



Effective Health Care Program

Progestogens for Prevention of Preterm Birth

Executive Summary

Introduction

Burden of Preterm Birth

Birth before completion of 37 weeks of pregnancy is considered preterm. These early births are associated with more than 85 percent of all perinatal morbidity and mortality and are the leading cause of infant mortality and long-term disability.¹⁻² Each year in the United States more than 475,000 infants are born preterm representing 12.5 percent of live births.³ Efforts to reduce preterm birth have been largely unsuccessful, with a 20 percent relative increase since 1990 in the proportion of births in the United States that are preterm.²

Morbidity and mortality associated with preterm birth represent untold distress for families, as well as significant costs to patients, health care systems, and payers. Average neonatal care costs are estimated to be \$17,300 greater for preterm infants relative to term infants, amounting to more than \$8.6 billion of annual medical spending in the United States.⁴ The ultimate goal in preventing preterm birth is to eliminate the risks of neonatal complications and death and to ensure normal development.⁵

In the last decade, accumulating evidence from randomized clinical trials (RCTs) has led professional organizations and an

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Institute of Medicine working group to endorse the use of progestogens for women with prior spontaneous preterm birth. However, these groups also note interest in assessing long-term safety because the



Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Effective
Health Care

legacy of diethylstilbestrol suggests caution and extended followup of mothers and infants after hormone use in pregnancy. Unresolved issues about choice of progestogen, optimal route of drug delivery, and other candidate high-risk populations for treatment remain. To review the current state of the evidence we answered the following Key Questions (KQs).

Key Questions

KQ1. In pregnant women who are at risk for preterm birth (which is birth before 37 weeks gestational age), does progestogen treatment, compared to a placebo, usual care, or other interventions improve maternal or fetal/neonatal health outcomes, including but not limited to:

- Complications during pregnancy (e.g., chorioamnionitis, antenatal hospitalizations and intrauterine growth restriction)?
- Mode of birth and complications during birth (e.g., cesarean birth and surgical complications)?
- Prematurity?
- Postpartum and neonatal complications (e.g., maternal postpartum hemorrhage and intraventricular hemorrhage)?
- Longer term outcomes (e.g., neurodevelopmental delay and future reproductive outcomes)?

KQ2. What is the nature and frequency of maternal and child adverse effects of progestogen treatment, including but not limited to:

- Complications during pregnancy (e.g. allergic reactions or development of gestational diabetes)?
- Mode of birth and complications during birth (e.g., unanticipated maternal harms)?
- Postpartum and neonatal complications (e.g., infections and sepsis)?
- Longer term outcomes?

KQ3. How do the effectiveness, adverse effects, and safety of progestogen treatment differ based on the maternal risk factors for preterm birth, such as severity of prior preterm birth, degree of cervical shortening, order of multiple gestations, fetal fibronectin status, preterm premature rupture of membranes (PPROM), threatened preterm birth, and socioeconomic predictors of prematurity, including race/ethnicity?

KQ4. How do the effectiveness, acceptability, adherence, adverse effects, and safety of progestogen treatment differ, based on the formulation, dose, frequency of

administration, and gestational age at initiation or discontinuation of progestogen therapy?

KQ5. How do the effectiveness, adverse effects, and safety of progestogen treatment differ based on cointerventions used to prevent preterm birth and its consequences, including antibiotics, corticosteroids, tocolysis, and surgical interventions such as cervical cerclage?

KQ6. What are the effects of health system and provider factors, including provider knowledge and attitudes, provider specialty, cost of drug, availability of drug in formularies, and Medicaid and private payer coverage, on the utilization of progestogens for eligible at risk women?

Methods

Literature Search

Our search included MEDLINE® and Embase. We also hand searched the references of included articles to identify additional studies. Controlled vocabulary terms served as the foundation of our search, complemented by additional keyword phrases to represent the myriad ways in which progestogens and preterm labor were referred to in the clinical literature. We also employed indexing terms within each database to exclude ineligible publication types and articles in languages other than English.

Article Selection Process

We examined article abstracts to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts for inclusion or exclusion. If one reviewer concluded the article could be eligible for the review based on the abstract, we retained it. Full publications were then jointly reviewed for final inclusion. Reasons and processes for exclusions are described in the full report.

Data Extraction

All team members shared the task of entering information into evidence tables. After initial data extraction, another member checked table entries for accuracy, completeness, and consistency. Abstractors reconciled inconsistencies.

Meta-Analysis

We conducted a Bayesian meta-analysis to provide aggregate estimates of the effectiveness of progestogen treatment for preventing preterm birth and reducing neonatal mortality. We constructed models to address two aspects of clinical utility—grouping the RCTs: (1) by the indications for which the progestogens were administered in the study (prior preterm birth, multiple gestations,

and current preterm labor) and (2) by the progestogen formulation used in the trial (intramuscular, oral, or vaginal).

Quality Assessment

We used a quality assessment worksheet to capture key elements of study design and conduct. Two reviewers independently assessed the quality and resolved differences through discussion, review of the publications, and consensus with the team. Quality scores for individual studies are listed in Appendix E (in the full report).

Evidence Synthesis

Text that summarizes the research evidence is organized by KQ. Within each KQ, we organized the evidence by aspects of the question, such as indication and formulation. In the full report, we include evidence tables and summary tables of common outcomes, and we provide extended analysis.

Results

Literature Search Yield

We identified 417 nonduplicate publications. Seventy articles met criteria and were included. The most common reasons for exclusion were irrelevance to the topic and ineligible study size. Included studies reflected 63 distinct study populations: 28 RCTs, 4 clinical trials, 14 cohort studies, 8 case series, 6 case-control studies, and 3 cross-sectional studies. Eight were good quality, 43 fair, and 19 poor. Seven articles reported secondary analyses or repeated surveys of the same provider group. Forty-six articles pertained to KQ1, 52 articles to KQ2, 19 articles to KQ3, 52 articles to KQ4, 18 articles to KQ5, and 11 articles to KQ6.

Interpretation of Meta-Analysis

In the Results section of the full report, we report the findings from meta-analysis as odds ratios (OR) from Bayesian models. It is important to note that when outcomes are common, such as preterm birth in these study populations, the OR is not a direct surrogate for the risk ratio (RR). For instance, in KQ1, below, consider these OR and comparable approximate RR pairings:

OR=0.66 (0.53, 0.82) → RR=0.78 (0.68, 0.90)

OR=0.52 (0.25, 0.96) → RR=0.53 (0.26, 0.96)

OR=0.26 (0.10, 0.49) → RR=0.41 (0.18, 0.66)

OR=1.18 (0.79, 1.39) → RR=1.09 (0.88, 1.17)

Thus the risk reduction is somewhat smaller than it may appear from the OR.

KQ1. Maternal, Fetal, and Neonatal Health Outcomes

Forty-six articles from 41 study populations provide data about progestogen use among women at risk for preterm birth. Indications for treatment varied, including a history of preterm birth in 10 investigations, preterm labor in the study pregnancy in 10, multiple gestation in 6, populations with a variety of risk factors in 11 studies, and unique indications (for example, abdominal surgery unrelated to pregnancy) in 4. Progestogen treatment included natural progesterone and synthetic progestins administered via injection, vaginally, or orally. The most common route and formulation was intramuscular 17 alpha-hydroxyprogesterone caproate (17OHP).

Among women with a history of preterm birth, progestogen treatment decreased the risk of preterm birth before 37 weeks (meta-estimate OR=0.66; 95% Bayesian credible interval [BCI]: 0.53, 0.82) and neonatal mortality (meta-estimate OR=0.52, 95% BCI: 0.25, 0.96). Among the trials in the meta-estimate, the risk of preterm birth was 46.6 percent among women in the placebo group and 37.2 percent among those receiving progestogens. In these same trials, the risk of neonatal death was 4.0 percent among women in the placebo group and 2.3 percent among those receiving progestogens. Thus, across studies, intervention is associated with a 9.4 percent overall reduction in preterm births and a 1.7 percent overall reduction in neonatal mortality. The largest RCT among women with prior preterm birth (n=611) did not find reduced risk of preterm birth or other benefits.⁶ Mean birth weight was not consistently reported. Infants of women treated with progestogens weighed an average of 239 gm more than those of women who received placebo, with poor precision (95% confidence interval [CI]: -44.5, 523.3 gm) and inconsistency across studies. These studies do not show consistent benefits in other maternal, fetal, neonatal, or child health outcomes.

Treatment of women with preterm labor was associated with prolonged time from treatment to birth in two uncontrolled trials.⁷⁻⁸ Two other trials, including a placebo-controlled double-blind study, reported nonsignificant differences and conflicting findings.⁹⁻¹⁰ Preterm birth findings were more consistent and supported by three studies. The aggregate estimate suggests progestogen treatment in women with preterm labor decreases the risk of preterm birth before 37 weeks (meta-estimate OR=0.26; 95% BCI: 0.10, 0.49). Among

74 comparison group members not receiving progestogens 50.0 percent had preterm births compared to 21.3 percent of the 75 women receiving progestogens, an overall decrease of 28.7 percent.

Moderately strong evidence based on trials and consistent findings indicates lack of effectiveness for multiple gestations (preterm birth at < 35 weeks OR=1.18; 95% BCI: 0.79, 1.39). Among the trials in the meta-estimate, the risk of preterm birth was 47.5 percent among women in the placebo group and 51.9 percent among those receiving progestogens. Thus, across studies, intervention is associated with a 4.4 percent overall increase in preterm births. The heterogeneity of the studies that included women with varied indications for progestogen treatment, combined with the lack of reporting outcomes by risk factors, makes it impossible to interpret their significance for specific indications. Among studies that examined unique indications for progestogen treatment, such as postoperative management or treatment of active-duty military personnel, none demonstrated improvements in maternal, fetal, or neonatal outcomes. One unique indication, asymptomatic short cervix, had a randomized trial of progesterone vaginal gel added to the literature after completion of our initial systematic review, bringing the total number of women studied for this indication to 708. The trials found benefit in preventing prematurity and neonatal mortality from preterm birth, while raising questions about what cervical length to use as a cutoff for treatment and when to screen.¹¹⁻¹²

Evidence supporting all uses other than those among women with prior spontaneous preterm birth is insufficient to inform clinical care. Evidence for benefits beyond prevention of preterm birth, such as increased birthweight, decreased infant morbidity, and improved childhood outcomes is insufficient across all groups in which progestogens have been studied.

KQ2. Adverse Effects of Progestogen Treatment for Mother or Child

Fifty-two studies from 47 study populations provided some information on adverse effects of progestogen treatment. Most studies do not indicate what categories of harms were systematically assessed, what operational definitions were used to define a specific harm, or what proportion of women or infants were assessed at each time period. It is not possible to determine with confidence whether the extreme ranges of incidence of adverse effects reported reflect differences in definitions, susceptibility among participants, dose or formulation, or methods for ascertainment. The latter seems likely to contribute since

potential harms were not uniformly sought. Similar small proportions of study participants withdrew from treatment and placebo groups; 0.6 to 3.2 percent and 0.3 to 1.6 percent respectively. In general, clinical trials have lacked statistical power to identify distinct differences in adverse effects between groups such as risk of fetal deaths prior to birth. Long-term effects have not been well studied. No high-quality surveillance studies of large populations of exposed women and/or children were identified. No data were available from large registries often developed for surveillance of rare outcomes. Numbers of gestations followed for rare outcomes such as genital tract anomalies, feminization of the male fetus, altered reproductive function, or other hormone-responsive changes in physiology are insufficient to assess risk.

KQ3. Modifiers of Treatment Outcomes by Maternal Factors

Nineteen studies with distinct populations provide information on modifiers of treatment outcomes. Data are limited and evidence is insufficient for understanding potential differences in effectiveness of progestogens for prevention of preterm birth based on maternal factors such as gestational age of the prior spontaneous preterm birth, number of prior spontaneous preterm births, gestational age at initiation of the intervention, or a short cervix. No evidence details whether there are differences in adverse effects or safety based on maternal factors. We found no data for women at risk of preterm birth due to prior PPROM, detection of fetal fibronectin, cerclage, or uterine malformations, or for women who conceived with assisted reproductive technologies.

KQ4. Modifiers of Outcomes by Type of Progestogen

Twenty-seven studies with distinct populations evaluated injected 17OHP; among these there were 23 distinct dose/interval combinations. The majority initiated treatment between 16 and 21 weeks. Two retrospective case series (n=156 and n=208) and one retrospective cohort (n=906) compared initiating 17OHP before, versus after, 21 weeks of gestation. Mean gestational age at birth and other outcomes did not differ. The relationship between number of injections and outcome was examined in a single database analysis; more than five injections prolonged gestation, while fewer did not confer benefit. However, this analysis does not take into account gestational age at birth, which is important because women who gave birth at term had greater opportunity to have more injections, leaving interpretation inconclusive.

Evidence is insufficient to determine whether there are different maternal and/or fetal outcomes or adverse effects based on dose, frequency or gestational age at initiation or discontinuation of treatment.

Seven studies with four dose/interval combinations evaluated progesterone vaginal gel or suppository; timing of initiation varied. The five studies using suppositories observed a statistically significant prolongation of gestation (total n=189). Two studies of gel (total n=556) did not. No adverse effects were recorded in studies of suppositories, while multiple adverse effects were reported in the two studies that used vaginal gel.

Five studies with five dose/interval combinations and varied timing of initiation evaluated oral micronized progesterone; one study administered 100 mg twice daily and documented prolongation of pregnancy and increase in birthweight. Four studies reported adverse effects; none were linked to dose or frequency of treatment.

Five studies, all conducted before 1980, used other progestogens. These include exogenous progestin and estrogen with and without thyroid hormone, diethylstilbestrol (DES) with natural and synthetic progesterone, 6-alpha-methyl-17-alpha-acetoxyprogesterone, and crystalline progesterone dissolved in vegetable oil. None described gestational age at initiation. Two reported adverse effects (interventions: DES with natural and synthetic progesterone and in utero exposure to exogenous progestin and estrogen) that include feminization of male children, potentially due to combined estrogen and progestin. These studies are noted for completeness, but are not included in the meta-analysis or the strength-of-evidence assessment.

We calculated meta-analysis estimates by using RCTs grouped by progestogen formulation (17OHP, oral, and vaginal) to access the effectiveness of each formulation at preventing preterm birth and neonatal mortality. These included 15 RCTs, 8 of which were for 17OHP, 3 for oral progestogens, and 4 for vaginal progestogens. For neonatal mortality, aggregate estimates indicated no formulation was effective at reducing risk ($OR_{17OHP}=1.11$, 95% BCI: 0.66, 1.73; $OR_{Oral}=0.68$, 95% BCI: 0.04, 2.17; $OR_{Vaginal}=0.77$, 95% BCI: 0.39, 1.27). However, all formulations were effective at reducing the risk of preterm birth (meta-estimates: $OR_{17OHP}=0.75$, 95% BCI: 0.60, 0.90; $OR_{Oral}=0.56$, 95% BCI: 0.36, 0.79; $OR_{Vaginal}=0.76$, 95% BCI: 0.57, 0.98).

Direct comparisons of routes, doses, and timing of initiation have not been investigated in randomized clinical trials of progestogens currently available to prescribe. No studies directly assessed adherence to treatment or evaluated whether varying frequency or dose influenced prolongation of pregnancy. We do not know whether patient preferences, adherence, and outcomes vary across route of administration. In total, the evidence is insufficient for choosing a target window for treatment and for selecting one form or dose of progestogen over another.

KQ5. Modifiers of Outcomes by Cointerventions

Ten studies with distinct populations reported using tocolytic treatments as a cointervention to prevent spontaneous preterm birth, either alone or in combination with another cointervention. Eight studies used other forms of cointerventions for their intervention group, including cortisol, daily nursing surveillance, nurses to administer drugs and be available to answer questions (but not daily), bed rest, cervical cerclage, estrogen, omega-3 fatty acid supplements, and DES. None of these studies provide data that allow determination of the separate and joint effects of the progestogen and the cointervention. We sought stratified analyses (grouped either by the cointervention or the progestogen placebo or control status), models with an interaction term, or models of independent effect from which effect modification could be calculated. However, evidence is insufficient for understanding the role of cointerventions in either amplifying or undermining the potential benefits of progesterone treatment. We could not assess adherence or harms because of small group sizes by combinations of progestogen and cointervention and because of limited reporting of adverse events. No evidence is available to guide choices of cointerventions.

KQ6. Effects of Provider and Health System Factors

Eleven studies with distinct populations assessed care provider knowledge, attitudes, and prescribing practices. Five of those surveyed providers. Among maternal–fetal medicine specialists (MFMS) in the United States, prescribing increased from 38 percent for preterm birth prevention in 2003 to 67 percent in 2005 ($p < 0.001$). If a prior spontaneous preterm birth is used as the primary criterion for eligibility, use of progestogens beyond this scope is rising, with 20 percent of MFMS reporting use for short cervix or preterm labor symptoms in 2003; 39 percent of MFMS by 2005; and 52 percent of generalist obstetricians in 2007. More than three-quarters of those

who prescribe progestogens use weekly injections, with vaginal next most common, and oral rare.

Obstacles reported by those who prescribe progestogens include lack of availability, lack of insurance coverage, lack of FDA approval, and need for greater information about long-term effects. Nonprescribers identified similar barriers, endorsing them in higher proportions. One survey addressed patient demand; 63 percent reported that patients “never request”; 35 percent, “infrequently request”; and 2 percent, “frequently request” progestogens.

Two studies outside the United States found little use of progestogens—2 percent in Australia/New Zealand and 7 percent in Canada. Seventy-one percent of Canadian obstetricians cited “evidence not convincing” as the primary reason they do not prescribe. Both Canadian and Australian/New Zealand obstetricians expressed willingness to participate in large-scale trials (84 and 65% respectively), indicating alignment of the perceived weakness of evidence with willingness to pursue additional data.

Among the six observational studies with data about use of progestogens, 40 to 52 percent of women eligible for treatment with progestogens do not receive treatment. Fifty-six percent of prescribing (at a National Institute of Child Health and Human Development 17OHP study site) was for vaginal suppositories, 25.5 percent for injections, and 18.6 percent unknown. Factors associated with use may be context specific; however, older maternal age, private insurance, earlier prior preterm birth, and earlier enrollment in prenatal care predict treatment in some settings. Categorization of indications in the largest database study found 79.5 percent had a prior preterm birth and 63.6 percent met eligibility criteria. Multiple gestations contributed 8 percent of “nonstandard use,” with current preterm labor treatment contributing 44.8 percent, and cerclage, 23.2 percent.

Current evidence is insufficient about provider, patient, or health system factors that determine prescribing. No published studies have examined interventions to change uptake or use patterns.

Discussion

Applicability

We used inclusion criteria intended to identify studies applicable to women receiving prenatal care in the United States, including research from settings with comparably advanced prenatal and neonatal care. Although the literature includes a high proportion of RCTs, 28 of

63 study populations (44%), heterogeneity of progestogen formulations, doses, intervals, outcomes reported, and populations recruited present challenges to combining results to develop more informative estimates of effectiveness of treatment. In general, studies have also been too small to provide valid estimates of factors that may modify treatment effects, such as additional maternal risk factors or cointerventions intended to further reduce risk of preterm birth.

Lack of direct comparisons of treatment options further hinders ability to know what findings will best extend to a specific patient or to decisions about care protocols within clinics or health systems. An additional, subtle factor is worthy of consideration in assessing whether and how findings apply to specific care populations: in some studies, observed rates of spontaneous preterm births among those who did not receive intervention exceeded that observed in population-level data about recurrent preterm birth. This discrepancy is not rare in research; an unknown degree and form of bias may result in selection of women who are higher risk than the larger set of women. This implies that observed absolute effects and anticipated improvements in numbers of preterm births may be lower in practice.

Update on Recently Completed Research

Use of progestogens to reduce preterm birth risk has been a rapidly developing area of investigation. After completion of this systematic review, results from a number of trials garnered attention at national meetings. We awaited publication of these reports, completing an additional update of the literature search in October 2011. Our update identified eight additional randomized trials, one for the indication of prior preterm birth, three for preterm labor, two for twin gestations, one for PPRM, and one for short cervix. Two of these trials demonstrated effectiveness for reducing risk of preterm birth. However, in the context of the larger literature, overall strength of evidence for the full report is not fundamentally modified by this update of studies. The full report includes details.

Summary Strength of Evidence and Findings

Progestogen treatment reduces risk of preterm birth in singleton pregnancies in women with prior preterm birth. Use of progestogens for this indication is based on evidence of moderate strength, based on small numbers of trials of varied progestogens. The largest trial, which used vaginal gel, found no evidence of effectiveness. Two RCTs report effectiveness in reducing preterm birth among women with short cervical length. Moderately strong

evidence indicates a lack of effectiveness for multiple gestations. Evidence is insufficient for evaluating all other uses and for understanding factors associated with patient preference and adherence to different routes of progestogens administration. Across indications, data are sparse to evaluate influence on near-term and long-term maternal and infant health outcomes. Overall evidence is insufficient for evaluating whether intervention has the ultimately desired outcome of preventing morbidity and promoting normal childhood development.

Conclusions

The strength of evidence for use of progestogens in singleton pregnancy with prior spontaneous preterm birth is moderate—four randomized trials, the largest of which had inconsistent findings. Two trials among women with short cervical length provide low strength of evidence for effectiveness. Moderate strength of evidence suggests a lack of effectiveness for multiple gestations. Evidence is insufficient for all other uses. Across indications, data are sparse to evaluate influence on near-term outcomes such as neonatal mortality and morbidities. Evidence is insufficient for understanding whether intervention has the ultimately desired outcome of preventing morbidity and promoting normal childhood development.

Many scenarios faced daily by care providers and women at risk of preterm birth and considering progestogen treatment are not backed up by consistent, high-quality evidence. Use is extending into groups for whom clear evidence of benefit is lacking. Pressure to intervene is amplified by the fact that no other prevention strategies are available. Lack of large-scale, systematic evidence about potential risks of treatment is concerning to providers and their concern is supported by the absence of high-quality followup data. Ultimately, providing data to support choice of an optimal form of progestogen, to determine whether long-term outcomes are improved, and to rule out longer term risks will require large-scale comparative effectiveness and surveillance research.

References

1. Behrman RE, Butler AS, Institute of Medicine (U.S.). Committee on Understanding Premature Birth and Assuring Healthy Outcomes. *Preterm birth: causes, consequences, and prevention*. Washington, D.C.: National Academies Press; 2007.
2. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2005. *Natl Vital Stat Rep*. 2007 Dec 5;56(6):1-103. PMID 18277471.
3. Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2007. *National vital statistics reports*, Web release. Released March 18, 2009 Released March 18, 2009;57(12).
4. Bailit JL, Votruba ME. Medical cost savings associated with 17 alpha-hydroxyprogesterone caproate. *Am J Obstet Gynecol*. 2007 Mar;196(3):219 e1-7. PMID 17346527.
5. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med*. 2007 Aug 2;357(5):477-87. PMID 17671256.
6. O'Brien JM, Adair CD, Lewis DF, 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 Oct;30(5):687-96. PMID 17899572.
7. Borna S, Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labour: a randomised controlled trial. *Aust N Z J Obstet Gynaecol*. 2008 Feb;48(1):58-63. PMID 18275573.
8. Facchinetti F, Paganelli S, Comitini G, et al. Cervical length changes during preterm cervical ripening: effects of 17-alpha-hydroxyprogesterone caproate. *Am J Obstet Gynecol*. 2007 May;196(5):453 e1-4; discussion 21. PMID 17466698.
9. Noblot G, Audra P, Dargent D, et al. The use of micronized progesterone in the treatment of menace of preterm delivery. *Eur J Obstet Gynecol Reprod Biol*. 1991 Jul 25;40(3):203-9. PMID 1879595.
10. Fonseca EB, Celik E, Parra M, et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Engl J Med*. 2007 Aug 2;357(5):462-9. PMID 17671254.
11. Kauppila A, Hartikainen-Sorri AL, Janne O, et al. Suppression of threatened premature labor by administration of cortisol and 17 alpha-hydroxyprogesterone caproate: a comparison with ritodrine. *Am J Obstet Gynecol*. 1980 Oct 15;138(4):404-8. PMID 7424996.
12. Briery CM, Veillon EW, Klauser CK, et al. Progesterone does not prevent preterm births in women with twins. *South Med J*. 2009 Sep;102(9):900-4. PMID 19668021.

Full Report

This executive summary is part of the following document: Likis FE, Andrews JC, Woodworth AL, Velez Edwards DR, Jerome RN, Fannesbeck CJ, McKoy JN, Hartmann KE. *Progestogens for Prevention of Preterm Birth. Comparative Effectiveness Review No. 74*. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I.) AHRQ Publication No. 12-EHC105-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

For More Copies

For more copies of *Progestogens for Prevention of Preterm Birth, Executive Summary No. 74* (AHRQ Pub. No. 12-EHC105-1), please call the AHRQ Publications Clearinghouse at 1-800-358-9295 or email ahrqpubs@ahrq.gov.

