

Preterm birth

Progesterone and pessary

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INTRODUCTION

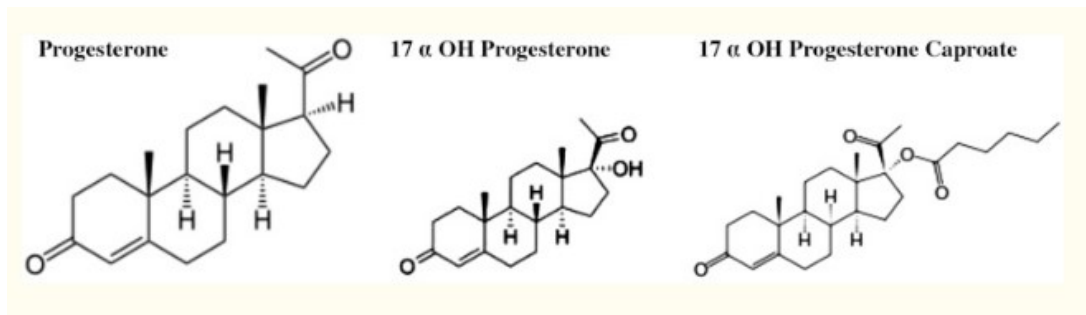
- ▶ Preterm birth complicates 1 in 8 deliveries and accounts for over 85 percent of all perinatal morbidity and mortality
- ▶ Efforts to delay delivery in patients presenting with acute preterm labor have been largely unsuccessful. For this reason, much attention has focused on preventive strategies, such as progesterone supplementation
- ▶ the name is derived from its function: pro-gestational steroidal ketone

supplemental progesterone appears to be effective in preventing preterm birth in some high-risk patients

Final points:

- ▶ Progesterone is effective in some high risk patients
- ▶ Progesterone in all patient with prior spontaneous PTD(36w singleton- 34w multifetus)
- ▶ Progesterone in all patient with short cervix
- ▶ Progesterone:17-OHP weekly IM from 16W.....vaginal.prog daily from diagnosis (16-24w) until 36w
- ▶ Progesterone,pessary and cerclage.....3 strategy in PTB prevention
- ▶ Multiple pregnancysame to singleton pregnancy
- ▶ Pessary.....??????????

- ▶ Progesterone is a steroid hormone which plays a crucial role in each step of human pregnancy. (pro-gestational steroidal ketone)



- ▶ In early pregnancy, progesterone is produced by the corpus luteum. This organ is fundamental for pregnancy maintenance until the placenta takes over its function at 7-9th week of gestation

ROLE OF PROGESTERONE IN PREGNANCY MAINTENANCE

- ▶ Corpus luteum progesterone production is critical for pregnancy maintenance until the placenta takes over this function at 7 to 9 weeks of gestation
- ▶ ● Progesterone maintains uterine quiescence in the latter half of pregnancy; mechanism is unclear
- ▶ Functional withdrawal of progesterone activity at the level of the uterus appears to occur proximate to the onset of labor both at term and preterm, without a significant change in serum progesterone levels
- ▶ ● Progesterone prevents apoptosis in fetal membrane explants under both basal and pro-inflammatory condition and thus may protect the membranes from preterm prelabor rupture and, in turn, preterm birth .
- ▶ Progesterone supplementation may enhance these actions .Other mechanisms may also be involved; for example, progesterone may act to counter the inflammatory response leading to preterm labor and birth .

➤ Preterm Labour

Efforts to delay delivery have been largely
unsuccessful:

Much attention has focused on
Preventive Strategies

Progesterone supplement therapy to reduce
the risk of spontaneous preterm birth

Efficacy of progesterone for prevention of PTB

- ▶ 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 (usually defined as <20 mm) during the midtrimester
- ▶ progesterone supplementation has no role in the treatment of acute preterm labor

Type, route, dose, and interval of progesterone supplement therapy for prevention of PTB

- ▶ Progesterone used for prevention of PTB is divided into 2 types:
 1. 17-alpha hydroxyprogesterone caproate (17 α -OHPC)
 2. Natural micronized progesterone

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

17 α -OHPC, 17-alpha hydroxyprogesterone caproate.

17 α -OHPC for prevention of PTB

- ▶ A synthetic derivative of 17 hydroxyprogesterone
- ▶ It is inactivated when orally administered, thus it is injected intramuscularly.
- ▶ The half-life is 7.8 days, and therefore it is usually administered once a week to maintain serum concentration.
- ▶ Weekly intramuscular injection of 250 mg was effective in preventing PTB in pregnant women with history of PTB.
- ▶ Higher dose or shorter interval was used in different studies and none these studies proved the efficacy of 17 α -OHPC in preventing PTB in these subsets of patients.

Micronized progesterone for prevention of PTB

- ▶ A natural progesterone, is similar to that produced in corpus luteum and placenta.
- ▶ 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 vaginal, 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.

Micronized progesterone for prevention of PTB

- ▶ A review study (2017) concluded that dose of 100 mg was used in trials that targeted pregnant women with history of PTB, while 200 mg was used in trials of women with short CL.
- ▶ 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.

Beginning time and duration of the progesterone supplement therapy for prevention of PTB

- ▶ Is varied depending on the indications and the medication type.
- ▶ The therapy usually began at 16 to 20 weeks of gestation for those who had history of PTB, whereas it begins upon diagnosis for those with short cervixes, as the CL is measured through transvaginal ultrasound conventionally after midtrimester.
- ▶ The therapy usually lasted until 36,6d weeks of gestation or rupture of membranes or delivery, whatever comes first.

Side effects of progesterone

- ▶ 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
- ▶ sleep disorders

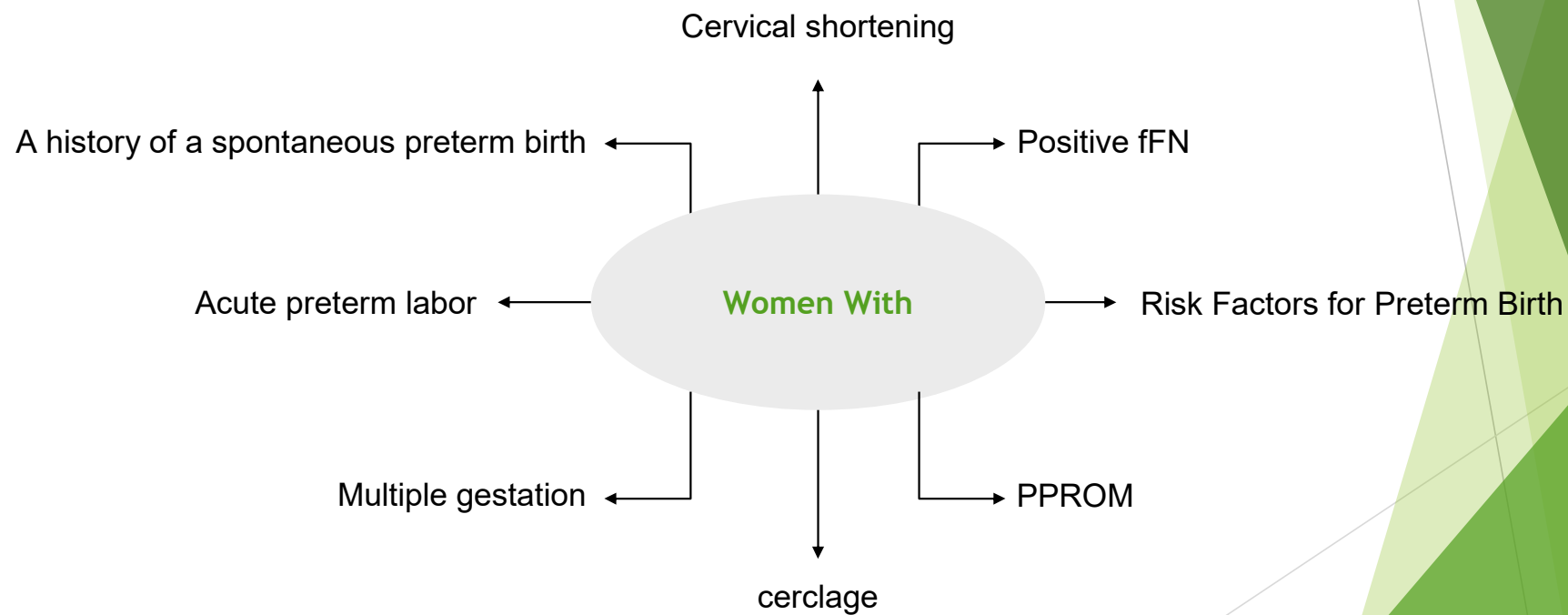
SIDE EFFECTS

- ▶ *Injection site reaction*
- ▶ *Vaginal irritation or discharge*
- ▶ *GDM*
- ▶ *G.HTN and Preeclampsia*
- ▶ *VTE*
- ▶ *Infection*

Side effects of progesterone

- ▶ The synthetic progesterone, 17 α -OHPC, has lower rates of these side effects than the natural micronized progesterone but hypospadias and increase in some malignancy such as colorectal and prostate cancer was reported(in first trimester description)-*FDA withdrawing Makena from the market-*
- ▶ Vaginal administration of micronized progesterone can help avoiding metabolism by the liver, thereby markedly reducing the risk of these side effects.
- ▶ 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

Indications of progesterone in preterm labour



Indications of progesterone in preterm labour

- ▶ Singleton pregnancy, normal CL, prior spontaneous singleton PTL



Progesterone supplementation indicated?

YES

- OH progesterone: 250 mg/IM weekly, 16-20 w until 36 weeks or delivery
- Monitor cervical length: short (<25 mm) cervix → perform cerclage
- Natural progesterone administered vaginally is a reasonable alternative

Indications of progesterone in preterm labour

- ▶ Singleton pregnancy, normal CL, prior spontaneous twin PTL



Progesterone supplementation possibly?

YES

- OH progesterone: 250 mg/IM weekly, 16-20 w until 36 weeks or delivery
- Monitor cervical length: short (<25 mm) cervix → perform cerclage
- Natural progesterone administered vaginally is a reasonable alternative

Indications of progesterone in preterm labour

- ▶ Short cervix ($\leq 20\text{mm}$), singleton pregnancy, no prior PTL



Progesterone supplementation indicated?

YES

- 90 to 200 mg supp.vaginally each night from diagnosis to 36w
- 100 -200 mg micronized vaginal progesterone
- 8 percent vaginal gel containing 90 mg micronized progesterone



Are commercially available, but no approved for prevention of preterm birth in cervical shortening

Indications of progesterone in preterm labour

► Multiple gestation

- most of the studies so far have revealed that progesterone supplement therapy in twin pregnancies did not significantly reduce the risk of PTB.
- The ACOG and the SMFM concluded that the effectiveness of progesterone supplement therapy in multiple pregnancy lacks sufficient evidence.
- A recent meta-analysis(2017) showed that twin pregnancy with short cervix(<25) vaginal progesterone supplement therapy was effective in improving perinatal outcomes of twin pregnancies.

Indications of progesterone in preterm labour

- ▶ Multiple pregnancy (twin or triple), no prior PTL, normal CL



Progesterone?
Cercelage?

NO

Indications of progesterone in preterm labour

- ▶ Twin pregnancy, prior preterm birth



Possibly?

YES

- OHPC: 250 mg/IM weekly, 16 and 20 weeks -36 weeks or until delivery
- Reasonable alternative: natural progesterone administered vaginally

Indications of progesterone in preterm labour

► Twin pregnancy



High dose vaginal progesterone?

(400 mg/day)

NO

Indications of progesterone in preterm labour

- ▶ After placement of a cerclage



A prior preterm birth, continuing 17P supp
Has not been proven to be useful

Continuing P supp
????

► Progesterone NOT indicated

- PPROM
- Positive fetal fibronectin test
- After an episode of PTL

Progesterone supplementation indicated?

NO

► Use of progesterone for indications **is not supported**:

- Placenta Previa
- Abruptio Placenta
- In obese women (BMI>30) is suggested that 17OHP may not be effective(?)

- ▶ Women with a history of preterm birth due to PPROM

Appear to benefit
YES

- ▶ Acute preterm labour

NO
Progesterone do not
routinely recommend

- ▶ Uterine anomaly or ART

NO

Main points of indications of progesterone in preterm labour

- Although supplemental progesterone does appear to be effective in preventing preterm birth in some high-risk women, *it should not be seen as a panacea*. At best, progesterone supplementation prevents only 20 percent of recurrent preterm births, and the long-term benefits of progesterone supplementation are not yet clear.
- The potential clinical benefits of progesterone supplementation appear large, whereas the risks seem small in comparison.

Final points:

- ▶ Progesterone is effective in some high risk patients
- ▶ Progesterone in all patient with prior spontaneous PTD(36w singleton- 34w multifetus)
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Recommendations for progesterone supplementation to prevent preterm birth

Indication	Progesterone supplementation indicated?	Management
Singleton pregnancy, prior spontaneous singleton preterm birth, normal cervical length	Yes	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks of gestation and continuing through 36 weeks of gestation or until delivery and monitor cervical length. Natural progesterone administered vaginally is a reasonable alternative. Short (≤ 25 mm) cervix → consider performing cerclage
Singleton pregnancy, prior spontaneous twin preterm birth, normal cervical length	Possibly	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks of gestation and continuing through 36 weeks of gestation or until delivery and monitor cervical length. Natural progesterone administered vaginally is a reasonable alternative. Short (≤ 25 mm) cervix → consider performing cerclage
Singleton pregnancy, no prior spontaneous preterm birth, short cervix (≤ 20 mm)	Yes	Progesterone suppository 90 to 200 mg vaginally each night from time of diagnosis through 36 weeks of gestation. A vaginal suppository can be prepared by a compounding pharmacy utilizing a commercially available standardized kit. Other options include a 100 mg micronized progesterone vaginal tablet or an 8 percent vaginal gel containing 90 mg micronized progesterone per dose. Both preparations are commercially available in US, but not approved for prevention of preterm birth in cervical shortening.
Multiple pregnancy (twins or triplets) without prior preterm birth, normal cervical length	No	No progesterone, no cerclage
Twins, prior preterm birth	Possibly	Hydroxyprogesterone caproate 250 mg intramuscularly weekly beginning between 16 and 20 weeks of gestation and continuing through 36 weeks of gestation or until delivery. Natural progesterone administered vaginally is a reasonable alternative.
Twins, short cervix	Possibly	Vaginal progesterone, no cerclage
Preterm premature rupture of membranes	No	–
Positive fetal fibronectin test	No	–
Undelivered after an episode of preterm labor	No	–

Adapted from: Committee on Practice Bulletins—Obstetrics, The American College of Obstetricians and Gynecologists. Practice bulletin no. 130: prediction and prevention of preterm birth. *Obstet Gynecol* 2012; 120:964. Reaffirmed 2018.

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pessary

- ▶ Current evidence does not support the use of cervical pessary to prevent preterm birth or to improve perinatal outcomes in singleton or twin gestations with a short cervix and in unselected twin gestations.

pessary

- ▶ The theory behind use of vaginal pessaries is that they alter the axis of the cervical canal and displace the weight of the uterine contents away from the cervix. By changing the angle of the cervix in relation to the uterus, the pessary also obstructs the internal os and thus may provide protection against ascending infection

Cervical pessary to prevent preterm birth in asymptomatic high-risk women: a systematic review and meta-analysis.

Conde-Agudelo A, Romero R, Nicolaides KH

Am J Obstet Gynecol. 2020;223(1):42. Epub 2020 Feb 3

RESULTS Twelve studies (4687 women and 7167 fetuses/infants) met the inclusion criteria: 8 evaluated pessary vs no pessary in women with a short cervix, 2 assessed pessary vs no pessary in unselected multiple gestations, and 2 compared pessary vs vaginal progesterone in women with a short cervix. There were no significant differences between the pessary and no pessary groups in the risk of spontaneous preterm birth <34 weeks of gestation among singleton and twin gestations with a cervical length ≤ 25 mm. Overall, no significant differences were observed between the pessary and no pessary groups in preterm birth <37, <32, and <28 weeks of gestation, and most adverse pregnancy, maternal, and perinatal outcomes.

CONCLUSION Current evidence does not support the use of cervical pessary to prevent preterm birth or to improve perinatal outcomes in singleton or twin gestations with a short cervix and in unselected twin gestations.

Pessary in twin pregnancy

- ▶ Role of pessary – Use of a cervical pessary may be considered in twin pregnancies with a short cervix, based on the favorable results and trends in the randomized trials . however, we are not advising our patients to use a pessary because no consistent benefit in composite neonatal morbidity has been documented for any cervical length cutoff. We believe that further study demonstrating a clear and consistent benefit is needed before recommending cervical pessary for a short cervix in asymptomatic patients or following threatened preterm labor.

Cervical pessary to prevent preterm birth in women with twin gestation and sonographic short cervix: a multicenter randomized controlled trial (PECEP-Twins).

Goya M, de la Calle M, Pratcorona L, Merced C, RodóC, Muñoz B, Juan M, Serrano A, Llurba E, Higuera T, Carreras E, Cabero L, PECEP-Twins Trial Group
Am J Obstet Gynecol. 2016;214(2):145. Epub 2015 Nov 25.

- ▶ In a multicenter randomized trial in Spain, placement of a pessary in 137 asymptomatic women with twin pregnancies and a short cervix (≤ 25 mm) at 18 to 22 weeks reduced the rate of sPTB <34 weeks: 16.2 (11/68) versus 39.4 percent (26/66) with expectant management (RR 0.41, 95% CI 0.22-0.76)

Cervical pessary for preventing preterm birth in twin pregnancies with maternal short cervix after an episode of threatened preterm labor: randomised controlled trial

Merced C, Goya M, Pratcorona L, Rodó C, Llurba E, Higuera T, Cabero L, Carreras E, PECEP-RETARD Trial Group

Am J Obstet Gynecol. 2019;221(1):55.e1. Epub 2019 Feb 28

RESULTS Significant differences were observed in the spontaneous preterm birth rate before 34 weeks between the pessary and routine management groups (11 of 67 [16.4%] in the pessary group vs 21 of 65 [32.3%] in the control group; relative risk, 0.51). No significant differences were observed in the preterm birth rate <28 weeks or <37 weeks between groups. Significant reduction was observed in the number of neonates weighing less than 2500 g

CONCLUSION Pessary use did significantly lower the spontaneous preterm birth rate before 34 weeks in twin pregnancies with maternal short cervix remaining after a threatened preterm labor episode. Pessary use also reduced the threatened preterm labor recurrence and neonates' weight less than 2500 g.

Pessary Compared With Vaginal Progesterone for the Prevention of Preterm Birth in Women With Twin Pregnancies and Cervical Length Less Than 38 mm: A Randomized Controlled Trial.

Dang VQ, Nguyen LK, Pham TD, He YTN, Vu KN, Phan MTN, Le TQ, Le CH, Vuong LN, Mol BW

Obstet Gynecol. 2019;133(3):459 .

- ▶ In a randomized trial in Vietnam comparing the effectiveness of cervical pessary with vaginal progesterone for the prevention of preterm birth in asymptomatic patients with twin pregnancies and short cervix (≤ 28 mm), the pessary reduced preterm birth < 34 weeks of gestation by 53 percent (21 [10/47] versus 46 [16/35] percent, RR 0.47, 95% CI 0.24-0.90) and a composite of poor perinatal outcomes by 62 percent (19 versus 50 percent, RR 0.38, 95% CI 0.12-0.47). For cervical length < 38 mm, the reduction in the composite of poor perinatal outcomes was statistically significant, but the reduction in preterm birth < 34 weeks was not.

