⁵⁾ (2011) / MC-RCT	Micronized progesterone 200 mg pessaries vagina daily	GA 20-24 to 34 wk / - Twin pregnancy and - Cervical length < 10 th centile, ≤ 30 mm at GA 20-24 wk or - Spontaneous delivery before 34 wk or miscarriage after 12 wk	Short cervix 17 / 30	Short cervix Delivery GA < 32 wk: 23.5%	Short cervix Delivery GA < 32 wk: 16.7%	Short cervix OR = 1.54 (0.35, 6.73) p = 0.57
				Delivery GA < 34 wk: 29.4%	Delivery GA < 34 wk: 40.0%	OR = 0.63 (0.18, 2.23) p = 0.47
				Previous preterm Delivery GA < 34 wk: 30.0%	Previous preterm Delivery GA < 34 wk: 22.2%	Previous preterm OR = 2.14 (0.34, 13.42) p = 0.42
			Previous preterm 10 / 18	Delivery GA < 34 wk: 30.0%	Delivery GA < 34 wk: 22.2%	OR = 1.50 (0.26, 8.64) p = 0.65

RCT: Randomized, placebo-controlled, double-blind study, MC-RCT: Multi-center, randomized, placebo-controlled, double-blind study, 17 OHP-C: 17 alpha-hydroxyprogesterone caproate, GA: gestational age

Recommendations for progesterone supplementation in clinical practice (Table 4)

The American College of Obstetricians and Gynecologists (ACOG) stated that progesterone supplementation should be offered to women with a singleton pregnancy with previous spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes and may be considered in pregnant women with short cervical length (<15 mm) during mid-trimester ultrasound screening⁽³⁶⁾. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommended progesterone supplement, either 17 OHP-C 250 mg intramuscular weekly or daily micronized progesterone 100 mg vaginally, in women

who had previous spontaneous preterm birth and recommended daily micronized progesterone 200 mg vaginally in women with short cervical length (<15 mm) detected at 22-26 weeks of gestation. The therapy should be started after 20 weeks' gestation and stopped when the risk of prematurity is low⁽³⁷⁾.

On February 4th, 2011, the U.S. Food and Drug Administration (FDA) approved Makena[®] (hydroxyprogesterone caproate) injection as a drug used to reduce the risk of preterm birth in pregnant women with a history of at least one spontaneous preterm birth. The FDA also stated that this drug is not intended for use in women with multiple gestations or other risk factors for preterm birth^(38,39).

Table 4. Recommendations for progesterone supplementation for prevention of preterm birth

Indication	Formulation, dose, route	FDA ^(38, 39) (2011)	ACOG ⁽³⁶⁾ (2008)	SOGC ⁽³⁷⁾ (2008)
Previous preterm birth	17 OHP-C 250 mg IM weekly or Micronized progesterone 100 mg vagina daily from GA 16-20 to 34-37 wk	Approved	Should be offered	Recommended
Short cervical length during mid-trimester (<15 mm)	Micronized progesterone 200 mg vagina daily from GA 16-20 to 34-37 wk	Not approved	May be considered	Recommended
Multiple gestations	-	Not approved	Not recommended	Not recommended

FDA: The U.S. Food and Drug Administration, ACOG: The American College of Obstetricians and Gynecologists, SGOC: The Society of Obstetricians and Gynaecologists of Canada, 17 OHP-C: 17 alpha-hydroxyprogesterone caproate, IM: intramuscular, GA: gestational age

Practical points

- The progesterone level does not decrease significantly in human pregnancy before the onset of labor. Functional withdrawal of progesterone may play a role directly at the uterus before the onset of labor.
- There were clear evidences that weekly, 17 alpha-hydroxyprogesterone caproate (17 OHP-C) supplementation should be offered to women who had previous spontaneous preterm birth before 37 weeks of gestation.
- There was no evidence from randomized, placebo controlled, double-blind studies that

17 OHP-C can reduce the rate of preterm birth in women with a short cervix. This synthetic progestin has been approved for use only in pregnant women with previous preterm birth.

- There were clear evidences that daily micronized progesterone vaginal suppository should be offered to women who had short cervical length on transvaginal ultrasound screening at mid-trimester, although it has not been approved by the U.S. FDA.
- There was no evidence supported the use of progesterone supplementation for prevention of preterm birth in multiple pregnancies.

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Exam for CME credits

- 1. Which one is true about the role of progesterone and initiation of labor in human species?**
 1. Progesterone withdrawal leads to cervical ripening and parturition.
 2. Administration of exogenous progesterone effectively prevents labor and delivery process.
 3. The levels of progesterone in the maternal blood, the fetal blood and the amniotic fluid are not changed before the onset of labor and delivery.
 4. Loss of progesterone receptors hypotheses has been proven to initiate parturition.
- 2. Which one is false about the effect of progesterone in the women at risk for preterm birth?**
 1. Intramuscular 17 alpha-hydroxyprogesterone caproate reduced preterm birth rate.
 2. Transvaginal progesterone administration reduced preterm birth rate.
 3. Progesterone administration reduced neonatal morbidity.
 4. Progesterone administration reduced neonatal mortality.
- 3. Which one is false about the effect of progesterone in the women who had short cervical length during mid-trimester?**
 1. Intramuscular 17 alpha-hydroxyprogesterone caproate reduced preterm birth rate.
 2. Transvaginal progesterone administration reduced preterm birth rate.
 3. Progesterone administration reduced neonatal morbidity.
 4. Progesterone administration reduced neonatal mortality.
- 4. Which one is true about the recommendations for progesterone supplementation in clinical practice of the American College of Obstetricians and Gynecologists (ACOG), the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the U.S. Food and Drug Administration (FDA)?**
 1. ACOG, SOGC and FDA recommended progesterone supplementation in women who had previous spontaneous preterm birth.
 2. ACOG, SOGC and FDA recommended progesterone supplementation in women with short cervical length.
 3. ACOG, SOGC and FDA recommended progesterone supplementation in women who had previous spontaneous preterm birth and in women with short cervical length.
 4. ACOG, SOGC and FDA recommended progesterone supplementation in women with multiple gestations.

ชื่อ นพ./พญ.นามสกุล.....
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สาขา.....โรงพยาบาล.....
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Exam for CME credits

1. Which one is true about the role of progesterone and initiation of labor in human species?

- A. Progesterone withdrawal leads to cervical ripening and parturition.
- B. Administration of exogenous progesterone effectively prevents labor and delivery process.
- C. The levels of progesterone in the maternal blood, the fetal blood and the amniotic fluid are not changed before the onset of labor and delivery.
- D. Loss of progesterone receptors hypotheses has been proven to initiate parturition.

2. Which one is false about the effect of progesterone in the women at risk for preterm birth?

- A. Intramuscular 17 alpha-hydroxyprogesterone caproate reduced preterm birth rate.
- B. Transvaginal progesterone administration reduced preterm birth rate.
- C. Progesterone administration reduced neonatal morbidity.
- D. Progesterone administration reduced neonatal mortality.

3. Which one is false about the effect of progesterone in the women who had short cervical length during mid-trimester?

- A. Intramuscular 17 alpha-hydroxyprogesterone caproate reduced preterm birth rate.
- B. Transvaginal progesterone administration reduced preterm birth rate.
- C. Progesterone administration reduced neonatal morbidity.
- D. Progesterone administration reduced neonatal mortality.

4. Which one is true about the recommendations for progesterone supplementation in clinical practice of the American College of Obstetricians and Gynecologists (ACOG), the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the U.S. Food and Drug Administration (FDA)?

- A. ACOG, SOGC and FDA recommended progesterone supplementation in women who had previous spontaneous preterm birth.
- B. ACOG, SOGC and FDA recommended progesterone supplementation in women with short cervical length.
- C. ACOG, SOGC and FDA recommended progesterone supplementation in women who had previous spontaneous preterm birth and in women with short cervical length.
- D. ACOG, SOGC and FDA recommended progesterone supplementation in women with multiple gestations.

	A	B	C	D
1.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4.	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

บริการธุรกิจตอบรับ

ใบอนุญาตเลขที่ ปณ.(น)/3148 ปณฝ.เพชรบุรีดีดีใหม่
ถ้าฝากส่งในประเทศไม่ต้องผูกตราไปรษณียากร

ราชวิทยาลัยสูตินรีแพทย์แห่งประเทศไทย

ตู้ ปณ.1067 ปณฝ.เพชรบุรีดีดีใหม่

กรุงเทพฯ 10311