



Grand Rounds: Can progesterone prevent preterm birth?

The research says that the drug can benefit women at risk, but how exactly should these data be applied in clinical practice? Two experts offer some valuable insights.

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No one has to remind ob/gyns that preterm birth (PTB) takes a heavy toll both medically and financially on the American public. Unfortunately, in recent decades clinicians have had little success in reining in this problem, which is no doubt why so much attention has been given to recent research on the preventative effects of 17-alpha-hydroxyprogesterone caproate (17P). But in order to achieve the most benefit from this therapy, several educational and logistical barriers need to be addressed, and both physicians and patients need to understand more about the appropriate use of the medication and compliance support with the therapy. With appropriate planning, overcoming these obstacles is possible within an organized education and support network.

Appreciating the scope of the problem

Preterm birth, birth prior to 37 completed weeks of pregnancy, complicates 12.3% of all births in the United States annually.¹ In 2002, that translated into an estimated 480,000 preterm infants. Although advances in neonatal care have improved survival for these newborns, the rate of prematurity has steadily increased over the past three decades.^{1,2} The incidence of delivery before 37 weeks' gestation increased from 9.4% of live births in 1981 to 11.0% in 1994 and 12.3% in 2004.^{1,2} These increases are attributed to increases in the multiple birth rate, although PTB is also increasing among singleton deliveries.¹ The rate of PTB in black women is nearly double the rate in white women.¹

National statistics indicate that PTB is the leading cause of perinatal mortality and morbidity in infants without birth defects. Prematurity causes an estimated 70% of all neonatal deaths of nonanomalous infants in the US.³ Mortality is directly correlated with gestational age at delivery. The mortality rate for infants born at less than 32 weeks is almost 70 times the rate of a term infant (2.6 per 1,000 live births).⁴ And for infants born less than 37 weeks it's 15 times the term infant rate.

Of course, morbidity is also a major concern, especially for infants born at less than 32 weeks' gestation. Complications include respiratory distress syndrome, intraventricular hemorrhage, sepsis, necrotizing enterocolitis, and cerebral palsy. Preterm infants are also at risk for associated medical conditions extending into childhood and adulthood. One prospective study found that 25% of very premature infants have significant long-term neuro-developmental impairments not improved by educational intervention.⁵ The extent of cognitive impairment extending into childhood for infants born at less than 26 weeks' gestation has been underestimated. New estimates suggest that 41% of these extremely preterm infants have serious cognitive deficits at 6 years of age.^{6,7}

In addition to the devastating toll on infant mortality and morbidity, prematurity exacts a heavy financial cost on the US health-care system. In 2001 alone, charges for hospital stays for infants with any diagnosis of prematurity were approximately \$13.6 billion or about 50% of all birth-related spending.⁸ Researchers have estimated that prematurity and low birthweight combined accounted for 35% of all direct infant care expenditures in the US.⁹ Aetna, a national health benefits company serving 13.7 million Americans and covering over 140,000 deliveries a year, estimates that the cost of care through the first year of life for infants born at less than 37 weeks' gestation is \$34,000 and for infants born at less than 32 weeks' gestation is \$119,000.¹⁰ This excludes the associated maternal care costs. By comparison, the average cost of care through the first year of life for a term birth is \$1,373. The financial cost of prematurity for the Medicaid population is no doubt greater because the proportion of births that are preterm is greater.

Understanding risk factors for spontaneous preterm birth

Preterm births are generally considered to be either "spontaneous" or "indicated." Spontaneous PTBs are initiated by spontaneous preterm labor with intact fetal membranes or preterm premature rupture of membranes (PPROM). Indicated PTBs result from either induction of labor or cesarean delivery without labor, most commonly in response to maternal complications of pregnancy such as hypertensive disorders or diabetes or fetal complications such as growth restriction or placental bleeding. Of all PTBs, about 20% are indicated while 80% are unanticipated or spontaneous.¹¹ As spontaneous and indicated PTB have different clinical presentations and probably different underlying causes as well, interventions to prevent one may not prevent the other.

While many demographic characteristics are associated with PTB, traditional risk scoring systems do not predict PTB very accurately.¹² In fact, over 50% of women who have a spontaneous PTB don't have any identifiable risk factors.¹³ The risk factor most consistently shown to predict PTB is history of a prior PTB. The estimated risk of having a subsequent PTB if a prior birth was preterm ranges from 15% to 80%, depending on the presence of other risk factors. The number of prior PTBs influences the risk of subsequent PTB. For example, women with one prior PTB are four times more likely to deliver another preterm infant and women with two prior PTBs have a sixfold increased risk of delivering preterm compared to multiparous women with no prior PTBs.¹⁴ For African-American women, a two- to fourfold increased risk results in rates of 35% to 70% of recurrent PTB.¹⁵

Additionally, the lower the gestational age of a prior spontaneous PTB, the greater the likelihood of subsequent PTB. For example, women who had a PTB at 23 to 27 weeks' gestation in the past had a 27.1% chance of delivering at less than 37 weeks in the current pregnancy. The corresponding probabilities when the prior delivery was at 28 to 34 weeks and 35 to 36 weeks were 24.0% and 20.9%. In comparison, women whose prior births occurred only at term had an 8.8% probability of delivering preterm in the current pregnancy.¹⁶

How do you prevent preterm births?

Efforts to avert a PTB can be categorized as primary, secondary, and tertiary prevention.¹⁷ Primary prevention aims to provide prenatal care to the general population with the goal of preventing disease. Secondary prevention provides health services to high-risk patients who have not yet presented with signs or symptoms—17P would fall into this category. Tertiary prevention offers health services to patients *after* a disease is diagnosed with the intended goal of avoiding complication of the disease. While tertiary interventions such as antepartum corticosteroid therapy, and maternal and neonatal transport are effective, others are less clearly beneficial. For example, antibiotics have been shown to have benefits in the setting of PPRM^{18,19} but not in women in preterm labor with intact membranes.²⁰ Tocolytics are effective at prolonging pregnancy for at least 48 hours, but their impact on neonatal morbidity and mortality appears minimal.¹⁷

There are few primary or secondary treatments known to be effective for PTB, but several that have proven disappointing, including the provision of enhanced prenatal care,^{21,22} psychosocial support,²³ nutritional supplementation,¹⁷ ambulatory tocodynamometry,²⁴ prophylactic bed rest in twin pregnancy,²⁵ and screening and treatment of genital tract infections in asymptomatic women.²⁶ Using 17P to reduce the risk of recurrent PTB, on the other hand, is the first approach to secondary prevention that has proven effective in a randomized placebo-controlled trial.

Reviewing the research on 17-alpha-hydroxyprogesterone

17P is a naturally occurring metabolite of progesterone. Both are produced in large amounts in human pregnancy; neither has androgenic activity. As long ago as 1964, progesterone's ability to prevent "prematurity" was described in several small clinical trials. A meta-analysis published in 1989 of 15 randomized controlled trials (RCTs) conducted between 1953 and 1985 involving 819 women treated with several different progestins found no significant reduction in the rate of PTB.²⁷ However, a subsequent meta-analysis of seven double-blind RCTs of women at high risk of PTB found a significant reduction in PTB in pregnancies that were treated specifically with 17P.²⁸

In 1998, the National Institute of Child Health and Human Development (NICHD), Maternal Fetal Medicine Units (MFMU) Network conducted an RCT to test the hypothesis that weekly intramuscular administration of 250 mg of 17P started at 15 to 20 completed weeks' gestation and continued through 36 completed weeks of pregnancy would reduce the risk of preterm birth in women who have previously experienced a spontaneous singleton preterm delivery.²⁹ Women eligible for the trial included those with a prior singleton spontaneous PTB between 20 and 37 weeks' gestation, singleton gestation in current pregnancy, and enrolled from 15 to 20 weeks of pregnancy. Women with anomalous fetuses, multiple gestations, planned or current cervical cerclage, and women on heparin or progesterone in the current pregnancy were excluded. There were 1,039 women eligible to participate in the trial, of whom 463 (44%) enrolled; 59% were African-American.

Women randomized to progesterone had a significantly lower rate of recurrent PTB at less than 37 weeks, less than 35 weeks, and less than 32 weeks of gestation than women treated with placebo (see Table 1). The benefit was seen for all racial groups. Additionally the infants of women treated with 17P had significantly fewer complications, including necrotizing enterocolitis, and the need for supplemental oxygen.

A sub-analysis of the NICHD data found that 17P prolonged pregnancy regardless of gestational age of the qualifying birth. The greatest benefit was seen in women with a prior spontaneous PTB at early gestational ages (less than 34 completed weeks).³⁰

	17P	Placebo	RR	CI
n	306	153		
Gestational age at delivery				
<37 weeks	30.3%	34.0%	0.88	0.74-1.05
<35 weeks	26.0%	30.7%	0.87	0.73-1.03
<32 weeks	18.4%	19.6%	0.98	0.77-1.24
BB < 2,500 g	27.2%	48.1%	0.66	0.51-0.87
BB < 1,500 g	0.6%	13.0%	0.62	0.39-1.01
Neonatal death	2.0%	5.0%	0.44	0.17-1.12
Neonatal morbidity	1.3%	5.2%	0.26	0.1-0.63
Intracranial hemorrhage	0	2.6%	NA	NA
Supplemental O₂	14.0%	23.8%	0.62	0.42-0.92
Respiratory distress syndrome	0.5%	15.1%	0.65	0.39-1.05

Table 1. Gestational age at delivery, fetal and neonatal outcome of women treated with either 17P or placebo in

Intramuscular progesterone was generally well-tolerated in the NICHD NICHD trial trial. Over 92% of women who started on the drug completed the trial. Although 50% reported some side effects, all were mild including local injection site reactions, soreness, swelling, or bruising. Adverse fetal effects did not differ significantly between 17P and placebo groups and no predominant defect was observed.

A second, smaller RCT by da Fonseca and associates in 2003 reported on the efficacy of progesterone vaginal suppositories in high-risk women treated between 24 and 34 weeks' gestation, and found that PTBs were significantly reduced, from 28.5% to 13.8% for births before 37 weeks, and from 18.6% to 2.8% for births before 34 weeks in the placebo versus the progesterone groups, respectively.³¹ This trial was complicated by a heterogeneous patient population (including women with a history of spontaneous prior PTB, uterine malformations, and prophylactic cervical cerclage placement in the current pregnancy); the relatively small number of participants (72 assigned to progesterone and 70 to placebo); and a relatively high rate of women who were lost to follow-up or dropped out of the study.

Applying the research 'in the trenches'

While the NICHD research represents a potential breakthrough, let's take a closer look at how it might apply in day-to-day practice. First, only 44% of eligible women consented to participate in the study. Those who did agree to enroll had a particularly high risk for recurrent PTB, as evidenced by the 55% rate of PTB in the placebo group. Although that rate is not surprising given their mean gestational age at first PTB (31 weeks) and the large percentage of enrollees with two or more prior PTBs (32%), these women may not have been representative of the population with prior PTB as a whole. Also bear in mind that the investigators did not have permission to collect information on those who declined to participate. [Paul Meis, personal communication January 4, 2005.]

Second, the rate of PTB in the intervention group was still high (36%), which means that 17P doesn't provide complete protection. Nonetheless, the authors estimated that in this very high-risk population, only 12 women with prior PTB would need to be treated to prevent one PTB at less than 32 weeks and 5 to 6 women treated to prevent one PTB at less than 37 weeks. A recent estimate of the impact of 17P on the national prematurity rate predicted that 10,000 PTBs could be prevented with a resultant decrease in the national prematurity rate by 2%.³² Although the reduction in the PTB rate is modest in absolute terms, the impact per case affected is significant.

Following publication of the NICHD trial, the ACOG Committee on Obstetric Practice published an opinion stating that 17P offers "apparent benefits in a high-risk population" and recommended that women who had had a previous preterm delivery be considered for treatment. But ACOG also said that the ideal formulation, optimal route of delivery, and long-term safety are still unknown.³³

What's the mechanism of action?

We still don't understand the mechanism of action by which 17P prevents PTB. It's possible that the drug works by relaxing uterine muscle; it may have anti-inflammatory effects; or it may affect the maternal-fetal pituitary/adrenal axis. Since the mechanism of action is not known, it is best to use only 17-alpha-hydroxyprogesterone, and to use it only in women for whom its benefit has been demonstrated (i.e., women with a prior spontaneous PTB).

17P has been studied in several animal species without evidence of teratogenicity. Likewise an extensive review of 17P in humans has failed to find teratogenic effects.³⁴ A meta-analysis of 186 articles by Raman-Wilms and colleagues showed no association between first-trimester exposure to sex hormones and genital malformations.³⁵ And studies with an average of 11.5 years of follow-up also found no anomalies.³⁶ The MFMU Network is currently conducting a follow-up study of the children born in the trial of 17P to prevent recurrent preterm delivery to evaluate their health status in the preschool years.

Is the drug being fully utilized?

Despite the encouraging news for recent RCTs, few ob/gyns seem to be using 17P. A survey of board-certified maternal-fetal medicine (MFM) specialists in the US conducted 6 months after the publication of the NICHD trial, for instance, found that only 38% of respondents were using the drug. Among those who were not, 25% said they were concerned with drug efficacy, 12% were concerned with safety, 12% were concerned with liability, and 81% were awaiting more data.³⁷ A follow-up survey of the SMFM membership to determine adoption trends is planned.

The limited use of 17P indicated in this survey has also been observed in broad practice settings. Aetna, for example, initiated coverage of 17P for this indication in November 2003, following the publication of the NICHD trial and the ACOG Committee Opinion. Aetna's data monitoring systems revealed, however, that fewer than one prescription per month for the medication was written for Aetna members in the subsequent 6 months.

A subsequent analysis was conducted by interviewing participating physicians, members of professional organizations, pharmacy partners, and others. In addition to those cited by the survey, other identified obstacles to expanded use included the lack of patient and physician awareness of the literature and eligibility criteria; lack of availability of a consistent and reliable supply of medication; lack of reimbursement by commercial health plans and Medicaid, and concern about patient adherence and support required for weekly injections.

Patient and provider education. Little patient and provider information has been disseminated on the potential value of 17P. A news release was published on the ACOG Web site in October 2003 describing the study findings.³⁴ Electronic searches of content in news media outlets also reveal relatively few "hits" when searched for key words progesterone, 17

progesterone, and preterm birth.³⁸ We don't fully understand why so little attention has been given to this subject but the barriers discussed further on in this article may be contributing factors.

Drug production and distribution. In the US, manufactured medications are regulated by the FDA in accordance with Good Manufacturing Practice (GMP) standards. By contrast, sterile compounded preparations like 17P (which are the combination of two or more finished dosage medications by a pharmacy rather than a manufacturer) are produced in accordance with requirements of the Federal Food, Drug and Cosmetic Act, not GMP standards. Oversight and regulation is the responsibility of State Boards of Pharmacy. Quality issues related to preparation, storage, and dispensing of compounded medications as a class are well-documented and have resulted in product recalls, patient injury, and even death.³⁹ A 2002 national survey by the American Society for Health-System Pharmacists indicated that few pharmacies are equipped with the controlled compounding environments needed for dispensing sterile preparations.

The survey also documented that many pharmacists are not performing critical quality assurance checks, such as end-product testing to ensure accuracy and consistency of product.⁴⁰ Efforts to improve the quality of pharmacy-prepared sterile preparations have been on-going. The first official and enforceable sterile preparation compounding requirements in the US, outlined in the US Pharmacopeias (USP) chapter 797, was made enforceable on January 1, 2004. The guidelines now set standards for sterile product compounding. The guidelines apply to all practice settings in which sterile preparations are compounded, including specialty pharmacies, hospitals, physician offices, or ambulatory care clinics.

The USP guidelines may be adopted and enforced by state boards of pharmacy and surveyable by accreditation organizations such as the Joint Commission Accreditation of Healthcare Organizations (JCAHO). Some states, such as Missouri, have now adopted standards that are more stringent than the USP. Some health plans, such as Aetna, require compounding pharmacies to comply with the new USP guidelines.

Pharmacies, unlike drug manufacturing organizations, are permitted to prepare a supply of compounded medications to meet the specific demands of their patients. They are prohibited from compounding a quantity that could be used by another pharmacy for their patients or for sale to physicians to dispense to their patients. Additionally, patient-specific compounded products prepared by a pharmacy may be shipped across state lines only if the pharmacy has an "out of state" license to sell pharmaceuticals in that state. At the present time, there are only a limited number of pharmacies that meet these requirements. (The drug is available from Freedom Drug, 12 Kent Way, Bayfield, MA 01922, Phone: 800- 660-4283.)

Reimbursement by commercial health plans and Medicaid. A few commercial health plans are providing coverage for 17P as well as the administration of the medication. Aetna, for example, initiated coverage for 17P shortly after the NICHD trial and the ACOG Committee Opinion were published. Government plans like Medicaid, however, generally do not cover the

medication for their insured members. One third of all live births in the US are reimbursed through Medicaid. This population probably has a higher rate of prematurity and extreme prematurity than the general population (due to the higher rate of risk factors for prematurity among Medicaid recipients including the African-American race, poverty, cigarette smoking, young maternal age, and unmarried status) and are likely to benefit the most from the medication. Although most Medicaid plans do not currently cover the cost of this therapy, the relatively low cost of approximately \$100 for an entire treatment course may prompt more plans to cover it in the future.

Patient adherence and challenge to self-administration. 17P is administered weekly as an IM injection. In the NICHD trial, patients generally made weekly clinic visits. A requirement for weekly visits may be a barrier to administration of treatment.

Liability issues. Some clinicians are not using 17P because they're concerned about liability. Although 60% of non-user MFM specialists in the above survey were "not or minimally concerned" with the 17P safety, 12% of non-users indicated liability concerns as a barrier to use.³⁷

ACOG has specifically advised "... further studies are needed to evaluate the use of progesterone in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length, or positive test results for cervicovaginal fetal fibronectin. When progesterone is used, it is important to restrict its use to only women with a documented history of a previous spontaneous birth at less than 37 weeks' gestation because unresolved issues remain, such as optimal route of drug delivery and long-term safety of the drug..."³³ Despite this recommendation, the survey indicated 20% of current 17P prescribers said they use 17P for indications not described in the NICHD trial, including women with a short cervix or symptomatic women. Conversely, there may also be a liability concern associated with *not* offering 17P to eligible women.

The hassle factor. When you combine the lack of information and education about the research findings with an uncertain or inconsistent supply of medication, lack of coverage or inconsistency of coverage by private and public payers, the logistics of administering the medication, and the compliance factor, it's understandable that many physicians don't want to deal with the hassle. Unfortunately, these obstacles mean many eligible patients won't benefit from the drug.

A system-wide approach to overcoming obstacles

NIH and ACOG have the opportunity to educate caregivers and patients regarding the potential benefits of and indications for effective new treatments. They can work with industry to encourage the widespread availability of an adequate supply of medication, and can support the needed long-term evaluations of safety and efficacy of such treatments.

Health-care organizations also have an opportunity to take an active role in promoting effective treatment for appropriate candidates. Aetna, for example, through a dedicated Women's Health unit, has developed a comprehensive initiative to: (1) increase member and physician awareness of the published literature and potential value of the therapy; (2) ensure access to a reliable and consistent supply of the medication for Aetna members; and (3) develop a case management program for women eligible for 17P therapy in accordance with the NICHD evidence. The insurer's experience in implementing this program may be useful for other companies contemplating this issue.

As a first step, Aetna surveyed compounding pharmacies within its pharmacy network to identify one that documented compliance with the USP guidelines and worked with that vendor to ensure that members who needed it would have an adequate supply of 17P. They also developed a tracking mechanism to monitor progesterone usage. A comprehensive educational outreach program was then developed for obstetrical care providers and neonatologists, to educate them about the research findings, indications for 17P therapy, and the process to obtain the medication.

Women who elect 17P are offered a single home nurse visit to teach the woman or a family member how to administer the medication. Additionally, women are offered compliance support services by obstetrical case managers throughout their pregnancies. Case management also includes the coordination of services for preterm labor education or specialty care. Through May 2005, 82 of 263 identified eligible women received 17P through this Aetna program. The most common reason for not using 17P was uncertainty by physicians and their patients about the indications for and availability of the drug.

While enrollment in the Aetna program is too small to draw statistically significant conclusions, the anecdotal information is instructive. To date, patient and physician feedback has been overwhelmingly positive. Preliminary experience with this program indicates that physicians and patients generally have been unaware of the literature, potential benefits, and eligibility criteria, and are uncertain about how to obtain the medication. In addition, physicians have used 17P in ways not supported by the literature—including as treatment for active preterm labor, or for multiple gestations, history of spontaneous abortions without prior PTBs, or uterine abnormalities.

Most members participating in this program have been able to administer the medication at home with the assistance of a family member and the aid of a single home nurse visit. It may be more difficult, however, for women with less support, such as young Medicaid patients, to self-administer medication, although this has not been formally evaluated.

Despite these positive developments, we remain uncertain about a number of issues. The NICHD trial didn't include women with multifetal gestation, short cervical length, and other women at known risk for PTB, so 17P is not currently recommended for them. A NICHD trial evaluating the drug in multifetal pregnancy is ongoing. It is also not known whether other progestins or less invasive forms of administration of the drug are equally effective.

We now know that 17P can prevent a significant number of PTBs in women who have had a prior spontaneous PTB. While promising, much is still unanswered about the mechanism of action and other population groups that may benefit. With these data in hand, it's important for physicians to be educated about the appropriate applications of the medication and it's important that they discuss it with women who may benefit. Of course, clinicians need to exercise caution in clinical settings not covered by the research. And finally, access to the medication and coordination of services necessary to support compliance is essential to overcoming the logistical barriers to its use. With appropriate planning, such obstacles can often be overcome.

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TABLE 1

Gestational age at delivery, fetal and neonatal outcome of women treated with either 17P or placebo in NICHD trial

	17P	Placebo	RR	CL
N	306	153		
Gestational age at delivery				
<37 weeks	36.3%	54.9%	0.66	0.54–0.81
<35 weeks	20.6%	30.7%	0.67	0.48–0.93
<32 weeks	11.4%	19.6%	0.58	0.37–0.91
BW < 2,500 g	27.2%	41.1%	0.66	0.51–0.87
BW < 1,500 g	8.6%	13.9%	0.62	0.36–1.07
Neonatal death	2.6%	5.9%	0.44	0.17–1.13
Necrotizing enterocolitis	1.3%	5.2%	0.25	0.8–0.82
Intraventricular hemorrhage	0	2.6%	NA	NA
Supplemental O ₂	14.9%	23.8%	0.62	0.42–0.92
Respiratory distress syndrome	9.5%	15.1%	0.63	0.38–1.05