FEATURE

Effective Prevention of Preterm Birth

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Although many studies have shown a lack of effective strategies for the primary and secondary prevention of spontaneous preterm delivery (SPTD), there are several strategies that are effective. SPTD encompasses preterm labor and premature rupture of membranes, which account for about 70% of all preterm deliveries. George A. Macones, MD, of Washington University, St. Louis, Missouri, USA, discussed the data behind several strategies that are effective in the prevention of preterm birth.

In 2011, the percentage of live preterm births in the United States ranged from less than 10.7% to more than 12.2%, with the greatest rates occurring in the southern states. The national average of live preterm births peaked in 2006 at 12.8% and decreased to 11.7% in 2011. Prof. Macones noted that this recent decrease was likely a result of the efforts of the American College of Gynecology and the March of Dimes to reduce the number of late preterm births (34 to 37 weeks of gestation).

Preterm birth is associated with substantial morbidity, such as respiratory distress syndrome, necrotizing enterocolitis, chronic lung disease, retinopathy, and sepsis, as well as high rates of mortality. Worldwide, it is estimated that there are 15 million preterm births per year, with about 500,000 of those occurring in the United States. Importantly, the United States ranks number 6 in the rate of preterm birth—the only developed nation to make the top 10 list. Prof. Macones suggested visiting the March of Dimes web site as an excellent source for statistics about preterm birth, including state-specific information.

Clearly, the prevention of preterm birth is of utmost importance. In general, there are 3 levels in the prevention of disease: (1) primary, which occurs pre-disease; (2) secondary, which occurs in asymptomatic disease; and (3) tertiary, which occurs in symptomatic disease.

Multiple studies have evaluated the primary prevention of SPTD. Many have produced negative results, however, including the screening and treating of infections like bacterial vaginosis and periodontal disease. Furthermore, home uterine activity monitoring or bed rest has been shown not to be effective in the primary prevention of SPTD.

Another strategy is the use of 17-hydroxyprogesterone (OHP). In a multicenter, controlled trial, women with a previous SPTD at gestational age >20 weeks were randomly assigned to receive 17-OHP or placebo [Meis PJ et al. *N Engl J Med* 2003]. Patients who received 17-OHP were less likely to deliver preterm, but a greater number of women experienced miscarriage (Table 1). Originally, 17-OHP was available at compound pharmacies, but once a pharmaceutical company gained conditional approval by the U.S. Food and Drug Administration (FDA), the price greatly increased. The price has subsequently decreased in response to a backlash from the obstetric community.

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Table 1. Reduction of Preterm Birth With 17-OHP

Outcome	17-OHP (n=306)	Placebo (n=153)	Relative Risk (95% CI)
Delivery at <35 wk	36.3%	54.9%	0.66 (0.54 to 0.81)
Spontaneous delivery at <37 wk	29.4%	45.1%	0.65 (0.51 to 0.83)
Delivery at <35 wk	20.6%	30.7%	0.67 (0.48 to 0.93)
Delivery at <32 wk	11.4%	19.6%	0.58 (0.37 to 0.91)
Miscarriage at <20 wk	1.6%	0%	—

17-OHP=17-hydroxyprogesterone.

For secondary prevention, it is important to screen patients for SPTD. Although fetal fibronectin can be used to screen asymptomatic women, Prof. Macones advised against it because there is currently no therapy that can be offered to those patients who screen positive and are at a greater risk of experiencing SPTD. One effective method of secondary prevention is the midtrimester measurement

of cervical length in asymptomatic women. In a study of 755 women who received cervical-length measurement at 23 weeks, 98% reported that they thought it was worth it to discover their SPTD risk [Clement S et al. *Ultrasound Obstet Gynecol* 2003]. In a randomized, controlled trial, women who underwent cervical-length screening received either 200 mg of vaginal progesterone or placebo if their cervix was considered short at ≤15 mm [Fonseca EB et al. *N Engl J Med* 2007]. Out of more than 24,000 cervical-length assessments, 1.7% of women had a short cervix. Patients who received progesterone experienced a significant reduction in risk of SPTD at <34 weeks (adjusted relative risk, 0.56; 95% CI, 0.32 to 0.91; p=0.02), with a similar rate of fetal death as compared with placebo (Table 2). In another trial, women with a short cervix (10 to 20 mm) were randomly assigned to receive 90 mg of progesterone gel or placebo [Hassan SS et al. *Ultrasound Obstet Gynecol* 2011]. The risk reduction (RR) of primary SPTD at <33 weeks was 45%, and the secondary RR at <28 weeks and <35 weeks was 50% and 38%, respectively. As a result, there was a significant decrease in the risk of any neonatal morbidity or mortality event (p=0.04), as well as low birth weight (<1500 g; p=0.01) and respiratory distress syndrome (Table 3; p=0.03). Another study, however, found different results with the use of 17-OHP. In this study, there were similar rates of SPTD at <37 weeks and <32 weeks, with a higher rate of fetal loss in the 17-OHP arm (Table 4) [Grobman WA et al. *Am J Obstet Gynecol* 2012]. Prof. Macones highlighted that the different outcomes were because the progesterone, which was used in the positive trials, is not the same as 17-OHP, which was used in the negative trial. In addition to improving outcomes, cervical-length screening is cost effective [Werner EF et al. *Ultrasound Obstet Gynecol* 2011]. The use of universal cervical-length screening has resulted in a cost savings of $12 billion.

Table 2. Vaginal Progesterone Reduces the Risk of Spontaneous Preterm Delivery

Outcome	Progesterone	Placebo	Adjusted Relative Risk (95% CI)	p Value
Spontaneous delivery at <34 wk	19.2%	34.4%	0.56 (0.32 to 0.94)	0.02
Fetal death	0.7%	0.7%	—	—
Composite adverse outcomes	8.1%	13.8%	0.59 (0.23 to 1.31)	0.19

There are some opponents of cervical-length screening and treatment of at-risk women with progesterone gel, however. One reason is that the number of women who must be screened to prevent 1 SPTD is high, ranging from 400 to 588, with the number to treat ranging from 7 to 14 women [Hassan SS et al. *Ultrasound Obstet Gynecol* 2011; Fonseca EB et al. *N Engl J Med* 2007]. Another issue is *mission creep*, which suggests that because the need is so high, unnecessary interventions are performed. To prevent mission creep, Prof. Macones stated that it is important to make sure that women with a cervical length of less than 22 mm are not treated with the progesterone gel. In addition, some may argue that there is a lack of availability of screening.

Table 3. Effect of Progesterone Gel on Neonatal Outcomes

Outcome	Vaginal Progesterone	Placebo	Risk Reduction	p Value
Any neonatal morbidity or mortality event	7.7%	13.5%	43%	0.04
Respiratory distress syndrome	3.0%	7.6%	61%	0.03
Birth weight <1500 g	6.4%	13.6%	53%	0.01

Table 4. Effect of 17-OHP on Secondary Prevention of Spontaneous Preterm Delivery

Outcome	17-OHP	Placebo	Risk Reduction (95% CI)
PTD at <37 wk	25.1%	24.2%	1.03 (0.79 to 1.35)
Fetal loss	0.3%	0%	—
Delivery at <32 wk	8.6%	9.7%	0.88 (0.54 to 1.43)
Composite	7.0%	9.1%	0.77 (0.46 to 1.30)

17-OHP=17-hydroxyprogesterone; PTD=preterm delivery.

As a result of the data on cervical-length screening, the Society for Maternal-Fetal Medicine (SMFM) developed a clinical guideline for the use of progesterone in preterm birth prevention [SMFM. *Am J Obstet Gynecol* 2012]. These guidelines state that a 90 mg gel or 200 mg suppository of vaginal progesterone is associated with the reduction of SPTD and perinatal morbidity and mortality in women with singleton gestations and no prior SPTD who have a short cervix (≤20 mm) at ≤24 weeks. Prof. Macones agrees with the recommendation, but he pointed out that training and implementation are keys to a successful screening program.

For the primary prevention of SPTD, smoking cessation and the administration of 17-OHP appear to be effective strategies. For the secondary prevention of SPTD, the application of progesterone gel or suppository results in a substantial reduction in the risk of preterm birth, as well as perinatal morbidity and mortality.