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Progesterone to Prevent Preterm Birth in Twin Gestations: What is the Next Step Forward?

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Progesterone is a key hormone for pregnancy maintenance, and a decline in progesterone action is considered to be central to the initiation of parturition in most mammalian species, including primates.^{1, 2} This hormone acts in all components of the common pathway of parturition¹⁻³ and promotes myometrial quiescence, inhibits cervical ripening, and down-regulates the production of chemokines [such as interleukin (IL)-8] by the chorioamniotic membranes.⁴ Importantly, the administration of progesterone receptor antagonists [i.e. mifepristone (RU486) or onapristone (ZK98299)] to pregnant women, non-human primates and guinea pigs can induce the onset of labor and cervical ripening.⁵ Thus, it is not surprising that many investigators have explored the use of progesterone for the prevention of preterm birth.

Two compounds with progestational action have been used in clinical trials: progesterone, the bioequivalent of the natural hormone, and 17-alpha-hydroxyprogesterone caproate (17OHP-C), a synthetic ester, in which the caproate is added to prolong the half-life of the compound.⁵ The two molecules have different physiologic properties⁶ and clinical effectiveness in the prevention of preterm birth (i.e. vaginal progesterone prevents preterm birth in women with a short cervix and singleton gestation,^{7, 8} but there is no evidence that 17OHP-C does⁹). Trials of 17OHP-C in twin^{10, 11} and triplet^{12, 13} gestations have indicated that this compound does not prevent preterm birth in multiple pregnancies. Three trials have explored the effects of vaginal progesterone in the prevention of preterm birth in twins. Two have used vaginal progesterone (90mg daily in a bioadhesive gel),^{14, 15} and one has used 200mg.¹⁶ All trials have been negative. A logical question is whether twin gestations require a larger dose of progesterone for the prevention of preterm birth.

In this issue of the Journal, Serra et al.¹⁷ report the results of an important randomized clinical trial which addressed this question. Women with dichorionic, diamniotic twin pregnancies, conceiving largely through assisted reproductive technologies (ART; ovarian stimulation, *in vitro* fertilization or intracytoplasmic sperm injection), were randomized to either placebo or two different doses of vaginal progesterone daily in pessaries (one group received 200mg, and another, 400mg). The primary endpoint of the study was preterm birth (<37 weeks). Eligible women were recruited at 11-13 weeks of gestation, but randomized at 20 weeks. If patients had been treated with vaginal progesterone during the first trimester for corpus luteum support, that treatment was stopped at the time of recruitment. The study was conducted in 5 centers in Spain and included 290 women (with complete follow-up data). The rate of preterm birth at <37, <34, <32 and <28 weeks was not significantly different among the 3 groups (placebo, 200mg of progesterone, or 400 mg of progesterone). The

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frequency of a sonographic short cervix (<25mm) in the trial of Serra et al.¹⁷ was low (1.7%; 5/290), and this may be one explanation for the negative results (see below for the relationship between a short cervix and response to progesterone).

The trial was well-designed in that it involved double-blind randomization, focused on dichorionic twins (excluding the possibility that results may be confounded by the complications of monochorionic twins), the patients were randomized and enrolled at approximately 20 weeks, and cervical length was routinely measured by transvaginal ultrasound at 20, 24 and 28 weeks of gestation. The authors appropriately acknowledged that while the effect size used for sample size estimation (50% reduction in preterm birth) was based on the best available evidence at the time of trial design,¹⁸ subsequent trials have not demonstrated such a benefit.¹⁴ Nonetheless, the trial is unique in that it is the only one to have compared different doses of progesterone with placebo for the prevention of preterm birth. The optimal dose of progesterone has been an open question for both singleton and twin gestations.

Two observations are noteworthy: first, a higher dose of vaginal progesterone (400mg vs. 200mg) did not yield efficacy. This is consistent with a subgroup analysis in an individual patient meta-analysis of singleton gestations with a short cervix in which a higher dose of vaginal progesterone (200mg vs. 90-100mg daily) did not result in further reduction of preterm birth compared to the lower dose.¹⁹ Second, higher doses of progesterone appear to have side effects. There was a non-significant dose-dependent trend toward a higher incidence of intrahepatic cholestasis among women treated with progesterone.¹⁷ This suggests that, even for a natural hormone present in high concentrations in peripheral blood during pregnancy, it is prudent to adhere to the principle of using the lowest effective dose. The available evidence from randomized clinical trials using progestins in twin gestations to prevent preterm birth has not yielded the desired outcome. Recent observations that progesterone does not inhibit stretch-induced MAPK activation of gene expression in human myometrial cells have been invoked as an explanation for the negative results of progestin trials in twins.² Whatever the reason for the lack of effectiveness, further randomized clinical trials of progestins in unselected twin gestations do not seem justified.

Why is vaginal progesterone ineffective in the prevention of preterm birth in women with twin gestations? Is it that this treatment just does not work, or rather, that randomized clinical trials have not focused on the population that may benefit from this treatment? Perhaps we can learn from the experience in singleton pregnancies.

Two large randomized clinical trials tested the effect of vaginal progesterone on patients with singleton gestations at “high risk” for preterm birth. Da Fonseca et al.¹⁸ reported that vaginal progesterone (100mg suppository daily) decreased the rate of preterm birth in a population of patients with a prior history, uterine malformation or a prophylactic cervical cerclage. However, in the largest trial to date (n=659 patients, excluding women with uterine malformations and a prophylactic cervical cerclage), O’Brien et al.²⁰ found that vaginal progesterone (90mg daily) in women with a history of preterm birth did not reduce the rate of preterm delivery. The different outcomes of the trials are unlikely to be due to the criteria for entry because the number of patients who had uterine malformations and a cervical cerclage comprised only 3.5% (5/142) and 2.8% (4/142) in the study of Da Fonseca et al.¹⁸ Similarly, the two trials used micronized progesterone – one as a suppository,¹⁸ and the other as a bioadhesive gel.²⁰ Therefore, it is likely that the difference lies elsewhere.

DeFranco et al.,²¹ in a secondary analysis of the O’Brien trial,²⁰ reported that the response to progesterone varied as a function of sonographic cervical length in the midtrimester, and that women with a cervix of <28mm had a lower rate of preterm birth and less neonatal

morbidity. This observation suggested that a short cervix may be a biomarker for patients who may respond to vaginal progesterone – this is biologically plausible, given the large body of evidence supporting that a suspension of progesterone action induces cervical ripening (review in reference⁵).

Subsequently, two independent randomized clinical trials demonstrated that vaginal progesterone reduced the rate of preterm birth (defined as <34 or <33 weeks) when given to women with a short cervix in the midtrimester by 44-45%.^{7, 8} Moreover, an individual patient meta-analysis showed that vaginal progesterone reduced admission to the Neonatal Intensive Care Unit, the rate of respiratory distress syndrome, the requirement for mechanical ventilation and composite neonatal morbidity/mortality.¹⁹ It seems that a short cervix can identify a subset of patients who may benefit from vaginal progesterone. Could this also be the case in twin gestations?

A sonographic short cervix is a powerful predictor of preterm birth in both singleton and twin gestations. Indeed, the same cervical length confers a greater risk for preterm birth in twin gestations than in singleton. For example, a cervical length of <15mm in singleton gestation confers a 50% risk of preterm delivery <32 weeks,²² while the same risk is conferred in twin gestation by a cervical length of <25mm.²³ A systematic review and meta-analysis²⁴ showed that, among asymptomatic women, a cervical length of <20mm at 20-24 weeks of gestation was a major predictor of preterm birth at <32 and <34 weeks (pooled positive likelihood ratios of 10.1 and 9.0, respectively). Thus, the logical question is whether vaginal progesterone given to women with a dichorionic pregnancy and a short cervix can prevent preterm birth. Data suggesting that this may be the case comes from a subgroup analysis of an individual patient meta-analysis indicating that administration of vaginal progesterone to women with twin gestations and a short cervix (<25mm) may reduce the rate of preterm birth by 30% (RR 0.70; 95% CI, 0.34 – 1.44) and nearly halve the rate of neonatal morbidity (RR 0.52; 95% CI, 0.29 – 0.93).¹⁹ It is noteworthy that the observations are based on a small number of patients, and therefore, the 30% decrease may not have reached significance due to the small sample size. Yet, neonatal morbidity/mortality was significant when the sample size was larger (more newborns than mothers in twin gestations). These findings need to be replicated in a well-designed, prospective randomized clinical trial.

We believe that such a trial should include women with dichorionic twin gestations and a short cervix (e.g., 10-25mm) stratified by history of preterm birth. Selection of the primary and secondary outcomes also requires considerable thought, given that the duration of gestation is different in twin than in singleton gestations. The sample size calculation needs to take into account that the prevalence of indicated preterm birth is higher in twins than in singletons, and that vaginal progesterone is not expected to reduce the frequency of preeclampsia, intrauterine growth restriction and other causes of indicated preterm birth (such as severe growth restriction in one of the twins, etc.). Other unique features of the design need to be taken into account. The statistical analysis plan requires additional considerations: for instance, the need to account for the lack of independence among neonates (i.e., they belong to the same pregnancy). The design of such a trial is well-advanced, and its complexity will require a multi-national effort to obtain a clear answer to this challenging question within an optimal timeline. Centers in the U.S., Europe, Latin America and Asia are participating in the design of this trial*, and institutions in which twin clinics are well-established are welcome to join. This effort is important because twin gestations contribute disproportionately to preterm birth, and, at present, there is no

*Investigators include Sonia S. Hassan, Andrew Combs, Thomas Garite, Roberto Romero (U.S.), Maria Teresa Gervasi (Italy), Bo Yoon (Korea), Enrique Oyarzun (Chile), and others.

intervention that can reduce the rate of preterm birth, including cerclage, 17-OHPC, or a cervical pessary.

Twin gestations comprise a heterogeneous population including patients with spontaneous conception, those who conceived using ART, monochorionic and dichorionic twins, etc. The causes of preterm birth differ in twins and singletons (e.g. twin-to-twin transfusion syndrome). Similarly, while the higher rate of spontaneous preterm birth has been attributed to uterine overdistension, other mechanisms, including infection/inflammation, play a role.^{25, 26} Given the syndromic nature of preterm parturition,³ just as in singleton gestation, progesterone is likely to benefit only a subset of women with twin gestations. Therefore, progress requires that we advance in understanding the mechanisms of disease and the pathology responsible for preterm birth in twin gestations. High-dimensional biology,²⁷ including pharmacogenomics, is likely to offer additional insight. More importantly, a fundamental philosophical change is necessary. Our discipline needs to evolve from the current classification of obstetrical disorders, which is fundamentally descriptive of symptoms and signs, to a new taxonomy of disease informed by underlying pathophysiology. This would assist us in identifying subgroups within the “great obstetrical syndromes”²⁸ that may benefit from specific therapeutic interventions. Twin gestation is an excellent example of this challenge.

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