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Review Article

The Up-to-date Informations of Progesterone Supplementation for Prevention of Preterm Birth

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Preterm birth (PTB) remains a major cause of neonatal mortality and morbidity, despite improvements in tocolytic treatment and neonatal care. Progesterone (17a-hydroxyprogesterone) produced naturally or synthetically can prevent PTB when applied vaginally and orally. Progesterone use may be a safe and cost-effective option in cases of singleton pregnancy with prior PTB, asymptomatically short cervix and arrested preterm labor.

Key Words: Cervical length, Preterm birth, Preterm labor, Progesterone

The World Health Organization has defined preterm birth (PTB) as birth before 37 completed weeks of gestation.[1] Spontaneous PTB, with or without prior rupture of the membranes (PPROM), accounts for two-thirds of PTBs, with the remainder due to obstetrically indicated conditions such as preeclampsia and intrauterine growth restriction (IUGR) (2). PTB represents 12% of all births in the United States.[2] PTB is associated with significant health care costs as well as neonatal morbidity and mortality. It is the leading cause of neonatal mortality in neonates without anomalies and is responsible for approximately 50% of cerebral palsy, 33% of visual impairment, 20% of mental retardation and an increased risk of long-term cardiovascular morbidity.[3] Costs related to care for infants with PTB or low birth weight is reported to exceed 11 billion dollars annually.[4]

Despite advances in obstetric care, the rate of PTB has not decreased over the past 40 years, with an increased prevalence reported in developed countries. Assisted reproductive techniques (ART) and the concomitant increase in multiple pregnancies have contributed to the rise of PTB. Nearly 60% of twins and nearly all triplet and higher-order multiple births represent PTBs. In the past, medical efforts focused on the prognosis of prematurity rather than preventing its occurrence. This approach had significant advances in neonatal medicine and use of antenatal corticosteroids, which markedly reduced neonatal morbidity and mortality. However, fewer advances have been made in primary prevention of PTB and effective tocolysis. Several tocolytic agents are currently used including β-adrenergic agonists, magnesium sulfate, nitric oxide donors, calcium channel blockers, cyclooxygenase inhibitors, and oxytocin receptor antagonists. These tocolytics inhibit myometrial contractility by altering intracellular transduction pathways responsible for cell contraction, inhibiting the synthesis of myometrial stimulants, or by blocking the actions of myometrial stimulants. However, they

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can-not reverse the processes leading to activation of the myometrium during labor at term or preterm.[5]

Increased understanding concerning the pathophysiology of preterm labor has changed the focus of PTB efforts from tocolysis to prevention. This review focuses on the evaluation of current reports on actions and routes of administration of various progestin formulations for prevention of PTB.

1. Role of progesterone

Progesterone has been important in maintaining pregnancy for more than 80 years, since the classic work of Allen et al.[5] In human parturition, progesterone is produced by the corpus luteum early in pregnancy, and mainly by the placenta in the remaining two-thirds of pregnancy. It has been proposed that labor is initiated by progesterone withdrawal, that is, a physiologically regulated decrease in progesterone levels. In most mammalian species, progesterone concentrations in the peripheral blood decrease before the onset of labor at term (i.e., progesterone withdrawal), although this has not been confirmed in human pregnancy.[4]

Progesterone has an important role in the maintenance of pregnancy by modulating the production of proinflammatory cytokines. Cytokines such as interleukin (IL)-1β, tumor necrosis factor-alpha (TNF-α) and IL-6 increase the production of matrix metalloproteinases including MMP-1, MMP-8 and MMP-9, which digest collagen type 1 in the extracellular matrix to induce cervical softening and effacement.[6] At term, spontaneous uterine activity may occur secondary to modulation of the progesterone receptors in the uterus, creating a 'functional' progesterone withdrawal that allows the release of cytokines. This process of cervical ripening precedes the myometrial contractions of labor by weeks. The most likely pathway for the initiation of preterm labor involves premature release of cytokines in the uterus.[7]

Progesterone exerts overall control on both cervical ripening and myometrial contractility. Therefore, supplementation of progesterone seems a very promising strategy for prevention of PTB.

2. Clinical studies of progesterone

1) Patients with prior PTB

Many studies have reported the efficacy of using progesterone to prevent PTB. One of the first randomized trials of progesterone for the prevention of PTB in women at increased risk was published by Papiernik et al. in 1970.[4] Ninety-nine women were randomized to 17 α-hydroxyprogesterone (17P) or placebo in the third trimester. The incidence of PTB was 4% in the 17P treated group and 18% in the placebo group. Thereafter, Johnson et al. reported that a significant reduction in the rate of PTB when 17P was administered from the second trimester.[8]

Since then, many other trials have been published. A recent reevaluation of the study data of Meis et al. was performed by the United States Food and Drug Administration (FDA) to assess the efficacy and safety of 17P in this population of women with a history of PTB.[9] In the prospective, double-blind, placebo-controlled trial of 463 women with prior spontaneous PTB, participants were randomizedto receive weekly intramuscular injections of 17P (n=306) or placebo (n =153) between 16 and 37 weeks of gestation or delivery. There was a reduction in rates of delivery at less than 37 weeks (36.3% in the 17P group vs 54.9% in the placebo group), at less than 35 weeks (20.6% vs 30.7%), and at less than 32 weeks (11.4% vs 19.6%) in women with progesterone. Treatment with 17P

reduced the incidence of neonatal complications (necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen) in the treated group. According to Petrini et al., weekly administration of 17P from 16-20 weeks of gestation in women with a history of PTB decreases the rate of PTB by up to 33%.[10] The study performed by Odibo et al. showed that administration of 17P in women with prior PTB at <32 weeks and at 32-37 weeks was effective in the prevention of PTB and also had cost savings.[11] Recently, Saghafi et al. reported that weekly administration of 17P to pregnant women with a history of PTB was associated with a decrease in PTB and improvement in birth weight.[12] The collective results show that progesterone supplementation reduces PTB in women with prior PTB.

17P is an artificially made caproate ester of 17-hydroxyprogesterone, a natural progestin produced during pregnancy. 17P is a long-acting progestin and can be administered once a week. The half-life of 17P is approximately 7.8 days, compared with 33-55 hours for natural progesterone.[5] However weekly intramuscular injection of 17P is invasive and has adverse effects such as pain, swelling, itching, and brusing. Natural progesterone can be used non invasive methods (intravaginal and oral dosing). The use of natural progesterone has also been studied for PTB prevention. The use of vaginal versus intramuscular progesterone has been advocated because of the "uterine first-pass effect". The efficacy of progesterone seems to be improved with an increase in the delivery to the endometrium with vaginal dosing. An increase of 14-times in the ratio of endometrial-to-serum concentrations after vaginal dosing than after systemic administration was presented.[13]

Many studies have reported a benefit from intravaginal dosing for the prevention of PTB. In a randomized, placebo-controlled trial of supplemental vaginal progesterone (100 mg daily) in 142 women at high risk for PTB, the authors found that rate of delivery at less than 34 weeks of gestationwas significantly lower among women receiving progesterone than among those receiving placebo (2.7% versus 18.6%).[14] But, in another study, prophylactic treatment with vaginal progesterone gel (90 mg, daily) did not reduce the frequency of recurrent PTB (≤32 weeks) in women with a history of spontaneous PTB.[15]

Sometimes, vaginal dosing is poorly accepted by many patients because of unpleasant vaginal discharge. For this reason, Rai et al. evaluated the effect of oral micronized progesterone to prevent PTB. At this randomized double-blind placebo-controlled trial, the mean gestational age at delivery in the patients received 100 mg of oral micronized progesterone was higher than placebo group ($P < 0.001$).[16]

2) Patients with short cervical length

Asymptomatic women found at midgestation to have a short cervix are at greatly increased risk for spontaneous PTB, but it is unknown whether progesterone reduces this risk in such women.

The first study of progesterone prophylaxis based on cervical length was carried out by Fonseca et al.[17] In this multicenter study, 24,620 women screened with vaginal ultrasonography between 20 weeks and 25 weeks of gestation. Of these, 413 women had a cervical length less than 15 mm (1.5%) and of them, 250 were randomly assigned (1:1) to daily vaginal progesterone (200 mg micronized progesterone capsules) or placebo from 24 weeks to 34 weeks of gestation. Overall, progesterone therapy significantly reduced the rate of PTB at less than 34 weeks of gestation (19.2% versus 34.3%). The second study randomized on the basis of

cervical length is from Hassan et al.[18] This was an international multicenter trial of women recruited from a screened population of 32,091 who had cervical length measurement at 19-24 weeks' gestation; 733 women (2.3%) had a cervical length between 10 and 20 mm, of whom 465 were randomized to receive 90 mg progesterone gel or a placebo gel vaginally daily. Analysis demonstrated a significant 45% reduction in deliveries <33 weeks (8.9% vs 13.1%), a 50% reduction in deliveries <28 weeks (5.1% vs 10.3%) and a 47% reduction in very low-birth weight infants (6.4% vs 13.6%) in the progesterone treated group. In the treatment group there was also a significant reduction in respiratory distress syndrome (3.0% vs 7.6%) and a composite of neonatal morbidity. So, some authors reported that doing universial cervical length screening and vaginal progesterone treatments is effective for prevention of PTB, reduction of neonatal morbidity, and cost saving.[7]

3) Patients with arrested preterm labor

The use of progesterone for patients who present preterm labor is not recommended. However, women with preterm labor that is arrested with tocolytic therapy are at increased risk of recurrent preterm labor. The efficacy of maintenance tocolytic therapy after successful arrest of preterm labor remains controversial.

In 2007, Facchinetti et al. evaluated the use of 17P in patients admitted with an acute episode of preterm labor who had yet to deliver. Undelivered patients (in these patients, cervical ripening and the cascade of preterm labor was already initiated) were randomly divided into treatment with intramuscular 17P (341 mg twice weekly) until 36 weeks and placebo. Cervical shortening, as measured by ultrasound performed 7 and 21 days post-randomization, was significantly less in the treated group with 17P as compared with placebo. They showed that cervical shortening is attenuated by treatment with 17P in women admitted for threatened preterm labor.[19] Borna et al. performed a similar study to determine whether supplementation of vaginal progesterone after inhibition of preterm labor is associated with an increased latency period and a decreased recurrent of preterm labor.[20] They reported that the use of vaginal progesterone suppository after successful tocolysis significantly associated with a longer latency until delivery (36 vs 24 days), reduced respiratory distress syndrome, low birth weight, birth weight between the two groups. But, no significant differences were found between recurrent preterm labor, admission to intensive care unit, and neonatal sepsis for the progesterone and control. In a 2011 study, Bomba-Opon et al. carried out a retrospective evaluation of vaginal progesterone efficacy in pregnant patients with symptoms of threatened preterm labor. The control group (n = 94) were treated with tocolytics and steroids, while the study group (n = 96) received additionally 200 mg of progesterone vaginally until delivery or week 34 of gestation. The administration of vaginal progesterone after to colysis in threatened preterm labor was associated with prolongation of pregnancy. The reduction of deliveries before 34 weeks was observed in patients presenting with contractions after 27 weeks gestation.[21]

3. Limitations and safeties of progesterone

While 17P has been shown to reduce the rate of recurrent PTB in singleton gestations, several recent studies have shown the lack of positive effect of 17P in women with twin gestation. Rouse et al. conducted a randomized, double-blind, placebo-controlled trial in 14 centers in healthy women with twin gestations. In this study, weekly 250 mg injections of 17P failed

to lower the rate of PTB, to prolong gestation, or to improve fetal or neonatal outcome.[22] Similarly, Caritis et al demonstrated no reduction in PTB in women with triplet pregnancies treated with 17P.[23]

In the case of pregnancies with PPROM, Briery et al. reported that 17P did not extend gestation versus placebo and cannot be recommended for treatment in such women.[24]

The use of progesterone and cerclage together is understudied and, therefore, is not recommended. Rafael et al. noted that prophylactic treatment of PTB with 17P in women with an ultrasound-indicated cerclage could not reduce the rate of PTB.[25]

Several studies have evaluated the safety of progesterone in pregnancy. 17P demonstrated no teratogenic, androgenic, or glucocorticoid effect, or virilization of female even higher dose including 1000 mg weekly in an the animal study.[4] Several studies reported on the safety of 17P in human pregnancy. Varma et al. did not find any evidence of adverse effects on fetuses in human pregnancies with in utero exposure to 17P.[26] In a battery of psychological tests on a group of adolescent males who were exposed in utero to 17P, Kesler et al. found no significant differences compared with controls.[27] In 2007, Northern et al. performed a follow-up study of children exposed in utero to 17P compared with placebo.[28] There was not a significant difference between two groups.

CONCLUSION

Despite extensive studies, we are still unable to effectively prevent preterm delivery. In some cases, the use of progesterone provides a significant reduction in the risk of PTB. Supplementation of progesterone for the prevention of PTB should be offered to singleton pregnant women with a prior spontaneous PTB due to spontaneous preterm labor or PPROM. Based on the current studies, prophylactic progesterone supplementations in asymptomatic women with short cervix and in women with arrested preterm labor may be also considered. The use of progesterone in women with multiple pregnancies, PPROM, and cerclage is not recommended. Progesterone is thought to inhibit cervical ripening. However, the exact mechanism of progesterone in treatment of these patients remains unclear. Further studies about a variety of application, effectiveness, and safety of progesterone supplementation for prevention of PTB are needed.

REFERENCE

1. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. Acta Obstet Gynecol Scand 1977;56:247-53.
2. Goldenberg RL. The management of preterm labor. Obstet Gynecol 2002;100:1020-37.
3. Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. Obstet Gynecol 2007;110:405-15.
4. Hall NR. What agent should be used to prevent recurrent preterm birth: 17-P or natural progesterone? Obstet Gynecol Clin North Am 2011;38:235-46.
5. Lucovnik M, Kuon RJ, Chambliss LR, Maner WL, Shi SQ, Shi L, et al. Progestin treatment for the prevention of preterm birth. Acta Obstet Gynecol Scand 2011;90:1057-69.
6. Watari M, Watari H, DiSanto ME, Chacko S, Shi GP, Strauss JF 3rd. Pro-inflammatory cytokines induce expression of matrix-metabolizing enzymes in human cervical smooth muscle cells. Am J Pathol 1999;154:1755-62.
7. Campbell S. Universal cervical-length screening and vaginal progesterone prevents early preterm births, reduces neonatal morbidity and is cost saving: doing nothing is no longer an option. Ultrasound Obstet Gynecol 2011;38:1-9.
8. Johnson JW, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17alpha-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med 1975;293:675-80.

9. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379-85.
10. Petrini JR, Callaghan WM, Klebanoff M, Green NS, Lackritz EM, Howse JL, et al. Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. Obstet Gynecol 2005;105:267-72.
11. Odibo AO, Stamilio DM, Macones GA, Polsky D. 17alpha-hydroxyprogesterone caproate for the prevention of preterm delivery: A cost-effectiveness analysis. Obstet Gynecol 2006; 108:492-9.
12. Saghafi N, Khadem N, Mohajeri T, Shakeri MT. Efficacy of 17α-hydroxyprogesterone caproate in prevention of preterm delivery. J Obstet Gynaecol Res 2011;37:1342-5.
13. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. Obstet Gynecol 2000;95:403-6.
14. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419-24.
15. O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007;30: 687-96.
16. Rai P, Rajaram S, Goel N, Ayalur Gopalakrishnan R, Agarwal R, Mehta S. Oral micronized progesterone for prevention of preterm birth. Int J Gynaecol Obstet 2009;104:40-3.
17. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462-9.
18. Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2011;38:18-31.
19. Facchinetti F, Paganelli S, Comitini G, Dante G, Volpe A. Cervical length changes during preterm cervical ripening: effects of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol 2007;196:453.e1-4; discussion 21.
20. Borna S, Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labour: a randomised controlled trial. Aust N Z J Obstet Gynaecol 2008;48:58-63.
21. Bomba-Opon DA, Kosinska-Kaczynska K, Kosinski P, Wegrzyn P, Kaczynski B, Wielgos M. Vaginal progesterone after tocolytic therapy in threatened preterm labor. J Matern Fetal Neonatal Med 2011 Oct 4.
22. Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med 2007;357:454-61.
23. Caritis SN, Rouse DJ, Peaceman AM, Sciscione A, Momirova V, Spong CY, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Obstet Gynecol 2009;113:285-92.
24. Briery CM, Veillon EW, Klauser CK, Martin RW, Magann EF, Chauhan SP, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. Am J Obstet Gynecol 2011;204:54.e1-5.
25. Rafael TJ, Mackeen AD, Berghella V. The effect of 17α -hydroxyprogesterone caproate on preterm birth in women with an ultrasound-indicated cerclage. Am J Perinatol 2011;28:389-94.
26. Varma TR, Morsman J. Evaluation of the use of Proluton-Depot (hydroxyprogesterone hexanoate) in early pregnancy. Int J Gynaecol Obstet 1982;20:13-7.
27. Kester PA. Effects of prenatally administered 17 alpha-hydroxyprogesterone caproate on adolescent males. Arch Sex Behav 1984;13:441-55.
28. Northen AT, Norman GS, Anderson K, Moseley L, Divito M, Cotroneo M, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol 2007;110:865-72.

Peer Reviewers' Commentary

Preterm birth (PTB) remains a major cause of neonatal mortality and morbidity, despite improvements in tocolytic treatment and neonatal care. Progesterone (17a-hydroxyprogesterone) produced naturally or synthetically can prevent PTB when applied vaginally and orally. Progesterone use may be a safe and cost-effective option in cases of singleton pregnancy with prior PTB, asymptomatically short cervix and arrested preterm labor. Supplementation of progesterone for the prevention of PTB should be offered to singleton pregnant women with a prior spontaneous PTB due to spontaneous preterm labor or PPROM. Based on the current studies, prophylactic progesterone supplementations in asymptomatic women with short cervix and in women with arrested preterm labor may be also considered. In this review, Up-to-date informations of Progesterone supplementation for prevention of preterm birth to make it easier to understand the summary and, in clinical practice is thought to be very helpful.

(Comment: Editorial Committee)