Progesterone supplementation to reduce the risk of spontaneous preterm birth

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Literature review current through: Oct 2018. | **This topic last updated:** Sep 28, 2018.

INTRODUCTION — Preterm birth (delivery prior to 37 weeks or 259 days of gestation) complicates 1 in 8 deliveries in the United States, but accounts for over 85 percent of all perinatal morbidity and mortality. Efforts to delay delivery in women 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).

Although supplemental progesterone appears to be effective in preventing preterm birth in some high-risk women, it should not be seen as a panacea. Even if all pregnant women in the United States with a history of preterm birth receive progesterone prophylaxis, it is estimated that the risk of preterm birth would be reduced by 20 percent and the absolute preterm birth rate would be reduced by only 0.01 percent because most preterm births are not recurrences and prophylaxis has limited efficacy [1-4]. If women with a short cervix are also identified and treated, an additional absolute risk reduction of 0.02 percent would be achieved [4].

This topic will review issues related to use of progesterone for prevention of preterm birth. Progesterone supplementation is only one component of risk reduction. Risk factors for preterm birth and other potential interventions for reducing risk are discussed separately. (See "Preterm birth: Risk factors, interventions for risk reduction, and maternal prognosis".)

ROLE OF PROGESTERONE IN PREGNANCY MAINTENANCE — Progesterone contributes to pregnancy maintenance in several ways:

- Corpus luteum progesterone production is critical for pregnancy maintenance until the placenta takes over this function at 7 to 9 weeks of gestation. In fact, removal of the corpus luteum [5] or administration of a progesterone receptor antagonist [6] readily induces abortion before 7 weeks (49 days) of gestation.

- Progesterone maintains uterine quiescence in the latter half of pregnancy; however, the mechanism is unclear [7-9]. 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 in the weeks preceding labor [7-14].

- Progesterone prevents apoptosis in fetal membrane explants under both basal and pro-inflammatory conditions [15,16] and thus may protect the membranes from preterm prelabor rupture and, in turn, preterm birth.

Progesterone supplementation may enhance these actions, which are likely mediated via progesterone-receptors [17]. Other mechanisms may also be involved (eg, alteration in the immune response).

EFFICACY OF PROGESTERONE FOR PREVENTION OF PRETERM BIRTH — The efficacy of progesterone supplementation for prevention of preterm birth depends primarily on appropriate patient selection (table 1). In vitro and animal research suggest that the type of progestin, formulation, dose, route of delivery, and plasma concentration (which varies among patients receiving progestins) also impact efficacy [18-20]. Emerging evidence suggests that the specific pathogenetic pathway leading to preterm birth is important as well [21,22]. These factors likely played a role in the discordant findings reported in the trials discussed below.

Pregnancies likely to benefit from progesterone supplementation — Progesterone supplementation appears to reduce the rate of spontaneous singleton preterm birth in women who have had a previous spontaneous preterm singleton birth and in women with a short cervix on ultrasound examination in the current pregnancy. Neonatal morbidity and neonatal mortality are also reduced.

Since spontaneous preterm birth is likely the final common pathway of several pathogenic processes, a single intervention such as progesterone supplementation is unlikely to benefit all women at risk. A logistic regression analysis demonstrated significant treatment-genotype interactions, which could result in either a beneficial or harmful treatment response [23]. Studies have also found that women with certain characteristics, such as vaginal bleeding, gonorrhea, or chlamydia in the current pregnancy; a late preterm birth in a past pregnancy; or penultimate preterm birth, are less likely to have a significant risk reduction [21,22].

Spontaneous singleton preterm birth in prior pregnancy — A 2013 meta-analysis analyzed 39 randomized trials of prenatal progesterone administration for prevention of preterm birth in women at increased risk of preterm birth by various criteria [24]. For women with a past history of spontaneous preterm birth (11 trials, n = 1899 women), progesterone supplementation resulted in lower risks for preterm birth and some neonatal morbidities compared with placebo/no treatment:

- Birth <34 weeks (relative risk [RR] 0.31, 95% CI 0.14-0.69)
- Birth <37 weeks (RR 0.55, 95% CI 0.42-0.74)
- Neonatal death (RR 0.45, 95% CI 0.27-0.76)
- Use of assisted ventilation (RR 0.40, 95% CI 0.18-0.90)
- Necrotizing enterocolitis (RR 0.30, 95% CI 0.10-0.89)
- Neonatal intensive care unit admission (RR 0.24, 95% CI 0.14-0.40)

Differences in risks for intraventricular hemorrhage, neonatal sepsis, and retinopathy of prematurity were not statistically significant.

The following two trials are the seminal trials supporting the benefit of progesterone supplementation for prevention of recurrent preterm birth, and were included in the meta-analysis

described above [24]. In contrast, the subsequent OPPTIMUM and PROGRESS trials, which were published after the meta-analysis, found no significant improvement in primary obstetric, neonatal, or childhood outcomes with vaginal progesterone supplementation [25,26]. These latter trials do not change the author's treatment approach (table 1). The results are concordant with findings from trials showing a benefit of hydroxyprogesterone caproate in patients with prior spontaneous preterm birth (see 'Pregnancies likely to benefit from progesterone supplementation' above) and with a systematic review showing a benefit of vaginal progesterone in patients with a short cervix. (See 'Short cervix in current pregnancy' below.)

- **Maternal fetal medicine units network trial (**hydroxyprogesterone caproate **injection)** – Meis and co-investigators randomly assigned 459 women with a documented history of spontaneous singleton preterm delivery <37 completed weeks to weekly intramuscular injections of hydroxyprogesterone caproate (250 mg) or placebo beginning at 16 to 20 weeks of gestation and continuing until 36 weeks [3]. Active prophylaxis significantly reduced the risk of delivery at all gestational ages studied:

  - <37 weeks (36 versus 55 percent in the placebo group [RR 0.66; 95% CI, 0.54-0.81]),
  - <35 weeks (21 versus 31 percent [RR 0.67; 95% CI, 0.48-0.93])
  - <32 weeks (11 versus 20 percent [RR 0.58; 95% CI, 0.37-0.91])

  Infants from progesterone supplemented pregnancies had less perinatal morbidity, with significantly reduced rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. There was no evidence of virilization of female offspring, which is a theoretic concern of this therapy.

  Secondary analysis of these data found that women with a history of a prior spontaneous preterm birth <34 completed weeks were most likely to benefit [27].

  The placebo group had a particularly high rate of preterm birth, which limits the generalizability of these findings to women at lower risk of recurrent preterm birth and raises a concern about potential imbalance among study groups despite randomization.

- **Brazilian trial (**progesterone **gel vaginally)** – da Fonseca and co-investigators randomly assigned 142 women at high-risk for preterm delivery (based on at least one previous spontaneous singleton preterm birth, prophylactic cervical cerclage, or uterine malformation) to daily supplementation with progesterone vaginal suppositories (100 mg) or placebo from 24 through 34 weeks of gestation [2]. Active prophylaxis significantly reduced the risk of delivery at all gestational ages studied:

  - <37 weeks (14 versus 29 percent in the placebo group)
  - <34 weeks (3 versus 19 percent in the placebo group)

  By monitoring all patients with an external tocodynamometer once a week for 60 minutes, the investigators were also able to demonstrate a significant difference in the frequency of spontaneous uterine contractions between the two groups, suggesting that progesterone supplementation exerts its effect by maintaining uterine quiescence in the latter half of pregnancy.

- **OPPTIMUM (**progesterone **capsules vaginally)** – In OPPTIMUM (vaginal progesterone prophylaxis for preterm birth study), 1228 women at high risk for preterm birth were randomly

assigned to receive either vaginal progesterone 200 mg daily or matching placebo, beginning at 22 to 24 weeks of gestation and ending at 34 weeks [25]. Inclusion criteria were previous spontaneous birth at ≤34 weeks, cervical length ≤25 mm, and/or a positive fetal fibronectin test combined with clinical risk factors for preterm birth (eg, history of second-trimester loss, preterm premature rupture of membranes, or cervical procedure to treat cervical intraepithelial neoplasia).

Major findings were:

- Vaginal progesterone supplementation did **not** significantly reduce the:
  - Primary obstetric outcome "fetal death or birth before 34 weeks" (adjusted odds ratio [OR] 0.86, 95% CI 0.61-1.22)
  - Primary neonatal outcome "death, brain injury, or bronchopulmonary dysplasia" (adjusted OR 0.62, 95% CI 0.38-1.03)
  - Primary childhood outcome "standardized cognitive score at two years of age" (difference in means -0.48, 95% CI -2.77 to 1.81)
- Although primary obstetric and neonatal composite outcomes were not improved, vaginal progesterone supplementation resulted in fewer neonatal deaths (1/600 versus 6/537; unadjusted OR 0.17, 95% CI 0.06-0.49) and a reduction in brain injury on neonatal ultrasound (3 versus 6 percent; unadjusted OR 0.50, 0.31-0.84).
- In subgroup analysis, "women with a history of a prior spontaneous preterm birth" had no significant treatment effect in obstetric and childhood outcomes, but a potential treatment effect was noted for the composite neonatal outcome (OR 0.48, 95% CI 0.29-0.79; P-interaction 0.053).

The study was well-designed, well-executed, and had a sample size larger than all previously published studies combined. Two-thirds of women in the progesterone group were compliant (ie, ≥80 percent of medication was taken).

While vaginal progesterone supplementation in this high-risk cohort did not significantly reduce preterm birth, it did reduce the frequency of neonatal death and sonographic evidence of brain injury. Why these early benefits did not lead to a difference in mortality or neurodevelopmental outcome at two years is unclear. The role of postnatal factors on these outcomes requires further study. In addition, the standardized cognitive score is a limited measure of neurodevelopmental outcome and may not have captured more subtle behavioral and cognitive outcomes.

- **PROGRESS** – The PROGRESS trial recruited nearly 800 women with a live singleton or twin pregnancy at 18 to <24 weeks of gestation and a history of prior preterm birth at <37 weeks of gestation in the preceding pregnancy, where labor occurred spontaneously or in association with cervical insufficiency or following preterm prelabor rupture of the membranes [26]. Randomization to use of a vaginal progesterone pessary did not reduce birth <37 weeks, neonatal respiratory distress syndrome, or secondary outcomes (other neonatal and maternal morbidities related to preterm birth) compared with placebo.

Short cervix in current pregnancy — Cervical shortening is a known risk factor for preterm birth in both low- and high-risk populations (see "Second-trimester evaluation of cervical length for prediction of spontaneous preterm birth").

A 2018 systematic review and meta-analysis of individual patient data from randomized trials (including OPPTIMUM) found that vaginal progesterone supplementation reduced the risk of preterm birth and neonatal morbidity and mortality in singleton gestations with midtrimester cervical length ≤25 mm [28]. For example, compared with placebo, vaginal progesterone:

- Reduced spontaneous preterm birth <34 weeks of gestation (15 versus 20 percent, RR 0.72, 95% CI 0.55-0.95; five trials, 974 women), as well as spontaneous preterm birth before 28, 30, 32, 35, and 36 weeks
- Reduced respiratory distress syndrome (RR 0.47, 95% CI 0.27-0.81)
- Reduced composite neonatal morbidity and mortality (RR 0.59, 95% CI 0.38-0.91)
- Reduced birth weight <1500 g (RR 0.62, 95% CI 0.44-0.86)
- Reduced admission to the neonatal intensive care unit (RR 0.68, 95% CI 0.53-0.88)

Neurodevelopmental outcomes at two years of age were similar for vaginal progesterone and placebo groups.

Use of vaginal progesterone rather than intramuscular hydroxyprogesterone caproate appears to be a critical factor for preventing preterm birth in women with a short cervix. In contrast to the above systematic review and meta-analysis of trials of vaginal progesterone [28], two trials in which women with singleton gestations and a short cervical length were randomly assigned to weekly intramuscular hydroxyprogesterone caproate (250 mg or 500 mg) or placebo through 36 weeks reported that treatment with hydroxyprogesterone caproate did not reduce the risk of preterm birth [29,30]. In addition to chance, methodological issues may have played a role. For example, both trials were stopped before completion because of lack of efficacy at the scheduled interim analysis. Also, one trial was limited to nulliparous women with a short cervix while the other included women with both a short cervix and risk factors for preterm birth (history of preterm delivery, cervical surgery, uterine malformation, or prenatal diethylstilbestrol exposure).

It is also possible that differences in the pharmacologic actions of the two progesterones may account for differences in effectiveness in women with a short cervix. Vaginal progesterone clearly inhibits cervical ripening; the effect of hydroxyprogesterone caproate on cervical ripening is less clear [31].

Pregnancies where the benefit of progesterone supplementation is unclear — The benefit of progesterone supplementation in women at high risk of preterm birth, but without a short cervix or a prior history of singleton spontaneous preterm birth, is not supported by strong evidence. Some of these clinical scenarios are reviewed below.

Singleton pregnancy with spontaneous twin preterm birth in prior pregnancy — A prior spontaneous preterm birth is a risk factor for a subsequent spontaneous preterm birth whether the initial preterm delivery was a singleton or a twin pregnancy [32-35]. No study has specifically evaluated whether progesterone supplementation decreases the risk of a preterm birth of a singleton after a previous spontaneous preterm birth of twins, but a benefit is plausible. The author provides hydroxyprogesterone caproate supplementation for women with a singleton pregnancy

who have had a prior spontaneous preterm birth, singleton or twin. Not providing progesterone supplementation in this setting is also reasonable.

Positive fetal fibronectin test — Although a positive cervicovaginal fetal fibronectin (fFN) test is a risk factor for preterm birth, minimal information on use of progesterone supplementation in such women is available. In OPPTIMUM, women with a positive fFN test and risk factors for preterm birth were included in the study population [25]. Progesterone supplementation did not improve obstetric, neonatal, or childhood outcomes in this trial. (See 'Pregnancies likely to benefit from progesterone supplementation' above.)

After cerclage — In women with a prior spontaneous preterm birth, continuing hydroxyprogesterone caproate supplementation after placement of a cerclage has not been proven to be useful in reducing preterm birth, but available data are limited to secondary analysis of one underpowered trial. Some UpToDate authors, including this author, continue hydroxyprogesterone caproate in the absence of good quality data showing lack of benefit after cerclage placement. (See "Cervical insufficiency", section on 'Cerclage placement and use of progesterone supplementation'.)

After preterm prelabor rupture of membranes — Beginning progesterone supplementation is not beneficial in women who develop preterm prelabor rupture of membranes (PPROM) in the current pregnancy. In a meta-analysis of randomized trials, progesterone supplementation did not prolong the latency period or increase the gestational age at delivery in singleton pregnancies with PPROM [36].

In contrast, women with a history of preterm birth due to PPROM appear to benefit from progesterone supplementation in subsequent pregnancies; these women were included in the prior randomized trials of the efficacy of progesterone supplementation in women with prior spontaneous preterm birth [2,3]. As discussed above (see 'Role of progesterone in pregnancy maintenance' above), progesterone appears to prevent apoptosis in fetal membranes in vitro under both basal and pro-inflammatory conditions [15], thereby providing a mechanism by which progesterone supplementation may prevent recurrent PPROM and preterm birth.

Treatment or cotreatment of threatened or established preterm labor — A 2014 meta-analysis of data from four small randomized trials in women with threatened or established preterm labor found that progesterone therapy did not reduce preterm birth <34 weeks or delivery of infants <2500 grams, but a possible reduction in delivery before 37 weeks was observed [37].

Maintenance therapy after threatened preterm labor — The use of progesterone in women who remain undelivered after an episode of threatened preterm labor is investigational and most providers (including the author) do not routinely recommend progesterone supplementation for maintenance tocolysis. Randomized trials evaluating various types of progesterone supplementation in this setting have reported disparate results, likely related to factors such as differences in size, type of progestin, route of administration, and inclusion of a placebo versus a no treatment arm. When only high quality trials were evaluated by 2016 meta-analysis, maintenance progesterone was not more effective than placebo [38]:

- Delivery <37 weeks – RR 0.91 (95% CI 0.67-1.25)
- Delivery <34 weeks – RR 1.21 (95% CI 0.85-1.70)
- Latency to delivery – RR 0.60 (95% CI -3.73 to 4.94)

A randomized trial that evaluated use of progesterone (vaginal progesterone or intramuscular hydroxyprogesterone caproate) after an episode of threatened preterm labor specifically in women with a short cervix also reported no reduction in preterm birth with either drug compared with untreated women [39].

Multiple gestation — Progesterone is not effective in unselected multiple gestations. One reason may be that the pathogenesis of preterm labor and delivery in multiples is different from that in singletons and less impacted by changes in progesterone.

- **Twin pregnancy**

  - **Unselected twin pregnancies** – In a 2017 meta-analysis of unselected twin gestations randomly assigned to receive progesterone supplementation (intramuscular or vaginal) or no treatment/placebo (17 trials, n = 4773 women), neither hydroxyprogesterone caproate nor vaginal progesterone reduced the risk of preterm birth <28, <34, or <37 weeks or improved neonatal outcomes [40]. Administration of a high versus a low dose did not appear to be a factor. These findings generally agree with those from a previous meta-analysis that used individual patient data [41].

  - **Twins in current pregnancy and prior singleton preterm birth** – The optimum management of a woman with a prior spontaneous singleton preterm birth who now has a twin pregnancy with normal cervical length is unclear. A prior spontaneous preterm birth of a singleton is an independent and additive risk factor for preterm birth of twins [42]. In the absence of data clearly showing harm or lack of efficacy in this specific setting, the author prescribes hydroxyprogesterone caproate to women with twin pregnancies who have had a previous unexplained spontaneous singleton preterm birth. However, this is controversial [43]. Not providing progesterone supplementation in this setting is also reasonable. A subgroup analysis of a meta-analysis using individual patient data found that vaginal progesterone was not effective in this setting, although data were limited; no data on hydroxyprogesterone caproate in this setting was available [41].

  - **Twin pregnancy with short cervix** – In a 2017 meta-analysis of individual patient data from six randomized trials of women with twin gestations and midtrimester cervical length ≤25 mm, vaginal progesterone reduced preterm birth <33 weeks compared with no treatment/placebo (relative risk [RR] 0.69, 95% CI 0.51-0.93; 50/159 [31 percent] versus 62/144 [43 percent]) [44]. The relative risks of neonatal death, respiratory distress syndrome, and birth weight <1500 g were also reduced significantly, on average by 30 to 50 percent. Based on these data, which should be confirmed in larger trials, the author treats twin pregnancies with a short cervix with vaginal progesterone. This is also controversial as the trials have involved a relatively small number of participants. Not providing progesterone supplementation in this setting is also reasonable.

    Intramuscular hydroxyprogesterone caproate does not appear to be beneficial for managing twin pregnancies with a short cervix. In a randomized trial, twice weekly injections of 500 mg hydroxyprogesterone caproate did not result in a reduction in preterm birth (<37, <34, or <32 weeks) or neonatal morbidity/mortality in women with twin pregnancy and a short cervix [45]. In fact, intramuscular hydroxyprogesterone caproate may increase adverse perinatal outcome in twin pregnancy [40,41,46].

- **Triplet pregnancy** – A 2015 individual patient data meta-analysis of three placebo-controlled randomized trials of hydroxyprogesterone caproate supplementation of asymptomatic women

with triplet pregnancies reported no benefit [47]. Supplementation did not result in a statistical reduction in preterm birth <28, 32, or 34 weeks or composite adverse perinatal outcome.

Uterine anomaly or ART — Women with some uterine anomalies and those who conceive with assisted reproductive technology (ART) appear to be at increased risk of preterm birth. The effectiveness of progesterone therapy for prevention of spontaneous preterm birth in these women is unknown [48]. (See "Pregnancy outcome after assisted reproductive technology" and "Congenital uterine anomalies: Clinical manifestations and diagnosis".)

Maternal obesity — In women with a history of prior spontaneous preterm birth and pre-pregnancy body mass index (BMI) >30 kg/m^2, a secondary analysis of data from the Maternal-Fetal Medicine Units Network Trial discussed above [3] suggested that hydroxyprogesterone caproate may not prevent recurrent preterm birth <37 weeks (RR of preterm birth 1.55, 95% CI 0.83-2.89) [49]. The threshold for efficacy appeared to be <165 pounds (74.8 kg). While this report has several weaknesses (eg, it was an unplanned post hoc analysis, pre-pregnancy weights were self-reported, no data were available on weight gain during pregnancy or hydroxyprogesterone caproate serum levels), it raises an important clinical question that needs to be addressed further. Until additional confirmatory studies are available, this author would suggest not limiting hydroxyprogesterone caproate supplementation by any BMI or weight criteria.

SAFETY, SIDE EFFECTS, AND ADVERSE EFFECTS — The OPPTIMUM study suggests that progesterone supplementation for preterm birth prophylaxis does not increase the risk of any major complication in women or offspring up to two years of age [25].

Minor side effects are related to the route of administration, and include injection site reactions and vaginal irritation or discharge. Specific side effects related to synthetic versus natural progesterone are described below. (See 'Hydroxyprogesterone caproate' below and 'Natural or micronized progesterone' below.)

We use progesterone to reduce the risk of spontaneous preterm birth, when indicated, in women with a history of venous thrombosis as there is no clinical evidence that vaginal progesterone or hydroxyprogesterone caproate are associated with an increased risk of venous thrombosis. The package inserts of all progesterone preparations and progestins in the United States carry a warning that a history of or current thrombophlebitis or venous thromboembolic disorders is a contraindication to use. The US Food and Drug Administration requires this warning because estrogen-progestin contraceptives are associated with an increased risk of venous thrombosis and they believe there is inadequate information to determine whether specific progesterone preparations or progestins used alone are also associated with an increased risk.

CHOICE OF PROGESTERONE PREPARATION — We recommend hydroxyprogesterone caproate 250 mg weekly (also known as 17-alpha-hydroxyprogesterone caproate or 17OHPC) administered intramuscularly for women with a history of spontaneous preterm birth and natural progesterone 100 mg daily administered vaginally for women with a short cervix (≤20 mm), based on the outcomes reported in the trials described above. This recommendation is consistent with that of the Society of Maternal Fetal Medicine [50].

Although a 2017 meta-analysis of randomized trials of intramuscular hydroxyprogesterone caproate or vaginal progesterone in women with a previous spontaneous preterm birth found that vaginal progesterone resulted in lower rates of spontaneous preterm birth <34 weeks (17.5 versus 25.0 percent; RR 0.71 95% CI 0.53-0.95) [51], this analysis does not influence our

approach as it included only three small trials (n = 680 women) and the quality of evidence was low.

Nevertheless, the reproductive effects of the two drugs are not identical [31]. Different progesterones may have different clinical effectiveness because synthetic hydroxyprogesterone caproate and natural progesterone have different biological activities in the myometrium and uterine cervix: Progesterone decreases myometrial contractility and prevents cervical ripening, but hydroxyprogesterone caproate does not [52], possibly because natural progesterone has greater binding affinity for nuclear progesterone receptors than hydroxyprogesterone acetate [53]. There also appear to be differential effects on prevention of membrane weakening and, in turn, preterm prelabor rupture of membranes. Large comparative trials are needed to determine whether one drug is superior to the other for all pregnancies at high risk for spontaneous preterm birth, whether the choice of drug should depend on the specific risk factor for spontaneous preterm birth (past history or short cervix), and whether the different outcomes observed in this analysis were due to differences in dosing, formulation, or route of delivery [18,20,54].

INITIATION AND DISCONTINUATION OF THERAPY — Based on the data from the randomized trials presented above (see 'Pregnancies likely to benefit from progesterone supplementation' above):

- In women with a previous preterm birth, we begin hydroxyprogesterone caproate in the second trimester (16 to 20 weeks) and continue it through 36+6 weeks of gestation. Ideally, progesterone is started earlier rather than later within this range for maximum effect [55]. We also follow their cervical length with serial ultrasound examinations until 24 weeks of gestation, and consider cerclage if cervical length is ≤25 mm. (See "Cervical insufficiency", section on 'Ultrasound-based cervical insufficiency'.)

- In women with no previous preterm birth and a short cervix ≤20 mm before 24 weeks, we begin natural progesterone upon diagnosis and continue the drug through 36+6 weeks of gestation.

PROGESTERONE PREPARATIONS AND DOSES

Hydroxyprogesterone caproate — Hydroxyprogesterone caproate is a synthetic progestogen with minimal to no androgenic activity. Doses have ranged from 25 mg every five days to 1000 mg weekly, beginning as early as 16 weeks of gestation. We use a 250 mg dose, administered intramuscularly. Standard contraindications to progesterone administration include hormone-sensitive cancer, liver disease, and uncontrolled hypertension.

Makena (United States brand name) is a hydroxyprogesterone caproate preparation approved by the US Food and Drug Administration to reduce the risk of recurrent preterm birth in women with a singleton pregnancy who have a history of a prior spontaneous preterm delivery [56]. Two methods for delivery are available: an autoinjector for subcutaneous administration of 275 mg and single- and multi-dose vials for intramuscular injection of 250 mg. Physicians may request a licensed pharmacist to compound a hydroxyprogesterone caproate preparation tailored to an individual patient's particular medical needs, but should be aware of regulations and spectrum of quality concerns related to this practice [57-61].

The safety of hydroxyprogesterone caproate in pregnancy has been supported by numerous epidemiologic studies [62-65] and clinical trials [2,3,66]. Although several studies have reported a nonstatistical increase in risk of miscarriage and stillbirth in pregnancies exposed to progestins

[3,67-69], others could not confirm this observation or observed a nonstatistical decrease in these risks [70-72]. This possible association requires further study [73].

Although both diabetogenic and anti-diabetogenic effects have been attributed to progesterone, weekly use of hydroxyprogesterone caproate by women at risk for preterm delivery does not appear to increase their risk for developing gestational diabetes. In a secondary analysis of data from two double-blind randomized placebo-controlled trials of hydroxyprogesterone caproate for prevention of preterm delivery, the incidence of gestational diabetes was similar in the intervention and placebo groups [74]. An observational study reported discordant findings, which may have been due to differences in patient characteristics (eg, race, ethnicity) between women who did and did not receive hydroxyprogesterone caproate [75].

A possible increase in risk of hypospadias in male offspring exposed to exogenous progestins before 11 weeks of gestation has been described [76,77]. Even if confirmed, the concern is not relevant to women with prior preterm delivery since they will receive the drug after 16 weeks of gestation.

Natural or micronized progesterone — Natural progesterone is typically administered vaginally. The advantage of vaginal progesterone is its high uterine bioavailability since uterine exposure occurs before the first pass through the liver. It has few systemic side effects, but vaginal irritation can be bothersome and the drug needs to be administered daily. Doses of 90 to 400 mg have been effective, beginning as early as 18 weeks of gestation. We use 100 mg administered vaginally each evening; however, in some areas a 200 mg suppository may be more readily available and less costly. A vaginal suppository can be prepared by a compounding pharmacy utilizing a commercially available standardized kit [78].

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 the United States, but not approved for prevention of preterm birth in cervical shortening. The FDA concluded the data in the manufacturer's application did not sufficiently support the efficacy of progesterone 8 percent gel compared with placebo in reducing the risk of preterm births before 33 completed weeks of gestation among women with a short cervical length, but the drug was safe in this population [79]. The FDA was critical of the statistical methods used in the key trial and noted that most of the apparent treatment benefit occurred in non-US centers.

The safety profile of vaginal progesterone in the first trimester of pregnancy is supported by extensive data from patients who received the drug for luteal support, while large trials during the second and third trimester in women at increased risk of preterm birth support its safety later in gestation [25,80,81].

Oral progesterone — An oral micronized preparation of natural progesterone also exists, but few studies have assessed its efficacy [82-84]. A daily dose of 400 mg is common [82,84], although doses have varied widely. Reported side effects, which are less than with synthetic progesterone, include sleepiness and fatigue [66,85].

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Preterm labor and birth".)

SUMMARY AND RECOMMENDATIONS

- Progesterone supplementation reduces the risk of preterm birth by about one-third in women with a singleton pregnancy who have had a previous spontaneous singleton preterm birth and in women with a short cervix on ultrasound examination in the current pregnancy. (See 'Pregnancies likely to benefit from progesterone supplementation' above.)

- For women with a singleton pregnancy who have had a previous spontaneous singleton preterm birth, we suggest progesterone treatment (**Grade 2B**). We suggest intramuscular injections of hydroxyprogesterone caproate rather than vaginal progesterone (**Grade 2C**), beginning in the second trimester (16 to 20 weeks) and continuing through 36 weeks of gestation. We prescribe 250 mg weekly. Daily natural progesterone administered vaginally is a reasonable alternative. (See 'Spontaneous singleton preterm birth in prior pregnancy' above.) We also follow their cervical length with serial ultrasound examinations until 24 weeks of gestation, and consider cerclage if cervical length is ≤25 mm. (See "Cervical insufficiency", section on 'Ultrasound-based cervical insufficiency'.)

  We manage women with a singleton pregnancy who have had a prior spontaneous preterm twin birth the same way. (See 'Singleton pregnancy with spontaneous twin preterm birth in prior pregnancy' above.)

- For women with midtrimester cervical shortening (defined as ≤20 mm before 24 weeks) and no prior spontaneous singleton preterm birth, we suggest daily vaginal progesterone treatment (**Grade 2B**) through 36 weeks of gestation. Reasonable options include a vaginal suppository (100 or 200 mg), gel (90 mg), or tablet (100 mg micronized progesterone). (See 'Short cervix in current pregnancy' above and 'Choice of progesterone preparation' above.)

- For multiple gestations, we recommend not administering progesterone supplementation routinely (**Grade 1B**) (see 'Multiple gestation' above). However:

  - For women with twin pregnancies and a previous spontaneous preterm birth, the author prescribes hydroxyprogesterone caproate. Not prescribing progesterone supplementation or prescribing natural progesterone vaginally is also reasonable. (See 'Multiple gestation' above.)

  - For women with twin pregnancies and a short cervix in the current pregnancy, the author prescribes vaginal progesterone. Not prescribing progesterone supplementation is also reasonable. (See 'Multiple gestation' above.)

- Routine progesterone supplementation does not appear to be useful for preventing preterm birth in the setting of preterm premature rupture of membranes or after an episode of arrested preterm labor. There is no information on efficacy in women with a positive fetal fibronectin test. The effect in women with a cerclage is unclear. (See 'After preterm prelabor rupture of membranes' above and 'Positive fetal fibronectin test' above and 'After cerclage' above and 'Treatment or cotreatment of threatened or established preterm labor' above.)

- For women who choose to take progesterone for preterm birth prophylaxis, it appears to be safe with no major adverse events noted in follow-up studies up to two years. (See 'Safety, side effects, and adverse effects' above.)

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GRAPHICS

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	–

Graphic 66456 Version 12.0

Contributor Disclosures

Errol R Norwitz, MD, PhD, MBA Grant/Research/Clinical Trial Support: Illumina [Preeclampsia (primary investigator on a prospective cohort study to collect samples from patients with preeclampsia to facilitate development of a biomarker test to predict/diagnose this disorder)]. Consultant/Advisory Boards: Hologic [Preterm birth (Fetal fibronectin test to predict preterm birth)]; Natera [Fetal aneuploidy testing (NIPT as a screening test for fetal aneuploidy)]; Seracare [Fetal aneuploidy testing (Developing controls for NIPT screening test for fetal aneuploidy)]; Bayer [Prediction test for preeclampsia (Use of urinary angiogenic factors to predict preeclampsia)]. **Charles J Lockwood, MD, MHCM** Nothing to disclose **Vanessa A Barss, MD, FACOG** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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