

Prevention of Preterm Birth - What Works and What Doesn't?

Abstract

Preterm birth is the leading cause of neonatal death and resulting handicap in survivors. Multiple conditions and mechanisms result in preterm birth to include infection or inflammation, uterine distension, physical or psychological stress, uterine bleeding, short or incompetent cervix, and genetics. Given the multitude of causes for preterm birth, it is not surprising there are many treatments to prevent preterm birth such as intramuscular progesterone, vaginal progesterone, cervical cerclage, and pessary. Determining the best treatment for a given patient can be confusing. The purpose of this manuscript is to clarify which treatment option is best suited for a given patient at risk for preterm delivery.

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Introduction

Since 2006, the U.S. early preterm birth (defined as birth prior to 34 weeks gestational age) rate has declined from 3.66% to 3.40%, and the late preterm birth (defined as birth between 34 and 36 weeks gestational age) rate has declined from 9.15% to 7.99%. Significant racial disparities exist in preterm birth rates with non-hispanic blacks having the highest rates and non-hispanic whites the lowest [1]. Most of the change in the preterm birth rate over the last two decades has been among infants born late preterm, which comprise the bulk of all preterm births (70.4 percent in 2012) [2].

Multiple conditions and mechanisms result in preterm birth to include infection or inflammation, uterine distension, physical or psychological stress, uterine bleeding, short or incompetent cervix, and genetics with the strongest risk factor being previous preterm birth [3]. Preterm birth can be reduced by preventing elective delivery preterm delivery; prescribing effective contraception to allow conditions associated with preterm birth such as short inter-delivery interval, tobacco use, illicit drug use, low pre-pregnancy weight, and poor nutritional status to be corrected prior to conception; and reducing the rate of multiple gestations. Given the multitude of causes for preterm birth, it is not surprising there are many treatments to prevent preterm

birth such as intramuscular progesterone, vaginal progesterone, cervical cerclage, and pessary. Determining the best treatment for a given patient can be confusing. The purpose of this manuscript is to clarify which treatment option is best suited for a given patient at risk for preterm delivery.

Progesterone

The exact manner by which progesterone prevents preterm birth is not known, but there are multiple proposed mechanisms with the evidence favoring two:

- 1) Progesterone has an anti-inflammatory effect that counteracts the inflammatory process leading to preterm birth and
- 2) Providing a local increase in progesterone in gestational tissues counteracts the functional decrease in progesterone leading to preterm birth [4].

Intramuscular (IM) injections of 17-alpha-hydroxyprogesterone caproate (17P) have been evaluated in several trials (Table 1). While weekly IM injections of 17P has been shown to decrease the risk of recurrent preterm birth [5], it has been shown not to be beneficial in the setting of short cervix, twin gestation, or following preterm labor successfully arrested with tocolysis [6-9].

Table 1: Select studies evaluating intramuscular 17-alpha-hydroxyprogesterone caproate (17P) to prevent preterm birth.

| Author | Preterm Birth Risk Factor | Gestational Age at Treatment Initiation (wks) | 17P dose | Outcome |
|----------------------|--|---|--------------------|---|
| Meis et al. [5] | Prior spontaneous PTB at 20 to 36-6/7 weeks, current singleton gestation | 16-0/7 to 20-6/7 | 250mg weekly | Decrease in PTB < 32, 35, and 37 weeks |
| Grobman et al. [6] | Nulliparous with CL<30mm, singleton gestation | 16-0/7 to 22-3/7 | 250mg weekly | No decrease in PTB < 35 or 37 weeks |
| Rouse et al. [7] | Twin gestation | 16-0/7 to 20-0/7 | 250mg weekly | No decrease in PTB < 35 weeks or composite morbidity |
| Combs et al. [8] | Dichorionic-diamniotic twin gestation | 16-0/7 to 24-0/7 | 250mg weekly | No improvement in mean gestational age at delivery or composite morbidity |
| Rozenberg et al. [9] | Singleton, Preterm labor successfully arrested with tocolysis, CL<25mm | 24-0/7 to 31-0/7 | 500mg twice weekly | No decrease in preterm birth < 32, 34, or 37 weeks |

CL: Cervical Length

Given its ease of administration as compared to intramuscular progesterone, the use of vaginal progesterone in patients at risk for preterm birth may be preferred. While vaginal progesterone gel 90mg qam did not decrease risk of recurrent preterm birth in women with a prior spontaneous preterm birth [10], use of progesterone gel in singleton gestations with no history of preterm birth but with sonographically short cervix (10-20mm at 19 to 23-6/7 weeks) was found to reduce the incidence of preterm birth prior to 28, 33, and 35 weeks [11]. Similarly, treatment of patients carrying a singleton gestation found to have cervical length <15mm at 20-25 weeks with micronized vaginal progesterone 200mg qhs resulted in a 44% decrease in preterm birth prior to 34 weeks [12]. The use of vaginal progesterone of different formulations to include 90mg gel [13], 200mg pessary [14] and 100mg suppository [15] to reduce the risk of preterm birth in twin gestations has been evaluated without success.

Cerclage

Cervical cerclage is used to provide extrinsic support to compensate for inherent cervical weakness as seen with cervical incompetence. Cerclage has been shown to reduce the incidence of recurrent preterm birth in women with a current singleton gestation and history of preterm birth when the cervix was found to be <15-25mm prior to 23-24 weeks [16-17]. Consequently, most experts use cervical length of 15-25mm as their threshold for cerclage placement in a patient with a prior spontaneous preterm birth [15,18]. Cerclage placement in women without a history of prior spontaneous preterm birth and short cervix has not been associated with a reduction in preterm birth [18] and use of cerclage in twin gestation with cervical length <25mm has been associated with a twofold increase in preterm birth [19].

Indications for cerclage in women with singleton gestations are:

1. History indicated
2. Physical examination indicated and
3. Ultrasound finding of short cervix with a history of prior preterm birth [18].

A history indicated (prophylactic) cerclage is placed in a patient with a history of one or more unexplained 2nd trimester loss related to painless cervical dilation in the absence of labor or abruption or a history of prior cerclage due to painless cervical dilation. Prophylactic cerclages are typically placed at 13-14 weeks gestation. Physical examination indicated (rescue or emergency) cerclage is placed in patients with advanced cervical dilation in the absence of labor or abruption. There is limited data from one small trial [20] which suggests benefit from rescue cerclage. Ultrasound indicated cerclage is placed in a patient with a prior history of spontaneous preterm birth with unclear history who is followed in a subsequent singleton pregnancy with serial sonographic evaluation of cervical length from 16-24 weeks gestation and found to have shortening less than 25mm before 24 weeks gestation. Cerclage placement should be limited to the 2nd trimester before viability and evidence is lacking for benefit of cerclage solely for prior surgery on cervix or Mullerian anomaly. Cerclage removal is recommended at 36 to 37 weeks but should be removed sooner for cervical change, painful uterine contractions, or vaginal bleeding associated with preterm labor [18].

Pessary

While no benefit to reducing preterm birth in twins have been found with the use of 17P, vaginal progesterone, or cerclage, recent studies have shown benefit of the vaginal pessary in reducing preterm birth in both singleton and twin gestations with cervical shortening [21]. Pessaries have been used for centuries for the non-surgical management of uterine or vaginal vault prolapse. Pessaries designed for the treatment of prolapse were the first pessaries used for the purpose of preventing preterm birth. More recently, however, pessaries designed specifically for this purpose have been designed [22,23]. There are several hypotheses as to how pessaries may prevent preterm birth. Ultrasound and MRI examinations have suggested that the pessary changes the angle of the cervix relative to the uterus to a more acute angle which might prevent direct pressure on the membranes at the level of internal os [24-26]. In addition, the pessary might prevent further dilation of the internal OS (Figure 1 & 2).

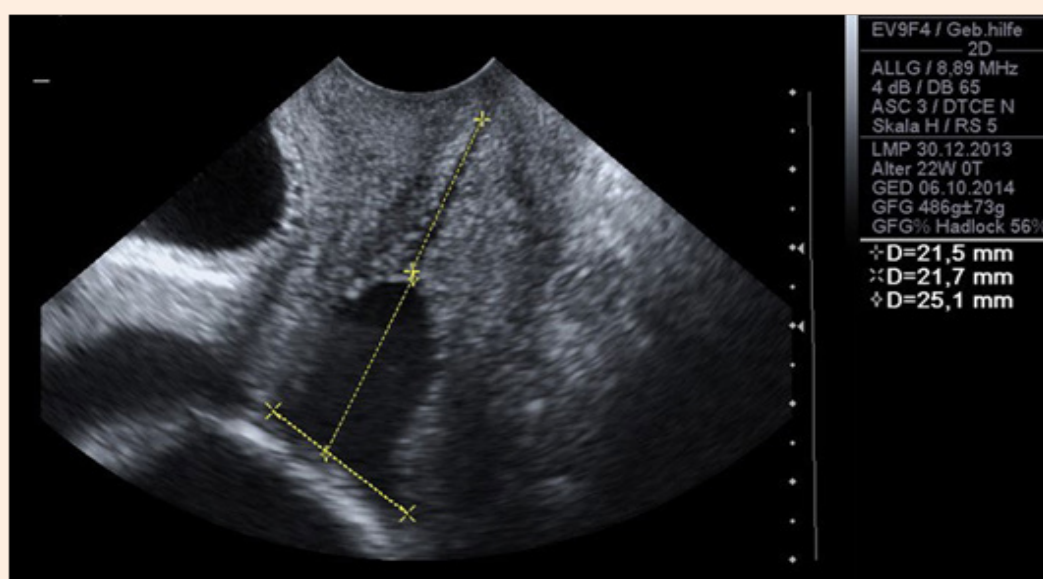


Figure 1: Transvaginal ultrasound showing cervical funneling in twin gestation at 22 weeks.

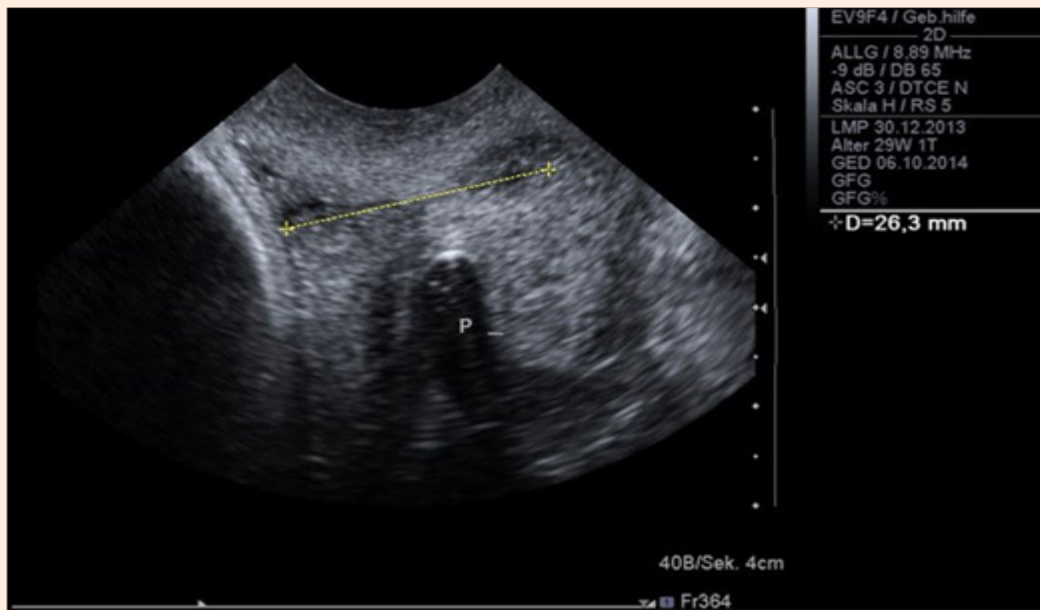


Figure 2: Transvaginal ultrasound showing improvement at 28 weeks with pessary (P) in place.

A large multicenter study recently found that use of a cervical pessary in nulliparous and multiparous patients (with and without a history of preterm birth) who were found to have a cervical length of less than 25mm at 20-23 weeks gestation reduced the risk of spontaneous preterm birth less than 28 weeks, 34 weeks, and 37 weeks. Another multicenter randomized trial was performed to assess whether a cervical pessary could effectively prevent poor pregnancy outcomes in twin gestations [21]. Subjects were randomized to cervical pessary placed between 16 and 20 weeks' gestation or no pessary. In unselected women with multiple pregnancy, prophylactic use of the cervical pessary did not reduce poor perinatal outcome. However, in a sub analysis the authors found benefit to pessary use in multiple gestations with CL <25th percentile (38mm) in regards to decrease in composite neonatal morbidity and decreased preterm delivery rate <32 weeks, but not before 37 weeks. Although promising, because this potential benefit was found in a secondary analysis of an otherwise negative study and after the criterion for a short cervix was revised, use of the pessary to reduce preterm birth in women with twins has not yet been widely adapted as the standard of care. There are

more than 10 ongoing studies in various countries-including the United States - comparing pessary with other methods to prevent preterm birth such as progesterone and cerclage in both singleton and twin pregnancies.

(Could do with a conclusions section, and perhaps a table of recommendations for when to use each Rx listed. Would also include something about importance of remembering to give steroids for standard indications, but not simply for risk of PTB.)

Conclusion

While 17P, vaginal progesterone, cerclage, and pessaries have all been shown to reduce the risk of preterm birth there are specific clinical situations for the use of each (Table 2). Data on pessary use for the prevention of preterm birth is limited but promising. If validated in the current on-going studies, cervical pessary placement may have additional benefit for prevention of preterm birth in women with a short cervix carrying twins and singletons.

Table 2: Summary of treatments available to reduce preterm birth.

| Treatment | Population that may Benefit in Reduction of Preterm Birth |
|----------------------|---|
| 17P | Prior spontaneous PTB at 20 to 36-6/7 weeks, current singleton gestation |
| Vaginal Progesterone | Short CL (10-20mm at 19 to 23-6/7 weeks [11] or <15mm at 20 - 25 weeks [12]), no history of PTB |
| Cerclage | Singleton gestation with prior PTB and CL<25mm prior to 24 weeks |
| | One or more prior 2 nd trimester losses related to painless cervical dilation in the absence of labor or abruption |
| Pessary* | Twin gestation with CL<38mm at 16 - 20 weeks |
| | Singleton gestation with CL<25mm at 20-23 weeks |

CL: Cervical Length

*Data from international studies. Several studies currently on-going in the United States.

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