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REVIEW

UPDATES ON MATERNAL FETAL MEDICINE

Effects of progestogens in women with preterm premature rupture of membranes

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ABSTRACT

Different strategies have been adopted for prevention of spontaneous preterm birth, including use of progestogens. So far, five randomized trials have been published evaluating the efficacy of progestogens in women with PPROM, including a total of 425 participants. All the five trials enrolled pregnant women with singleton pregnancies randomized between 20 and 34 weeks of gestation. In four trials women were randomized to either weekly intramuscular 250 mg 17α-hydroxyprogesterone-caproate or placebo, while Mirzaei *et al.* was a three arms trials in which women received weekly intramuscular 250 mg 17α-hydroxyprogesterone-caproate, or rectal progesterone 400 mg daily, or no treatment. In all the trials, latency antibiotics were used, and tocolysis was used permitted for first 48 hours at discretion of attending physician. Recently a meta-analysis including the five trials has been published. They found that when compared to placebo weekly intramuscular 250 mg 17α-hydroxyprogesterone-caproate did not alter the latency period to delivery in singleton gestations with PPROM. Additionally, there was no difference in gestational age at delivery between groups or in mode of delivery. No significant differences were reported in maternal or neonatal outcomes, with latency not significantly altered in sensitivity analyses. So far, no trials have been published evaluating natural vaginal progesterone in women with PPROM.

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KEY WORDS: Cerclage - Pessary - Progesterone - Cesarean delivery.

Preterm birth is defined as birth before 37 weeks of gestation.[1] An estimated 15 million infants are born preterm every year, with short- and long-term complications in the survivors.

Preterm birth includes elective delivery for maternal or fetal indications, defined as iatrogenic or medically indicated preterm birth, and spontaneous preterm birth, including either spontaneous onset of preterm labor or preterm premature rupture of membranes (PPROM).

About 25-30% of all spontaneous preterm deliveries follow PPROM, which is the most commonly cause of preterm birth in black women.[1] In women with PPROM, antibiotics have been shown to safely extend latency and decrease the risks of maternal and neonatal infection.[2, 3]

Progestagens, progestins, and natural progesterone

Different strategies have been adopted for prevention of spontaneous preterm birth, including use of progestogens.[3-31] Progestogens, also known as progestagens or gestagens, are a class of steroid hormones that bind to and active the progesterone receptor. Progestogens include

natural progesterone, and progestins. Progestins are synthetic progestogens. Major examples of progestins include the 17α-hydroxyprogesterone derivative medroxyprogesterone acetate, and the 19-nortestosterone derivative norethisterone. 17α-hydroxyprogesterone-caproate is an ester of the 17α-hydroxyprogesterone.

Progestogen administration has been studied in different at-risk women. High quality evidence from randomized controlled trials supports use of vaginal natural progesterone in asymptomatic women with short transvaginal ultrasound cervical length, in both singletons, at dose of 200 mg daily,[4] and twins, at dose of 400 mg daily,[31] while efficacy as maintenance tocolysis is actually still a subject of debate.[8, 16] In women with prior spontaneous preterm birth progestogens given from about 16 weeks to 36 weeks of gestation have been shown to be effective,[4] with daily vaginal progesterone, either suppository or gel, better alternative to weekly intramuscular 17α-hydroxyprogesterone-caproate.[24]

Preterm premature rupture of membranes

The membranes surrounding the amniotic cavity are composed of the amnion and the chorion. Membranes normally rupture during labor. Premature rupture of membranes (PROM) refers to rupture of the fetal membranes prior to the onset of labor irrespective of gestational age. Preterm prelabor rupture of membranes (preterm PROM) is defined membrane rupture prior to 37 weeks gestational age. Its frequency is about 3% of pregnancies. PPROM is associated with several maternal and perinatal complications, including chorioamnionitis, operative delivery low birth weight, low APGAR score, respiratory distress syndrome, sepsis, necrotized enterocolitis, admission to NICU, intrauterine fetal death and neonatal death.[32]

A prior PPROM, vaginal infections, collagen vascular disorders (such as Ehlers-Danlos Syndrome, systemic lupus erythematosus), direct abdominal trauma, preterm labor, cigarette smoking, illicit drugs (cocaine), anemia, low body mass index (BMI<20 kg/m^2), nutritional deficiencies of copper and ascorbic acid, low socioeconomic status, are associated risk factors for PPROM.[32] Uterine malformations may also be involved.

Progestagens and PPROM

So far, five randomized trials have been published evaluating the efficacy of progestagens in women with PPROM, including a total of 425 participants (Table I).[33-37] All the five trials enrolled pregnant women with singleton pregnancies randomized between 20 and 34 weeks of gestation. In four trials women were random-

TABLE I.—*Trials evaluating progestogens for women with PPROM.*

	Briery,[33] 2011	Combs,[34] 2011	Combs,[35] 2015	Mirzaei,[36] 2014	Langen,[37] 2018
Study location	USA	USA	USA	Iran	USA
Number of patients*	69 (33/36)	12 (4/8)	152 (74/78)	171 (57, 17-OHPC; 57, rectal progesterone; 57 control)	21 (10/11)
Progestogens treatment	17-OHPC	17-OHPC	17-OHPC	17-OHPC or rectal progesterone	17-OHPC
Dose, route, frequency	250mg IM, q week	250 mg IM, q week	250 mg IM, q week	17OHPC: 250 mg IM, q week; Rectal progesterone: 400 mg daily	Not reported
Control	Placebo (castor oil)	Placebo (castor oil)	Placebo (castor oil)	No treatment	Vehicle without progestin component
Included range gestational age at randomization (weeks^{days})	20^0 - 30^0	23^0 - 31^6	23^0 - 30^6	24^0 - 34^0	24^0 - 32^0

*Total number (number in the progesterone group/number in the control group).

ized to either weekly intramuscular 250 mg 17α-hydroxyprogesterone-caproate or placebo, while Mirzaei *et al.* was a three arms trials in which women received weekly intramuscular 250 mg 17α-hydroxyprogesterone-caproate, or rectal progesterone 400 mg daily, or no treatment. In all the trials, latency antibiotics were used, and tocolysis was used permitted for first 48 hours at discretion of attending physician. In four trials women already on progestogens prior PPROM were excluded, but in Coombs *et al.* those women were included but recommended to have progestogens (vaginal progesterone) discontinued after randomization.

Recently a meta-analysis including the five trials has been published.[38] They found that when compared to placebo weekly intramuscular 250 mg 17α-hydroxyprogesterone-caproate did not alter the latency period to delivery in singleton gestations with PPROM. Additionally, there was no difference seen in gestational age at delivery between groups or in mode of delivery. No significant differences were reported in maternal or neonatal outcomes, with latency not significantly altered in sensitivity analyses.

So far, no trials have been published evaluating natural vaginal progesterone in women with PPROM.

Conclusions

Progesterone therapy usually starts in the second trimester when the risk of preterm birth is investigated by ultrasound evaluation and clinical history. Currently, progestogens that are recommended by guidelines to prevent preterm birth in singleton gestations are: vaginal micronized progesterone administered daily in case of women with short cervix (sonographic cervical length at 25 mm or less); intramuscular 17a-hydroxyprogesterone caproate in oil administered weekly from the 16th to the 36th week of gestation in women with a history of prior spontaneous preterm birth.

In women with PPROM, progestogens, at least as studied so far, do not seem to prolong pregnancy. These results should encourage continued research into other interventions that could benefit this population.

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