Clinical, Family, and Cost Outcomes of Preterm Births: An Overview of the Problem and Prevention Opportunities

Joanne Armstrong, MD, MPH, and Paul J. Meis, MD

Abstract

- **Objective:** To describe the impact of preterm birth on morbidity and mortality rates and costs to society as well as to review prevention strategies, specifically focusing on the use of 17α-hydroxyprogesterone caproate (17P).
- **Methods:** Review of the literature.
- **Main results:** Preterm birth is the leading cause of infant death and pediatric neurodevelopmental disability in the United States and an important cause of chronic illness in children. The incidence of preterm birth has been slowly rising despite advances in obstetric health care. Preterm birth exacts an enormous societal economic toll, estimated at $26.2 billion in 2005 or $51,600 per preterm infant. A woman who has a spontaneous preterm birth is at high risk for a subsequent preterm birth. Recent trials have confirmed the use of progesterone beginning in the second trimester as an effective intervention.
- **Conclusion:** Effective interventions to prevent preterm birth remain elusive. Use of 17P has shown efficacy for reducing the risk of a recurrent preterm delivery.

Preterm birth is defined as a live birth before 37 completed weeks of gestation. Compared with other developed countries, the rate of preterm birth in the United States is high, and the rate has been increasing steadily over the past 2 decades. In 2004, over 500,000 births, or 12.5% of all births in the United States, were delivered prior to term, representing an increase of more than 30% since the government began tracking preterm births in 1981 [1]. Compared with singleton births, twin and triplet births in the United States are approximately 6 times and 9 times more likely to be preterm, respectively [1].

Preterm birth demonstrates a marked racial disparity. The rate of preterm birth for black infants in the United States is 17.6% compared with 10.7% for white infants. However, the rate of preterm birth for white infants in the United States remains high compared with rates of 6% to 8% in most European countries [2].

**Medical Consequences of Preterm Birth**

Preterm birth is the leading cause of infant death in the United States, and mortality is directly correlated with gestational age [3]. Infants born at less than 37 weeks’ gestation and less than 35 weeks’ gestation are 15 times and 70 times more likely to die compared with an infant born at term [4]. Advances in neonatal intensive care have greatly improved the survival rates for very preterm infants but have been accompanied by an increase in medical complications, many occurring later in the neonatal period than previously experienced. In a cohort of extremely premature infants born in 1995 at 20 to 25 weeks of gestation, 39% of infants survived. Among nonsurvivors, many deaths occurred as late as 100 days of hospitalization [5].

Medical complications associated with preterm birth include respiratory distress syndrome, chronic lung disease, injury to the intestines, immune system compromise, cardiovascular disorders, hearing and vision problems, and neurologic injury including cerebral palsy. As with neonatal mortality, morbidity associated with prematurity is gestational age–dependent. Among survivors born at less than 25 weeks’ gestation, rates of severe, moderate, and mild disability at age 6 years are 22%, 24%, and 34%, respectively [6]. Near-term infants (born 35–36 6/7 weeks of gestation) experience greater rates of mild complications (eg, temperature instability, hypoglycemia, respiratory distress, jaundice) compared with full-term infants [7].

Prematurity-associated medical complications experienced in the neonatal period may herald health, educational, and occupational impairments that extend beyond infancy into childhood and adulthood. In a long-term follow-up

From Aetna and the Department of Obstetrics and Gynecology, Baylor College of Medicine, Sugar Land, TX (Dr. Armstrong); and the Department of Obstetrics and Gynecology, Wake Forest University School of Medicine, Winston-Salem, NC (Dr. Meis).
study of very low-birth weight (VLBW) infants (< 1500 g) who were born between 1977 and 1979, the survival at 1 year of age was 64% [8]. At age 9, 10% of the children demonstrated a major neurologic abnormality and 21% had a low IQ (compared with 16% of controls of normal birth weight). These impairments were reflected in lower academic achievement in reading, math, and spelling skills [8]. The same cohort of VLBW young adults was assessed again at age 20 years [9]. Fewer VLBW young adults had graduated from high school (74% vs. 83%), and mean IQ scores and academic achievement was lower as compared with young adults of normal birth weight [9,10].

**Societal Costs of Prematurity**

A number of investigators have examined the impact of a preterm baby on family stress. Singer et al [11] evaluated psychologic distress for 3 years after childbirth in 3 groups of mothers of infants who weighed less than 1500 g: (1) mothers of preterm infants defined as high risk due to the diagnosis of bronchopulmonary dysplasia; (2) mothers of preterm infants defined as low risk due to the absence of the diagnosis of bronchopulmonary dysplasia; and (3) mothers of babies born at term. At age 1 month, mothers of both high-risk and low-risk preterm infants experienced more psychologic distress than mothers of term infants. At age 2 years, psychologic distress of mothers of low-risk preterm infants did not differ from the mothers of term infants, whereas mothers of high-risk preterm infants continued to experience more psychologic distress. At age 3 years, the 3 groups of mothers did not differ in regard to levels of psychologic distress, but mothers of high-risk preterm infants described more parenting stress than either of the other 2 groups. In mothers of both high-risk and low-risk preterm infants, the severity of maternal depression was related to lower child developmental scores [11].

The effects of preterm birth on the families of school-age children was examined in a study by Taylor et al [12], which evaluated psychologic stress among families of infants born at less than 750 g, 750 to 1499 g, and infants weighing more than 2500 g (full term). Families of infants born at less than 750 g experienced more stress than families of term-born infants. Families of infants born at less than 1500 g who were sociodemographically advantaged experienced more stress than families of infants weighing less than 1500 g who were sociodemographically disadvantaged. Higher neonatal medical risk negatively impacted the family but only in sociodemographically advantaged families.

In a survey of parents of children aged 12 to 16 years who had birth weights of less than 1000 g, Saigal et al [13] found that the child’s health status had an impact on parents’ emotional health and had other negative impacts on the family, such as stresses and strains on the marriage and negative effects on other siblings. In some cases, the child’s health status brought the couple closer together, but in others it was a major factor in separation and divorce.

**Financial Cost of Prematurity**

Preterm birth exacts an enormous financial toll. The Institute of Medicine (IOM) recently completed a comprehensive analysis of the cost of prematurity [14], which estimated that the societal economic burden associated with preterm birth in the United States in 2005 was at least $26.2 billion, or $51,600 per preterm infant. This estimate greatly exceeded prior cost estimates because it included costs beyond the short-term direct medical costs of neonatal and maternity care upon which prior estimates were established. The IOM estimates included longer-term direct medical costs, indirect medical costs (eg, disability care), and nonmedical costs (eg, educational interventions, lost individual and family productivity). Although direct medical costs for care of the infant account for two thirds of the total economic burden of premature birth, significant additional costs include direct maternal medical care costs ($1.19 billion or $3800/ preterm infant), early intervention costs ($611 million or $1203/preterm infant), educational interventions costs ($1.09 billion or $2150/preterm infant), and lost household productivity ($5.7 billion or $11,214/preterm birth). At a minimum, preterm birth and low birth weight infants accounted for approximately 35% of all infant care spending in the United States [15].

Not surprisingly, the per-case cost of preterm birth is correlated with gestational age at birth. The IOM estimated that the average total medical care cost through age 6 years per infant born at less than 28 weeks, 28 to 31 weeks, 32 to 36 weeks, and more than 37 weeks of gestation is approximately $198,000, $101,000, $41,000, and $3300, respectively [14]. The per-case cost of preterm birth is greatest at the earliest gestational ages; however, most preterm births occur near term (32–36 completed weeks) and the resulting aggregated costs are comparable with the aggregated costs for infants born between 28 and 32 weeks of gestation and those born at less than 26 weeks of gestation weeks ($4.9 billion, $5.1 billion, and $6.1 billion, respectively). Thus, preterm birth prevention strategies targeted at a wide range of gestational ages, including near-term births, have the potential to improve infant health in the United States as well as achieve substantial medical cost savings [16,17].

**Risk Factors for Spontaneous Preterm Birth**

Preterm births can be classified by their apparent etiology as either spontaneous or indicated. Spontaneous preterm births represent approximately 80% of all preterm births and are initiated either by spontaneous labor or preterm premature rupture of membranes (PPROM) [18]. Based on common risk factors for their occurrence, it may be appropriate to consider...
births due to spontaneous preterm labor and PPROM as a single entity and likely caused by similar pathogeneses. Indicated preterm births represent approximately 20% of all preterm births and result from induction of labor or Caesarean delivery without labor, most commonly in response to maternal or fetal complications of the pregnancy. As spontaneous and indicated preterm birth have different clinical presentations and underlying causes, interventions to prevent one may not effectively prevent the other.

Attempts to predict preterm birth with the assistance of risk scoring systems have not been successful [19]. Several risk factors for preterm birth have been described (eg, prior preterm delivery, short cervical length, black race, extremes of maternal age, cigarette smoking, low maternal weight); however, more than 50% of women who have a spontaneous preterm delivery do not have any identifiable risk factors [20]. Among women with risk factors for preterm birth, a history of a preterm delivery is the risk factor most consistently shown to predict recurrent preterm birth. Women with a prior preterm delivery have a 15% to 80% likelihood of recurrence. Likelihood of recurrence increases with the number of prior preterm deliveries. Compared with multiparous women with no prior preterm deliveries, women with 1 prior preterm delivery have an estimated fourfold increased risk of recurrent preterm birth, and women with 2 prior preterm deliveries have a sixfold increased risk of recurrent preterm birth [21].

For African-American women, a two- to fourfold increased risk results in rates of recurrent preterm birth of 35% to 70%, respectively [22]. In addition, the lower the gestational age of an infant born via prior spontaneous preterm delivery, the greater the likelihood of subsequent preterm birth.

**Prevention of Preterm Delivery**

Many attempts have been made to find ways to reduce the incidence of preterm birth. Beginning in the 1970s, drug therapy for the prevention of preterm delivery became widely used and focused mainly on the use of tocolytic drugs to halt preterm labor. Although tocolytic drugs have been effective in halting labor for up to several days, their use has not reduced the incidence of preterm delivery or resulted in improvements in perinatal outcome [23].

Cervical cerclage has long been employed in women thought to have a weakness of cervical integrity, but randomized trials of cervical cerclage have generally not demonstrated its effectiveness for preventing preterm delivery [24]. Although vaginal infections are known to be associated with an increased risk of preterm delivery, large controlled trials in low-risk women found no improvement in rates of preterm birth as a result of screening for and treating vaginal infections [25,26]. Despite many trials of reduced physical activity, the use of tocolytic drugs to halt labor, antibiotic therapy, and other strategies for prevention, no effective and reproducible method of preventing preterm birth has been discovered [27]. Thus, the enigma of preterm birth is widely considered to be the greatest problem in obstetrics in the developed world.

**Progesterone Therapy**

The use of progesterone to prevent preterm delivery is not new. A randomized trial of progesterone by Papiernik [28] in 1970 demonstrated that progesterone therapy was effective for preventing preterm delivery. Several small trials of progesterone therapy were conducted over the next 2 decades [29]. Recently, interest in this therapy has been reinvigorated as evidenced by the recent publication of 5 review articles and an American College of Obstetricians and Gynecologists (ACOG) committee opinion [30–35]. The origin of this new enthusiasm and interest in progesterone was sparked by 2 randomized trials, one using progesterone vaginal suppositories and the other using 17α-hydroxyprogesterone caproate (17P) injections to prevent recurrent preterm delivery [36,37].

In 2003, da Fonseca and colleagues [36] reported the results of randomized, placebo-controlled trials of vaginal progesterone suppositories in 142 women considered at high risk for preterm birth. In over 90% of patients, the risk factor was a previous preterm delivery. Patients were randomly assigned to a daily 100-mg progesterone suppository or a placebo suppository. The treatment period was 24 to 34 weeks of gestation. Several patients were excluded from analysis because of PPROM or were lost to follow-up, leaving 72 progesterone-treated and 70 placebo-treated patients. The rate of preterm delivery at less than 37 weeks in progesterone-treated patients was 13.8%, significantly less than the rate of 28.5% observed in placebo-treated patients. The rate of preterm delivery at less than 34 weeks of gestation in the progesterone group was 2.8% compared with 18.6% in the placebo group. These differences were statistically significant. Intention-to-treat analysis showed smaller differences between the groups, but these differences remained statistically significant.

Meis et al [37] reported the results of a large multicenter trial of 17P conducted by the Maternal Fetal Medicine Units Network of the National Institute of Child Health and Human Development. The study enrolled women with a documented history of a previous spontaneous preterm delivery, which occurred as a consequence of either spontaneous preterm labor or PPROM. Participants were randomly assigned to weekly injections of 250 mg 17P or placebo administered between 16 and 20 weeks of gestation, which was continued until delivery or 37 weeks of gestation, whichever came first. Enrollment was halted early with 463 patients enrolled after the data safety and monitoring committee found evidence of efficacy for the primary outcome. In this study, delivery at less than 37 weeks’ gestation was reduced from 54.9% in the placebo group to 36.3% in the 17P
group. Similar reductions were seen in delivery at less than 35 weeks of gestation (from 30.7% to 20.6%) and in delivery at less than 32 weeks of gestation (from 19.6% to 11.4%). All of these differences were statistically significant. Rates of birth weight less than 2500 g, neonatal complications of intraventricular hemorrhage, necrotizing enterocolitis, and need for supplemental oxygen and ventilatory support were significantly reduced. Rates of neonatal death were reduced from 59% in the placebo group to 2.6% in the 17P group, although this difference was not statistically significant. Women enrolled in this study had unusually high rates of preterm birth, which could be explained in part by the fact that the mean gestational age of their previous preterm delivery was early (31 weeks). In addition, one third of the women had more than 1 previous spontaneous preterm delivery. A majority of the women were black, but treatment with 17P showed equal efficacy in black women and in nonblack patients.

In 2003, the ACOG committee opinion on use of progesterone to reduce preterm birth recognized the benefit of progesterone demonstrated in the 2 trials for women with a prior spontaneous preterm delivery [35]. However, the opinion cautioned that progesterone should not be recommended for women with other high-risk conditions (eg, twin gestation, shortened cervix) outside of randomized trials. Although women enrolled in the Meis et al [37] study initiated 17P between 16 and 20 weeks of gestation, 1 trial has demonstrated efficacy up to 26.9 weeks of gestation [38]. These results require confirmation and until such efficacy data are available, therapy should be initiated as close to 15 weeks’ gestation as possible.

In a 2005 meta-analysis of 10 trials (including the 2 recent trials) of progesterational agents to prevent preterm births, Sanchez-Ramos et al [34] found that women who received progesterational agents had a 55% lower rate of preterm delivery compared with women randomized to placebo (26.2% vs. 35.9%; odds ratio, 0.45 [95% confidence interval, 0.25–0.80]). The difference in rates of perinatal mortality in progesterone-treated patients compared with placebo-treated patients was not statistically significant.

Although 17P has shown efficacy for reducing the rate of recurrent preterm delivery for women at risk due to a prior preterm delivery, the usefulness of progesterone for women with other high-risk problems is unproven. A Maternal Fetal Medicine Units Network trial of 17P in 655 women with twin gestation found no benefit [39]; the results of this trial confirmed results from an earlier Finnish trial by Hartikainen-Sorri and colleagues [40].

The efficacy of vaginal progesterone treatment is uncertain. Although the study by da Fonseca et al [36] showed efficacy, a subsequent trial of vaginal progesterone gel in 611 women with a prior preterm delivery at less than 35 weeks demonstrated no difference in rates of preterm delivery between the treatment and placebo groups [41].

Safety of 17P

The safety of 17P administered in human and nonhuman pregnancy has been well studied. Among well-controlled studies examining the safety of 17P in human pregnancy, none has demonstrated any adverse effect on the outcome of the pregnancy, the fetus, or the newborn, including increased perinatal mortality, congenital anomalies, or cognitive impairments [42–49]. In one of the largest studies, Ressegue et al [44] examined 24,000 deliveries in Olmstead County, Minnesota (1936–1974), and found that 649 offspring exposed to 17P showed no increase in congenital anomalies or other ill effects compared with matched controls. A notable feature of this study was the long period of follow-up of the children (mean, 11.5 years) [44]. Providing further support to these findings, a study by Northen [49] that evaluated 278 children (age, 4 years) who were exposed to 17P in utero found no significant differences in health status, physical examination findings, including genital anomalies, or developmental assessment in children exposed to 17P in utero versus children exposed to placebo.

Societal and Medical Cost Reductions with 17P

An analysis by Petrini and colleagues [50] estimated that if all eligible women in the United States were treated with 17P, approximately 10,000 spontaneous preterm births would be prevented annually, thereby reducing the overall preterm birth rate by approximately 2% (from 12.1% to 11.8%). Although the absolute rate reduction of preterm birth may be modest, the medical impact per case prevented is significant, and the potential medical cost savings associated with 17P is large. A recent analysis that combined data from 6 studies evaluating the costs of preterm births and 7 evaluating the effectiveness of 17P estimated that the initial neonatal hospital costs could be reduced by $3800 per woman treated and could lead to a reduction in lifetime medical costs of $15,900 per child [17]. Furthermore, it is estimated that if all pregnant women eligible for 17P were universally treated, discounted lifetime medical costs of their offspring could be reduced by more than $2 billion annually [17]. These estimates likely underestimate the potential economic benefit of 17P because prematurity-associated medical costs employed in the estimates excluded some categories of direct medical costs (eg, outpatient infant care), indirect medical costs (eg, disability care), and nonmedical costs (eg, educational interventions) [51]. Similarly, a recent cost-effectiveness analysis found that 17P was associated with cost savings when used to prevent preterm birth in women with prior preterm deliveries less than 32 weeks and 32 to 37 weeks [52].
Barriers to Use
A 2003 survey of board-certified U.S. perinatologists found that 38% of respondents used 17P for the prevention of preterm birth [53]. A repeat of this survey in 2005 found that 67% of respondents reported using 17P in practice [54]. Among respondents who reported using 17P, 41% said the most frequent indication for use was a prior spontaneous preterm birth at less than 34 weeks. Sixty-three percent of respondents who used 17P reported using it for the indication of a prior spontaneous preterm birth at less than 37 weeks, with the remaining respondents reporting nonevidence-based use of the medication [54]. Given the number of preterm births between 34 and 37 weeks of gestation and the associated morbidity and cost of preterm births in this gestational age-group, further understanding of nonuse of 17P is warranted. The survey indicated that approximately 50% of patients offered 17P by their physician declined its use [54]; the most commonly cited reason is lack of insurance coverage. Indeed, about one third of physicians who reported using the medication noted the lack of coverage for 17P by insurance companies as the most concerning barrier to its use. Although many commercial insurance companies include 17P as a covered benefit, Medicaid rarely does. Only a few states (e.g., North Carolina) cover the medication. This is a significant lost opportunity because approximately one third of all live births in the United States are reimbursed through Medicaid [55]. Compared with the general population, the population insured by Medicaid likely has a higher rate of prematurity and extreme prematurity due to the higher rate of risk factors for prematurity (e.g., black race, poverty, cigarette smoking, young maternal age, unmarried status) and may therefore experience the greatest positive impact from the medication. Recent data describing the cost-effectiveness of 17P [17,52] may influence other payers, including Medicaid, to expand access to the medication.

Even when insurance reimbursement is available for 17P, access to a reliable supply of the drug may be limited. Compounded drugs are created by the combination of 2 or more finished dosage medications by a pharmacy rather than a manufacturer. The local production and oversight of compounded drugs may limit their access as compared with U.S. Food and Drug Administration (FDA)–approved manufactured drugs. Additionally, the quality and consistency of compounded medications may be uneven. Indeed, in the Meis et al [37] study, the pharmaceutical company that supplied the study drug was forced to recall it due to poor quality control. (The trial was started anew with a new drug manufacturer.) In January 2007, the FDA granted orphan drug status for 17P for the prevention of preterm birth in women with a history of preterm delivery [56]. Full FDA review of 17P is underway. If approved, access and consistency of the product will likely be improved, but the cost of 17P will likely increase. Currently, in its compounded form, the cost of 17P throughout pregnancy is less than $200. Available cost-benefit analyses are based on the current cost and would need to be recalculated if the cost of the drug increased significantly.

Another barrier to the use of 17P is the lingering safety concerns and the potential legal issues surrounding the use of a non-FDA-approved drug in early pregnancy [53]. Full FDA approval probably would allay these concerns. These concerns underscore the importance of only using 17P in clinical settings where effectiveness has been demonstrated. It is of concern that 1 physician survey found that 39% of respondents reported using 17P in pregnant women with risk factors other than a prior spontaneous preterm birth [54]. Although safety data are reassuring, this nonevidenced use of 17P may reflect the relative paucity of alternative effective therapies for high-risk individuals. A trial sponsored by the National Institute of Child Health and Human Development is underway to evaluate the impact of 17P on the prevention of preterm birth in nulliparous women with a shortened cervix in the second trimester of pregnancy.

Summary
There are few treatments known to be effective for preventing preterm birth. Randomized, placebo-controlled trials have demonstrated that 17P can be used to reduce the risk of recurrent preterm birth in patients with approved risk factors. Modeled data suggest that universal use of 17P in eligible women would result in a modest reduction in the overall rate of preterm births as well as significant medical cost savings of up to $2 billion annually. On a per-case basis, the prevention of preterm birth would result in the avoidance of significant medical and social costs. Continued work to understand the mechanism of action of prematurity and of 17P will expand the scientific knowledge base. The existing science is helpful to guide policy and practice decisions today.

Corresponding author: Joanne Armstrong, MD, MPH, One Prudential Cir, Sugar Land, TX 77478, Armstrongmj@aetna.com. Author contributions: conception and design, JA, PJM; analysis and interpretation of data, JA, PJM; drafting of the article, JA, PJM; critical revision of the article, JA, PJM.

References
3. Callaghan WM, MacDorman MF, Rasmussen SA, et al. The contribution of preterm birth to infant mortality rates in the
20:249–52.


Copyright 2007 by Turner White Communications Inc., Wayne, PA. All rights reserved.