Preventing Preterm Birth

The Role of 17α Hydroxyprogesterone Caproate

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Compiled in January 2009

Dear Member,

On behalf of the American College of Obstetricians and Gynecologists, District II (ACOG), we are pleased to provide you with *Preventing Preterm Birth*, a resource guide offering relevant physician education regarding preterm birth. The guide's first chapter, *The Role of 17a Hydroxyprogesterone Caproate*, provides the following:

- A Review of Relevant Clinical Trials and Research
- ACOG Guidelines
- A Protocol Outline for In-Office Use
- Case Vignettes

After reading this chapter, please complete the evaluation on page 29 to help ACOG assess the effectiveness of this educational piece.

New York's preterm birth rate is nearly 60% higher than the Healthy People 2010 goal of 7.6% and increased by 13% between 1995 and 2005.[1] This consistent increase in preterm birth in New York State underscores an urgent need for comprehensive, sustained provider education regarding these alarming rates and the opportunity 17P offers to prevent prematurity. ACOG District II partnered with the March of Dimes in 2006 to survey New York obstetricians on their use of 17P. Survey results show only 25% offer, recommend or refer patients for 17P in accordance with ACOG guidelines. Due to these findings, the goal of this chapter is to provide physician education regarding preterm birth incidence and complications, the mechanism of progesterone action and the appropriate use of 17P.

We would like to extend our appreciation to the task force of medical experts who offered their expertise throughout the creation of this chapter. Their knowledge and dedication were invaluable.

If you have any questions regarding the chapter or ACOG's initiatives, please contact the ACOG District II office at: info@ny.acog.org or (518) 436-3461.

Sincerely,

Scott D. Hayworth, MD, FACOG
Chair, ACOG District II

Peter Bernstein, MD, MPH, FACOG
Chair, 17P Task Force

[1]March of Dimes. 2008 Premature Birth Report Card, www.marchofdimes.com.

Introduction

Project Overview

With one in eight babies born preterm in the United States, prematurity continues to be one of the leading obstetric challenges facing our country.[2] Despite medical advances in obstetric care, such as the emergence of 17P, New York's prematurity rate has risen by over 10% since 1995.[3]

Due to startling survey results in 2006 showing only 25% of responding District II obstetricians offer, recommend or refer patients for 17P in accordance with ACOG guidelines, ACOG District II launched a prematurity initiative to address these identified educational needs.

The goal of this initiative is to provide multi-media physician education regarding the scope of preterm birth, the mechanism of 17P action and its appropriate use for preterm birth prevention. In 2008, the 17P task force of nationally recognized experts utilized District II's survey results to develop and deliver grand rounds education to hospitals across New York State. To compliment this activity, the task force assembled this comprehensive 17P chapter. While evaluation is ongoing, preliminary initiative results have been favorable.

Although this 17P chapter provides up-to-date medical information, it is also important for individuals to remain current with the continuous advances in 17P and preterm birth.

[2] March of Dimes. Quick Facts. Peristats. 2005.

[3] March of Dimes. 2008 Premature Birth Report Card, www.marchofdimes.com.

17P Overview

This 17P chapter contains information regarding the mechanisms for progesterone action, clinical trials and research and a review of current guidelines. Practical advice for addressing barriers to care and implementing an office protocol are also offered. Additionally, case vignettes are provided to highlight teaching points and clinician resources help solidify the education.

Table of Contents

The rate of preterm birth in the United States has been rising over the last 15 years.

I. Background

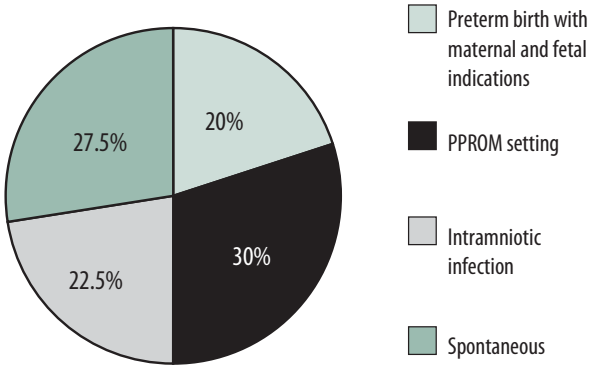
Definitions:

Preterm Birth- A live birth before 37 completed weeks gestation. Further definition includes late preterm (34-36 weeks), moderately preterm (32-36 weeks) and very preterm (<32 weeks).

Spontaneous Preterm Birth- Unintentional, unplanned labor before 37 completed weeks gestation. While the cause of spontaneous preterm birth is unknown, a history of spontaneous preterm birth is one of the strongest predictors for a preterm birth in a subsequent pregnancy.

Medically Indicated Preterm Birth- Intentional delivery due to a serious medical condition before 37 completed weeks gestation.

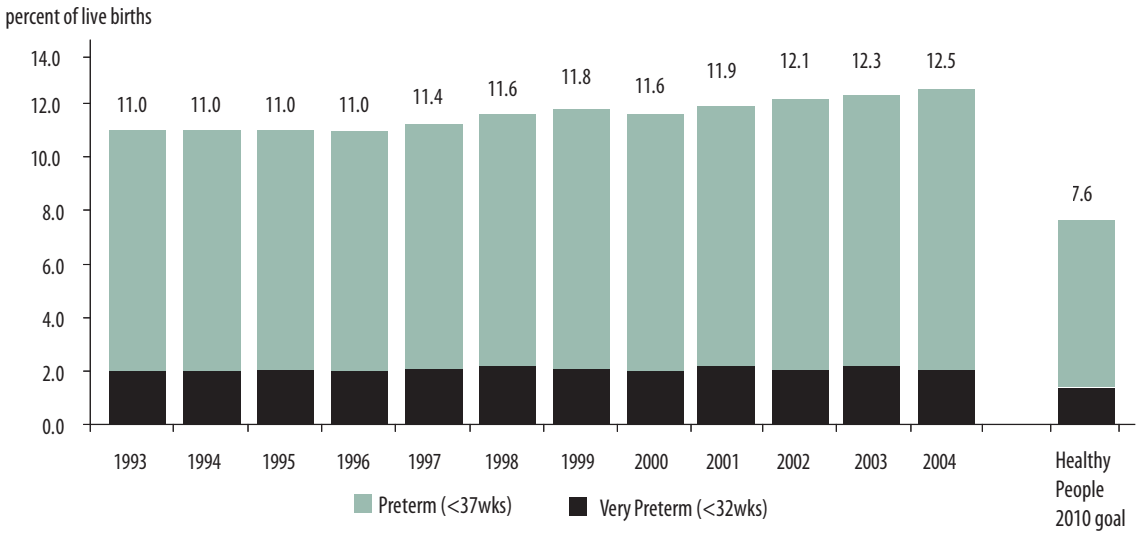
Preterm Birth in the United States



Arias, Pediatrics 2003

The rate of preterm birth in the United States has been rising over the last 15 years. Nationally, preterm birth affects 12% of all babies delivered in the United States or approximately 480,000 births. In the last decade, preterm birth has increased by 27% in the United States and accounts for 85% of all perinatal morbidity and mortality. Preterm birth is the leading cause of perinatal mortality among African Americans and the second leading cause among the overall American population. Examples of women at greatest risk for preterm birth include a history of preterm delivery, maternal weight less than 50 kilograms, African American race, bleeding, sexually transmitted infection during the pregnancy and multiple gestation.

Preterm and Very Preterm Births, United States, 1993-2004



National Center for Health Statistics, final natality data
Prepared by March of Dimes Perinatal Data Center, 2008

Cost of Preterm Birth

In 2005, the annual societal economic cost (medical, educational, and lost productivity) associated with preterm birth in the United States was at least $26.2[4] billion. There are many reasons to prevent preterm birth. Besides the burden on individuals and families from the morbidity and mortality related to this condition, there is also a societal cost. Reducing preterm birth could save numerous healthcare dollars, reduce education and health care budget strains and increase our society's productivity.

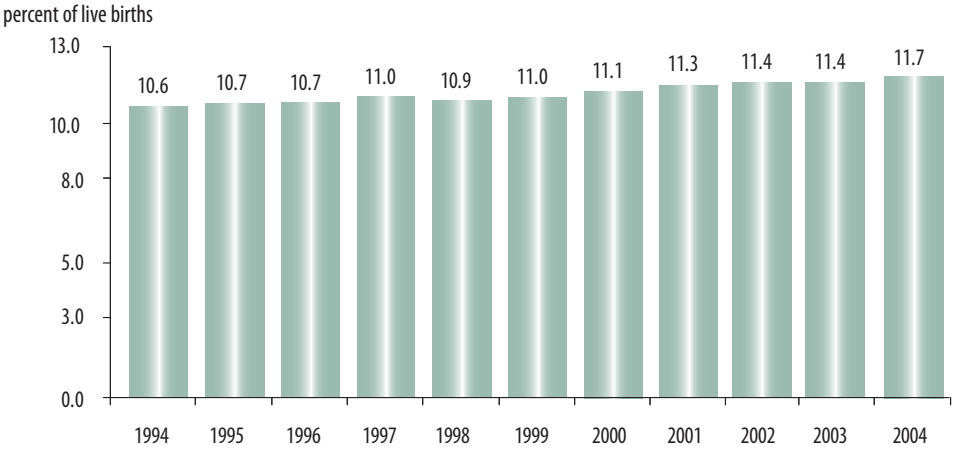
Preterm Birth in Our Back Yard

In an average week in New York State:

- 563 Babies are born preterm
  - 392 born low birth weight (<2,500 g)
- 97 Babies are born very preterm
  - 75 very low birth weight (<1,500 g)

March of Dimes, Birth Defects Foundation, January 2008

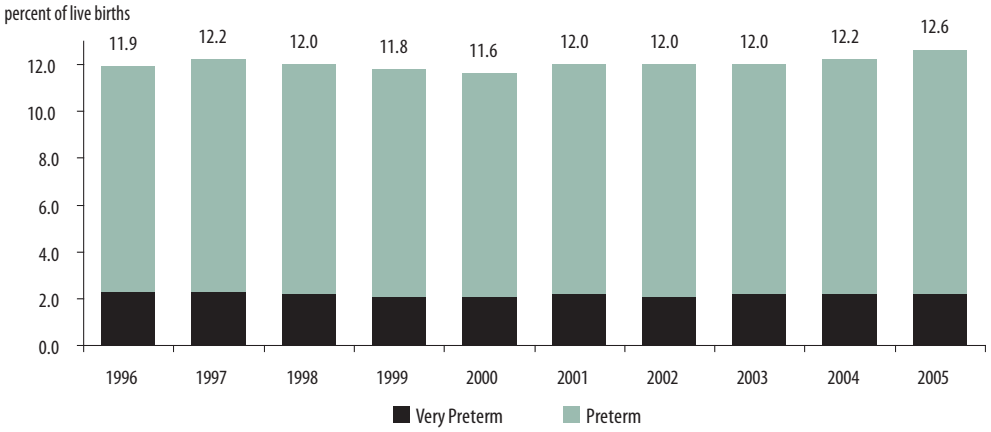
Preterm Births, New York State, 1994-2004



National Center for Health Statistics, final natality data
Prepared by March of Dimes Perinatal Data Center, 2008

[4]Preterm Birth: Causes, Consequences, and Prevention. (2006) Institute of Medicine. National Academies Press, Washington, D.C.

Preterm and Very Preterm Births, New York City, 1996 - 2005



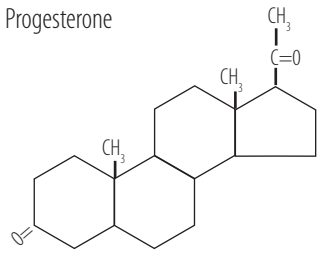
National Center for Health Statistics, final natality data
Prepared by March of Dimes Perinatal Data Center, 2008

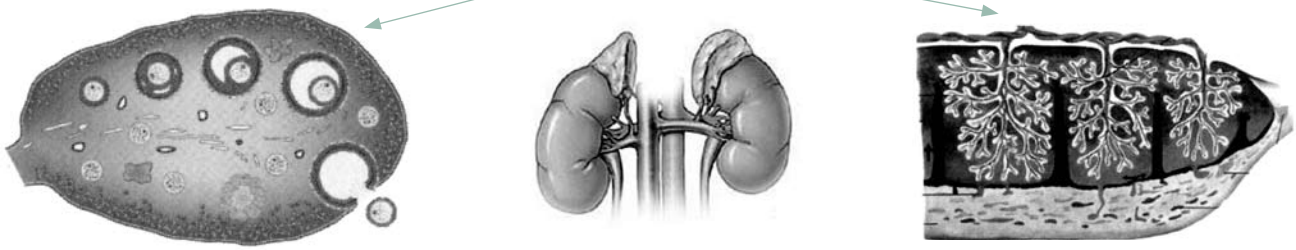
Between 1994 and 2004, the rate of infants born preterm in New York increased more than 10 percent. In 2004, 1 in 9 babies (11.7% of live births) were born preterm in New York. The preterm birth rate rose again in 2005 and preliminary data for 2006 show a continued increase, underscoring the urgent need for a sustained, comprehensive plan. New York City's preterm rates are slightly higher than the national average but mimics the national upward trend.

Progestogens for Preventing Preterm Birth

- Steroid Hormone
  - Isolated in 1934 from the corpus luteum
- Natural or Synthetic formulations
- Oral, Intramuscularly, and Vaginal administration
- Uses
  - Hormonal supplementation
  - Replacement
  - Contraception

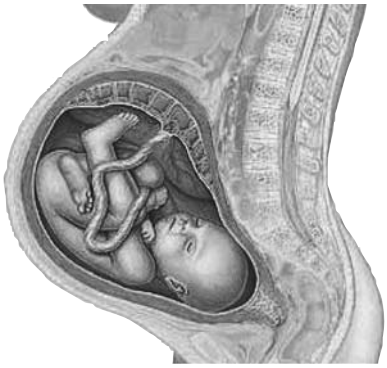
Progesterone is synthesized in the Ovaries, Adrenal Glands, and Placenta





Progesterone Action in Normal Pregnancy

- May suppress immunity to prevent rejection of fetal cells
- Induces myometrial quiescence
  - Suppresses contractile genes
  - Promotes relaxation systems
  - Suppresses cytokines, prostaglandins and response to oxytocin
  - Prevents formation of gap junctions



In 2005, the annual societal economic cost (medical, educational, and lost productivity) associated with preterm birth in the United States was at least $26.2 billion.

II. Clinical Trials and Research

This section offers a review of significant trials and research regarding 17P as well as references for further education.

Progesterone and Prevention of Preterm Birth

- Used since the 1970's for prevention of preterm labor
- Lack of clinical use due to conflicting results
  - Inclusion of mixed populations (i.e. recurrent pregnancy losses, active preterm labor)
  - Small number of patients
- Meta-analysis of 17P use
  - Seven placebo-controlled trials
  - 15% to 70% reduction in preterm birth
  - No significant reduction in perinatal mortality or morbidity

Keirse, Br J Obstet Gynaecol 1990

For more information on this topic:

Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Br J Obstet Gynaecol. 1990; 97:149-54.

There is increasing evidence that progesterone supplementation can reduce the rate of preterm birth in high-risk women. 17P has been used since the 1970s for prevention of preterm labor. Over many decades, despite several randomized trials, conflicting evidence has resulted in limited use in clinical practice.

The conflicting evidence might be explained by the inclusion of mixed populations such as women with recurrent pregnancy loss and those presenting with active preterm labor. Additionally, some of the trials included only a small number of patients.

In 1990, a meta-analysis of seven placebo-controlled trials involving prophylactic administration of 17P found that use of this agent was associated with a 15 to 70 percent reduction in occurrence of preterm birth, but no significant reduction in perinatal mortality or morbidity, or miscarriage.

The pooled odds ratios found no significant effect on rates of miscarriage, perinatal death or neonatal complications. However, the odds ratio for reduction of preterm birth was significant, 0.5 (95% confidence interval [CI] 0.30–0.85), as was the odds ratio for birth weight < 2,500 g, 0.46 (95% CI 0.27–0.80).

The National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medical Units (MFMU) Trial

463 patients at high risk for preterm birth because of a prior preterm birth randomized to weekly 17P or placebo at 16-20 weeks until 37 weeks.

- Significantly reduced the risk of preterm delivery (RR=relative risk, CI= confidence interval)
  - <37weeks (36% v 55% [RR, 0.66; 95% CI 0.54-0.81])
  - <35weeks (21% v 31% [RR, 0.67; 95% CI 0.48-0.93])
  - <32weeks (11% v 20% [RR, 0.58; 95% CI 0.37-0.91])
- 17P exposed infants
  - Less perinatal morbidity
  - Reduced rates of necrotizing enterocolitis, intraventricular hemorrhage and need for supplemental oxygen
- No evidence of virilization of female offspring

Meis, N Engl J Med 2003
Northen, Obstet Gynecol 2007

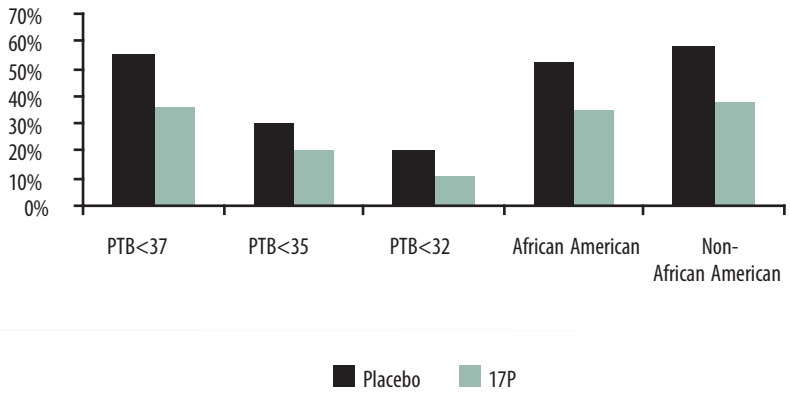
For more information on this topic:

Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003; 348:2379.

Northen AT, Norman GS, Anderson K, et al. for the National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network. Follow-up of children exposed in utero to 17 [alpha]-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. 2007; 110(4):865-872.

NICHD MFMU Trial- Key Results

p<0.01 all groups compared to placebo
PTB= Preterm Birth



Meis, N Engl J Med 2003

Benefits of 17P in reducing rates of preterm delivery were seen regardless of the cutoff used for defining a preterm birth. This finding was observed both for African and non African Americans.

However, it is surprising that more than 50% of the patients in the placebo group delivered before 37 weeks of gestation. This high percentage is substantially more than the reported incidence of preterm birth. It is likely due to the population studied being of higher risk as shown by the mean gestational age of prior preterm birth, at 30 weeks. The design of the study requiring an intramuscular injection may have changed the composition of the group to one of higher risk. Thus extraordinarily high risk women may have preferentially been enrolled in the study making it difficult to generalize the findings to all women with a prior preterm birth.

For more information on this topic:

Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003; 348:2379.

Northen AT, Norman GS, Anderson K, et al. for the National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network. Follow-up of children exposed in utero to 17 [alpha]-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. 2007; 110(4):865-872.

For more information on this topic:

Dodd J, Flenady V, Cincotta R, Crowther C. Prenatal administration of progesterone for preventing preterm birth. Cochrane Database Syst Rev 2006; :CD004947.

Mackenzie R, Walker M, Armson A, Hannah ME. Progesterone for the prevention of preterm birth among women at increased risk: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol 2006; 194:1234.

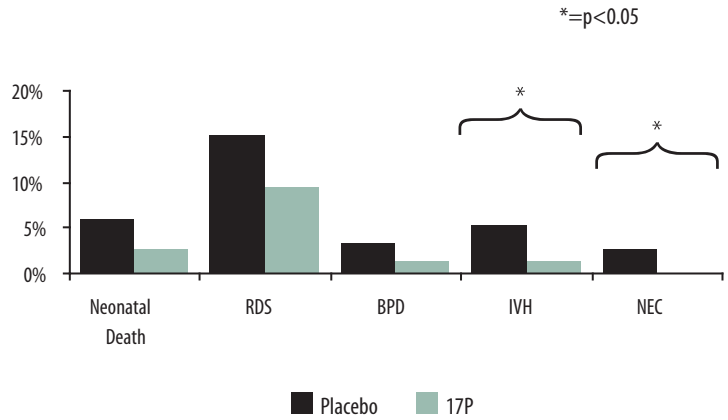
Sanchez-Ramos L, Kaunitz AM, Delke I. Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. Obstet Gynecol 2005; 105:273.

Spong CY. Prediction and prevention of recurrent spontaneous preterm birth. Obstet Gynecol 2007; 110:405-15.

Spong CY, Meis PJ, Thom EA, et al. Progesterone for prevention of recurrent preterm birth: impact of gestational age at prior delivery. Am J Obstet Gynecol, 2005; 193:1127-31.

Thornton JG. Progesterone and preterm labor--still no definite answers. N Engl J Med 2007; 357:499.

17P and Neonatal Complications



Meis, N Engl J Med 2003

RDS= Respiratory Distress Syndrome
BPD= Bronchopulmonary Dysplasia
IVH= Intraventricular Hemorrhage
NEC= Necrotizing Enterocolitis

The benefits of 17P extended beyond merely prolonging the length of gestation. As demonstrated above there were significant declines in the rate of intraventricular hemorrhage and necrotizing enterocolitis as well as trends toward reduced incidence of neonatal death, respiratory distress syndrome and bronchopulmonary dysplasia.

Other Studies of Progesterone

Meta-analyses of randomized controlled trials (RCTs) confirms decreased risk of preterm birth: 25-31% vs 33-47%
Secondary analysis of the RCT by the MFMU

- 17P decreases recurrent preterm birth if previous preterm births <34 weeks
- 17P does not decrease recurrence in women with previous preterm birth >34weeks

Spong, Obstet Gynecol 2005

Follow up studies of 17P confirmed its benefits. More recent meta-analyses of 17P, now including the 2003 NICHD MFMU trial demonstrated the effectiveness of 17P, and a secondary analysis of the NICHD MFMU trial found that the benefit of 17P appeared to be most pronounced among women whose prior spontaneous preterm birth occurred before 34 weeks of gestation.

Study of 17P's Estimated Effect

For more information on this topic:

Petrini JR, Callaghan WM, Klebanoff M, et al. Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. Obstet Gynecol 2005; 105:267.

Estimated Effect

2002 national birth certificate analysis:

- If all eligible women received progesterone, the overall preterm birth rate in the United States would be reduced by ~2%.
- 10,000 preterm births would have been prevented in 2002 if all eligible women were given progesterone.
- 22.5% of preterm births in 2002 were recurrent and prophylaxis could reduce that incidence of preterm birth by 33%.

Petrini JR, Obstet Gynecol 2005

Using 2002 national birth certificate data, approximately 30,000 recurrent preterm births occurred in women eligible for 17P. Using the 33% reduction rate from the NICHD MFMU trial, if 17P therapy were delivered to all of these women, nearly 10,000 spontaneous preterm births would have been prevented, thereby reducing the overall United States preterm birth rate by approximately 2%, from 12.1% to 11.8% ($P < .001$), with higher reductions in targeted groups of eligible pregnant women.

Vaginal Progesterone Trials

For more information on this topic:

da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003; 188:419.

- 142 high risk women randomized to daily progesterone vaginal suppositories (100mg) from 24-34 weeks versus placebo
- Inclusion criteria: history of at least one previous spontaneous preterm birth, prophylactic cervical cerclage, and uterine malformation
- 90% had previous preterm birth
- Progesterone group had:
  - Lower preterm birth <37weeks (14% v 29%, p<0.05)
  - Lower preterm birth <34weeks (3% v 19%, p<0.05)

da Fonseca, AJOG 2003

The use of daily vaginally-administered progesterone as an alternative to weekly injections of 17P has also been studied. A trial by da Fonseca, et al which included a heterogeneous group of women at risk for preterm delivery, found a significant benefit to the study drug.

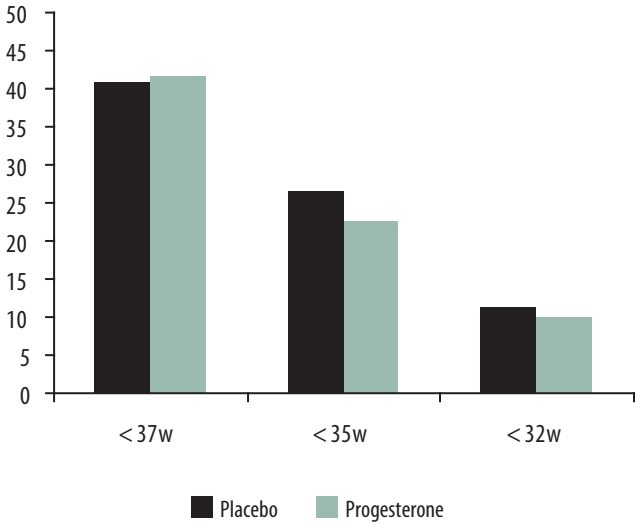
However, a larger trial of vaginal progesterone in a different vehicle did not find a similar benefit.

- Multinational randomized control trials of >600 women with history of preterm birth.
- Daily vaginal progesterone gel (90 mg) or placebo starting at 18-23 weeks of gestation did not result in a reduced rate of preterm birth.

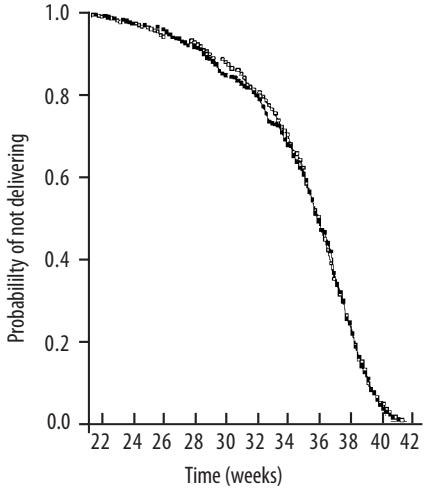
For more information on this topic:

O'Brien JM, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007; 30(5):687-96.

Vaginal Progesterone



O'Brien, Ultrasound Obstet Gynecol 2007



O'Brien, Ultrasound Obstet Gynecol 2007

Progesterone and Short Cervix

In a sub analysis, vaginal progesterone reduced the rate of preterm delivery (<32 weeks) only in women with cervical length <28mm at enrollment.

For more information on this topic:

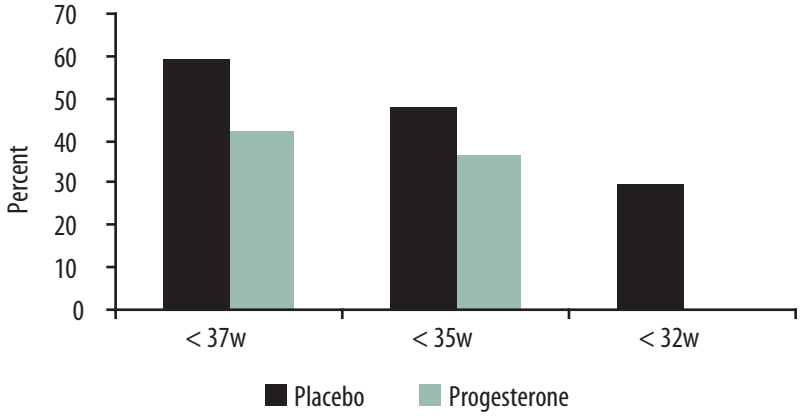
DeFranco EA, O'Brien JM, Adair CD, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007; 30(5):697-705.

Sub-analysis of 46 women with cervical length ≤ 28 mm

- 19 progesterone
  - 4 without preterm birth
  - 15 with preterm birth
- 27 placebo
  - 5 without preterm birth
  - 22 with preterm birth

DeFranco, Ultrasound Obstet Gynecol 2007

Progesterone and the Short Cervix



DeFranco, Ultrasound Obstet Gynecol 2007

". . . these conclusions must be considered tentative...(and) hypothesis generating. . . (and) . . . further investigation is necessary. Specifically randomized clinical trials designed to test the effect of progesterone in women with a short cervix. . ."

DeFranco, Ultrasound Obstet Gynecol 2007

For more information on this topic:

da Fonseca EB, Celik E, Parra M, et al, for the Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007; 357:462-9.

Other Studies of Vaginal Progesterone

Randomized trial of 250 asymptomatic women at 20-25 weeks

- Cervical length <15 mm
- Vaginal progesterone 200 mg vs. placebo
- Preterm Birth <34 weeks: 19.2% vs. 34.4% (RR 0.56, 95 % CI 0.36-0.86)
- Neonatal morbidity: 8.1% vs. 13.8% (RR 0.59, 95% CI 0.26-1.25)
- One fourth of patients had prior preterm birth
- 10-15% of patients were having twins

da Fonseca, N Engl J Med. 2007

This randomized trial, which was conducted by da Fonseca, et al of 250 asymptomatic women with cervical length less than 15 mm between 20-25 weeks and which randomized women to vaginal progesterone 200 mg or placebo, reported a decreased incidence of preterm birth and a nonsignificant decrease in neonatal morbidity. Approximately 10% of the women in the placebo and 8.4% in the treatment group had multiple gestations. The exclusion criteria were major fetal abnormalities, painful regular uterine contractions, a history of ruptured membranes or a cervical cerclage. Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group (19.2% vs. 34.4%; relative risk, 0.56; 95% confidence interval [CI], 0.36 to 0.86). Progesterone was associated with a nonsignificant reduction in neonatal morbidity (8.1% vs. 13.8%; relative risk, 0.59; 95% CI, 0.26 to 1.25; P=0.17). There were no serious adverse events associated with the use of progesterone.

Twin Gestations

Randomized control trial of 661 twins given 17P weekly intramuscularly 250 mg vs placebo

- Delivery <35 weeks or fetal death similar in both groups: 41.5 % vs 37.3%
- No effect of 17P on preterm birth

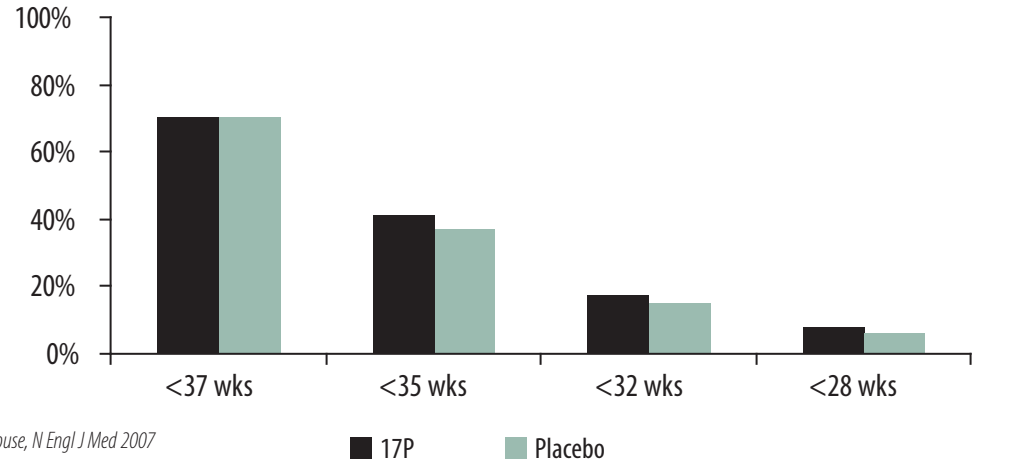
Rouse, N Engl J Med 2007

For more information on this topic:

Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med 2007; 357:454-61.

Twins are another high risk group for preterm birth. A randomized controlled trial conducted by the NICHD MFMU Network that was similar in design to the Maternal-Fetal Medicine Network study of singleton gestations reported no differences in preterm birth rate before 35 weeks or fetal death in a group of 661 twin pregnancies. Delivery or fetal death before 35 weeks occurred in 41.5% of pregnancies in the 17P group and 37.3% of those in the placebo group (relative risk [RR], 1.1; 95% confidence interval [CI], 0.9 to 1.3). Thus no benefit was found to support using 17P in multiple gestations.

Progesterone and Twins



Rouse, N Engl J Med 2007

Triplet Gestations

For more information on this topic:

Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Obstet Gynecol 2009; 113:285-92.

Randomized control trial of 134 women carrying triplet gestations were given 17P weekly intramuscularly 250 mg vs placebo

- Delivery <35 weeks or fetal loss were similar in both groups: 83% vs 84%
- No effect of 17P on preterm birth rates for deliveries <28 weeks or <32 weeks

Caritis, Obstet Gynecol 2009

Similar findings for triplet gestations as for twins were recently demonstrated in another randomized controlled trial also conducted by the NICHD MFMU Network. It reported no differences in preterm birth rate before 28, 32, or 35 weeks of gestation or fetal death in a group of 134 triplet gestations. Delivery or fetal death before 35 weeks occurred in 83% of pregnancies in the 17P group and 84% of those in the placebo group (relative risk [RR], 1.0; 95% confidence interval [CI], 0.9 to 1.1). Thus no benefit has been found to support using 17P in twin or triplet gestations.

Safety of Progestins in Pregnancy

For more information on this topic:

Anonymous. Reprotox 1997, Vol. 92, Micromedex Inc.

Raman-Wilms L, Tseng AL, Wighardt S, et al. Fetal genital effects of first trimester sex hormone exposure: a meta-analysis. Obstet Gynecol 1995; 85:141.

Schardein JL. Congenital abnormalities and hormones during pregnancy: a clinical review. Teratology 1980; 22:251.

Several extensive reviews of the literature have been published regarding the safety of progestins in pregnancy. Schardein in a very extensive review found "no justification (exists) for undue concern over the induction of nongenital malformations through hormone use in pregnancy." This review found that although some androgenic compounds have the potential for masculinization of the female fetus, progesterone and 17P have no such potential. Raman-Wilms, et al performed a meta-analysis of the literature after reviewing the 186 published articles. The meta-analysis showed no association between first trimester exposure to sex hormones and external genital malformations. In the current Reprotox computer database, supported by Micromedex, the review of hydroxyprogesterone concluded that, "there is no available evidence that the administration of this agent (17P) during pregnancy is harmful."

Additional Safety Studies

Additionally, a number of authors have reported the results of well-controlled clinical studies to examine the safety of 17P in human pregnancy. Varma and Morsman examined the outcome of 150 pregnancies treated with hydroxyprogesterone because of threatened abortion, and compared them with 150 patients who experienced early pregnancy bleeding but were not treated with the drug. No evidence was found that the drug had any adverse effect on the fetus or the outcome of the pregnancy. Michaelis, et al in a cohort study of 13,643 pregnancies in West Germany found no increase in malformations in infants exposed in utero to 17P compared with controls. Resequie, et al examined a cohort of 24,000 pregnancies delivered in Olmstead County, Minnesota in 1936-1974 and found that the 649 offspring exposed to 17P showed no increase in congenital anomalies or other ill effects compared with controls. A notable feature of this study was the long period of follow-up of the children, with a mean of 11.5 years.

Check, et al performed a follow-up study by questionnaire of 382 women treated with progestins during pregnancy and found no increase in anomalies compared with control offspring. Katz, et al studied 1,608 infants exposed to progestins in utero and compared them to 1,146 control infants. No difference was found in rates of all malformations, (120/1,000) and 123.9/1,000, respectively). Castro examined a group of adolescent males who were exposed in utero to 17P and performed a battery of psychological tests on the subjects and on matched control subjects. They found no significant differences between the groups in psychological testing.

For more information on this topic:

Check JH, Rankin A, and Teichman M. The risk of fetal anomalies as a result of progesterone therapy during pregnancy. Fertility and Sterility 1986; 45:575.

Katz Z, Lancet M, Skornik J, et al. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol 1985; 65:775.

Michaelis J, Michaelis H, Gluck E, Koller S. Prospective studies of suspected association between certain drugs administered in early pregnancy and congenital malformations. Teratology 1983; 27:57.

Resseguie LJ, Hick JF, Bruen JA, et al. Congenital malformations among offspring exposed in utero to progestins, Olmstead County, Minnesota 1936-1974. Fertility and Sterility 1985; 43:514.

Varma T, Morsman J. Evaluation of the use of proluton-depot (hydroxyprogesterone hexanoate) in early pregnancy. Int J Gynecol Obstet 1982; 20:13.

III. Guidance for Appropriate Use

ACOG's 2008 committee opinion acknowledges the benefits of progestrone in high risk populations with prior preterm birth. However, optimal formulation and route of delivery is still unknown.

ACOG Committee Opinion No. 419 October 2008

ABSTRACT: Preterm birth affects 12% of all births in the United States. Recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women. Despite the apparent benefits of progesterone, the ideal progesterone formulation is unknown. The American College of Obstetricians and Gynecologists Committee on Obstetric Practice and the Society for Maternal Fetal Medicine believe that further studies are needed to evaluate the optimal preparation, dosage, route of administration, and other indications for the use of progesterone for the prevention of preterm delivery. Based on current knowledge, it is important to offer progesterone for pregnancy prolongation to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation.

For the complete Committee Opinion, go to page 22.

Eligibility Criteria for 17P

Based on current research and guidelines, below are commonly accepted elibility criteria for 17P.

Eligibility Criteria:

- History of a spontaneous preterm birth (<37 weeks)
- Singleton pregnancy
- Initiate treatment between 16 weeks, 0 days and 20 weeks, 6 days

Exclusion Criteria:

- Known fetal anomaly
- Current or planned cervical cerclage
- Hypertension
- Seizure disorder

17P is not for women with:

- Multi-fetal pregnancy
- Short cervix and no prior preterm birth
- Previous medically indicated preterm birth

Recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women.

Frequently Asked Questions

Current 17P data and research are limited. Many questions regarding 17P remain. Below are commonly asked questions and answers based on current 17P research findings.

When is the optimal time to initiate 17P therapy? When is most effective- 16-20 weeks, less than 24 weeks or 21-27 weeks?

Different studies use varying times in pregnancy to start the medication such as between 16 and 20 weeks or less than 24 weeks. Another study reported the effect is similar when the medication is started between 21-27 weeks vs. 16-20 weeks. While more research is needed in this area, initiation of between 16 weeks, 0 days and 20 weeks, 6 days is commonly accepted.

For more information on this topic:

How HY, Barton JR, Istwan NB, Rhea DJ, Stanziano GJ. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? Am J Obstet Gynecol, 2007; 197(3):260.

When should I stop giving 17P? At 35 or 36 weeks? Does early discontinuation of 17P (less than 32 weeks) increase the risk of preterm delivery?

Limited evidence suggests early discontinuation can be associated with an increased risk of preterm birth. While further studies are needed, weekly intramuscular injections could continue until 36 weeks, 6 days gestation or until the patient gives birth- whichever comes first.

For more information on this topic:

How HY, Barton JR, Istwan NB, Rhea DJ, Stanziano GJ. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? Am J Obstet Gynecol, 2007; 197(3):260.

Meis PJ for the Society of Maternal-Fetal Medicine. 17 hydroxyprogesterone for the prevention of preterm delivery. Obstet Gynecol 2005; 105:1128-1135.

Rebarber A, Ferrara LA, Hanley ML, et al. Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2007; 196:224.e1-4.

What is the optimal 17P dose? Which is more effective-17P 250 mgs intramuscularly weekly or vaginal progesterone 100-200 mg daily?

Varying doses and regimens have been used in different studies with 17P- 250 mg given intramuscularly weekly and vaginal progesterone in doses between 100 and 200 mg daily being the most common. Further studies are needed to evaluate optimal dosage, route and formulation (e.g. gel or suppository).

For more information on this topic:

(also see page 15-16 for 'Safety of Progestins in Pregnancy' and 'Additional Safety Studies'):

Dudas I, Gidai J, Czeizel AE. Population-based case-control teratogenic study of hydroxyprogesterone treatment during pregnancy. Congenital Anomalies, 2006; 46(4):194-8.

Elizur SE, Tulandi T. Drugs in infertility and fetal safety. Fertility & Sterility, 2008; 89(6):1595-602.

Northen AT, Norman GS, Anderson K, et al. for the National Institute of Child Health and Human Development (NICHD) Maternal–Fetal Medicine Units (MFMU) Network. Follow-up of children exposed in utero to 17 [alpha]-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. 2007; 110(4):865-872.

Can 17P be used as a tocolytic agent?

The use of progesterone in established preterm labor, ie, as a tocolytic agent has been shown not to be effective. Although the design of trials and drugs used varies, no studies have demonstrated any efficacy in prolonging pregnancy. Thus, the use of progesterone as a tocolytic drug, or as an adjunct to tocolytic agents for patients in preterm labor, is to be discouraged outside of randomized trials. It is likely that once the physiologic or pathologic processes that precede labor (such as the formation of gap junctions or activation of the inflammatory cascade) have occurred, treatment with progesterone is not effective in halting this process.

Is 17P safe? Can it harm the mother or child?

To date, there are many studies following the exposure of mothers and children to 17P. Currently, no adverse consequences have been found in either mother or child.

Inappropriate Use of 17P

For more information on this topic:

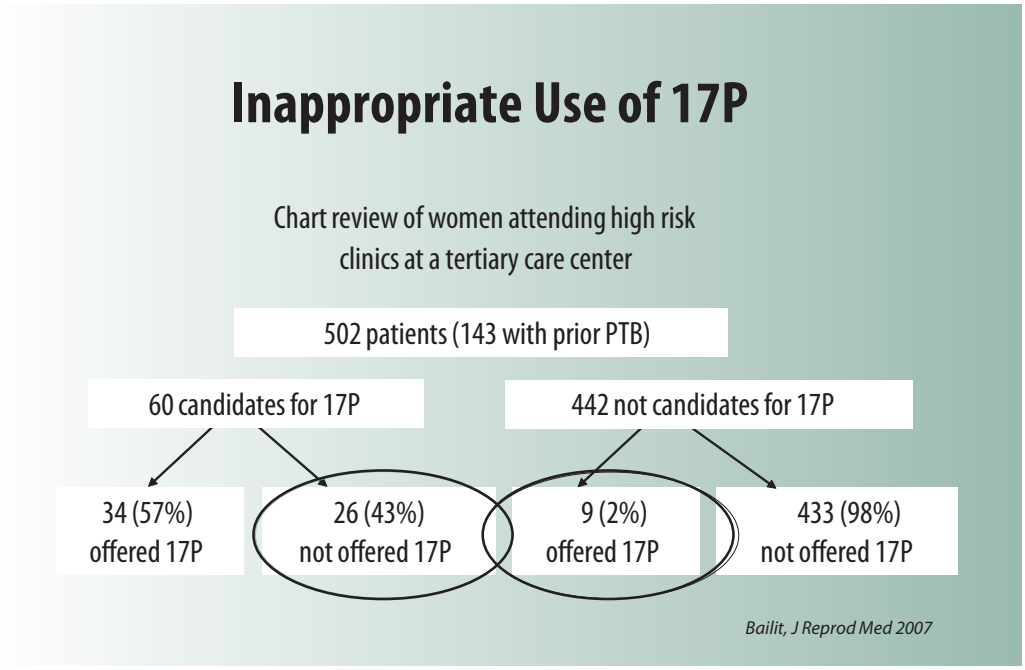
Rittenberg C, Sullivan S, Istwan N, et al. Clinical characteristics of women prescribed 17 alpha-hydroxyprogesterone caproate in the community setting. Am J Obstet Gynecol 2007; 197:262. e1-262.e4.

While 17P has potential to reduce preterm birth for a specific set of women, misuse of 17P is not uncommon. A 2007 article published in the American Journal of Obstetrics and Gynecology performed a review of nearly 2,000 women enrolled in an outpatient program to receive 17P weekly for the prevention of preterm delivery between April 2004 and Jan. 1, 2006. The authors (Rittenberg, et al) noted that many women were receiving 17P inappropriately. Some even had twin gestations or a cervical cerclage in a prior pregnancy—two situations where there has been no demonstrated benefit to 17P.

Another study conducted by Bailit, et al noted that many patients were not offered 17P who were potential candidates--and some were offered it who were not appropriate candidates.

For more information on this topic:

Bailit JL, Berkowitz R, Thorp JM, et al. Use of progesterone to prevent preterm birth at a tertiary care center. J Reprod Med. 2007; 52(4):280-4.



Based on current knowledge, it is important to offer progesterone for pregnancy prolongation to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation.

For more information on this topic:

Henderson Z, Power M, Lackritz E, et al. Use of progesterone to prevent preterm births: attitudes and practices of U.S. obstetrician-gynecologists. Am J Obstet Gynecol, 2007; 197(6):S206-S206.

Survey of Prenatal Care Providers (n=345)

- 74% reported that they recommend or offer 17P.
- 55% of those that offer 17P reported they recommend it to women without a prior preterm birth but who had other risk factors for preterm delivery such as cervical changes on examination or ultrasound or those requiring cervical cerclage.

Barriers to Care

While 17P has the potential to reduce preterm birth, barriers exist for the provider and patient. 17P is currently only available at compounding pharmacies and some hospital pharmacies. Not all insurance companies cover 17P and compounding pharmacies often require direct patient payment. Without insurance coverage, 17P may be unaffordable to some patients.

While some retrospective data has shown 17P initiation before 27 weeks may still be efficacious, it is generally accepted practice that 17P initiation should occur between 16 weeks, 0 days and 20 weeks, 6 days. Eligible women who initiate prenatal care late in pregnancy are missed opportunities for this therapy.

Eligible women using intramuscular injections must also be willing and able to either make consistent weekly visits to the provider's office or perform home injections. Home injections could be self-administered or assisted by a trained friend or family member. These weekly injections must occur to optimize the effectiveness of 17P.

As research continues, it is important to continuously provide physician education to encourage appropriate use.

Case Vignettes

The following case vignettes are provided to help solidify knowledge of 17P and its appropriate use.

Case #1

- 30 year old para 0101 at 16 weeks gestation with a history of a spontaneous preterm birth at 28 weeks.
- She had no past medical or past surgical history.
- Last pregnancy was without complications, but at 28 weeks, patient felt cramping, went into the hospital and had contractions q 4 minutes and was not leaking fluid nor bleeding vaginally.
- Patient received antenatal steroids and magnesium sulfate, but progressed in labor and had spontaneous vaginal delivery of 1,500 gram infant.

Points of Learning

- Data supports use of 17P in patients at risk for recurrent spontaneous preterm birth.
- No treatable etiology was identified.
- Treatment regardless of the neonatal outcome.

Case #2

- 33 year old para 1121 at 20 weeks with a history of chronic hypertension and last pregnancy complicated by superimposed severe preeclampsia with HELLP syndrome at 24 weeks.
- Required cervical dilation with neonatal demise at day of life 7.
- Currently taking two medications for hypertension. No other medical or surgical problems.
- Wants to prevent preterm delivery.

Points of Learning

- Indicated preterm delivery is not an indication for 17P.
- 17P not appropriate for a patient with hypertension.

Case #3

- 38 year old para 0 at 12 weeks, s/p invitro fertilization, with dichorionic/diamnionic twins.
- Obesity is the only co-morbidity.
- Patient wants to decrease her risk for preterm delivery of twins.

Points of Learning

- No reliable evidence that 17P is effective in women with multiple gestation.

ACOG COMMITTEE OPINION

Number 419 • October 2008 *(Replaces No. 291, November 2003)*

Use of Progesterone to Reduce Preterm Birth

Committee on Obstetric Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

ABSTRACT: Preterm birth affects 12% of all births in the United States. Recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women. Despite the apparent benefits of progesterone, the ideal progesterone formulation is unknown. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the Society for Maternal Fetal Medicine believe that further studies are needed to evaluate the optimal preparation, dosage, route of administration, and other indications for the use of progesterone for the prevention of preterm delivery. Based on current knowledge, it is important to offer progesterone for pregnancy prolongation to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation.

The Society for Maternal Fetal Medicine Publications Committee

The American College of Obstetricians and Gynecologists

Women's Health Care Physicians

Preterm birth affects 12% of all births in the United States. This statistic has led multiple investigators to identify those women at greatest risk (eg, those with prior preterm delivery, multiple gestation, short cervical length, maternal weight less than 50 kg, bleeding, and those of African American race). Recent randomized trials comparing progesterone with placebo have been conducted using several groups at high risk and low risk for preterm delivery. The purpose of this Committee Opinion is to review these results.

A large randomized placebo-controlled trial investigating the use of 17α-hydroxyprogesterone caproate ("17P") therapy (250 mg administered intramuscularly) for the prevention of preterm birth in a select, high-risk group of women (with a documented history of a previous spontaneous singleton preterm birth at less than 37 weeks of gestation) was conducted for the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (1). A total of 459 women with a history of previous spontaneous singleton births at less than 37 weeks of gestation were enrolled between 16 weeks and 20 weeks of gestation. Of note, the mean gestational age of their previous preterm deliveries was 30.7 weeks. They were randomly assigned to receive weekly intramuscular injections of 17α-hydroxyprogesterone caproate (n = 306) or placebo (n = 153) from enrollment to 37 weeks of gestation or delivery. The study was stopped early when results showed a significant protection against recurrent preterm birth for all races of women who received 17α-hydroxyprogesterone caproate. This study demonstrated significant reductions in preterm and early preterm birth, low birth-weight, as well as significant reductions in infant complications (intraventricular hemorrhage, necrotizing enterocolitis, neonatal intensive care unit admissions, and the need for supplemental oxygen therapy) with progesterone therapy (Table 1). Four-year follow-up found no adverse health outcomes of surviving children (2).

In a randomized placebo-controlled trial of supplemental vaginal progesterone (100 mg daily) in 142 women at high risk for preterm birth (more than 90% of whom had a previous spontaneous singleton preterm birth) the authors found that for delivery at less than 34 weeks of gestation, the preterm birth rate was significantly lower among women receiving progesterone than among those receiving placebo (2.7% versus 18.6%) (3). The results of this study and the NICHD trial support the hypothesis that proges-

Table 1. Rates of Preterm Labor With Progesterone Therapy or Placebo

Gestation	Placebo Group (n = 153)	Progesterone Group (n = 306)	Relative Risk	Confidence Interval	*P*
Less than 37 weeks	54.9%	36.3%	0.66	0.54–0.81	.001
Less than 35 weeks	30.7%	20.6%	0.67	0.48–0.93	.0165
Less than 32 weeks	19.6%	11.4%	0.58	0.37–0.91	.0180

Data from Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348:2379–85.

terone supplementation reduces preterm birth in women at risk for preterm birth, with a prior preterm birth.

The effectiveness of progesterone supplementation has been evaluated in several other high-risk groups for preterm delivery, with conflicting results. A randomized trial of 17α-hydroxyprogesterone caproate in 661 women with twin gestations found no benefit of progesterone supplementation for the prevention of preterm delivery (4). A randomized trial of 659 women with a history of spontaneous preterm delivery randomized and treated between 18 weeks and 23 weeks of gestation with 90 mg of natural progesterone vaginal gel or placebo found no improvement in preterm birth at less than 37 weeks, less than 35 weeks or less than 32 weeks of gestation. (5). Another randomized trial evaluated asymptomatic women with a short cervix and singleton and twin gestations. Of 24,620 women screened with endovaginal ultrasonography between 20 weeks and 25 weeks of gestation, 413 women had a cervical length less than 15 mm (1.5%) and of those women, 250 were randomized (1:1) to daily vaginal progesterone (200 mg micronized progesterone capsules) or placebo from 24 weeks to 34 weeks of gestation. Of note, 15% of the study population had a history of a prior preterm delivery and 10% of the study population had a twin gestation. Overall, progesterone therapy significantly reduced the rate of spontaneous preterm birth at less than 34 weeks of gestation (19.2% versus 34.3%) [6].

Despite the apparent benefits of progesterone in some situations, the ideal formulation is unknown. The 17α-hydroxyprogesterone caproate used in the NICHD trial was specially formulated for the trial and is not currently commercially available. Although the initial trial (3) used 100 mg vaginal suppositories and demonstrated pregnancy prolongation with treatment, vaginal progesterone gel was not beneficial in reducing preterm birth in women with a history of spontaneous preterm delivery randomized and treated between 18 weeks and 23 weeks of gestation (5). Micronized progesterone capsules (200 mg vaginally daily) were used in the trial of progesterone for asymptomatic women with a very short cervix (less than 15 mm), and appeared to be effective for this indication (6). Whether the differences seen in efficacy of the recently studied vaginal preparations reflects differences in dosages (100 mg versus 200 mg), variation in absorption and bioavailability with different preparations (gel versus capsule versus suppository), or differences in study populations remain to be elucidated. Progesterone has not been studied as a supplemental treatment to cervical cerclage for suspected cervical insufficiency, as a preventive agent for asymptomatic women with a positive cervicovaginal fetal fibronectin screen result, as a tocolytic agent, or as a therapeutic agent after tocolysis, and it should not be used at this time for these indications alone.

Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes. Current evidence does not support the routine use of progesterone in women with multiple gestations. Progesterone supplementation for asymptomatic women with an incidentally identified very short cervical length (less than 15 mm) may be considered; however, routine cervical length screening is not recommended. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the Society for Maternal Fetal Medicine believe that further studies are needed to determine if there are other indications for progesterone therapy for the prevention of preterm delivery.

References

1. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network [published erratum appears in N Engl J Med 2003;349:1299]. N Engl J Med 2003;348:2379–85.
2. Northen AT, Norman GS, Anderson K, Moseley L, Divito M, Cotroneo M, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Obstet Gynecol 2007;110: 865–72.
3. da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol 2003;188:419–24.

4. Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. N Engl J Med 2007;357:454–61.
5. O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007;30:687–96.
6. da Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462–9.

Use of progesterone to reduce preterm birth. ACOG Committee Opinion No. 419. American College of Obstetricians and Gynecologists. Obstet Gynecol 2008;112:963–5.

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IV. Protocol for In-Office Use

This section is adapted from the University of North Carolina (UNC) Center for Maternal and Infant Health.

When implementing any new methods or medications in one's practice, it is essential to train staff, trouble shoot and implement protocols for a smooth transition. A comprehensive 17P protocol should include information regarding ordering, storing, administering, coding and patient education. The following protocol is for utilizing 17P intramuscularly.

Ordering

17P is currently only available at compounding pharmacies and at some hospital pharmacies. While ACOG does not endorse any particular compounding pharmacy, below is a list of suggested suppliers of 17P.

Alere (formerly known as Matria): 1-800-999-0225
Wedgewood Pharmacy: 1-800-331-8272
Vitality: 1-800-397-5899
Freedom Pharmacy: 1-800-660-4283
Pine Pharmacy Compounding & Wellness Center: 716-332-2288
Fallon Wellness: 1-800-890-1137

Notes:

- Check with hospital pharmacies as some may also dispense 17P.
- Alere will come to the patient's home to give the weekly injections.
- Wedgewood and Vitality will ship the medication to the physician's office or patient's home depending on to whom and where the injections will be given.
- Freedom will ship to provider's office. It will contact the patient to request credit card information for payment. When patient arrives at the office for medication, staff can give her a copy of her receipt.

Storing

The shelf life of 17P is six months. 17P is typically delivered in 5 ml vials. The medication can be kept at room temperature and does not need refrigeration. For best results, 17P should be kept in a dry place away from direct heat and sunlight. Patients can transport vials to and from the office visit. If the medication looks cloudy it may have been stored for too long.

Administering

- Initiate treatment between 16 weeks, 0 days and 20 weeks, 6 days gestation.
- If an eligible woman presents to prenatal care late, 17P may be initiated as late as 26 weeks, 6 days--although the data to support this is inconclusive.
- Weekly injections could continue until 36 weeks, 6 days gestation or until the patient gives birth- whichever comes first.
- 17P can be administered into the gluteus muscle, alternating sides each week. It may also be given in the anterior thigh.
- The weekly intramuscular dosage of 17P is a 250mg (1 ml) injection, ideally given at the same time each week.
- The suggested range of time in between injections is 5 to 9 days- should it be necessary to plan around holidays or other delays.

Patients must be counseled about how to reduce the risk of preterm birth and ways to recognize the signs of preterm labor.

- Many patients can successfully find a friend or family member to give them the weekly injection once they have been trained.
- The injection is not unusually painful. It has been compared to a Depo-Provera injection with less medication but a thicker consistency.
- Patients can take acetaminophen and/or soak in a warm tub if they are sore, but this is usually not necessary.

Additional administration tips

- Clean the vial top with an alcohol swab before use.
- Clean the injection site with an alcohol swab before administration.
- Draw up 1 ml of 17P in a 3cc syringe with an 18-gauge needle.
- Change the needle to a 21-gauge 1½ inch needle before injecting 17P.
- The 17P medication is extremely thick. Careful technique is required to avoid overfilling the syringe and subsequent wastage.

Missed Doses

Progesterone stays in the body for approximately 7 days. Therefore, it is important that a woman receives a dose of 17P every week. The suggested range of time in between injections is 5 to 9 days .

If a week is missed, be sure that the patient receives the next dose. If a woman has difficulty making her weekly appointments, consider teaching her or a family member how to give the injection. It is important that a patient receive the injections until 36 weeks, 6 days in order to help carry her pregnancy as close to full term as possible. If the patient is experiencing signs and symptoms of preterm labor, continue to give her 17P until she delivers or until 36 weeks, 6 days of pregnancy.

Side effects are very rare, but include soreness, swelling, itching and bruising.

Coding

ICD9 codes

Diagnosis	Code
Preterm labor, personal history	V13.21

Helping Patients Understand 17P

It is essential that patients understand the importance of their commitment to maintaining the weekly injection regime and that 17P does not guarantee a full-term pregnancy. Patients must be counseled about how to reduce the risk of preterm birth and ways to recognize the signs of preterm labor.

If a patient goes into preterm labor, other measures will be needed to delay birth. These might include tocolytics to stop contractions and steroids to help develop the baby's lungs. In some circumstances, bed rest may be recommended. If a woman is going to deliver early, it may be best that she gives birth in a facility that has a high-level Neonatal Intensive Care Unit (NICU).

V. Resources and Research

Websites

American Academy of Pediatrics- aap.org
American College of Obstetricians and Gynecologists, District II- acogny.org
American College of Obstetricians and Gynecologists- acog.org
Center for Disease Control and Prevention-cdc.gov
Institute of Medicine- iom.edu
March of Dimes- marchofdimes.com
UNC Center for Maternal and Infant Health- mombaby.org

Research

While more research is needed, numerous preterm birth studies and trials have helped determine appropriate uses of 17P. Please utilize the listing below to further your understanding of this subject.

Anonymous. Reprotox 1997; 92, Micromedex Inc.

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Mackenzie R, Walker M, Armson A, Hannah ME. Progesterone for the prevention of preterm birth among women at increased risk: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol 2006; 194:1234.

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Michaelis J, Michaelis H, Gluck E, Koller S. Prospective studies of suspected association between certain drugs administered in early pregnancy and congenital malformations. Teratology 1983; 27:57.

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VI. Evaluation and Future Education

1) Do you currently offer or recommend 17P to any of your pregnant patients for the prevention of recurrent preterm birth or refer them elsewhere for this therapy? (Circle all that apply)
   Yes, I:
   a) Offer
   b) Recommend
   c) Refer eligible women for 17P therapy

   d) No (Skip to question 3)

2) If Yes, what section of this chapter was most helpful to you in your practice? Least helpful to you in your practice? (Upon completing question 2, skip to Question 5)

Most Helpful	Least Helpful
Background	Background
Clinical Trials and Research	Clinical Trials and Research
Guidance for Appropriate Use	Guidance for Appropriate Use
Protocol for In-Office Use	Protocol for In-Office Use
Resources and Research	Resources and Research

   Please elaborate:_____

3) If No, what section of this chapter was most helpful to you in your practice? Least helpful to you in your practice?

Most Helpful	Least Helpful
Background	Background
Clinical Trials and Research	Clinical Trials and Research
Guidance for Appropriate Use	Guidance for Appropriate Use
Protocol for In-Office Use	Protocol for In-Office Use
Resources and Research	Resources and Research

   Please elaborate:_____

4) If you do not currently offer or recommend 17P to any of your pregnant patients, after reading this chapter would you now consider offering it? Why or why not?

   _____
   _____
   _____
   _____

continued on reverse

5) In what formats(s) do you prefer to receive medical education? (please circle all that apply)
   a) Grand Rounds
   b) Conferences
   c) Toolkits and Resource Guides
   d) Webcasts
   e) Podcast
   f) Other:_____

6) What clinical topics regarding preterm birth would you like to receive more medical education on?

_____

_____

_____

_____

Thank you!

Return completed evaluation to:
ACOG District II
Attn: Medical Education Department
152 Washington Avenue
Albany, NY 12210
FAX: 518-426-4728