Use of *17 Alpha-Hydroxyprogesterone Caproate* in Clinical Practice

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Former British Prime Minister Winston Churchill once described the political agenda of the Post World War II Soviet Union as "a riddle wrapped in a mystery inside an enigma". Many obstetricians feel the same way about prematurity secondary to preterm labor leading to spontaneous preterm birth. In fact, some may even say the same about *17 alpha-hydroxy-progesterone* based on the plethora of studies being done on this medication and other forms of progesterone used as an adjunct or as the primary treatment modality in the prevention of preterm birth in patients with signs and symptoms of preterm labor or who are at increased risk of preterm birth based on factors in the current or previous pregnancy.

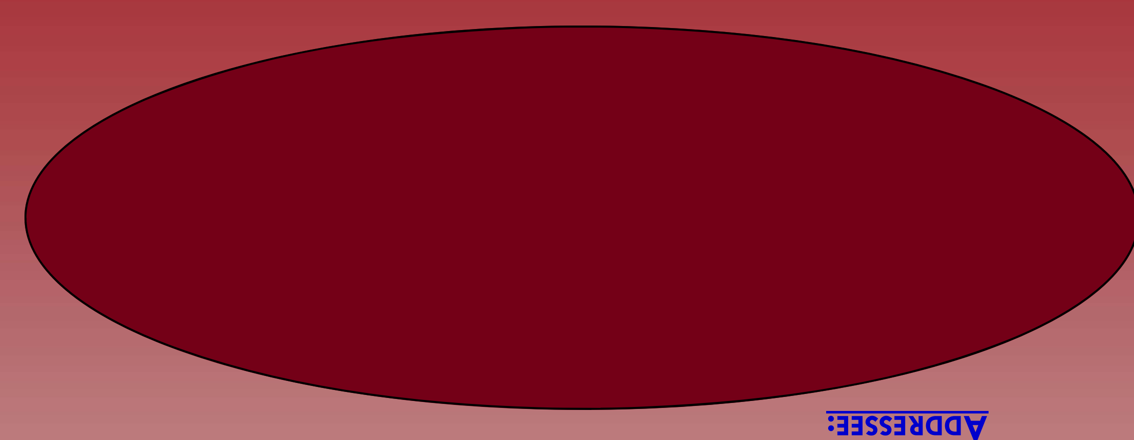
Physiology

Progesterone plays a key role in the physiological process that leads to preterm birth. Progesterone has multiple actions on the myometrium during the second and third trimester of pregnancy that leads to a down regulation of the contractile mechanism in the myometrial smooth muscle cell. It has an inhibitory effect starting from decreasing the number of receptors to oxytocin, which increases the threshold of stimulation leading to contraction, to decreasing the propagation of contractions once such activity has been initiated by preventing the formation of gap junctions. This is the scientific basis for the clinical use of progesterone. However important its inhibitory role may be, it is not a panacea to the treatment and/or the prevention of uterine contractions specifically and preterm labor along with preterm birth generally. Unfortunately for us, the contractile process is so complex that no one molecule will never be a panacea because so much more goes into the pathway leading to preterm birth.

Pre-Term Birth

When preterm birth is defined as a birth occurring at less than 35 weeks of gestation, it accounts for 10% of total births. If we use this 10% as the risk of preterm birth for the general population, and therefore as a starting point where we can separate women into two distinct categories such as *high risk* (where the rate of preterm birth is significantly greater) or *low risk* (where the risk of preterm birth is less than or equal to this value). This value has proved to be unattainable. In other words, using this value as a goalpost or measuring stick has been unattainable in terms of all methods of screening or treatments for preterm labor where following such a treatment, the rate of preterm birth has been significantly decreased to a value below 10%.

The goalpost has definitely been moved, so that the current measure of the effectiveness of a therapeutic model is whether or



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- *In December 2007, we partnered with the Woman's Hospital of Texas Auxiliary, and purchased thousands of dollars worth of medications to donate to a woman's & children's hospital in Southern Iraq. These medications were shipped before Christmas and arrived safely at their destination to benefit all of those woman & children who had been without substantial hospital care.*
- *In March of 2008, we donated several cases of medical supplies to Medical Bridges in Houston, for use in their outreach programs in several Latin American countries.*
- *We have begun to donate tickets to our suite at the Toyota Center (Houston, Texas) to several local charities, so that their less fortunate clients might partake of an evening of entertainment despite their illnesses or infirmities.*

We hope that through your referrals to our company you realize that not only will your patients receive a superior homecare experience, but that your trust in us extends outward to benefit those much less fortunate.

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not the treatment has resulted in a significant reduction in preterm birth when compared to no treatment. This methodology has been applied to the following conditions associated with women who are considered high risk for preterm birth. If we examine recurrent preterm birth for example, it occurs in 26% of black women compared with 15–20% of white women. The gestational age of subsequent preterm delivery is similar to the initial preterm birth, with 50% delivering within 1 week and 70% delivering within 2 weeks of the previous preterm delivery. In addition, there is also an additive effect where women with one prior preterm delivery before 35 weeks of gestation have a 16% recurrence risk, those with two early preterm deliveries have a 41% risk, and those with three prior preterm deliveries have a 67% risk of subsequent preterm birth before 35 weeks. Investigators tried using progesterone beginning in the second trimester in an attempt to ameliorate this risk.

Clinical Studies

In the most publicized study, 459 patients at high-risk for preterm delivery due to a prior preterm birth at less than 35 weeks were randomly assigned to weekly intramuscular injections of *17 alpha-hydroxy-progesterone caproate* (250 mg) or placebo beginning at 16 to 20 weeks of gestation and continuing until 36 weeks. Prophylaxis with *17 alpha-hydroxyprogesterone* significantly reduced the risk of delivery at less than 37 weeks (36% versus 55% in the placebo group [RR, 0.66; 95% CI, 0.54-0.81]), delivery at less than 35 weeks (21% versus 31% [RR, 0.67; 95% CI, 0.48-0.93]), and delivery at less than 32 weeks (11% versus 20% [RR, 0.58; 95% CI, 0.37-0.91]). In 2003, an ACOG committee opinion recommended progesterone supplementation be used in patients presenting with this condition; its use should be restricted to women with a previous history of spontaneous preterm birth of a singleton at less than 37 weeks of gestation based on the result of this trial. I would be remiss if I failed to state one glaring fact: *one must keep in mind that the majority of preterm births are not recurrent*. As a result, we can take a look at what would happen if we applied this 33% reduction theoretically in our national model for a specific calendar year. In 2002, for example only 22.5 percent of preterm births in 2002 were recurrent. In 2002, the overall preterm birth rate was 12.1 %. Therefore, if all eligible women received progesterone prophylaxis, it would only reduce the overall preterm birth rate in the United States by approximately 2% (from 12.1% to 11.8%). This doesn't sound like much but when preterm birth surpasses birth defects as the leading cause of neonatal mortality in 2001 and is the leading cause of black infant mortality, I would consider this a good start.

Pre-Term Birth Prevention

Progesterone alone is not all that we can offer to prevent recurrent preterm birth, other treatment modalities that can be done in women with a prior history of preterm birth where studies have demonstrated a significant reduction in the rate of recurrent preterm birth include placing a cerclage, being discouraged from initiating smoking, delaying subsequent pregnancy for 18 months, and early reporting of symptomatic contractions. But in addition to the risk factor of a previous history of preterm birth, investigators have illustrated that progesterone use can reduce the rate of preterm birth in women with other known risk factors for preterm birth. For example, one randomized trial of women who remained undelivered after an episode of acute preterm labor with a closed cervix showed that treatment with high-dose *17 alpha-hydroxyprogesterone caproate* was associated with both less shortening of the cervix and a reduced rate of preterm delivery compared to observation alone. Another trial showed that progesterone reduced the rate of spontaneous preterm birth in asymptomatic women noted to have a short cervix (≤15 mm) on ultrasound at 20 to 25 weeks of gestation (delivery before 34 weeks 19.2% versus 34.4 % in controls receiving placebo,

(RR 0.54, 95% CI 0.36-0.86). Although these two studies didn't categorize women based on a history of preterm, these two studies cast light on the fact that multiple risk factors can be found in patients with preterm birth. Women with recurrent preterm births are also more likely to note symptoms of contractions in the late second trimester (43% compared with 19–22%, *P*=.001). In women with prior preterm births and a cervical lengths less than 25 mm at 22–24 weeks, 35% delivered before 37 weeks. If you add a positive fetal fibronectin (+ FFN), 60% delivered before 37 weeks and 50% delivered before 32 weeks. And finally, in one of the more publicized trials where high risk patients were given a daily supplementation with progesterone vaginal suppositories (100 mg) from 24 through 34 weeks of gestation, not only was the rate of delivery before 34 weeks significantly lower (3% versus 19%), there was a significant difference in spontaneous uterine contractions noted in monitoring by an external tocodynomanometer once a week for 60 minutes between the progesterone and control groups. In most of these studies, progesterone was continued until 36 weeks of gestation with early discontinuation of therapy leading to an increase in the risk of recurrent preterm birth

On the flip side, progesterone supplementation did not reduce the rate of preterm birth in multiple gestations randomly assigned to receive this therapy. In addition I do not feel that there is enough evidence that you can extrapolate the benefits found in singleton pregnancies complicated by acute preterm labor, a short cervix, or a history of preterm birth to patients with multiple gestations. In conclusion, I feel that in order for women with singleton pregnancies to benefit from progesterone therapy that the timing, duration, and dosage of *17 alpha-hydroxyprogesterone caproate* therapy should reflect that found in the clinical studies.

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