Effective Health Care Program

Comparative Effectiveness Review
Number 74

Progestogens for Prevention of Preterm Birth

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations with their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see the Web site www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. CERs will be updated regularly.

We welcome comments about this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Dr. Melissa McPheeters, Associate Director of the Evidence-based Practice Center, was crucial in providing advice and in guiding review methods, including searches, data extraction, quality rating, strength-of-evidence reporting, and applicability assessment. She was especially helpful as a neutral adjudicator and as a sounding board for challenging decisions about scope and focus.

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Mr. Jeffrey Seroogy joined the team at a crucial time, bringing to bear his considerable organizational skills and experience with evidence report production. He worked tirelessly to format documents, check summary tables, compile quality scores, and complete critical details of the report as a whole.

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Progestogens for Prevention of Preterm Birth

Structured Abstract

Objectives: The Vanderbilt Evidence-based Practice Center systematically reviewed evidence addressing administration of progestogens to prevent preterm birth.

Data Sources: We searched MEDLINE® and Embase for articles published in English from January 1966 to October 2010. A focused update was added through October 2011.

Review Methods: We excluded publications that did not address a Key Question, were not research, or had fewer than 20 participants. We included 70 publications: 8 were good quality; 43, fair; and 19, poor. Sixteen randomized controlled trials (RCTs) contributed data for Bayesian meta-analysis. The update netted eight additional RCTs.

Results: Among women with prior preterm birth and a singleton pregnancy (four RCTs), progestogen treatment decreased the risk of preterm birth (Odds Ratio [OR]=0.66, 95% Bayesian credible interval [BCI]: 0.53, 0.82), corresponding to an absolute reduction in risk of preterm birth between 0 and 26 percent across studies. In this population, progestogens also reduced neonatal death (OR=0.52, 95% BCI: 0.25, 0.96). Two trials of progestogen administration among women with short cervical length, one identified in the main portion of the review and the latter in the focused update, report reduction of risk of preterm birth with an absolute reduction in risk of 8.8 and 15.2 percent. Evidence of benefit for other maternal, fetal, or neonatal health outcomes is inconsistent or absent. In multiple gestations, progestogen treatment does not prevent prematurity (preterm birth OR=1.18, 95% BCI: 0.79, 1.39), enhance birthweight, or improve other outcomes.

No maternal factors, such as number or severity of prior preterm births, have been definitively shown to modify effects of progestogen treatment. Similarly, direct comparisons have not been made between routes of administration or doses in RCTs. Across RCTs (n=15), no formulation was effective at reducing risk for neonatal mortality, but all were effective at reducing the risk of preterm birth (meta-estimates: OR_{17OHP}[1]=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). Evidence is insufficient to determine whether time of initiation and adherence to treatment influence outcomes. Factors associated with adherence to treatment have not been systematically studied.

Potential adverse effects (harms) were not uniformly assessed in this literature. Study participants withdrew from treatment and placebo groups in similar small proportions. Long-term maternal and infant effects have not been well studied. No data were available from large registries for surveillance of rare outcomes such as fetal death. Publications about provider- and system-level factors confirm wide variability in use of progestogens, use in populations that lack clear evidence of benefit, and desire for data about longer term benefits and risk of harms.

Conclusions: Progestogens prevent preterm birth when used in singleton pregnancy in which the mother has had a prior spontaneous preterm birth or in which cervical length is short. The strength of the evidence supporting its use for these indications is moderate and low,

[1] 17 alpha-hydroxyprogesterone caproate

respectively. In contrast, moderate strength of evidence suggests 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.

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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 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 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.

Key Questions

1. 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)?
2. 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?

3. 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?
4. 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?
5. 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?
6. 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 Key Question (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 cut-off 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, as well as 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-acetoxy-progesterone, 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 PPROM, 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.

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Introduction

Background

Burden of Preterm Birth

Births before the 37th week of pregnancy are considered preterm. Risks of complications from preterm birth are related to how early the birth is with the earliest births at greatest risk. Preterm births contribute to 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 more than 475,000 infants are born preterm in the United States, representing 12.5 percent of live births.[3] Efforts to reduce occurrence of preterm births have been unsuccessful, with a 20 percent relative increase in the proportion of preterm births in the United States since 1990.[2]

The morbidity and mortality associated with preterm birth represent untold distress for families, as well as significant costs to patients, health care systems, and payers. Mean neonatal costs are estimated to be $17,300 (in 2004 dollars) greater for preterm infants relative to term infants, amounting to more than $8.6 billion of annual medical spending in the United States.[4] Preterm birth occurs disproportionately in populations of low socioeconomic status. Because many public programs serve these populations the costs of preterm birth in the public arena are substantial. It is estimated that 40 percent of the medical costs associated with preterm births are paid by Medicaid.[1]

Approaches to prevent preterm births by intervening at the time a woman has symptoms of preterm labor have proven elusive and only minimally effective. Attention has increasingly focused on methods to prevent preterm birth using earlier interventions to reach women based on risks rather than symptoms. Some paths such as treating bacterial vaginosis or periodontal disease as a route to decrease immune system activation and reduce systemic inflammation, both linked with preterm birth risk, have proven ineffective. Others, such as maternal administration of corticosteroids to enhance fetal lung development when there is a risk of preterm birth have proven fruitful for mitigating neonatal effects but not for delaying births. Progestogen administration has been investigated as a preventive intervention that may be useful for more women, earlier in pregnancy, offering options for prevention across several groups of women with increased risk of preterm birth—those with prior preterm birth, multiple gestation, a short cervix, symptoms of preterm labor, or a variety of risk factors.

Use of Progestogens

Within the last decade, accumulating evidence from randomized clinical trials (RCTs) led professional organizations and an Institute of Medicine working group to endorse the use of 17 alpha-hydroxyprogesterone caproate (17OHP) for women with prior spontaneous preterm births. Indeed during the course of completing this review, the U.S. Food and Drug Administration (FDA) approved a 17OHP formulation for the indication of prevention of preterm birth among women with a prior preterm birth.[5]

Other progestogens may also be effective. Progesterone is a hormone that inhibits the uterus from contracting and is involved in maintaining pregnancy, especially early in gestation. The exact mechanism for pharmaceutical effects is not well understood.

In the United States, approximately 133,000 expectant mothers annually have a history of preterm birth and are potential candidates for progestogens. If the results of the largest U.S. trial

for that indication are used, an estimated 10,000 preterm births might be prevented annually by use of progestogens in this group.[4]

Rates of preterm birth are higher among low-income and other vulnerable populations, and thus a larger ratio of this population relative to the general population may benefit from progestogen treatment. A recent study to assess the impact of a specific progestogen treatment, 17OHP, on future medical costs for expectant mothers with a prior preterm birth found that potential cost savings substantially exceed the cost of treatment.[4] The cost of a typical 17OHP treatment regimen is relatively modest; one study estimates it to be about $400 per treated patient.[4] This estimate factors in the cost of each dose of drug, the number of injections needed, and the hourly wage of a registered nurse needed to administer the injections. If all at-risk pregnant women were treated with 17OHP, the aggregate medical cost savings could be sizeable. The cost of treating eligible women would be approximately $53 million annually, and is projected to reduce initial neonatal medical costs by more than $505 million each year. In this scenario annual net savings would be $452 million, and over the lifetime of affected infants the discounted annual medical savings could be more than $2 billion.[4]

The ultimate goal in preventing preterm birth is to eliminate the risks of neonatal death or complications in order to prevent longstanding health consequences and to promote normal childhood development.[6] Progestogen treatment with 17OHP has been shown to prolong pregnancy for women who have had a prior preterm birth. However, the long-term safety of this intervention is not well understood, and the legacy of diethylstilbestrol (DES) suggests the need for caution and extended followup of mothers and infants.

This topic includes important components of variation in care and clinical controversy. Progesterone treatment for preventing preterm birth was first studied in several small trials during the 1960s.[7] In the context of decades of research on progestogens with mixed results, clinical use outside specialized settings has recently begun to increase for prevention of preterm birth in women at risk.[7] In 2003, the American Congress of Obstetricians and Gynecologists stated it is important to restrict use of 17OHP to women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation, because unresolved issues such as optimal route of drug delivery and long-term drug safety remain.[8-9] In a 2005 survey, both prescribers and non-prescribers of 17OHP for the prevention of preterm birth noted concerns about the need for more data on safety and efficacy and also on long-term neonatal effects, as well as about the lack of FDA approval.[10] We undertook this review to systematically update what is known about use of progestogens for prevention of preterm birth.

Treatment Options

Progestogens are substances with biologic activity similar to the endogenous sex steroid progesterone.[11] Progestogens include natural progesterone, synthetic progesterone, and synthetic progestins that are similar but not identical in chemical structure.[12] Natural progesterone and synthetic progestins can be administered orally, vaginally, or via injection. Oral and vaginal preparations may be micronized to improve absorption.

Any progestogen used to treat pregnant women at risk for preterm birth was eligible for inclusion in this review, regardless of formulation or route. The most common progestogen in the studies in this review is the synthetic progestin 17OHP. Other injectable forms of progesterone used include crystalline progesterone and natural progesterone. Vaginal progestogens used in these studies were administered via suppositories, gel, and capsules. Oral progestogens included medroxyprogesterone acetate (trade names Provera® and Perlutex®), allylestrenol, and oral

chlormadinone acetate. Of these three oral formulations, only medroxyprogesterone acetate is currently available in the United States. Five studies used other progestogens.[13-16] These include exogenous progestin and estrogen with and without thyroid hormone, DES with natural and synthetic progesterone, 6-alpha-methyl-17-alpha-acetoxy-progesterone, and crystalline progesterone dissolved in vegetable oil.

Scope of This Report

Key Questions

We have synthesized evidence in the published literature to address these Key Questions (KQs):

1. In pregnant women who are at risk for preterm birth (which is birth before 37 weeks gestational age), does progestogen treatment, compared to 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)?

2. 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?

3. 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, threatened preterm birth, and socioeconomic predictors of prematurity, including race/ethnicity?
4. 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?
5. 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?
6. 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?

Organization of This Report

The Methods chapter describes our methods, including our search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and methods for extracting data into evidence tables and compiling evidence. We also describe our approach to grading the quality of the literature and to describing the strength of the literature.

The Results chapter presents the results of the literature search and the review of the evidence by KQ, synthesizing the findings across treatment types. We report the number and type of studies identified and we differentiate between total numbers of publications and unique studies to bring into focus the number of duplicate publications in this literature in which multiple publications are derived from the same study population. The Discussion chapter discusses the results and enlarges on the methodologic considerations relevant to each KQ. We also outline the current state of the literature and challenges for future research on the use of progestogens to prevent preterm birth.

Uses of This Report

We anticipate this report will be of value to all health care practitioners who take care of women of childbearing age, including members of the American Congress of Obstetricians and Gynecologists, the Association of Women's Health, Obstetric and Neonatal Nurses, the American College of Nurse-Midwives, the American Academy of Family Physicians, the American Academy of Nurse Practitioners, and other clinical professional organizations. In addition, this review will be of use to the National Institutes of Health, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, and the Health Resources and Services Administration—all of which have offices or bureaus devoted to women's health issues. This report can bring practitioners up to date about the current state of evidence, and it provides an assessment of the quality of studies that aim to determine the outcomes of progestogens use for the prevention of preterm birth. It will be of interest to individual women and the general public because of the burden that preterm birth places on families and society as a whole, and the recurring need for women and their health care providers to make the best possible decisions among numerous options. We also anticipate it will be of use to private sector organizations concerned with women's health, such as Childbirth Connection, March of Dimes, the National Women's Health Network, and Our Bodies Ourselves.

Researchers can obtain a concise analysis of the current state of knowledge in this field. They will be poised to pursue further investigations that are needed to advance research methods, understand risk factors, develop prevention strategies, develop new treatment options, and optimize the effectiveness and safety of clinical care for those women who are at risk for preterm birth.

Methods

In this section we document the procedures that the Vanderbilt Evidence-based Practice Center used to produce a complete evidence report on the use of progestogens to prevent preterm birth. We first describe the assistance provided by the technical expert panel throughout the topic refinement and review process. We then present the Key Questions (KQs) and analytic framework. We also discuss our strategy for identifying articles relevant to our six KQs, our inclusion and exclusion criteria, and the process we used to abstract pertinent information from the eligible articles and generate our evidence tables. In addition, we discuss our method for grading the quality of individual articles and for rating the strength of the evidence. Finally, we describe the peer review process.

Technical Expert Panel (TEP)

We identified technical experts on the topic of the use of progestogens to prevent preterm birth in the fields of obstetrics and gynecology, midwifery, nursing, epidemiology, pharmacology, primary care, and patient advocacy to provide assistance during the project. The TEP was expected to contribute to AHRQ's broader goals of (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included eight members serving as technical or clinical experts. To ensure robust scientifically relevant work, we called on the TEP to provide reactions to work in progress and advice on substantive issues or possibly overlooked areas of research. TEP members participated in conference calls and discussion through email to:

- Refine the analytic framework and KQs during topic refinement;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Provide input on the information and domains included in evidence tables;
- Develop a hierarchy of participant characteristics and outcomes to systematically assess;
- Advise about the clinical availability, use, and doses of progestational agents.

Because of their extensive knowledge of the literature, including numerous articles authored by TEP members themselves, and their active involvement in professional societies and trial networks, and as practitioners in the field, we also asked TEP members to participate in the external peer review of the draft report.

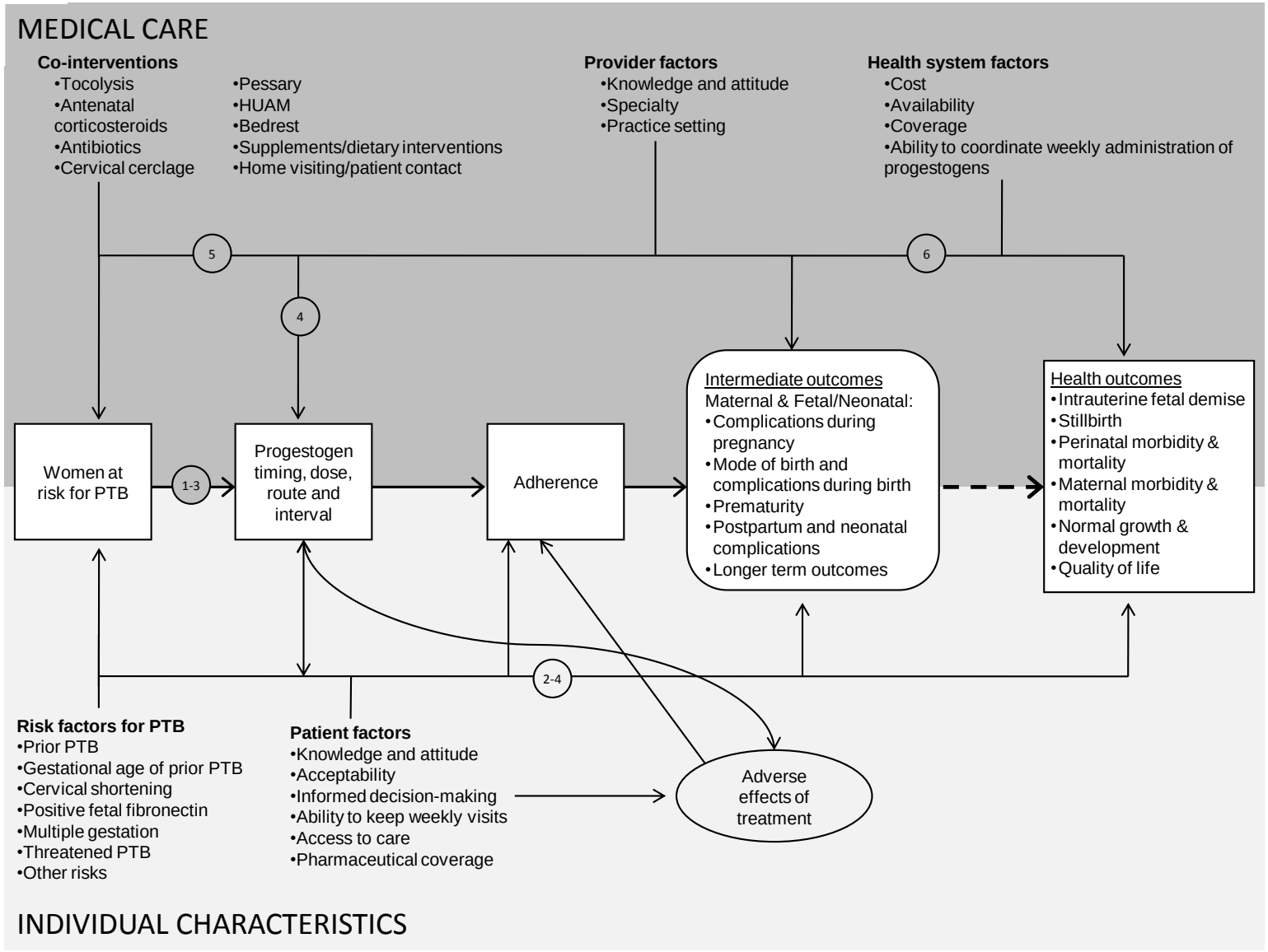
Analytic Framework for Progestogens for the Prevention of Preterm Birth

The analytic framework in Figure 1 summarizes the conceptual model used to guide this systematic review by focusing the KQs on the critical health care-related pathways and decision points. Our analytic framework emphasizes that care takes place at the interface of the health care system and the individual. The pathway through care is indicated in the boxes along the center line where the person and care meet. Each KQ is indicated within the framework at the relevant point of influence in care. Each of the domains listed among individual and system factors, such as patient factors, use of cointerventions, provider factors, and health system factors, has been shown to influence care trajectories and outcomes. Making these domains explicit as they influence the care pathway provides the framework in which the review team and

technical expert panel conducted this review. To the degree that individuals or care settings vary in context-specific points of influence, this framework may or may not be applicable.

Overall, the figure represents the population of interest, women at risk for preterm birth, and how the intervention of progestogens, at various timings, doses, routes, and intervals, (KQs 1–3) affects adherence, as well as intermediate and health outcomes (KQs 2–4). Adverse effects of treatment are examined in KQ 6. Finally, we sought to examine factors within the central care pathway as well as selected contextual domains like health system factors (KQs 5 and 6), and influence of individual characteristic on outcomes as a step towards enhancing applicability of the results (KQ 3). Portions of the framework that are unexplored in the scientific literature are highlighted in the discussion of future research needs.

Figure 1. Analytic framework for progestogens for the prevention of preterm birth



Literature Review Methods

Literature Search and Retrieval Process

Databases. Our search included examination of results in MEDLINE® and Embase. We also hand-searched the reference lists of included articles to identify additional studies for review.

Search terms. Controlled vocabulary terms served as the foundation of our search in each database, complemented by additional keyword phrases to represent the myriad ways in which progestogens and preterm labor are referred to in the clinical literature. We also employed indexing terms within each of the databases to exclude undesired publication types (e.g., reviews, case reports, Continuing Medical Education handouts) and items published in languages other than English.

Appendix A outlines our search terms and results. Our searches were executed between August 2009 and October 2010, prior to FDA approval of a dedicated progestogen product for preterm birth prevention among women with prior preterm birth,[5] and were not limited by date.

Inclusion and Exclusion Criteria

Our inclusion and exclusion criteria were developed in consultation with the TEP to capture the literature most tightly related to the KQs. Criteria are summarized in Table 1.

Table 1. Criteria for inclusion and exclusion of studies in the review

Category	Criteria
Study population	Adult females
Publication languages	English only
Admissible evidence	Study design • Controlled trials • Prospective trials with historical controls • Prospective or retrospective cohort studies • Case control studies • Case series with n ≥ 20 Other criteria • Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of data and results • Abstraction of relevant outcomes from data presented in papers must be possible • Sample sizes must be appropriate for study aims; single case reports or small case series (< 20 participants) are excluded

The study population is adult females. We did not have translation services available to us to review non-English papers, and our TEP agreed that the vast majority if not all of the relevant literature would be published in English. Furthermore, this review is intended to inform United States health care and most research in this population is published in English language journals. Empirical evidence on the potential for bias created by excluding non-English studies also suggests little effect.[17] Appendix B contains the list of excluded articles along with the reason for exclusion.

Article selection process. Once we identified articles through the electronic database searches, review articles, and bibliographies, we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts for inclusion

or exclusion, using an Abstract Review Form (Appendix C). If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it. The group included two physicians (KH, JA), a certified nurse-midwife and nurse practitioner (FL), two health services researchers (AW, JM) and two library scientists (RJ, TS).

Literature Synthesis

Development of Evidence Tables and Data Abstraction Process

The staff members and clinical experts who conducted this review jointly developed the evidence tables. We designed the tables to provide sufficient information to enable readers to understand the studies and to determine their quality; we gave particular emphasis to essential information related to our KQs. We based the format of our evidence tables on successful designs used for prior systematic reviews.

The team was trained to abstract by abstracting several articles into evidence tables and then reconvening as a group to discuss the utility of the table design. We repeated this process through several iterations until we decided that the tables included the appropriate categories for gathering the information contained in the articles. All team members shared the task of initially entering information into the evidence tables. Another member of the team also reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. The two abstractors reconciled disagreements concerning the information reported in the evidence tables. The full research team met regularly during the article abstraction period and discussed global issues related to the data abstraction process. In addition to outcomes related to treatment effectiveness, we abstracted all data available on adverse effects (harms). Harms encompass the full range of specific negative effects, including the narrower definition of adverse events.

The final evidence tables are presented in their entirety in Appendix D. Studies are presented in the evidence tables alphabetically by the last name of the first author. When possible, studies resulting from the same study population were grouped into a single evidence table.

Synthesis of the Evidence

Conduct of meta-analysis. We conducted a Bayesian meta-analysis[18-19] in order 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: (1) grouping RCTs by the indications for which the progestogens were administered in the study (prior preterm birth, multiple gestations, current preterm labor, and study populations with various risk factors) and by (2) the progestogen formulation used in the trial (intramuscular, oral, or vaginal). Data were too sparse to create models addressing the interaction of indications and formulation for the two primary outcomes.

A total of 16 studies were included in the meta-analyses: seven related to effectiveness for preventing preterm birth before 37 weeks and four for reducing mortality in singletons; four for preventing preterm birth before 35 weeks and five for reducing mortality in multiple gestations; and 15 for estimation of effectiveness by formulation.

In order for inferences from meta-analyses to be valid, it must be reasonable to assume the studies are in some way comparable. In the context of Bayesian analysis, we assume an exchangeable model, whereby the units of analysis (here, individual studies), are neither considered to be identical replicates nor entirely unrelated to one another.[20] The meta-analysis

attempts to parametrically estimate both the aspects of the studies that are similar and those which cause them to differ. For understanding the influence of formulation, we estimated an overall effect of varying the formulation of progestogen in relation to both outcomes.

The sampling model for the data expressed both the number of preterm births ($y_i^{(p)}$) and the number of neonatal mortalities ($y_i^{(m)}$) for each of $p^{(preterm)}$=30 and $m^{(mortality)}$=22 groups (either treatment or control) by study combinations as binomial random variables, where the θ values represent the group- and study-specific probabilities of each event. In this model, we posit that the specific values of these parameters vary according to (1) random (unmeasured) processes causing heterogeneity among studies, (2) a treatment effect of administering progestogen during pregnancy, and (3) the specific formulation of the progestogen treatment.

$$y_i^{(p)} \sim \mathrm{Bin}(n_i^{(p)}, \theta_i^{(p)})$$
$$y_i^{(m)} \sim \mathrm{Bin}(n_i^{(m)}, \theta_i^{(m)})$$

To implement this structure, we used a logit-linear mixed model to describe the variation in θ among the studies. The first component of this model, irrespective of whether formulation or indications was used as covariates, is a study-specific random effect $\beta_{0,s[i]}$, where s[i] denotes the study corresponding to observation i. This allows the model intercept for each study to be drawn from a "population" of studies, the distribution of which describes the variability due to any number of factors that are not measured or otherwise cannot be modeled. We chose a normal distribution as the sampling distribution for these parameters.

$$\beta_{0,s[i]}^{(p)} \sim N(\mu^{(p)}, \tau^{(p)})$$
$$\beta_{0,s[i]}^{(m)} \sim N(\mu^{(m)}, \tau^{(m)})$$

To account for potential covariance between the probabilities of preterm birth and neonatal death, these were initially modeled as bivariate normal random variates, with non-zero covariance. However, results from this model gave no indication of substantial covariance, and hence the model was simplified to assume independence. Note that τ_p and τ_m, inverse-variance parameters for the study random effects, are a measure of the heterogeneity among studies for each metric. Hence, large values of τ_p suggest relative homogeneity, while values close to zero indicate a high level of heterogeneity. For ease of interpretation, these were converted to standard deviations, via an inverse square-root transformation.

For estimating the study-specific means of preterm birth probability, we accounted for varying threshold values for determining incidences of preterm birth, which ranged from less than 34 weeks to less than 37 weeks across studies. The mean of the random effect was estimated as a linear function of the threshold value for each study.

The threshold values $w_{s[i]}$ were expressed as additional weeks relative to the lowest threshold value, making the lowest value a baseline, simply equal to γ_0.

$$\mu_{s[i]}^{(p)} = \gamma_0 + \gamma_1 w_{s[i]}$$

The second component of the logit-linear model for formulation effects is an array of fixed

$$\text{logit}(\theta_i^{(p)}) = \beta_{0,s[i]}^{(p)} + \beta_{1,j[i]}^{(p)} I(x_i = j)$$
$$\text{logit}(\theta_i^{(m)}) = \beta_{0,s[i]}^{(m)} + \beta_{1,j[i]}^{(m)} I(x_i = j)$$

effects $\{\beta_{1,\text{ im}}, \beta_{1,\text{oral}}, \beta_{1,\text{ vaginal}}\}$ that account for the effect of progestogen treatment by formulation. Here, *I* is the indicator function, which indexes the appropriate formulation effect parameter for each study. The sum of these components are logit-transformed, to ensure they fall in the [0, 1] interval. Clearly, the $\beta_{1,j[i]}$ are the parameters of interest, and since they are parameters in a logistic regression model they can be interpreted as the log-odds ratio for the effect of treatment via formulation *j*.

$$\delta_j^{(p)} = \exp[\beta_{i,j[i]}^{(p)}]$$
$$\delta_j^{(m)} = \exp[\beta_{i,j[i]}^{(m)}]$$

Similarly, the second component of the logit-linear model for maternal factors consists of a fixed effect for the progestogens treatment for each of three indications.

The models for the indication of multiple gestation included an additional level of hierarchical structure, which accounted for whether the multiple gestation comprised twins or triplets. Specifically, the β_2 parameters were modeled as:

$$\beta_1^{(p)} = \alpha_0^{(p)} I(mgest_i) + \alpha_1^{(p)} I(triplets_i)$$
$$\beta_1^{(m)} = \alpha_0^{(m)} I(mgest_i) + \alpha_1^{(m)} I(triplets_i)$$

where *I* is the indicator function. In other words, the effect of twins would be α_0 and the effect of triplets $\alpha_0 + \alpha_1$. Thus, the parameter α_1 can be interpreted as the marginal increase in effect of triplets on either response variable relative to twins.

Prior distributions. In each model, we sought to minimize the influence of prior information by specifying vague prior distributions for all unknown parameters. For logit-linear model coefficients, this was implemented via normal priors with mean zero and variance 100 (precision 0.01); on the probability scale, this resulted in suitably diffuse priors. To model heterogeneity, the standard deviation (sigma) parameters were given uniform priors over the interval [0, 100], implying equal prior probability for all values in this interval, which exceeds the expected range of variation for the random effects. To examine sensitivity to prior specification for the logit-linear model covariates, models were also run with Cauchy prior distributions with scale parameters set to 2.5. This distribution, with broader tails, is more robust to extreme values. The parameter estimates did not change as a result of using this alternative prior specification.

Estimation. Each model was implemented in PyMC version 2.1,[21] which fits Bayesian hierarchical models using Markov chain Monte Carlo (MCMC) algorithms. One million samples were generated for each model, with the first 900,000 iterations conservatively discarded as burn-in. The remaining samples were thinned by a factor of 10, leaving 10,000 samples for posterior inference. Model outputs showed no evidence of lack of convergence, based on inspection of the posterior samples and on R-hat values (Gelman-Rubin statistics). To check the fit of the model, we conducted posterior predictive checks, which generate simulated datasets

based on the fitted model. The distribution of simulated datasets was then compared to the observed data from the studies in the meta-analysis. The observed data fell within the 95 percent intervals of the simulated datasets for each study, suggesting an acceptable fit of the model to the data.

Rating Quality of Individual Studies

Internal Validity

Randomized allocation to treatment. This assessment combines randomization and method of randomization into a single criterion with a three-point scale.

Rationale: By randomly assigning groups to the intervention of interest, other factors that may confound the results are equally distributed between groups (assuming a large enough sample size). This equal distribution minimizes the chances of over- or under-estimation of treatment effect based on unequal distribution of confounding factors.

If randomized, we also evaluated the study for randomization methods, using the rationale described in Matchar and colleagues, 2001.[22]

Rationale: "Pseudo-randomization" methods may be susceptible to bias, as demonstrated by evidence of unequal distribution of participant characteristics[23] and larger effect sizes compared to studies using more rigorous methods.[24] In addition, methods of allocation concealment are also important in preventing bias (e.g., use of prepared sealed envelopes).

We combined these elements into a single operational definition, as described below:

Operational definition: Criterion met if randomization methods were not susceptible to bias, such as computer-generated numbers in sealed sequentially numbered envelopes (+). Criterion not met by studies that either used methods more prone to bias, such as alternate medical record numbers, or did not describe randomization methods or methods of allocation concealment (-). Criterion not applicable if treatment was not randomly allocated (NA).

Masking. Rationale: Masking, also known as blinding, refers to the concealment of treatment allocation from the care provider, the assessor, and the patient. In certain trials, particularly surgical trials, masking the patient or the surgeon from the treatment allocation can be challenging or impossible. Similarly, masking the assessor assigned to record immediate post-procedural outcomes such as wound healing can also be difficult. Nevertheless, when possible, masking prevents expectations from influencing findings.

Operational definition: Criterion was met if assessors and participants were masked to treatment or group (+). Criterion was not met if either care provider, assessor, or patient were not masked (-). Criterion not applicable if treatment was not randomly allocated.

Adequate description of participants and control selection criteria. Rationale: Patient characteristics that might affect outcomes (such as history of prior preterm birth, gestational age at initiation of treatment, multiple gestation) are likely to differ between two interventions. If these differences are not characterized, then erroneous conclusions may be drawn.

Operational definition: Criterion met if inclusion and exclusion criteria for participation in the study were well described.

We expected that the study population should be adequately described to make clear the potential for confounding in the analysis. We expected the study authors to adequately describe the study population such that it could theoretically be reproducible by another investigator. We expected comparable methods to be used to identify and screen participants across exposure or treatment groups. In addition, where applicable, we expected the study authors to provide a

participant flow diagram; reporting numbers of participants randomly assigned, number of those who received the intended treatment, completed the study protocol, and were included in the analysis of the primary outcome.

Description of loss to followup. Rationale: Failing to account for participants lost to followup may lead to erroneous conclusions, especially if the loss to followup is related to either the underlying disease or the intervention (e.g., participants seeking care elsewhere because of continuing symptoms or unacceptable side effects of treatment).

Operational definition: Criterion met for adequate followup (+) if (a) loss to followup was explicitly reported and (b) no more than 20 percent of any study arm was lost to followup. Those studies with less than 10 percent lost to followup were given an extra (+). Studies with greater than 20 percent loss to followup were considered inadequate for this measure (-).

Description of dropout rates. Rationale: Dropout rates may reflect differences in clinically important variables, such as side effects or treatment response. Failure to account for dropouts may result in erroneous conclusions similar to those seen with failure to account for loss to followup.

Operational definition: Criterion met if (a) participants dropping out of the study prior to completion were reported and (b) no more than 10 percent in any study arm left the study for reasons related to the study intervention or withdrawal of consent. Those studies with less than 5 percent in any study arm who left the study for reasons related to the study intervention or withdrawal of consent were given an extra (+).

Power calculation provided. Rationale: Many studies, especially case series, lack sufficient power to detect clinically important differences in outcomes or patient characteristics.

Operational Definition: Criterion met if a power calculation (pre or post) was provided.

Recognition and description of statistical issues. Rationale: Use of inappropriate tests may lead to misleading conclusions. For example, variables such as birth weight are often not normally distributed; use of means instead of medians when data may be affected by outlying observations can be misleading.

Operational definition: Criterion met if (a) appropriate statistical tests were used (e.g., nonparametric methods for variables with nonnormal distributions, or survival analysis techniques to account for loss to followup and dropouts) and (b) potential study limitations regarding design and analysis were discussed. Criterion not met if (a) inappropriate statistical tests were used or (b) study limitations were not discussed. An intention-to-treat (ITT) analysis was required of clinical trials.

External Validity

Baseline characteristics. We created a composite score for adequacy of the description of baseline characteristics. At minimum, we expected prior preterm birth and multiple gestation information to be presented. If either of these were omitted, criteria were not met. In order to receive a (+) study authors had to provided information on prior preterm birth and multiple gestation as well as at least three of the following: gestational age at initiation, race/ethnicity, body mass index (BMI), parity, smoking status, and outcome of the immediately preceding pregnancy.

Prior Preterm Birth. Rationale: Prior preterm birth is the strongest known predictor of a preterm birth and differences in prevalence in treatment groups would be likely confounders of observed relationships.

Operational definition: Criterion met if summary statistics of a history of preterm birth were given by comparison group or if study inclusion and exclusion criteria state that participants were included or excluded due to a history of preterm birth. Criterion not met if summary statistics were not provided.

Multiple gestation. Rationale: Similarly to prior preterm birth, multiple gestation is a strong risk factor for prior preterm birth and could confound an observed relationship between the treatment and the outcome. Therefore it is important that the distribution of this covariate be equivalent in the treatment groups.

Operational definition: Criterion met if summary statistics or inclusion and exclusion criteria related to multiple gestations were presented by group.

Adequate description of the intervention provided to participants. Rationale: The ability to replicate study results is dependent on adequate description of methods. Additionally, readers should be aware of aspects of clinical care that might influence outcomes.

Operational definition: Criterion met if (a) a detailed description of the therapy (dose, dosing schedule, protocols for behavioral interventions, and route of administration for medications and/or techniques for invasive therapies) was provided; (b) a reference to another publication describing the procedure was provided; or (c) statistical adjustment was made for likely sources of variation in clinical care (e.g., site where care was given, type of specialist providing care, individual provider, dose and timing).

Criterion not met if (a), (b), or (c) was not provided.

Adequate description of the outcomes. Rationale: Studies should designate a "called shot" or intended a priori primary outcome, and should provide group level data on that outcome at a minimum. Therefore, those that purport to attempt to change rates of preterm birth and birthweight should provide data by group on gestational age and birthweight.

Adequate length of followup for infant. Rationale: In an effort to capture longer term maternal and neonatal outcomes, we required that studies include followup information for the infant. In order to get a (+), studies needed to include outcome measures up to and including discharge from the hospital. Studies that included outcomes after hospitalization received (++). In addition, studies that only included measures up to the birth of the infant received (-).

Adequate description of methods used for outcome measurement. Rationale: Comparison between studies requires common methods of measurement, which in turn requires adequate description of the methods used to assess comparability.

Operational definition: Criterion met if (a) methods used to measure outcomes were adequately described or referenced, (b) definitions were given (e.g., definition of criteria for gestational age dating), or (c) outcomes were unambiguous (e.g., birth weight). Criterion not met if (a), (b), or (c) was not present.

Adequate description of reliability of outcome measurement. Rationale: Measurements of outcomes are only useful if changes in the outcome being measured are reflected in changes in the measurement (validity) and if these changes are reasonably consistent between the same observer measuring at different times or between different observers (reliability). For example, changes in a scale to assess menstrual blood flow should correlate with some other physiological measure of menstrual blood loss, and this correlation should be consistent when different women apply the same scale.

Operational definition: Criterion met if (a) a description of the methods used to assess validity and reliability of at least one outcome measure was provided, (b) a reference to another article documenting validity and reliability was provided, or (c) only unambiguous outcomes were included as primary outcomes. Criterion not met if none (a), (b), or (c) was not present.

Composite Quality Scores

A composite quality score of good, fair, or poor was calculated for both internal and external validity. The internal validity score was based on ten measures (see list above). In order to receive a rating of good, studies could not have any negative (-) scores. Studies were considered fair if they received three or fewer negative scores, or had intermediate levels of loss-to-followup or drop out. Studies were rated poor quality if they (1) had the highest level of loss-to-followup or dropout, (2) received four or more negative scores, or (3) had both three negative scores and intermediate loss-to-followup. The external validity score was based on eight measures, including the composite score for baseline scores (see list above). In order to receive a rating of good, studies could not have any negative (-) scores. The designation of fair quality was given to those studies that received one to three negative (-) scores. Poor quality scores were given to studies with four or more negative (-) scores.

Scores for internal and external validity were combined in order to determine overall quality. Studies with both good internal and external validity were characterized as good. Studies with any combination of good and fair, good and poor, or fair and fair for each measure were considered fair quality overall. Studies receiving any combination of poor and fair or those receiving poor for both internal and external validity were considered poor quality. The scoring algorithm for rating the quality of individual studies is included in Table 2. Quality scores for individual studies are presented in Appendix E.

Table 2. Scoring algorithm for quality rating

Definition and Scoring Algorithm	Rating
Score Algorithm for Internal Validity Quality Rating	
• No negative scores, lowest loss-to-followup score, and lowest dropout rate	Good internal validity
• One to three negative scores or intermediate loss-to-followup score or dropout rate	Fair internal validity
• High loss-to-followup score or high dropout rate ***OR***	Poor internal validity
• Four negative scores ***OR***	
• Three negative scores and intermediate loss-to-followup score	
Score Algorithm for External Validity Quality Rating	
• No negative scores	Good external validity
• One to three negative scores	Fair external validity
• Four or more negative scores	Poor external validity
Score Algorithm for Overall Quality Rating	
• Good internal validity and good external validity	Good overall
• Fair internal validity and fair external validity ***OR***	Fair overall
• Good internal validity and fair external validity ***OR***	
• Good internal validity and poor external validity ***OR***	
• Fair internal validity and good external validity ***OR***	
• Poor internal validity and good external validity	
• Poor internal validity and poor external validity ***OR***	Poor overall
• Fair internal validity and poor external validity ***OR***	
• Poor internal validity and fair external validity	

Grading Strength of Evidence

Strength of evidence is typically assigned to reviews of medical treatments after assessing four domains: risk of bias, consistency, directness and precision.[25-26] Although these categories were developed for assessing the strength of treatment studies, the domains apply also to studies of prevalence and screening. Available evidence for each KQ was assessed for each of these four domains; the domains were combined qualitatively to develop the strength of evidence for each KQ.

We graded the body of literature for each KQ and present those ratings as part of the Discussion section (below). The possible grades were:

I. High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.

II. Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

III. Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.

IV. Insufficient: Evidence is either unavailable or does not permit a conclusion.

Applicability

For decision makers to use this report to inform clinical care, it is important to consider the degree to which findings of the included research might be expected to apply in the types of populations and settings in which prenatal care is provided in the United States. Our assessment of applicability took place in two steps: (1) summary of similarity or lack of comparability of populations, interventions, comparison groups, outcomes, and settings represented in the available literature for each KQ (see Appendix E) and (2) eight questions on external validity on each study during quality assessment:

1. Were baseline characteristics related to the risk of preterm birth reported in sufficient detail to allow the reader to assess similarities or differences from a clinical population of interest?
2. Was the intervention adequately described to the degree that it could be replicated?
3. Was the primary outcome indicated and relevant to the use of progestogens in clinical care to prevent preterm birth?
4. Was a summary measure of gestational age at birth provided by group?
5. Was a summary measure of birth weight provided by group?
6. What was the timing of outcome measurement from initiation of treatment?
7. Do the authors define timing, approach, and tools for collection of outcome information?
8. Has the measurement approach/tool used for the primary outcome(s) been characterized in this or prior publications with respect to reliability and repeatability?

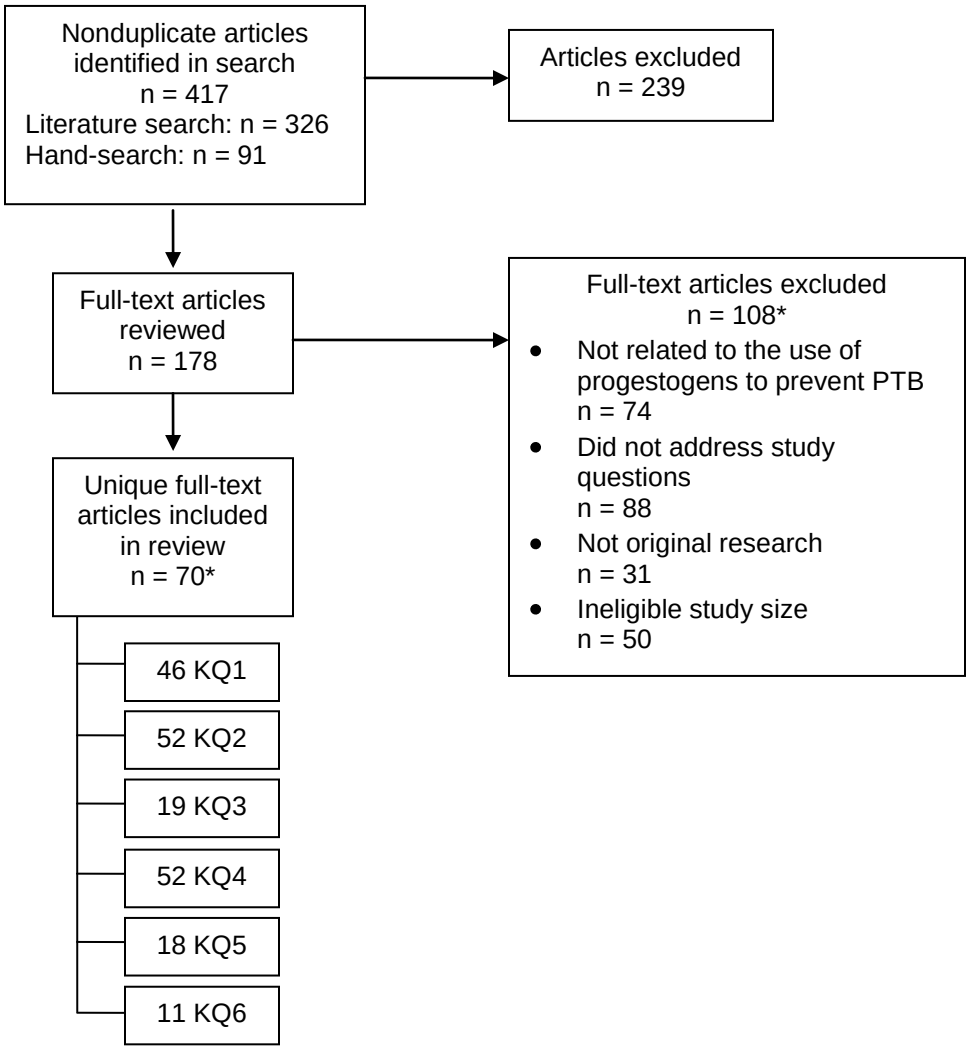
Peer Review and Public Commentary

Experts were invited to provide external peer review. The draft report was posted for four weeks to elicit public comment (Appendix F). We addressed all reviewer comments by revising the text as appropriate. We responded to each comment submitted from peer and public review in a disposition of comments report. This report will be available on the AHRQ Web site 3 months after the posting of this final CER.

Results

We identified 417 nonduplicate publications through the search process, with 178 proceeding to full text review (Figure 2). Seventy articles were included in the review, representing 63 distinct study populations: 28 RCTs, four clinical trials, 14 cohort studies, eight case-series, six case-control studies, and three cross-sectional studies. The most common reasons for exclusion were irrelevance to the topic and ineligible study size. Forty-six articles pertain to Key Question (KQ) 1, 52 articles to KQ2, 19 articles to KQ3, 52 articles to KQ4, 18 articles to KQ5, and 11 articles to KQ6. Table 3 provides a summary of the progestogen interventions represented in this review in reverse chronologic order. The progestogen interventions include 31 distinct combinations of formulations, route, and dose.

Figure 2. Disposition of articles identified by the search strategy



KQ=Key Question
*The number of articles addressing KQs and those excluded exceed the total number of articles in each category because some articles fit multiple exclusion categories or addressed more than one KQ.

Table 3. Summary of progestogen interventions

Study Country Total N	Progestogen	Form	Dose & Interval	Target EGA, start; end (weeks)	Indication
Mason et al.[27] 2010 U.S. N=253	17OHP	NR	NR	≤ 28 6/7; NR	Prior PTB
Harper et al.[28] 2010 U.S. N=852	17OHP	IM	250 mg q 7d	16-21.9; 36.9	Prior PTB
Gonzalez-Quintero et al.[29] 2010 U.S. N=4,238	17OHP	IM	250 mg q 7d	≤ 26; 36	Prior PTB
Combs et al.[30] 2010 U.S. N=89	17OHP	IM	250 mg q 7d	16-22; 34	Triplets
Cetingoz et al.[31] 2010 Turkey N=160	Progesterone†	Vaginal Supp	100 mg qd	24; 34	Varied risk factors
Berghella et al.[32] 2010 U.S. N=300	17OHP	IM	250 mg q 7d	16; 36	Varied risk factors
Rittenberg et al[33]. 2009 U.S. N=770	17OHP	IM	250 mg q 7-10d	< 21 (80.4%); 36	Prior PTB
Rai et al.[34] 2009 India N=150	Progesterone†	Oral	100 mg b.i.d.	18-24; 36	Prior PTB
Norman et al.[35] 2009 UK N=500	Progesterone	Vaginal Gel	90 mg qd	24; 34	Twins
Majhi et al.[36] 2009 India N=100	Progesterone†	Vaginal Cap	100 mg qd	20-24; 36	Prior PTB
Keeler et al.[37] 2009 U.S. N=91	17OHP	IM	250 mg q 7d	16-24; 36	Varied risk factors
Gyamfi et al.[38] 2009 U.S. N=1,094	17OHP	IM	250 mg q 7d	16-20.9; 34-36	Prior PTB Twins
Durnwald et al.[39] 2009 U.S. N=200	17OHP	IM	NR	15.0 ± 4.1; 36	Prior PTB
Caritis et al.[40] 2009 U.S. N=134	17OHP	IM	250 mg q 7d	16-21; 35	Triplets
Briery et al.[41] 2009 U.S. N=30	17OHP	IM	250 mg q 7d	20-30; NR	Twins
Ventolini et al.[42] 2008 U.S. N=606	17OHP	IM	250 mg q 7d	16-20.9; NR	Prior PTB

Table 3. Summary of progestogen interventions (continued)

Study Country Total N	Progestogen	Form	Dose & Interval	Target EGA, start; end (weeks)	Indication
Rittenberg et al.[43] 2008 U.S. N=166	17OHP	IM	250 mg q 7d	16-26; NR	Prior PTB
Rebarber et al.[44] 2008 U.S. N=1,882	17OHP	IM	250 mg q 7d	16-29; NR	Prior PTB
Mason et al.[45] 2008 U.S. N=104	17OHP	IM	250 mg q 7d	16-21 or > 21; NR	Prior PTB
Facchinetti et al.[46] 2008 Italy N=45	17OHP	IM	341 mg q 4d	25-34; 36	PTL
Borna et al.[47] 2008 Iran N=70	Progesterone†	Vaginal Supp	400 mg qd	24-34; NR	PTL
Rouse et al.[48] 2007 U.S. N=661	17OHP	IM	250 mg q 7d	16-20; 36	Twins
Rittenberg et al.[49] 2007 U.S. N=2,159	17OHP	IM	250 mg q 7d	16-20.9 (56.5%); NR	Health system
Rebarber et al.[50] 2007 U.S. N=2,081	17OHP	IM	250 mg q 7d	16-20.9; NR	Health system
Rebarber et al.[51] 2007 U.S. N=481	17OHP	IM	250 mg q 7-10 d	16-20.9; 37	Health system
O'Brien et al.[52] 2007 Multinational N=669	Progesterone	Vaginal Gel	90 mg qd	16-23; 37	Prior PTB
How et al.[53] 2007 U.S. N=906	17OHP	IM	Unknown q 7d	16-20.9 (66%); NR	Prior PTB
Gonzalez-Quintero et al.[54] 2007 U.S. N=515	17OHP	IM	Unknown q 7d	16-20.9 (56.7%); NR	Prior PTB
Fonseca et al.[55] 2007 Multinational N=250	Progesterone†	Vaginal Cap	200 mg qd	24; 34	Short cervix
Facchinetti et al.[56] 2007 Italy N=60	17OHP	IM	341 mg q 4d	25-34; 36	PTL
Bailit et al.[57] 2007 U.S. N=502	Progesterone	IM, Vaginal	NR	NR	Health system
Dudas et al.[58] 2006 Hungary N=60,994	17OHP	IM	250 mg qd	NR	Varied risk factors

Table 3. Summary of progestogen interventions (continued)

Study Country Total N	Progestogen	Form	Dose & Interval	Target EGA, start; end (weeks)	Indication
Mason et al.[59] 2005 U.S. N=38	17OHP	IM	250 mg q 7d	16-21; 36	Health system
Meis et al.[60] 2003 U.S. N=463	17OHP	IM	250 mg q 7d	16-21; 36	Prior PTB
da Fonseca et al.[61] 2003 Brazil N=157	Progesterone	Vaginal Supp	100 mg qd	24; 34	Varied risk factors
Corrado et al.[62] 2002 Italy N=584	Progesterone	IM	200 mg qd for 3 d after amniocentesis	16.7 ± 0.8 at amniocentesis; NR	Other
	17OHP	IM	340 mg twice a week until 2nd week after amniocentesis		
Bacq et al.[63] 1997 France N=100	Progesterone† (68.0%)	Oral	200-1,000 mg qd	NR	Other
Hobel et al.[64] 1994 U.S. N=3,459	Provera	Oral	20 mg (NR)	> 20; NR	Varied risk factors
Noblot et al.[65] 1991 France N=44	Ritodrine	IV drip	0.2 mg/min for 1h	NR	PTL
	Progesterone†	Oral	4x 100 mg q6h for 24h; 4x 100 mg q8h for 24h; 3 100 mg q8h		
Suvonnakote[66] 1986 Thailand N=75	17OHP	IM	250 mg q 7d	16-20; 38	Varied risk factors
Erny et al.[67] 1986 France N=7	Progesterone†	Oral	4, 100 mg capsules (NR)	30-36; NR	PTL
Yemini et al.[68] 1985 Israel N=80	17OHP	IM	250-12,500 mg over 36 wks (NR)	12.2 ± 3.3; 37	Varied risk factors
Resseguie et al.[69] 1985 U.S. N=4,719	17OHP	NR	NR	8.6 (median); NR	Other
	Progesterone	NR	NR	8.5 (median); NR	
Kester et al.[70] 1984 U.S. N=50	17OHP	IM	250 mg q 7d	4-24; NR	Other
Szekeres-Bartho et al.[71] 1983 Hungary N=33	17OHP	IM	250 mg q 7d	27-30; 34	PTL
Hauth et al.[72] 1983 U.S. N=246	17OHP	IM	1,000 mg q 7d	16-20; 36	Varied risk factors
Kauppila et al.[73] 1980 Finland N=48	17OHP	IM	250 mg day 1 and 3; 250 mg q 7d	27-36; 37	PTL

Table 3. Summary of progestogen interventions (continued)

Study Country Total N	Progestogen	Form	Dose & Interval	Target EGA, start; end (weeks)	
Hartikainen-Sorri et al.[74] 1980 Finland N=77	17OHP	IM	250 mg q 7d	28-33; 36	Twins
Cortes-Prieto et al.[75] 1980 Spain N=415	Allylestrenol	Oral	10-40 mg qd	NR; 1-2 before term	Varied risk factors
Kester et al.[13] 1980 U.S. N=62	DES	NR	50-14,000 mg (NR)	6, 36	Other
	DES; Progesterone	NR	56-14,215 mg (NR); 100-1,890 mg (NR)		
	Natural Progesterone	NR	25-1,955 mg (NR)		
	Synthetic Progesterone	NR	125-2,198 mg (NR)		
Johnson et al.[76] 1979 U.S. N=21	17OHP	IM	250 mg q 7d	16; 36	Varied risk factors
Breart et al.[77] 1979 France N=211	17OHP	IM	500 mg 2x/wk	20-34; 37	PTL
	Chlormadinone acetate	Oral	25 mg qd		
Reinisch & Karrow[78] 1977 U.S. N=141	Unspecified progestin	NR	Total: 478-10,650 mg (NR)	4.0; 36.1	Other
Meyer-Bahlburg et al.[15] 1977 U.S. N=204	Unspecified	NR	NR	NR	Other
Johnson et al.[79] 1975 U.S. N=50	17OHP	IM	250 mg q 7d	< 24; 37	Prior PTB
Hill et al.[80] 1975 U.S. N=73	17OHP	NR	250-7,500 mg (NR)	13.6; NR	Other
	Progesterone	IM	100 mg (NR)		
Øvlisen & Iversen[16] 1963 Denmark N=63	6α-methyl-17α-acetoxy-progesterone	NR	180 mg qd for 3 d, then 60 mg qd for 4 d	NR	PTL
Fuchs & Stakemann[14] 1960 Denmark N=126	Progesterone	NR	200 mg qd for 3 d, then 150 mg for 2 d, & then 100 mg qd	NR	PTL

† Micronized progesterone

17OHP = 17 alpha-hydroxyprogesterone caproate; Cap = capsule; IM = intramuscular; mg = milligrams; NR = not reported; PTB = preterm birth; PTL = preterm labor; q = every; qd = every day; Supp = suppository; wk = week.

KQ1. Maternal, Fetal, and Neonatal Health Outcomes

In this section we provide an overview of the content of the literature focused on the types of studies, settings, and study populations that make up the current state of the science. Then in turn, we summarize the evidence that relates progestogen use to antenatal and maternal outcomes, risk of preterm birth, and fetal and neonatal outcomes. Within each of these outcome categories we have organized the research findings by the risk factors that made the study participants eligible for progestogen treatment. These indications included prior preterm birth, multiple gestations, symptomatic preterm labor, short cervix, and treatment of those women with multiple risk factors. We organized outcomes by the risk factors of the study populations, since applicability is a central question for women, clinicians, and payers who want to know: does this research apply in this situation? Is this intervention likely to provide benefit if used for an individual with specific characteristics that make her at higher risk of preterm birth? Where a sufficient number of studies with some common elements allowed, we have provided aggregate estimates of effects from meta-analyses.

Content of the Literature

Forty-six publications address maternal, fetal, and neonatal health outcomes of progestogen treatment for prevention of preterm birth. They represent 41 unique study populations. These 41 studies include 26 RCTs;[14, 30-32, 34-37, 39, 41, 46-48, 52, 55-56, 60-62, 64-65, 67-68, 72, 77, 79] four clinical trials;[66, 71, 73-74] and eleven observational studies, including seven retrospective cohort studies,[27, 29, 33, 39, 44, 59, 80] two prospective cohort studies,[75-76] one prospective case series;[16] and one case-control study.[58] Of the 41, 18 were conducted in the United States, 15 in Europe, three in Asia, three in the Middle East, one in South America, and one on multiple continents including U.S. centers.

The preterm birth risk factor prompting progestogen treatment varied. Ten studies focused on women with a history of preterm birth;[27, 29, 33-34, 36, 39, 44, 52, 59-60] ten on preterm labor;[14, 16, 46-47, 56, 65, 67, 71, 73, 77] six on multiple gestations (four studies of twin pregnancies[35, 41, 48, 74] and two with triplets);[40, 81] eleven studies enrolled populations with a variety of risk factors;[31-32, 37, 58, 61, 64, 66, 68, 75-76, 79] one focused on asymptomatic women with a short cervix on midgestation ultrasound;[55] one on active-duty military personnel;[72] one on abdominal surgery during but unrelated to the pregnancy;[80] and one on midtrimester amniocentesis.[62] Studies of populations with varied risk factors included previously mentioned indications, such as history of preterm birth, as well as other conditions, such as previous spontaneous abortion, threatened spontaneous abortion, uterine anomaly, short cervical length and incompetent cervix.

The 41 studies include 23 unique combinations of progestogen formulation, route, and dose. The intramuscular route was most common with 25 studies using intramuscular 17OHP, one using crystalline progesterone, and one using a combination of natural progesterone and 17OHP injections. Seven studies used vaginal progestogens including three with suppositories, two with gel, and two with capsules. Six studies administered oral progestogens including micronized progesterone in three, medroxyprogesterone acetate (trade names Provera® and Perlutex®) in two, and allylestrenol in one. One study compared two progestogens, intramuscular 17OHP and oral chlormadinone acetate.

Maternal Health Outcomes

Preterm birth is associated with significant maternal morbidity and health care utilization. Progestogen treatment is aimed at not only preventing preterm birth and its associated fetal and neonatal health outcomes, but also improving maternal health outcomes. Thirty-two studies reported maternal health outcomes other than preterm birth (studies for which preterm birth is the only maternal health outcome reported can be found below in the discussion of preterm birth findings). The most clinically significant and frequently reported outcomes for complications during pregnancy and mode of birth are presented in Tables 4-7, of note each of these is mediated by the care provider as part of the process of care; none are patient reported or longer term. Within each table, studies are grouped by progestogen route (intramuscular, vaginal, and oral). Within each route, RCTs are listed first followed by clinical trials and observational studies, and each group of study types is in reverse chronological order.

In addition to those presented in Tables 4-7, other reported maternal health outcomes include spontaneous abortion;[60, 62, 68] changes in cervical length;[39, 46, 56] cerclage placement;[37, 40, 48, 79] contraction frequency in women diagnosed with preterm labor;[61, 65, 67] details of tocolysis use, such as timing, quantity, and duration;[65, 77] use of antenatal steroids;[30, 40-41, 48, 52, 60] hypertensive disorders;[30, 40, 48, 72] gestational diabetes;[30] placental abruption;[37] premature rupture of membranes;[62] chorioamnionitis;[30, 35, 37, 40, 48, 60] sepsis;[30] timing of birth in relation to treatment using categorical measures for time;[14, 16] duration of labor stages;[35] postpartum endometritis;[30] and postterm pregnancy.[72]

History of preterm birth. Among studies reporting maternal health outcomes, eight examined progestogen treatment in women with a history of preterm birth, including four RCTs[34, 36, 52, 60] and four observational studies.[29, 33, 39, 44] Seven of these studies reported maternal outcomes presented in Table 4, and one reported maternal outcomes not presented in the table.[39] Of the seven studies presented in Table 4, the intervention was intramuscular 17OHP in four,[29, 33, 44, 60] a vaginal micronized progesterone capsule in one,[36] vaginal progesterone gel in one,[52] and oral micronized progesterone in one.[34] Three of the RCTs had a placebo arm,[34, 52, 60] and the fourth had a no-treatment arm.[36] In the three retrospective cohort studies,[29, 33, 44] the women not receiving progesterone had daily nursing surveillance.

Table 4. Maternal outcomes for women with a history of preterm birth

Author Year Study Type	Intervention (N)	Antenatal Admission (%)	Preterm Labor (%)	Tocolysis (%)	PPROM (%)	Cesarean Birth (%)
Meis et al.[60] 2003 RCT	IM (305)	16.0	NR	17.3	NR	25.2
	Placebo (153)	13.8	NR	15.9	NR	26.8
González-Quintero et al.[29] 2010 Retrospective cohort	IM (2,978)	NR	NR	13.9*	NR	NR
	Daily outpatient nursing contact (1,260)	NR	NR	75.0	NR	NR

Table 4. Maternal outcomes for women with a history of preterm birth (continued)

Author Year Study Type	Intervention (N)	Antenatal Admission (%)	Preterm Labor (%)	Tocolysis (%)	PPROM (%)	Cesarean Birth (%)
Rittenberg et al.[33] 2009 Retrospective cohort	IM (342)	12.6*	39.2*	12.9*	7.3	NR
	Daily outpatient nursing contact (342)	43.0	60.8	49.7	8.5	NR
Rebarber et al.[44] 2008 Retrospective cohort	IM (232)	45.7*	45.7*	NR	8.6	NR
	Daily outpatient nursing contact (1,650)	70.8	70.8	NR	8.1	NR
Majhi et al.[36] 2009 RCT	Vaginal (50)	2.0	NR	NR	NR	8.0
	None (50)	6.0	NR	NR	NR	14.0
O'Brien et al.[52] 2007 RCT	Vaginal (309)	25.6	NR	11.3	12.0	29.0
	Placebo (302)	24.8	NR	10.3	12.6	27.8
Rai et al.[34] 2009 RCT	Oral (74)	NR	NR	20.3	NR	NR
	Placebo (74)	NR	NR	27.0	NR	NR

*Findings are statistically significant across treatment and placebo groups. IM = intramuscular; NR = not reported; PPROM = preterm premature rupture of membranes; RCT = randomized control trial.

Five studies reported antenatal hospitalizations. Three RCTs did not find a significant difference in antenatal hospitalizations with progestogen treatment compared to no treatment.[36, 52, 60] One of these trials[36] found the rate of antenatal hospitalizations was lower with vaginal progesterone compared to no treatment (2% vs. 6%, p=0.30). The other two trials found a higher rate of antenatal hospitalizations with progestogens, including one[60] with intramuscular 17OHP versus placebo (16.0% vs. 13.8%; risk ratio (RR)=1.14; 95% confidence interval (CI): 0.72, 1.86) and another[52] with vaginal progesterone versus placebo (25.6% vs. 24.8%; RR=1.14; 95% CI: 0.38, 3.37). The two retrospective cohort studies[33, 44] that compared progesterone with daily nursing surveillance did find a significantly lower rate of antenatal hospitalizations in women treated with intramuscular 17OHP ($p < 0.001$ in both). One study[44] found a 45.7 percent hospitalization rate in the 17OHP group compared to 70.8 percent in the control group, and the other study[33] had a 12.6 percent hospitalization rate in the 17OHP group compared to 43.0 percent in the control group.

These two retrospective cohort studies[33, 44] also found a significantly lower rate of preterm labor in women treated with intramuscular 17OHP versus daily nursing surveillance ($p < 0.001$ for both). One study[44] found a 45.7 percent rate of preterm labor in the 17OHP group compared to 70.8 percent in the control group, and the other study[33] had a 39.2 percent preterm labor rate in the 17OHP group compared to 60.8 percent in the control group. None of the other studies reported preterm labor rates.

Five studies reported the rates of tocolysis. Three RCTs did not report a significant difference in tocolysis when women received progestogens.[34, 52, 60] The rate of tocolysis was higher with progestogen treatment in a trial[60] comparing intramuscular 17OHP to placebo (17.3% vs. 15.9%; RR=1.09; 95% CI: 0.70, 1.69) and a trial[52] comparing vaginal progesterone to placebo (11.3% vs. 10.3%; odds ratio (OR)=1.12; 95% CI: 0.67, 1.86). The third RCT with nonsignificant findings[34] found a lower rate of tocolysis with oral progesterone compared to placebo (20.3% vs. 27. 0%, p=0.686). Two of the retrospective cohort studies[29, 33] found a significantly lower rate of tocolysis in women treated with intramuscular 17OHP compared to those who received daily nursing surveillance (12.9% vs. 49.7%, $p < 0.001$[33] and 13.9% vs. 75.0%, $p<0.001$).[29]

Three studies reported PPROM rates,[33, 44, 52] and did not find a significant difference. The PPROM rate was minimally higher in one study[44] comparing intramuscular 17OHP to placebo (8.6% vs. 8.1%, p=0.770). The other studies found a lower PPROM rate with progestogen treatment, including one study[52] with vaginal progesterone versus placebo (12.0% vs. 12.6%; OR=0.95; 95% CI: 0.58, 1.53) and another study[33] with intramuscular 17OHP versus outpatient nursing surveillance (7.3% vs. 8.5%, p=0.677).

Three studies reported cesarean rates[36, 52, 60] and did not find a significant difference. One study[52] found a higher cesarean rate with vaginal progesterone compared to placebo (29.0% vs. 27.8%; OR=1.06; 95% CI: 0.75, 1.51). The other studies found a lower rate of cesarean with progestogen treatment, including one study[36] with vaginal progesterone versus no treatment (8% vs. 14%; p=0.33) and another study[60] with intramuscular 17OHP versus placebo (25.2% vs. 26.8%; RR=0.94; 95% CI: 0.68, 1.30).

Preterm labor. Preterm labor was the indication for progestogen treatment in nine studies reporting maternal health outcomes, including seven RCTs,[14, 46-47, 56, 65, 67, 77] one clinical trial,[73] and one observational study.[16] Five of these studies reported maternal outcomes presented in Table 5, and four reported maternal outcomes not presented in the table.[14, 16, 46, 67, 71] Enrollment sizes for studies not included in Table 5 ranged from 45 to 126 participants. Each the five trials in Table 5 used a different dose and route of progestogens. The second trial arm was placebo in one trial;[65] no treatment in two trials;[47, 56] and a different intervention in two trials, including a different progestogen in one[77] and a tocolytic[73] in the other.

Table 5. Maternal outcomes for women with preterm labor

Author Year Study Type	Intervention (N)	Antenatal Admission (d)	PTL Recurrence (%)	Tocolysis (%)	PPROM (%)	Latency From PTL to Birth Days ± SD	Cesarean Birth (%)
Facchinetti et al.[56] 2007 RCT	IM (30)	NR	NR	NR	NR	35.3 ± 19.1*	NR
	None (30)	NR	NR	NR	NR	25.5 ± 15.1	NR
Bréart et al.[77] 1979 RCT	IM (105)	NR	NR	37.0	NR	NR	NR
	Oral (106)	NR	NR	35.0	NR	NR	NR

Table 5. Maternal outcomes for women with preterm labor (continued)

Author Year Study Type	Intervention (N)	Antenatal Admission (d)	PTL Recurrence (%)	Tocolysis (%)	PPROM (%)	Latency From PTL to Birth Days ± SD	Cesarean Birth (%)
Kauppila et al.[73] 1980 CT	IM (24)	NR	NR	0	NR	38.1 ± 4.3	NR
	Ritodrine (24)	NR	NR	100	NR	35.9 ± 5.7	NR
Borna et al.[47] 2008 RCT	Vaginal (33)	NR	35.1	NR	NR	36.1 ± 17.9	NR
	None (37)	NR	57.6	NR	NR	24.5 ± 27.2	NR
Noblot et al.[65] 1991 RCT	Oral with Ritodrine (22)	13.6 (n=21)*	NR	100	4.5	42	NR
	Placebo with Ritodrine (22)	17.8 (n=18)	NR	100	13.6	45	NR

*Findings are statistically significant.
CT = clinical trial; IM = intramuscular; NR = not reported; PPROM = preterm premature rupture of membranes; PTL = preterm labor; RCT = randomized control trial; SD = standard deviation.

One trial[65] reported on antenatal hospitalizations by mean days hospitalized and found a significantly shorter duration in women treated with oral micronized progesterone and Ritodrine versus placebo and Ritodrine (13.6 days vs. 17.8 days, $p < 0.05$). One trial[47] evaluated the recurrence rate of preterm labor and found it was lower with vaginal progesterone compared to no treatment (35.1% vs. 57.6%), but this difference was not statistically significant (p=0.092). Tocolysis could not be assessed as an outcome in two trials, because it was part of the intervention[65] or second arm.[73] The other trial[77] with tocolysis data analyzed rates in women receiving two progestogens (oral chlormadinone acetate vs. intramuscular 17OHP) and found a nonsignificant difference between the two treatments (35% for oral vs. 37% for intramuscular, p-value not reported). One trial[65] reported rates of PPROM and found a nonsignificant difference between groups treated with oral micronized progesterone and Ritodrine versus placebo and Ritodrine (4.5% vs. 13.6%, p-value not reported).

Four trials reported on the latency period from preterm labor treatment to birth. In two trials, the latency period was significantly longer in women treated with progestogens, including one[47] with vaginal progesterone versus no treatment (36.1 ± 17.9 days vs. 24.5 ± 27.2 days, p=0.037) and another[56] with intramuscular 17OHP versus no treatment (35.3 ± 19.1 days vs. 25.5 ± 15.1 days, p=0.003).[56] These two trials had a significant risk of bias; they did not have a placebo control, the event numbers were small, and the confidence intervals were wide. The other two trials found nonsignificant differences in the latency period (p-values not reported) with a longer latency period in the progestogen group (38.1 ± 4.3 days vs. 35.9 ± 5.7 days) in one trial[73] and in the placebo group (6.0 weeks with progestogen vs. 6.4 weeks with placebo) in the other trial.[65]

Multiple gestation. Multiple gestation was the indication for progestogen treatment in six studies, including five RCTs[30, 35, 40-41, 48] and one clinical trial,[74] all of which reported maternal health outcomes presented in Table 6. Four trials included twin gestations,[35, 41, 48, 74] and two trials included triplet gestations.[30, 40] The intervention was intramuscular 17OHP 250 mg weekly in five trials[30, 40-41, 48, 74] and vaginal progesterone gel 90 mg in one trial.[35] All of the trials included a placebo arm.

Table 6. Maternal outcomes for women with multiple gestation

Author Year Study Type	Intervention (N)	Antenatal Admission (%)	Preterm Labor (%)	Tocolysis (%)	PPROM (%)	Cesarean Birth (%)
Combs et al.[30] 2010 RCT	IM (56, triplets)	NR	NR	78.6	NR	92.9
	Placebo (25, triplets)	NR	NR	68.0	NR	100
Briery et al.[41] 2009 RCT	IM (16, twins)	NR	45.0	45.0	6.0	NR
	Placebo (14, twins)	NR	35.0	35.0	7.0	NR
Caritis et al.[40] 2009 RCT	IM (71, triplets)	NR	NR	47.0	8.0	100
	Placebo (63, triplets)	NR	NR	44.0	11.0	98.0
Rouse et al.[48] 2007 RCT	IM (325, twins)	NR	NR	21.9	NR	61.7
	Placebo (330, twins)	NR	NR	29.4	NR	62.2
Hartikainen-Sorri et al.[74] 1980 CT	IM (39, twins)	94.9	NR	NR	NR	NR
	Placebo (38, twins)	89.5	NR	NR	NR	NR
Norman et al.[35] 2009 UK RCT	Vaginal (250, twins)	NR	NR	NR	NR	59.2*
	Placebo (250, twins)	NR	NR	NR	NR	64.4

*Findings are statistically significant.
CT = clinical trial; IM = intramuscular; NR = not reported; PPROM = preterm premature rupture of membranes; RCT = randomized control trial.

One trial of twin pregnancies[74] reported antenatal admission rates and duration of hospitalization. More women treated with intramuscular 17OHP (94.9%) than placebo (89.5%) were hospitalized, but the length of stay was shorter for the 17OHP group (23.5 ± 10.9 days) than the placebo group (31.2 ± 16.0 days). A test of statistical significance was not reported for the admission rates, but the difference for hospitalization duration was significant ($p < 0.01$).

One RCT of twin pregnancies[41] reported rates of preterm labor and found a higher, but not statistically significant difference, in women treated with intramuscular 17OHP compared to placebo (45% vs. 35%, p=0.98). Four multiple gestation trials reported tocolysis rates.[30, 40-41, 48] Two RCTs of triplet pregnancies[30, 40] found a higher rate of tocolysis with intramuscular 17OHP compared to placebo (47% vs. 44%; RR=1.0; 95% CI: 0.7, 1.5 and 79% vs. 68%; OR=1.73; 90% CI: 0.51, 5.55) as did a RCT of twin pregnancies[41] comparing intramuscular 17OHP to placebo (45% vs. 35%, p=0.98). The third RCT reporting tocolysis rates[48] found a lower rate of tocolysis with intramuscular 17OHP in twin pregnancies compared to placebo (21.9% vs. 29.4%; RR=0.7; 95% CI: 0.6, 1.0).

Two trials reported rates of PPROM[40-41] and both found a slightly lower rate with progestogen treatment, including a RCT of triplet pregnancies[40] comparing intramuscular 17OHP to placebo (8% vs. 11%; RR=0.8; 95% CI: 0.3, 2.1) and a RCT of twin pregnancies[41]

comparing intramuscular 17OHP to placebo (6% vs. 7%, p=0.525). Four trials reported cesarean birth rates.[30, 35, 40, 44] One RCT[35] found significantly lower cesarean birth rates with treatment with vaginal progesterone gel versus placebo (59.2% vs. 64.4%, p=0.006). The other three trials that reported cesarean birth rates did not find a significant difference with progestogen treatment, including two RCTs of triplet pregnancies[30, 40] comparing intramuscular 17OHP to placebo (100% vs. 98%; RR=1.0; 95% CI: 1.0, 1.1 and 93% vs. 100%; p > 0.99) and a RCT of twin pregnancies[48] comparing intramuscular 17OHP to placebo (61.7% vs. 62.2%; RR=1.0; 95% CI: 0.9, 1.1).

Study populations with varied risk factors. Among studies reporting maternal outcomes other than preterm birth, five examined progestogen treatment in populations with varied risk factors (a variety of indications within a single study). Four were RCTs[31, 37, 61, 68] that included outcomes presented in Table 7, and one was an observational study (n=50) that reported maternal outcomes not presented in the table.[79] Of the trials presented in Table 7, two used a vaginal progesterone suppository,[31, 61] two used intramuscular 17OHP,[37, 67] three had a placebo arm, and one had a cerclage arm.[37]

Table 7. Maternal outcomes for study populations with varied risk factors

Author Year Study Type	Intervention (N)	Antenatal Admission (%)	Preterm Labor (%)	Tocolysis (%)	PPROM (%)	Cesarean Birth (%)
Keeler et al.[37] 2010 RCT	IM (37)	NR	NR	NR	37.1	NR
	Cerclage (42)	NR	NR	NR	32.5	NR
Yemini et al.[68] 1985 RCT	IM (39)	NR	29.0*	NR	6.4	NR
	Placebo (40)	NR	59.4	NR	8.1	NR
Cetingoz et al.[31] 2010 RCT	Vaginal (70)	25.0*	NR	NR	3.8	NR
	Placebo (80)	45.7	NR	NR	2.9	NR
da Fonseca et al.[61] 2003 RCT	Vaginal (72)	19.4	NR	NR	NR	NR
	Placebo (70)	31.4	NR	NR	NR	NR

*Findings are statistically significant.
IM = intramuscular; NR = not reported; PPROM = preterm premature rupture of membranes; RCT = randomized control trial.

Two trials analyzed the rate of antenatal hospitalizations among women receiving vaginal progesterone suppositories. One trial[31] found they were significantly lower among women who received progesterone than those who received placebo (25% vs. 45.7%; OR=2.5; 95% CI: 1.27, 5.04), and the other trial[61] found no significant difference between women who received progesterone and placebo (19.4% vs. 31.4%, p-value not reported). One trial[67] evaluated preterm labor rates and found they were significantly lower among women treated with intramuscular 17OHP compared to those who received placebo (29.0% vs. 59.4%, p < 0.025). Three trials[31, 37, 68] reported PPROM rates and did not find a significant difference between treatment and placebo or cerclage arms. One trial[68] compared intramuscular 17OHP and placebo (6.4% vs. 8.1%, p-

value not reported), and the other trial[31] compared vaginal progesterone suppositories and placebo (3.8% vs. 2.9%, p > 0.05).

Active-duty military personnel. In the one study (n=246)[72] in which intramuscular 17OHP was given to active-duty military personnel, the only maternal health outcome reported was preterm labor rates. There was no significant difference between treatment and placebo groups (6.3% vs. 5.7%, p-value not reported).

Abdominal surgery unrelated to pregnancy. In the one study (n=73)[80] in which intramuscular 17OHP was given to women who had abdominal surgery unrelated to pregnancy, the only maternal health outcome reported was preterm labor rates. The rate was lower in the treatment group than placebo, 2.9 percent versus 8.6 percent respectively, but no test of statistical significance was provided.

Preterm Birth Outcomes

Thirty-three studies reported preterm birth outcomes by gestational age. In some, a continuous outcome of mean gestational age birth was reported. Most reported the mean gestational age for all births; a few studies differentiated mean gestational age for preterm and term births. Others reported categorical outcomes by various cut points of gestational age. A number of cut points were used including 37, 36, 35, 34, 32, 30, 28, and 24 weeks. Specific cut points varied slightly depending on whether the day of the cut point was or was not included (for example, ≤ 35 weeks vs. < 35 weeks). A few studies reported categories by a range of gestational age (e.g., 32-34 weeks). The majority of studies reported the total preterm birth rate while a few differentiated spontaneous preterm births from preterm births for which there was an indication.

Preterm birth findings are presented in Tables 8–11. For 34, 32, and 28 weeks' gestation, cut points have been combined when studies did or did not include the day of the cut point (e.g., ≤ 34 weeks includes studies who reported by ≤ 34 weeks and < 34 weeks). All of the outcomes are for total preterm births, including spontaneous and indicated, unless otherwise noted. Within each table, studies are grouped by progestogen route (intramuscular, vaginal, and oral). Within each route, RCTs are listed first followed by clinical trials and observational studies, and each group of study types is in reverse chronological order.

History of preterm birth. Among studies reporting preterm birth outcomes, ten examined progestogen treatment in women with a history of preterm birth, including four RCTs[34, 36, 52, 60] and six retrospective cohort studies.[27, 29, 33, 39, 44, 59] Eight of these studies are presented in Table 8. One retrospective cohort study (n=38)[59] is not included because gestational age data were incomplete for the women who received progestogen treatment, and no specific gestational age data were provided for controls. Another retrospective cohort study (n=4,238) is not included because gestational age data are provided according to gestational age at prior preterm birth rather than by progestogen treatment and comparison groups.[29] Of the eight studies in Table 8, five used intramuscular 17OHP,[27, 33, 39, 44, 60] one used a vaginal progesterone capsule,[36] one used vaginal progesterone gel,[52] and one used oral micronized progesterone.[34] Three of the RCTs had a placebo arm,[34, 52, 60] and the fourth had a no-treatment arm.[36]

Table 8. Preterm birth outcomes for women with a history of preterm birth

Author Year Study Type	Intervention (N)	Mean GA ± SD (weeks)	PTB < 37 wk (%)	PTB < 35 wk (%)	PTB ≤ 34 wk (%)	PTB ≤ 32 wk (%)	PTB ≤ 28 wk (%)
Meis et al.[60] 2003 RCT	IM (306)	NR	36.3*	20.6*	NR	11.4*	NR
	Placebo (153)	NR	54.9	30.7	NR	19.6	NR
Mason et al.[27] 2010 Retrospective cohort	IM (193)	NR	46.6	26.4*	NR	13.5	NR
	No treatment or OB case management (60)	NR	51.7	41.7	NR	21.7	NR
Durnwald et al.[39] 2009 Retrospective cohort	IM (105)	NR	42.9	NR	NR	NR	NR
	None (95)	NR	35.8	NR	NR	NR	NR
Rittenberg et al.[33] 2009 Retrospective cohort	IM (342)	36.6 ± 3.0	45.9	12.0†	NR	3.8†	NR
	Daily perinatal nursing surveillance (342)	36.7 ± 2.9	42.7	10.8	NR	5.0	NR
Rebarber et al.[44] 2008 Retrospective cohort	IM (232)	35.4 ± 4.7	40.5†	25.9†	NR	13.4*†	NR
	Daily outpatient nursing surveillance (1,650)	36.0 ± 3.0	46.2	21.5	NR	7.9	NR
Majhi et al.[36] 2009 RCT	Vaginal (50)	NR	12.0*	NR	4.0	NR	NR
	None (50)	NR	38.0	NR	6.0	NR	NR
O'Brien et al.[52] 2007 RCT	Vaginal (309)	36.6 ± 3.8	41.7	22.7	NR	10.0	3.2
	Placebo (302)	36.6 ± 4.2	40.7	26.5	NR	11.3	3.0
Rai et al.[34] 2009 RCT	Oral (74)	36.1 ± 2.6*	39.2*	NR	27.0	2.7*	0
	Placebo (74)	34.0 ± 3.25	59.5	NR	25.7	20.3	4.0

*Findings are statistically significant.
GA = gestational age <weeks>; IM = intramuscular; NR = not reported; OB = obstetrical; PTB = preterm birth; RCD = randomized control trial; SD = standard deviation.
†Includes only spontaneous preterm births, total preterm birth rate not reported

Four studies[33-34, 44, 52] reported mean gestational age at birth. One RCT[52] found the mean gestational age to be virtually identical among women treated with vaginal progesterone compared to placebo (36.6 ± 3.8 weeks vs. 36.6 ± 4.2, mean difference=0.0). Two retrospective cohort studies found a minimally lower, and not statistically significant, mean gestational age in women given intramuscular 17OHP versus daily nursing surveillance with findings of 35.4 ± 4.7

weeks versus 36.0 ± 3.0 weeks (p=0.388) in one study[44] and 36.6 ± 3.0 weeks versus 36.7 ± 2.9 weeks (p=0.842) in the other.[33] One RCT[34] found mean gestational age at birth was significantly higher in women who received oral progesterone versus placebo (36.1 ± 2.66 weeks vs. 34.0 ± 3.25 weeks, p < 0.001).

All eight studies reported the proportion of births at less than 37 weeks. Three RCTs found the rate was significantly lower among women who received progestogen treatment, including one[36] comparing women using vaginal progesterone to no treatment (12% vs. 38%; RR=0.315; 95% CI: 0.14, 0.72; p=0.0027), one[60] comparing intramuscular 17OHP to placebo (36.3% vs. 54.9%; RR=0.66; 95% CI: 0.54, 0.81; p=0.001), and one[34] comparing oral progesterone to placebo (39.2% vs. 59.5%, p=0.002). Two retrospective cohort studies[27, 44] also found a lower rate of preterm birth at less than 37 weeks. One compared intramuscular 17OHP to daily nursing surveillance (40.5% vs. 46.2%), and this difference was not significant (p=0.121).[44] The second compared intramuscular 17OHP with either no treatment or obstetric case management (46.6% vs. 51.7%) and did not report a test of statistical significance.[27] Three additional studies found a higher, but not statistically significant, rate of preterm birth at less than 37 weeks with progestogen treatment. One of these[52] was a RCT comparing vaginal progesterone to placebo (41.7% vs. 40.7%; OR=1.08; 95% CI: 0.76, 1.52). The other two were retrospective cohort studies, including one[33] comparing intramuscular 17OHP to daily nursing surveillance (45.9% vs. 42.7%, p=0.436) and another[39] comparing women who did and did not receive intramuscular 17OHP (42.9% vs. 35.8%, p=0.31).The meta-estimate of the four RCTs reporting the proportion of births at less than 37 weeks is an OR of 0.66 (95% Bayesian credible interval (BCI): 0.53, 0.82). 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. Thus across studies, intervention is associated with a 9.4 percent overall reduction in preterm births.

Five studies[27, 33, 44, 52, 60] reported the occurrence of preterm birth at less than 35 weeks, and one RCT[60] found a significantly lower rate with intramuscular 17OHP compared to placebo (20.6% vs. 30.7%; RR=0.67; 95% CI: 0.48, 0.93; p=0.02). Another RCT[52] also found a lower rate of preterm birth at less than 35 weeks in women who received vaginal progesterone compared to placebo (22.7% vs. 26.5%), but this difference was not statistically significant (OR=0.9; 95% CI: 0.61, 1.34). One retrospective cohort study[27] found a significantly lower occurrence with intramuscular 17OHP compared to either no treatment or obstetric case management (26.4% vs. 41.7%, p=0.024). Two retrospective cohort studies found a higher, but not statistically significant, rate of preterm birth at less than 35 weeks with intramuscular 17OHP compared to daily nursing surveillance with rates of 25.9 percent vs. 21.5 percent (p=0.152) in one study[44] and 12.0 percent vs. 10.8 percent (p=0.712) in the other study.[33]

Two RCTs[34, 36] reported the rate of preterm birth at ≤ 34 weeks, and both found it was lower with progestogen treatment. One trial[36] compared vaginal progesterone to no treatment (4 percent vs. 6 percent; RR=0.666; 95 percent CI: 0.116, 3.82; p=0.64), and the other trial[34] compared oral progesterone to placebo (29.7% vs. 50%, no test of statistical significance reported).

Six studies[27, 33-34, 44, 52, 60] reported the rate of preterm birth at ≤ 32 weeks. One RCT[60] comparing intramuscular 17OHP to placebo found a significantly lower rate of preterm birth at ≤ 32 weeks with progestogen treatment (11.4% vs. 19.6%; RR=0.58; 95% CI: 0.37, 0.91; p=0.02). Four additional studies found a lower rate of preterm birth at ≤ 32 weeks that was not significant or did not have significance reported. These include a retrospective cohort study[33] comparing intramuscular 17OHP to daily nursing surveillance (3.8% vs. 5.0%, p=0.584), a retrospective

cohort[27] study comparing intramuscular 17OHP to either no treatment or obstetric case management (13.5% vs. 21.7%, no test of statistical significance reported), a RCT[52] comparing vaginal progesterone to placebo (10.0% vs. 11.3%; OR=0.9; 95% CI: 0.52, 1.56), and a RCT[34] comparing oral progesterone to placebo (2.7% vs. 20.3%, no test of statistical significance reported). One retrospective cohort study[44] found a significantly higher rate of preterm birth at less than 32 weeks among women treated with intramuscular 17OHP compared to those who did not receive 17OHP (13.4% vs. 7.9%, p=0.008). The authors attribute this to the fact that there was a higher incidence of pregnancy loss prior to 24 weeks' gestation in women receiving 17OHP.

Two RCTs reported the rate of preterm birth at ≤ 28 weeks, and neither found a significant difference with progestogen treatment. One trial[52] compared vaginal progesterone to placebo (3.2% vs. 3.0%; OR 1.07; 95% CI: 0.38, 2.96), and the other[34] compared oral progesterone to placebo (0% vs. 4%, p=0.25).

Preterm labor. Preterm labor was the indication for progestogen treatment in seven studies reporting preterm birth outcomes, including five RCTs,[46-47, 56, 65, 77] one controlled trial[73] and one observational study.[71, 73] Five of these studies are included in Table 9. Of these five studies, three used intramuscular 17OHP at varying doses and frequency.[46, 56, 73] The other two used a vaginal progesterone suppository[47] and oral progesterone.[65] Three of the RCTs had a no-treatment arm, and the fourth used placebo treatment.

Table 9. Preterm birth outcomes for women with preterm labor

Author Year Study Type	Intervention (N)	Mean GA ± SD (weeks)	PTB < 37 wk (%)	PTB < 35 wk (%)	PTB ≤ 34 wk (%)	PTB ≤ 32 wk (%)	PTB ≤ 28 wk (%)
Facchinetti et al.[46] 2008 RCT	IM (23)	NR	22.0*	NR	NR	NR	NR
	None (22)	NR	54.0	NR	NR	NR	NR
Facchinetti et al.[56] 2007 RCT	IM (30)	NR	16.0*	10.0	NR	NR	NR
	None (30)	NR	57.0	23.0	NR	NR	NR
Kauppila et al.[73] 1980 CT	IM (24)	39.1 ± 0.3*	NR	NR	NR	NR	NR
	Ritodrine (24)	37.7 ± 0.4	NR	NR	NR	NR	NR
Borna et al.[47] 2008 RCT	Vaginal	36.7 ± 1.5*	NR	NR	NR	NR	NR
	None (33)	34.5 ± 1.2	NR	NR	NR	NR	NR
Noblot et al.[65] 1991 RCT	Oral (22)	NR	27.3	NR	NR	NR	NR
	Placebo plus Ritodrine (22)	NR	36.4	NR	NR	NR	NR

*Findings are statistically significant.
†Includes only spontaneous preterm births, total preterm birth rate not reported.
CT = clinical trial; GA = gestational age <weeks>; IM = intramuscular; NR = not reported; PTB = preterm birth; RCT = randomized control trial; SD = standard deviation.

Two studies reported mean gestational age at birth, and both found it to be significantly higher among women who were treated with progestogen compared to those who were not. One was a RCT[47] comparing a vaginal progesterone suppository to no treatment (36.7 ± 1.5 weeks versus 34.5 ± 1.2 weeks, p=0.041), and the other was a clinical trial[73] in which women received intramuscular 17OHP or Ritodrine (39.1 ± 0.3 weeks vs. 37.7 ± 0.4 weeks, $p < 0.01$). Three RCTs reported the rate of preterm birth at less than 37 weeks.[46, 56, 65] Two found a significantly lower rate of preterm birth at less than 37 weeks with intramuscular 17OHP compared to no treatment, with rates of 22 versus 54 percent (p=0.049) in one trial,[46] and rates of 16 percent versus 57 percent (p=0.004) in another trial.[56] The third trial[65] found no statistically significant difference between women treated with oral progesterone and placebo (27.3% vs. 36.4%, p-value not reported). The meta-estimate combining these three trials is an odds ratio of 0.26 (95% BCI: 0.10, 0.49).[46, 56, 65] 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. One study[56] reported the rate of preterm birth at less than 35 weeks and did not find statistically significant differences at this cut point between women receiving intramuscular 17OHP or no treatment (10.0% vs. 23.3%, p-value not reported).

Two additional studies that reported preterm birth outcomes are not shown in Table 9 because no definition of preterm birth was provided, thus the gestational age cut point could not be determined. One of these studies (n=211)[77] compared oral chlormadinone acetate to intramuscular 17OHP and did not find a statistically significant difference in the rate of preterm birth between the two progestogens (4% vs. 8% respectively, p-value not reported). The other

study (n=33)[71] found a significantly lower rate of preterm birth among women treated with beta-mimetic drugs plus intramuscular 17OHP compared to women treated only with beta-mimetic drugs (27.3% vs. 69.2%, $p < 0.05$).

Multiple gestation. Multiple gestation was the indication for progestogen treatment in six studies, including five RCTs[30, 35, 40-41, 48] and one clinical trial[74], all of which reported preterm birth outcomes presented in Table 10. Four trials included twin gestations,[35, 41, 48, 74] and two trials included triplet gestations.[30, 40] The intervention was intramuscular 17OHP 250 mg weekly in five trials[30, 40-41, 48, 74] and vaginal progesterone gel 90 mg in one trial.[35] All of the trials included a placebo arm.

Table 10. Preterm birth outcomes for women with multiple gestation

Author Year Study Type	Intervention (N)	Mean GA ± SD (weeks)	PTB < 37 wk (%)	PTB < 35 wk (%)	PTB ≤ 34 wk (%)	PTB ≤ 32 wk (%)	PTB ≤ 28 wk (%)
Combs et al.[30] 2010 RCT	IM (56, triplets)	31.9 ± 4.1	NR	76.8	NR	33.9	16.1
	Placebo (25, triplets)	31.8 ± 2.9	NR	84.0	NR	52.0	8.0
Briery et al.[41] 2009 RCT	IM (16, twins)	33.9 ± 4.0	NR	44.0	NR	NR	NR
	Placebo (14, twins)	33.1 ± 2.9	NR	79.0	NR	NR	NR
Caritis et al.[40] 2009 RCT	IM (71, triplets)	32.4	NR	83.1	NR	41.0	10.0
	Placebo (63, triplets)	33.0	NR	84.1	NR	30.0	11.0
Rouse et al.[48] 2007 RCT	IM (325, twins)	34.6 ± 3.9	69.5	41.5	NR	16.9	8.0
	Placebo (330, twins)	34.9 ± 3.6	70.3	37.3	NR	14.5	6.1
Hartikainen-Sorri et al.[74] 1980 CT	IM (39, twins)	36.9 ± 2.6	30.8[†]	NR	NR	NR	NR
	Placebo (38, twins)	37.3 ± 2.4	23.7	NR	NR	NR	NR
Norman et al.[35] 2009 RCT	Vaginal (250)	35.4 ± 3.5	NR	NR	24.7	NR	NR
	Placebo (250, twins)	35.7 ± 3.0	NR	NR	19.4	NR	NR

[†]Includes only spontaneous preterm births, total preterm birth rate not reported.
CT = clinical trial; GA = gestational age <weeks>; IM = intramuscular; NR = not reported; PTB = preterm birth; RCT = randomized control trial; SD = standard deviation.

None of the trials found any significant difference in preterm birth outcomes with progestogen treatment. All of the trials reported mean gestational age at birth. Mean gestational age was higher with intramuscular 17OHP than placebo (33.9 ± 4 weeks vs. 33.1 ± 2.9 weeks, p=0.190) in one trial of twins[41] and another trial of triplets[30] (31.9 ± 4.1 weeks vs. 31.8 ± 2.9 weeks, p=0.36). In the other four trials, mean gestational age was slightly lower with

progestogen treatment compared to placebo with findings of 32.4 versus 33.0 weeks (p=0.527) in one trial,[40] 35.4 ± 3.5 weeks versus 35.7 ± 3 weeks (p=0.31) in one trial,[35] 34.6 + 3.9 weeks versus 34.9 ± 3.6 weeks (no test of statistical significance reported) in one trial,[48] and 36.9 ± 2.6 weeks versus 37.3 ± 2.4 weeks (p-value not reported) in one trial.[74]

Two trials, one with adequate power, reported no difference in preterm births using a 37-week cutpoint.[48, 74] Four trials[30, 40-41, 48] reported the preterm birth risk at less than 35 weeks. Three trials found the rate of preterm birth at less than 35 weeks was lower with progestogen treatment, including one trial of twin pregnancies[41] comparing intramuscular 17OHP to placebo (44% vs. 79%, p=0.117) and two trials of triplet pregnancies[30, 40] also comparing intramuscular 17OHP to placebo (83.1% vs. 84.1%; RR=1.0; 95% CI: 0.9, 1.1 and 76.8% vs. 84.0%; RR=0.9; 95% CI: 0.7, 1.1). One trial[48] found the rate of preterm birth at less than 35 weeks was higher with intramuscular 17OHP compared to placebo (41.5% vs. 37.3%; RR=1.1; 95% CI: 0.9, 1.3). The meta-estimate combining the two twin trials is an odds ratio of 1.07 (95% BCI: 0.80, 1.40) for preterm birth prior to 35 weeks.[41, 48] Combining the two triplet trials produces an odds ratio of 4.40 (95% BCI: 0.32, 11.57).[30, 40] When all twin and triplet trials are combined, the meta-estimate is 1.18 (95% BCI: 0.79, 1.39).[30, 40-41, 48] 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% overall increase in preterm births.

One trial[35] reported the rate of preterm birth at ≤ 34 weeks and found the rate was higher with vaginal progesterone compared to placebo (24.7% vs. 19.4%; OR=1.36; 95% CI: 0.89, 2.09; p=0.16). Three trials[30, 40, 48] reported the preterm birth rate at ≤ 32 weeks, and two found it was higher with progestogen treatment. One trial[40] compared intramuscular 17OHP and placebo in triplet pregnancies (41% vs. 30%; RR=1.4; 95% CI: 0.8, 2.2), and the other trial[48] compared intramuscular 17OHP and placebo in twin pregnancies (16.9% vs. 14.5%; RR=1.2; 95% CI: 0.8, 1.7). The third trial[30] compared intramuscular 17OHP and placebo in triplet pregnancies and found the preterm birth rate at ≤ 32 weeks was lower with progestogen treatment (33.9% vs. 52.0%; RR=0.7; 95% CI: 0.4, 1.1). Three trials[30, 40, 48] reported the preterm birth rate at ≤ 28 weeks. A trial of triplet pregnancies[40] found the rate was lower with intramuscular 17OHP compared to placebo (10% vs. 11%; RR=0.9; 95% CI: 0.3, 2.4). Two trials found the rate was higher with intramuscular 17OHP compared to placebo including one trial of twin pregnancies[48] (8.0% vs. 6.1%; RR=1.3; 95% CI: 0.8, 2.3) and one trial of triplet pregnancies[30] (16.1% vs. 8.0%; RR 2.0; 95% CI: 0.5, 8.6).

Study populations with varied risk factors. Among studies reporting preterm birth outcomes, ten examined progestogen treatment in study populations with varied risk factors (a variety of indications within a single study). Five RCTs,[32, 37, 61, 64, 79] one clinical trial,[66] and one case-control study[58] included preterm birth outcomes presented in Table 11. Three additional studies[32, 68, 76] are not included in the table but are discussed in the text at the end of this section. Of the seven studies included in Table 11, four used intramuscular 17OHP,[37, 58, 66, 79] two used a vaginal progesterone suppository,[31, 61] and one used an oral progestin.[64]

Five studies reported mean gestational age at birth.[31, 37, 58, 61, 79] Two RCTs found a significantly higher gestational age at birth among women treated with progestogens, including one trial[31] comparing vaginal progesterone to placebo (36w6d ± 2w3d vs. 35w6d ± 3w2d, p < 0.05) and one trial[79] comparing intramuscular 17OHP to placebo (38.6 ± 1.4 weeks vs. 35.2 ± 6.2 weeks, p < 0.025). A third RCT found a higher, but not statistically significant gestational age among women using vaginal progesterone compared to placebo (37.0 ± 2.8 weeks vs. 26.0 ± 3.3

weeks, p=0.029).[61] One RCT comparing intramuscular 17OHP to cerclage[37] found a similar gestational age at birth (33.0 ± 5.9 weeks vs. 32.9 ± 6.4 weeks, p=0.96). A case-control study[58] found a lower gestational age among women who received intramuscular 17OHP compared to women who did not (38.8 ± 2.4 weeks vs. 39.4 ± 2.0 weeks), and this result was significant in unadjusted and adjusted models (p < 0.0001 for both).

Five studies reported the rate of preterm birth at less than 37 weeks.[31, 37, 61, 64, 66] The rate was significantly lower with progestogen treatment in two RCTs[31] comparing vaginal progesterone to placebo, with rates of 40 percent versus 57.2 percent (OR=2.0; 95% CI: 1.04, 3.83; p=0.036) in one study[31] and 13.8 percent versus 28.5 percent (p=0.03) in the other.[61] The rate of preterm birth at less than 37 weeks was also significantly lower with progestogen treatment in a RCT[66] comparing intramuscular 17OHP to no treatment (14.3% vs. 48.7%, p=0.0036). The RCT[71] comparing intramuscular 17OHP to cerclage found the occurrence of preterm birth at less than 37 weeks was higher with progestogen treatment, but the difference was not significant (59.4% vs. 52.4%; RR=1.14; 95% CI: 0.77, 1.68). The fifth study[64] found a nonsignificant but higher rate of preterm birth at less than 37 weeks among women who received an oral progestin (Provera) compared with placebo (11.2% vs. 7.3%). This difference was attributed to the fact that many women did not take the progestogen. Further analysis demonstrated the preterm birth rate was 17.6 percent among 182 women who did not take the medication and 6.1 percent among 228 women who did.

Table 11. Preterm birth outcomes for study populations with varied risk factors

Author Year Study Type	Intervention (N)	Mean GA ± SD (weeks)	PTB <37 wk (%)	PTB <35 wk (%)	PTB ≤34 wk (%)	PTB ≤32 wk (%)	PTB ≤28 wk (%)
Keeler et al.[37] 2010 RCT	IM (37)	33.0 ± 5.9	59.4	43.2	NR	35.1	18.9
	Cerclage (42)	32.9 ± 6.4	52.4	38.1	NR	35.7	23.8
Johnson et al.[79] 1975 RCT	IM (18)	38.6 ± 1.6*	NR	NR	NR	NR	NR
	Placebo (25)	35.2 ± 6.7	NR	NR	NR	NR	NR
Suvonnakote[66] 1986 CT	IM (35)	NR	14.3*	NR	11.4	NR	0
	None (39)	NR	48.7	NR	17.9	NR	5.1
Dudas et al.[58] 2006 Case-control	IM (433)	38.8 ± 2.4*	NR	NR	NR	NR	NR
	Controls (37,718)	39.4 ± 2.0	NR	NR	NR	NR	NR
Cetingoz et al.[31] 2010 RCT	Vaginal (70)	36.9 ± 2.4*	40.0*	NR	8.8*	NR	NR
	Placebo (80)	35.9 ± 3.3	57.2	NR	24.3	NR	NR

*Findings are statistically significant

Table 11. Preterm birth outcomes for study populations with varied risk factors (continued)

Author Year Study Type	Intervention (N)	Mean GA ± SD (weeks)	PTB <37 wk (%)	PTB <35 wk (%)	PTB ≤34 wk (%)	PTB ≤32 wk (%)	PTB ≤28 wk (%)
da Fonseca et al.[61] 2003 RCT	Vaginal (72)	37.0 ± 2.8	13.8*	NR	2.8*	NR	NR
	Placebo (70)	36.0 ± 3.3	28.5	NR	18.6	NR	NR
Hobel et al.[64] 1994 RCT	Oral (411)	NR	11.2	NR	NR	NR	NR
	Placebo (412)	NR	7.3	NR	NR	NR	NR

*Findings are statistically significant

†Includes only spontaneous preterm births, total preterm birth rate not reported.

CT = clinical trial; GA = gestational age <weeks>; IM = intramuscular; NR = not reported; PTB = preterm birth; RCT = randomized control trial; SD = standard deviation.

One RCT reported preterm births at less than 35 weeks.[37] The rate was higher with intramuscular 17OHP than cerclage, but the difference was not statistically significant (43.2% vs. 38.1%; RR=1.14; 95% CI: 0.67, 1.93).

Three studies reported the preterm birth rate at ≤ 34 weeks.[31, 61, 66] The rate was significantly higher in the placebo group in two RCTs[31] comparing vaginal progesterone to placebo, with rates of 24.3 percent versus 8.8 percent (OR=3.35; 95% CI: 1.30, 8.63; p=0.010) in one study[31] and 18.6 percent versus 2.8 percent (p=0.002) in the other.[61] The third study[66] reported a lower preterm birth rate at ≤ 34 weeks with intramuscular 17OHP compared to no treatment (11.43% vs. 17.95%) but did not report a statistical test result for this finding.

One RCT reported the preterm birth rate at less than 32 weeks.[37] The rate was lower with intramuscular 17OHP than cerclage, but the difference was not statistically significant (35.1% vs. 35.7%; RR=0.98; 95% CI: 0.54, 1.79).

Two studies[37, 66] reported the birth rate at ≤ 28 weeks. One found it was lower with intramuscular 17OHP compared to no treatment (0% vs. 5.13%) but did not report a statistical test result for this finding.[66] The other found it was lower with intramuscular 17OHP than cerclage, but the difference was not statistically significant (18.9% vs. 23.8%; RR=0.79; 95% CI: 0.34, 1.88).[37]

One study (n=80)[68] is not included in Table 11 because it used an uncommon cut point for preterm birth (less than 36 weeks). Among the 31 women in that study who received intramuscular 17OHP, 16.1 percent gave birth at less than 36 weeks compared to 37.8 percent who received placebo, which was statistically significant ($p < 0.05$). A second study (n=21)[74] is a prospective cohort study that includes participants whose results are reported in a RCT[79] included in Table 11. The data from the two studies are combined in a way that makes it impossible to confidently provide results for preterm birth outcomes specific to participants in the prospective cohort study who were not in the RCT. A third study (n=300)[32] is a secondary analysis of a cerclage RCT in which there was an additional randomization stratum reflecting the patient's stated intent to use 17OHP. Outcomes for progestogen treatment are reported by initial randomization to cerclage or no cerclage. Preterm birth rates at less than 37, 35, 32, and 28 weeks did not differ significantly with 17OHP or no 17OHP in both cerclage and no-cerclage groups.

Asymptomatic short cervix on midgestation ultrasound. In the one study (n=250)[55] in which women who had an asymptomatic short cervix on midgestation ultrasound were given

vaginal progesterone, the rate of preterm birth prior to 34 weeks was 20.8 percent in the progesterone group and 36.0 percent in the placebo group (RR=0.58; 95% CI: 0.38, 0.87; p=0.008 and adjusted relative risk (ARR)=0.60; 95% CI: 035, 0.94; p=0.02).

Midtrimester amniocentesis. In the one study (n=584)[62] in which intramuscular natural progesterone and 17OHP were given to women who had midtrimester amniocentesis, there was no significant difference in the rate of preterm birth at less than 37 weeks in the treatment group compared to women who did not receive treatment (8.7% vs. 7.3%, p-value not reported).

Fetal and Neonatal Health Outcomes

Thirty-two studies reported fetal and neonatal outcomes other than gestational age (studies for which gestational age was the only neonatal outcome reported can be found in the previous discussion on preterm birth). Intrauterine fetal death, neonatal death, infant birth weight, and neonatal intensive care unit (NICU) outcomes are presented in Tables 12–16. Outcomes for neonatal conditions associated with prematurity are presented in Table 13. Each of Tables 12 and 14-16 is for a specific indication, while Table 13 includes multiple indications that are organized by risk factor in the order the indications are discussed in the text. Within all of the tables, studies are grouped by progestogen route (intramuscular, vaginal, and oral). Within each route, RCTs are listed first followed by clinical trials and observational studies, and each group of study types is in reverse chronological order.

In addition to those presented in Tables 12–16, other reported neonatal characteristics include Apgar scores,[35, 40-41, 48, 52, 62, 65, 73] cord pH,[36] placenta weights,[76] head circumference,[30, 52] very low birth weight,[40, 48, 55, 60] small for gestational age,[40] birth weight differences across groups,[76] neonatal age at birth per Ballard score,[34] and total days of hospital stay.[30] In addition, several studies present findings for a variety of neonatal health conditions, which may or may not be associated with prematurity, including transient tachypnea,[60] need for supplemental oxygen,[30, 60] bronchopulmonary dysplasia,[40, 48, 60] pneumonia,[30, 40, 48] pulmonary infection,[74] respiratory problems (nonspecific),[74] apnea/bradycardia,[68] patent ductus arteriosus,[40-41, 48, 60, 68] periventricular leukomalacia,[30, 40, 48]asphyxia,[30] seizures,[40, 48] hyperbilirubinemia,[36, 68, 74] phototherapy,[55] blood transfusion,[55] omphalitis,[74] anemia,[68] and the financial impact of the number of days in the NICU.[59]

History of preterm birth. Among studies reporting fetal and neonatal outcomes, six examined progestogen treatment in women with a history of preterm birth, including four RCTs[34, 36, 52, 60] and two retrospective cohort studies.[27, 59] All six of these studies are presented in Table 12, and three are included in Table 13. Three of the studies used intramuscular 17OHP,[27, 59-60] one used a vaginal micronized progesterone capsule,[36] one used vaginal progesterone gel,[52] and one used oral micronized progesterone.[34] Three of the RCTs had a placebo arm,[34, 52, 60] and the fourth had a no-treatment arm.[36]

Table 12. Fetal and neonatal outcomes for women with a history of preterm birth

Author Year Study Type	Intervention (N)	IUFD (%)	Neonatal Death (%)	Weight, Mean g ± SD	LBW, % (<2500g)	NICU Admission (%)	NICU Days, Mean ± SD
Meis et al.[60] 2003 RCT	IM (306)	2.0	2.6	NR	27.2*	NR	NR
	Placebo (153)	1.3	5.9	NR	41.1	NR	NR
Mason et al.[27] 2010 Retrospective cohort	IM (193)	NR	NR	NR	NR	33.7*	NR
	No treatment or OB case management (60)	NR	NR	NR	NR	45.0	NR
Mason et al.[59] 2005 Retrospective cohort	IM (24)	NR	NR	NR	NR	8.3	149.0*
	None (14)	NR	NR	NR	NR	14.3	231.0
Majhi et al.[36] 2009 RCT	Vaginal (50)	NR	0	2813.0 ± 501.0*	NR	0	NR
	None (50)	NR	0	2599.0 ± 421.0	NR	8.0	NR
O'Brien et al.[52] 2007 RCT	Vaginal (309)	1.6	1.9	2680.0 ± 710.0	NR	17.5	14.2 ± 16.6
	Placebo (302)	1.3	2.3	2661.0 ± 738.0	NR	21.5	20.5 ± 30.7
Rai et al.[34] 2009 RCT	Oral (74)	NR	4.1	2400.0 ± 650.0*	NR	13.5	NR
	Placebo (74)	NR	9.5	1890.0 ± 560.0	NR	51.3	NR

*Findings are statistically significant. g = gram; IM = intramuscular; IUFD = intrauterine fetal death; LBW = low birth weight; NICU = neonatal intensive care unit; NR = not reported; OB = obstetrical; RCT = randomized clinical trial; SD = standard deviation

Table 13. Neonatal conditions associated with prematurity

Author Year Study Type Indication	Intervention (N)	RDS (%)	NEC (%)	IVH (%)	Sepsis (%)	Vent (%)	ROP (%)
Meis et al.[60] 2003 RCT History of PTB	IM (306)	9.5	0*	1.3*	3.0	8.6	1.6
	Placebo (153)	15.1	2.6	5.2	2.6	14.6	3.3
Majhi et al.[36] 2009 RCT History of PTB	Vaginal (50)	NR	0	NR	0	NR	NR
	None (50)	NR	2.0	NR	6.0	NR	NR

Table 13. Neonatal conditions associated with prematurity (continued)

Author Year Study Type Indication	Intervention (N)	RDS (%)	NEC (%)	IVH (%)	Sepsis (%)	Vent (%)	ROP (%)
O'Brien et al.[52] 2007 RCT History of PTB	Vaginal (309)	11.0	1.0	1.9	NR	NR	NR
	Placebo (302)	11.9	1.7	1.6	NR	NR	NR
Borna et al.[47] 2008 RCT PTL	Vaginal (37)	10.8*	0	0	18.2	18.2	NR
	None (33)	36.4	0	0	5.4	5.4	NR
Combs et al.[30] 2010 RCT Multiple gestation	IM (168, triplets)	28.4	5.2	2.7	2.6	NR	2.8
	Placebo (75, triplets)	37.3	4.0	4.0	5.3	NR	6.5
Briery et al.[41] 2009 RCT Multiple gestation	IM (32, twins)	31.0	3.0	9.0	NR	NR	NR
	Placebo (28, twins)	32.0	0	14.0	NR	NR	NR
Caritis et al.[40] 2009 RCT Multiple gestation	IM (212, triplets)	31.0	0.9	0.9	9.0	33.0	0
	Placebo (183, triplets)	27.0	3.0	2.0	7.0	31.0	0
Rouse et al.[48] 2007 RCT Multiple gestation	IM (632, twins)	15.2	0.5	1.1	3.8	11.1	0
	Placebo (648, twins)	13.4	0.6	0.9	4.0	11.9	0
Yemini et al.[68] 1985 RCT Various risk factors	IM (5)	20.0	NR	NR	20.0	NR	NR
	Placebo (14)	28.6	NR	NR	14.3	NR	NR
Fonseca et al.[55] 2007 RCT Short cervix	Vaginal (125)	8.1	0	0.7	2.2	11.8	1.5
	Placebo (125)	13.8	0.7	1.4	8.0	18.1	0

*Findings are statistically significant.
IM = intramuscular; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; NR = not reported; PTB = preterm birth; PTL = preterm labor; RCT = randomized control trial; RDS = respiratory distress syndrome; ROP = retinopathy; Vent = mechanical ventilator.

Two RCTs[52, 60] reported intrauterine fetal death rates, and four RCTs[34, 36, 52, 60] reported neonatal death rates. No significant differences were reported with progestogen treatment. The meta-estimate for neonatal death is an odds ratio of 0.52 (95% BCI: 0.25, 0.96). Among the trials in the meta-estimate, 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 1.7 percent overall reduction in neonatal mortality.

Three RCTs reported mean birth weight. Two of these[34, 36] found a significantly higher birth weight in infants whose mothers received progestogens, including vaginal progesterone capsules ($p=0.023$) and oral progesterone ($p < 0.001$).The third[52] used vaginal progesterone gel and did

not find a significant difference. The meta-estimate of the change in mean birth weight is a mean difference of 239 g (95% CI: -44.5, 523.3).

One RCT[60] found a significantly lower rate of low birth weight (< 2,500 gm) in infants whose mothers were treated with intramuscular 17OHP (RR=0.66; 95% CI: 0.51, 0.87). Five studies[27, 34, 36, 52, 59] reported NICU admission rates, and two[52, 59] reported mean days in NICU. The only significant finding from the NICU outcomes was a lower number of days in the retrospective cohort in which women were treated with intramuscular 17OHP ($p < 0.000$ [sic]).[59] Three RCTs reported rates of neonatal conditions associated with prematurity, including respiratory distress syndrome,[52, 60] necrotizing enterocolitis,[36, 52, 60] intraventricular hemorrhage,[52, 60] sepsis,[36, 60] mechanical ventilation,[60] and retinopathy.[60] One trial[60] found significantly lower rates of necrotizing enterocolitis ($p=0.01$) and intraventricular hemorrhage ($RR=0.25$; $p < 0.05$) in infants whose mothers received intramuscular 17OHP. None of the others reported significant findings related to neonatal conditions associated with prematurity.

Preterm labor. Preterm labor was the indication for progestogen treatment in seven studies reporting fetal and neonatal outcomes, including five RCTs[14, 47, 56, 65, 77] and two observational studies.[16, 73] All seven of these studies are included in Table 14, and one is included in Table 13. Each of these seven studies used a different type, dose, and route of progestogens.

Table 14. Fetal and neonatal outcomes for women with preterm labor

Author Year Study Type	Intervention (N)	IUFD (%)	Neonatal Death (%)	Weight, Mean g ± SD	LBW, % (< 2500g)	NICU Admission (%)	NICU Days Mean ± SD
Facchinetti et al.[56] 2007 RCT	IM (30)	NR	NR	3103.0 ± 468.0	NR	NR	NR
	None (30)	NR	NR	2809.0 ± 317.0	NR	NR	NR
Bréart et al.[77] 1979 RCT	IM (105)	NR	NR	3156.0	NR	NR	NR
	Oral (106)	NR	NR	3099.0	NR	NR	NR
Fuchs & Stakemann[14] 1960 RCT	IM (63)	0	NR	NR	55.6	NR	NR
	Placebo (63)	3.2	NR	NR	55.6	NR	NR
Kauppila et al.[73] 1980 CT	IM (24)	NR	4.5	3460.0 ± 119.0*	8.3	NR	NR
	Ritodrine (24)	NR	0	3106.0 ± 118.0	12.5	NR	NR
Øvlisen et al.[16] 1963 Case series	IM (63)	NR	NR	NR	55.6	NR	NR
	Oral (63)	NR	NR	NR	61.9	NR	NR
	Placebo (63)	NR	NR	NR	55.6	NR	NR

Table 14. Fetal and neonatal outcomes for women with preterm labor (continued)

Author Year Study Type	Intervention (N)	IUFD (%)	Neonatal Death (%)	Weight, Mean g ± SD	LBW, % (< 2500g)	NICU Admission (%)	NICU Days Mean ± SD
Borna et al.[47] 2008 RCT	Vaginal (37)	NR	NR	3101.5 ± 587.9	27.0*	24.3	3.4 ± 7.6
	None (33)	NR	NR	2609.4 ± 662.9*	51.5	39.4	3.8 ± 8.2
Noblot et al.[65] 1991 RCT	Oral (22)	NR	NR	3077.0	NR	NR	NR
	Placebo (22)	NR	NR	2832.0	NR	NR	NR

*Findings are statistically significant.
g = grams; IM = intramuscular; IUFD = intrauterine fetal death; LBW = low birth weight; NICU = neonatal intensive care unit; NR = not reported; RCT = randomized control trial; SD = standard deviation.

One RCT[14] reported the rate of intrauterine fetal death, and one clinical trial[73] reported the rate of neonatal death. Neither reported if the difference in rate between intervention and placebo groups was significant. Five studies reported mean birthweight. Two studies found a significant difference in mean birth weight between infants whose mothers did and did not receive progestogens, p-values were 0.002 with vaginal progesterone suppositories[47] and < 0.05 with intramuscular 17OHP.[73] Two studies[65, 77] found no significant difference in birth weight with progestogen treatment, and one[56] did not report statistical findings for this outcome. Four studies analyzed the rate of low birth weight. One[47] found a significant difference between infants whose mothers did (27.0%) and did not (51.5%) receive vaginal progesterone suppositories (p=0.040), one[73] found the difference was not significant with intramuscular 17OHP (p-value not reported), and two[14, 16] did not report statistical findings for this outcome. One study[47] analyzed the rate of NICU admission and mean days of NICU stay, and found no significant differences in NICU outcomes with treatment with vaginal progesterone suppositories. One study[47] reported rates of five conditions associated with prematurity, including respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, sepsis, and mechanical ventilation. Respiratory distress syndrome was the only condition for which there was a significantly lower rate (p=0.021) among infants whose mothers received vaginal progesterone suppositories.

Multiple gestation. Multiple gestation was the indication for progestogen treatment in six studies, including five RCTs[30, 35, 40-41, 48] and one clinical trial,[74] all of which reported fetal and neonatal health outcomes presented in Tables 13 and 15. Four trials included twin gestations,[35, 41, 48, 74] and two trials included triplet gestations.[30, 40] The intervention was intramuscular 17OHP 250 mg weekly in five trials[30, 40-41, 48, 74] and vaginal progesterone gel 90 mg in one trial.[35] All of the trials included a placebo arm.

Table 15. Fetal and neonatal outcomes for women with multiple gestation

Author Year Study Type	Intervention (Maternal N/ Fetal N)	IUFD (%)	Neonatal death (%)	Weight, Mean g ± SD	LBW, % (<2500g)	NICU Admission (%)	NICU Days, Mean ± SD
Combs et al.[30] 2010 RCT	IM (56/168)	7.7*[†]	3.9	1719.0 ± 554.0	NR	NR	16.0 ± 23.2
	Placebo (25/75)	0	2.7	1609.0 ± 472.0	NR	NR	18.8 ± 30.1

Table 15. Fetal and neonatal outcomes for women with multiple gestation (continued)

Author Year Study Type	Intervention (Maternal N/ Fetal N)	IUFD (%)	Neonatal Death (%)	Weight, Mean g ± SD	LBW, % (<2500g)	NICU Admission (%)	NICU Days, Mean ± SD
Briery et al.[41] 2009 RCT	IM (16/32)	0	6.0	1968.8 ± 679.0	NR	NR	18.4 ± 65.8
	Placebo (14/28)	0	0	1934.7 ± 549.0	NR	NR	17.3 ± 29.8
Caritis et al.[40] 2009 RCT	IM (71/212)	0.4	2.0	1650.0 ± 554.0	91.0	NR	NR
	Placebo (63/183)	3.3	1.0	1754.0 ± 494.0	96.0	NR	NR
Norman et al.[35] 2009 RCT	Vaginal (250/494)	1.2	1.6	NR	NR	33.8	26.9 ± 33.5
	Placebo (250/494)	0.8	1.2	NR	NR	32.0	23.6 ± 29.5
Rouse et al.[48] 2007 RCT	IM (325/632)	3.7	3.1	NR	60.0	NR	NR
	Placebo (330/648)	2.7	1.8	NR	64.0	NR	NR
Hartikainen-Sorri et al.[74] 1980 CT	IM (39/78)	1.3	3.8	NR	NR	NR	NR
	Placebo (38/76)	1.3	1.3	NR	NR	NR	NR

*Findings are statistically significant.
†Includes miscarriages.
CT = clinical trial; g = grams; IM = intramuscular; IUFD = intrauterine fetal death; LBW = low birth weight; NICU = neonatal intensive care unit; NR = not reported; RCT = randomized control trial; SD = standard deviation.

All of the trials reported intrauterine fetal deaths and neonatal deaths. One RCT of triplet pregnancies[30] comparing intramuscular 17OHP to placebo found a statistically significant higher rate of intrauterine fetal death with progestogen treatment (7.7% vs. zero%, p=0.01). In this study, the intrauterine fetal death rate was only reported in combination with the miscarriage rate. Thus the 7.7 percent result includes some miscarriages after 16 weeks' gestation.[30] The meta-estimate for neonatal death combining the three twin trials is an odds ratio of 1.64 (95% BCI: 0.83, 2.67). Combining the two triplet trials produces an odds ratio of 2.09 (95% BCI: 0.14, 5.66). When the twin and triplet trials are combined, the meta-estimate is 1.75 (95% BCI: 0.93, 2.80). Among the trials in the meta-estimate, the risk of neonatal death was 1.5 percent among women in the placebo group and 2.8 percent among those receiving progestogens. Thus across studies, intervention is associated with a 1.3 percent overall increase in neonatal mortality.

Three trials[30, 40-41] reported mean birth weights, and two[40, 48] reported the rate of low birth weight. One trial[35] reported the rate of NICU admissions, and three[30, 35, 41] reported the mean number of NICU days. Four trials[30, 35, 41, 48] reported rates of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. Three trials[30, 40, 48] reported rates of sepsis and retinopathy. Two trials[40, 48] reported rates of mechanical ventilation. The only significant difference in fetal or neonatal outcomes with progestogen treatment was the higher

rate of miscarriage and stillbirth among participants who received 17OHP in a RCT of triplet pregnancies.[30]

Study populations with varied risk factors. Among studies reporting fetal and neonatal health outcomes, seven examined progestogen treatment in populations with varied risk factors (a variety of indications within a single study). Three RCTs[31, 68, 79] and three observational studies[58, 66, 75] included outcomes presented in Tables 13 and 16. One observational study reported other neonatal outcomes.[76] Two additional studies[32, 37] are not included in the table but are discussed in the text at the end of this section. Of the studies in Tables 13 and 16, four used intramuscular 17OHP[58, 66, 68, 79], one used a vaginal progesterone suppository,[31] and one used oral allylestrenol.[75]

Table 16. Fetal and neonatal outcomes for study populations with varied risk factors

Author Year Study Type	Intervention (Maternal N/ Fetal N)	IUFD (%)	Neonatal Death (%)	Weight, Mean g ± SD	LBW, % (<2500g)	NICU Admission (%)	NICU Days, Mean ± SD
Yemini et al.[68] 1985 RCT	IM (39)	0	0	3111.9 ± 905.5*	NR	NR	NR
	Placebo (40)	0	0	2680 ± 813.4	NR	NR	NR
Johnson et al.[79] 1975 RCT	IM (18)	0	0	2836.0 ± 412.0*	NR	NR	NR
	Placebo (22)	22.7	9.0	2361.0 ± 108.0	NR	NR	NR
Suvonnakote[66] 1986 CT	IM (35)	NR	NR	NR	31.4	NR	NR
	None (39)	NR	NR	NR	48.7	NR	NR
Dudas et al.[58] 2006 Case-control	IM (433)	NR	NR	3194.0 ± 555.0	9.0	NR	NR
	None (37,718)	NR	NR	3277.0 ± 511.0	5.6	NR	NR
Cetingoz et al.[31] 2010 RCT	Vaginal (80)	NR	3.8	NR	NR	16.3*	NR
	Placebo (70)	NR	4.3	NR	NR	37.1	NR
Cortes-Prieto et al.[75] 1980 Prospective cohort	Oral (25)	NR	NR	3455.0	NR	NR	NR
	None (40)	NR	NR	3186.0	NR	NR	NR

*Findings are statistically significant.
CT = clinical trial; g = grams; IM = intramuscular; IUFD = intrauterine fetal death; LBW = low birth weight; NICU = neonatal intensive care unit; NR = not reported; RCT = randomized control trial; SD = standard deviation.

One RCT[79] combined intrauterine fetal death and neonatal death rates to obtain a perinatal mortality rate and found this was significantly lower with intramuscular 17OHP compared to placebo ($p < 0.05$). There were no intrauterine fetal deaths or neonatal deaths in the other RCT reporting both these death rates.[68] A third RCT[31] only reported the neonatal death rate and did not find a significant difference with vaginal progesterone suppositories compared to no

treatment (p=0.867). Two RCTs[68, 79] found a significantly higher mean birth weight among infants whose mothers received intramuscular 17OHP ($p < 0.025$ and $p < 0.05$ respectively). One case-control study[58] found lower mean birth weight in infants whose mothers were treated with intramuscular 17OHP, which was significant when unadjusted (p=0.002) but lost significance when adjusted (p=0.09). The fourth study with mean birth weight data was a clinical trial that reported no significant findings.[75] Two studies reported the rate of low birth weight infants. One case-control study[58] found a higher rate of low birth weight in infants whose mothers were treated with intramuscular 17OHP, which was significant when unadjusted (OR=1.7; 95% CI: 1.2, 2.3) but lost significance when adjusted (OR=1.4; 95% CI: 0.9, 2.0). The other study, which was a clinical trial,[66] reported no significant findings with regard to with low birth weight. One RCT[31] found NICU admission rates were three times higher in newborns whose mothers received placebo than those whose mothers received vaginal progesterone suppositories (OR=3.04; 95% CI: 1.41, 6.54; p=0.004). One RCT[68] reported rates of neonatal conditions associated with prematurity, including respiratory distress syndrome and sepsis, with no significant findings when mothers received intramuscular 17OHP.

One RCT (n=79) only reported stratified neonatal morbidity and a perinatal death rate that combined intrauterine fetal deaths and neonatal deaths (10.8% with intramuscular 17OHP vs. 11.9% with cerclage, no test of statistical significance reported).[37] Another study (n=300) is a secondary analysis of a cerclage RCT in which there was an additional randomization stratum reflecting the patient's stated intent to use 17OHP.[32] Outcomes for progestogen treatment are reported by initial randomization to cerclage or no cerclage. The perinatal death rate, which includes stillbirths and postnatal deaths prior to hospital discharge, was significantly lower with 17OHP compared to no 17OHP in the group randomized to no cerclage (4% vs. 23%; OR=0.14; 95% CI: 0.03, 0.61; p=0.0029). The perinatal death rate did not differ significantly with 17OHP compared to no 17OHP in the group randomized to no cerclage(6% vs. 10%; OR=0.62; 95% CI: 0.16, 2.37; p=0.76).

Asymptomatic short cervix on midgestation ultrasound. In the one study[55] in which women who had an asymptomatic short cervix on midgestation ultrasound were given vaginal progesterone, there were no significant differences in treatment and placebo groups in rates of intrauterine fetal death (0.7% vs. 0.7%), neonatal death (1.5% vs. 5.1%), low birth weight (41.2% vs. 42.8%), respiratory distress syndrome (8.1% vs. 13.8%), necrotizing enterocolitis (0% vs. 0.7%), intraventricular hemorrhage (0.7% vs. 1.4%), sepsis (2.2% vs. 8.0%), mechanical ventilation (11.8% vs. 18.1%), and retinopathy (1.5% vs. 0%).

Active-duty military personnel. In the one study[72] in which progesterone was given to active-duty military personnel, there was no significant difference in rates of intrauterine fetal death (1.3% vs. 3.4%), neonatal death (2.5% vs. 0%), or low birth weight (7.5% vs. 9.0%) with intramuscular 17OHP compared to placebo (p-values not reported).

Abdominal surgery unrelated to pregnancy. In the one study[80] in which intramuscular 17OHP was given to women who had abdominal surgery unrelated to pregnancy, the intrauterine fetal death and neonatal death rates were lower in the treatment group than placebo, 2.9 percent versus 0 percent and 2.9 percent versus 8.6 percent respectively. No test of statistical significance was reported.

Midtrimester amniocentesis. In the one study[62] in which intramuscular natural progesterone and 17OHP were given to women who had midtrimester amniocentesis, the intrauterine fetal death rate was lower (0.6% vs. 1.1%) and the mean birth weight was higher (3138.9 ± 665.9 gm vs. 3073.6 ± 618.9 gm) in the treatment group compared to women who did not receive

treatment. The differences in these outcomes were not statistically significant (p-values not reported).

KQ2. Harms of Progestogen Treatments

Surveillance for adverse effects (harms) of progestogens use varied widely across studies with few explicitly describing a universal approach to inquiring about or establishing operational definitions of harms. Fourteen treatment studies, six RCTs[32, 46, 61, 64-65, 77] and eight other study types,[27, 29, 33, 39, 43-45, 71] did not include any reporting of harms associated with therapy in the methods or results of their study. In RCTs that addressed harms, incidence of any harm ranged from zero to 69 percent for the treatment group and zero to 65 percent for the placebo groups (Table 17).[14, 30-31, 34-36, 38, 40-41, 47-48, 52, 55-56, 60, 62, 67-68, 72, 79, 82-83] Harms were less likely to be reported by other types of studies and are especially challenging to compile in retrospective research. When reported, treatment groups had documented drug-related adverse events in zero to 13 percent of those treated compared to zero to 7 percent in comparison groups. Reported harms were generally mild and varied depending upon route of progestogen administrations (e.g., injection site reactions and vaginal irritation). In the RCTs, withdrawal due to drug or placebo treatment effects occurred in up to three percent and two percent of participants in the treatment and placebo arms respectively. In other studies, withdrawal occurred in up to 9.4 percent of participants in the treatment and comparison groups.

Table 17. Side effects and harms of progestogen treatment

	Placebo-Controlled RCT Arms				Other Studies by Treatment			
Range (Number of studies reporting)	**Placebo (n=27)**	**Injection (n=15)**	**Vaginal (n=8)**	**Oral (n=4)**	**Comparison Group (n=16)**	**Injection (n=23)**	**Vaginal (n=0)**	**Oral (n=2)**
Reaction/discomfort with suppository	0-17% (3)		0-24% (3)					
Injection site discomfort	7.8-62.3% (3)	17.2-61.6% (3)				58.6% (2)		
Urticaria/pruritus	1.2-2% (2)	3.4% (1)	4% (1)					0 (1)
Nausea	0-12% (3)	1.6% (1)	5% (1)	0 (1)				0 (1)
Vaginal discharge	9.2-24% (2)		8.4-32% (3)					
Gestational diabetes	6.9-12% (2)	6.7-16% (2)			4.9% (1)	5.5-12.9% (2)		
Hypertension (PIH)	0-29% (5)	12.5-21% (4)		0 (1)		4.8% (1)		
Chorioamnionitis	0-8% (5)	1.4-9% (2)	0-3.6% (3)		28.6% (1)	21.6% (1)		
Cesarean birth	14-100%[a] (7)	93-100%[a] (2)	8-59.2%[a] (5)		4% (1)	12% (1)		

[a]Includes multiple gestation studies.

Table 17. Side effects and harms of progestogen treatment (continued)

Range (Number of studies reporting)	Placebo-Controlled RCT Arms				Other Studies by Treatment			
	Placebo (n=27)	Injection (n=15)	Vaginal (n=8)	Oral (n=4)	Comparison Group (n=16)	Injection (n=23)	Vaginal (n=0)	Oral (n=2)
Bleeding disorders postpartum (maternal)	0-4% (3)	0 (1)	0.6 (1)	0 (1)		12.5% (1)		
Other complication in pregnancy (maternal)	0-21% (7)	5.3-7.5% (2)	0-17% (3)	0-6.8% (2)	32.2 (1)	33.8 (1)		0% (1)
Neonatal infection/sepsis	2.6-18.2% (8)	3.0-20% (5)	0-5.4% (3)		5.3% (1)	0.7-2.6% (2)		
Fetal/neonatal death[b,d]	0-27% (16)	0-11% (10)	0-3.8% (5)	4.1% (1)	0-25% (5)	1.5-10.8% (8)		3.8% (1)
Congenital anomalies	0-12% (8)	0.5-11% (5)	0-0.6% (3)		0-8% (6)	0-12% (6)		1.6% (1)
Reproductive teratogenic effects	1.2% (1)	2.1% (1)			0-2.1%[c] (2)	3.4%[c] (1)		0-1.6%[c] (2)
Any adverse event	64.4-65% (2)	65.9-69% (2)						
Withdrawals due to adverse events	0.3-1.6% (4)	0.6-3.2% (3)	1.6% (1)		7.3% (1)	8.3-9.4% (2)		
Not reported*	9	4	3	2	5	7		

[a]Includes multiple gestation studies
[b]Fetal/Neonatal Deaths for all causes including complications of prematurity
[c]Includes fetuses exposed to progestogens in first trimester
[d]Includes participants with cervical length < 25 mm.
*One "other" study type did not report formulation or dosage information and is not included in the table

The most commonly reported progestogen-related harm in RCTs was injection site discomfort, in 17 to 62 percent of the treatment group and 8 to 62 percent of the placebo group;[40, 48, 60] one prospective study reported injection site reactions in eight percent of participants.[59] Vaginal irritation and/or discharge was the next most common, occurring among up to 28 percent of women receiving vaginal progesterone and up to 24 percent of participants receiving a vaginal placebo. Two other studies mentioned injection or vaginal site discomfort, but did not report a specific number or proportion of participants.[66, 79] Urticaria or pruritus, reported in two RCTs, were experienced by up to four percent of progestogen treated participants and two percent receiving placebo.[35, 48] Nausea was assessed in three RCTs. Nausea was reported by two percent of participants receiving 17OHP injections, five percent of participants receiving progesterone via vaginal suppository, and up to 12 percent of participants receiving placebos via vaginal or injected route.[35, 48, 67]Neither of the trials using oral progesterone had any participants with nausea in the placebo or treatment arms.

Three studies investigated occurrence of gestational diabetes in women receiving 17OHP injections with conflicting results. In a pooled analysis of two RCTs (n=1,094), seven percent of the treatment and placebo groups developed gestational diabetes during the study.[38] In a second RCT, 16 percent of treated compared to 12 percent of control participants (RR=1.43; 95% CI: 0.31, 9.01) developed gestational diabetes in a cohort of women pregnant with triplets. While not

statistically different, the authors caution that this could be significant in a larger study population.[30] A retrospective cohort found a statistically significant association between 17OHP injections and gestational diabetes with 13 percent of progesterone treated participants (n=557) receiving the diagnosis compared to five percent of comparison participants (RR=3.09; 95% CI: 2.2, 4.4).[50]

Five RCTs[30, 40, 48, 67, 72] assessed occurrence of pregnancy-induced hypertension (PIH) in their participants. In four trials[30, 40, 48, 72] 13 to 21 percent of participants receiving progesterone and up to 29 percent of participants receiving placebo met criteria. In one trial[67] none of the women in either group had PIH. Five RCTs reported incidence of chorioamnionitis,[60] with ranges from 1.4 up to 9 percent among participants receiving injectable or vaginal progestogens, compared to zero to 8 percent of participants receiving the related placebos. Cesarean birth varied widely among seven RCTs reporting this outcome.[52, 60] Proportions of women having a cesarean spanned eight to 100 percent of treatment groups and 14 to 100 percent of placebo groups. These numbers are skewed higher than one might expect because of trials that included multiple gestations. Among studies with singleton pregnancies, cesareans were performed in eight to 29 percent of women in the treatment group and 14 to 28 percent of placebo group participants. Generally risk of cesarean was not reported in a way that allowed taking into account the proportion of cesareans attributable to prematurity and/or higher proportions of malpresentation among preterm fetuses.

Eight RCTs[30, 34-35, 47-48, 55, 67, 79] and one other study[84] tracked other maternal harms in pregnancy. These included milder effects like headache, fatigue, dizziness, and uterine contraction, as well as more severe effects such as sepsis, postpartum endometritis, cardiac rhythm abnormalities and jaundice. Events ranged in frequency from zero to 34 percent of participants in the progestogen arms to zero to 32 percent of participants receiving placebo or in the comparison group. Two RCTs[67, 79] assessed postpartum bleeding disorders, including postpartum hemorrhage and prolonged bleeding. Fewer than one percent of participants treated with vaginal progesterone and up to four percent of placebo group members reported disorders. No bleeding disorders were reported in women treated with 17OHP injections or oral progesterone therapy.

Among adverse effects reported in the fetus or newborn, fetal and/or neonatal mortality was the most common. A total of 15 RCTs[14, 30-31, 34-36, 40-41, 48, 52, 55, 60, 68, 72, 79] and ten other studies[28, 37, 42, 53, 69, 73-76, 80] noted mortality in eleven percent of the progestogen treatment arms and up to 27 percent of the placebo or comparison groups. This discrepancy likely reflects differences in preterm births between treatment and comparison arms, suggesting that in some cases, mortality is due to side effects of prematurity and not a risk of progestogen treatment. Because of small numbers for any single study, analyses were not reported that assessed risk of mortality adjusting for gestational age at birth. Neonatal infection and/or sepsis were reported by eight RCTs[30, 36-37, 47-48, 55, 60, 68] with similar broad ranges of incidence between participants receiving 17OHP (three to 20%), and placebo injections or suppositories (2 to 18%). Congenital anomalies among neonates were reported by eight RCTs[35-36, 48, 52, 60, 68, 72, 79] and seven other studies.[16, 58, 66, 69-70, 74, 76] In the RCTs of vaginal progesterone, up to 0.6 percent of those treated had a fetus or neonate with a congenital defect; compared to 0.7 percent in the placebo groups.[35-36, 52] Among women receiving 17OHP or placebo, anomaly rates were zero to 11 percent in the treatment groups and zero to 12 percent in the placebo groups.[48, 60, 68, 72, 79] The high percentage in this group is due to the inclusion of a study with only 43 participants and five affected by anomalies including accessory digits and functional cardiac murmurs.[79] Among the other study types, zero to 12

percent of fetuses or neonates in the treatment group and zero to eight percent in the comparison groups were affected by an anomaly. The high percentage in this group is due to the inclusion of a study with only 50 participants and five affected by anomalies including accessory digits and a loper.[70] One study not included in this analysis demonstrated a higher incidence of hypospadias in participants receiving oral progesterone, however this effect was not statistically significant at the gestational age when these develop and not viewed to be caused by the therapy, but by underlying infertility.[85]

None of the studies collected information about macrosomia as an adverse outcome of progestogen therapy. A more recent study found that 4 percent of infants born to women receiving 17OHP injections were > 90 percent for size, suggesting potential for reduced risk relative to population norms in which 10 percent would be expected to be above the 90th percentile. However all women in the study received a progestogen so there is no internal comparison group.[28]

Long-term effects of progestogen therapy could not be discerned because few studies collected followup beyond hospital discharge. One poor quality study reports an increase in "femininity" in boyhood and erectile failure and low sex drive in adulthood in males whose mothers received progesterone during pregnancy at any point between 6 and 35 weeks of gestation. These findings were not quantified and required 30 year recall to report on exposure.[13] One study[83] reports followup of 278 children (mean age 48 months) whose mothers were in an RCT of intramuscular 17OHP versus placebo.[60] Scores on the Ages and Stages Questionnaire were not different for the two groups of children, both for overall scores and the five domains this instrument includes: communication, gross motor, fine motor, problem solving, and personal-social. There were also no significant differences between groups in the nature and rate of diagnoses by health professionals, caregivers' assessment of the children's health, physical examinations, and genital or reproductive anomalies.[83]

In summary, most harms were rare, and studies that did track them were primarily conducting safety monitoring and ultimately underpowered to determine if the treatment or placebo group experienced a meaningfully disproportionate burden of adverse events. Most harms that are common, such as injection site pain with intramuscular preparations or vaginal discharge with vaginal preparations, appear to be a side effect of route and are experienced in similar high proportions across treatment and placebo groups. Others, like cesarean, are entangled with multiple pregnancies and would require additional modeling within study data to evaluate for any independent effect of the drug on risk. For most remaining harms that would be of interest, heterogeneity across aspects of study design, variation in progestogens and routes studied, and level of detail provided about harms measured prevents calculation of meaningful aggregate estimates.

KQ3. Maternal Risk Factors as Modifiers of Outcomes

In the context of this report, we use the term modifier to mean a characteristic that may interact with progestogen treatment to change the expected outcomes within the group who have that characteristic compared to a group who do not. For instance as an unrelated example of modification: pregnant women with Type 1 diabetes have higher risk of intrauterine fetal demise than women with Type 2 diabetes even when their insulin treatment achieves similar levels of blood sugar control. In this example the type of diabetes is said to modify the outcome of insulin treatment for reducing risk of fetal demise. Modifiers can have either a negative or a positive effect; some groups may get more benefit from an intervention than others.

A crucial factor in study of modifiers is that it requires a sufficient number of study participants with and without the characteristic who did and did not receive the treatment. Even studies that are sufficiently large to address the effectiveness of treatment with excellent statistical confidence in the findings may have groups that are too small to provide reliable analysis of the effects of modifiers. To directly assess whether a characteristic acts as a modifier requires specific statistical approaches. For instance, researchers could use either a stratified analysis – comparing treatment effects among women with the trait and without; or multivariate analysis that captures and compares the joint effects for each of the four (or more) possible groups: with trait and treatment, with trait and placebo, without trait and with treatment, and without trait and with placebo. Other sorts of comparisons among groups of women with specific traits across the findings of separate studies are descriptive and may lead to new hypotheses but are generally not definitive for making care decisions.

Gestational Age at Birth of Prior Spontaneous Preterm Birth

We sought evidence about whether gestational age of a prior preterm birth modifies outcomes, among women receiving progestogen for the indication of a current singleton pregnancy and a history of prior spontaneous preterm. Clinical discussion often gravitates toward whether women with a more severe prior preterm birth—meaning earlier in gestation—achieve more or less advantage from progestogens compared with women with a less severe, later prior preterm birth. Two publications aimed to address this question.[36, 86]

A secondary, subgroup analysis of an RCT of intramuscular 17OHP among women with a prior spontaneous preterm birth (n=459) reported greater effectiveness for prevention of preterm birth defined as birth before 37 weeks gestation if the prior preterm birth was less than 34 weeks.[86] By gestational age of the most severe prior preterm birth, the odds ratios for preterm birth comparing 17OHP to placebo were:

- OR=0.43 (95% CI: 0.19, 0.98) if between 20+0 and 27+6 weeks
- OR=0.44 (95% CI: 0.23, 0.85) if between 28+0 and 33+6 weeks
- OR=0.62 (95% CI: 0.29, 1.32) if between 34+0 and 36+6 weeks

While the trend in point estimates suggests greater benefit among those with earlier prior preterm birth, it is important to note that all the OR estimates of risk reduction fall within the confidence bounds of the other groups, meaning there is insufficient statistical precision to be confident of a conclusion that prior preterm birth severity modifies response to treatment.

A secondary, subgroup analysis of a non-blinded controlled trial of intravaginal micronized progesterone in women with a prior spontaneous preterm birth also did not have sufficient power.[36] Subdivision of the study population into three subgroups resulted in groups with, n=39, n=27, and n=9, insufficient for definitive conclusions.

A retrospective report[29] of 2,338 women subdivided the subjects according to gestational age of prior spontaneous preterm birth. A small effect of progestogens, less than one week of prolonged pregnancy, was reported for each of the three groups.

The body of evidence is fair for consistent effectiveness of progestogens for prevention of preterm birth, based upon gestational age (GA) of the prior spontaneous preterm birth. There is no evidence for different adverse effects or safety, based upon GA of the prior spontaneous preterm birth.

Number of Prior Spontaneous Preterm Births

Number of prior preterm births has also been a candidate of interest as a modifier of response to progestogens treatment. Two secondary analyses from the same trials described above also examined the potential influence of the number of prior preterm births on response to progestogens.[36, 87] Both evaluated preterm birth risk among women with one prior preterm birth, compared to more than one by progesterone versus placebo groups.

To establish a common metric across the two studies we have summarized the observed absolute risks and risk reduction by number of prior preterm births:

One prior preterm birth

- 17OHP (National Institute of Child Health and Human Development [NICHD] Maternal Fetal Medicine Units Trial)[87]
  - Treated: 31.8 percent preterm (99/310); placebo 44.4 percent (68/153)
  - Absolute risk difference: 12.6 percent lower among women treated
- Oral Micronized Progesterone[36]
  - Treated: 11.1 percent preterm (5/45); no treatment 35.0 percent (14/40)
  - Absolute risk difference: 23.9 percent lower among women treated

More than one prior preterm birth

- 17OHP (NICHD Maternal Fetal Medicine Units Trial)[87]
  - Treated: 47.7 percent preterm (148/310); placebo 69.8 percent (107/153)
  - Absolute risk difference: 22.1 percent lower among women treated
- Oral Micronized Progesterone[36]
  - Treated: 20 percent preterm (1/5); no treatment 50 percent (5/10)
  - Absolute risk difference: 30.0 percent lower among women treated

Multivariate models using the NICHD trial data suggested that receiving 17OHP reduced the excess risk of a history of more than one prior spontaneous preterm birth and that the outcome of the immediate prior pregnancy exerted more influence. However for formal analysis of number of prior preterm births as an effect modifier, even this larger trial lacks sufficient precision of the estimates across strata to document a clear difference. As in the examples of risk estimates by strata for severity of prior preterm birth, the estimates of effect are nested within each others' confidence intervals: for women with one prior spontaneous preterm birth, the absolute risk reduction was 13 percent (95% CI: -2.7, 28.8%) and for those with more than one prior, absolute risk reduction was 22.7 percent (95% CI: 9.5, 36.0%). The purpose of the logistic regression analysis was to detect differences in the association of a risk factor for preterm birth and the event of preterm birth between women treated with 17OHP and those treated with placebo. The logistic regression analysis yielded an odds ratio of 3.38 (95% CI: 1.36, 8.40) when comparing participants who had more than one prior spontaneous preterm to participants who had one prior within the placebo group. This indicates that in the absence of treatment number of prior spontaneous preterm births is a risk predictor. However, within the treatment group, the logistic regression analysis yielded an odds ratio of 1.54 (95% CI: 0.85, 2.79) when comparing participants who had more than one prior spontaneous preterm birth with participants who had one prior preterm birth, not a statistically significant difference.[87]

The post hoc subgroup analysis of data from a nonblinded controlled trial of intravaginal micronized progesterone did not have sufficient power to examine effect modification. The sample size of the original study was adequate for main effects, but subdivision of the study population into two subgroups resulted in inadequate power.[36]

A double-blind randomized controlled trial of weekly 17OHP injections in 168 women had only three percent of women with a history of prior spontaneous preterm birth. These five women were an inadequate sample size for comparative analysis of effectiveness.[72] A retrospective analysis of 906 women treated with weekly 17OHP injections did not include an untreated comparison group. No conclusion could be drawn about differences in effectiveness. The preterm birth rate was higher in participants with a higher number of prior spontaneous preterm births; this risk factor has already been established.[53]

The body of evidence is poor for determining if the effectiveness of progestogen for prevention of preterm birth varies by the number of prior spontaneous preterm births. No data evaluated other maternal, neonatal, or childhood outcomes. No evidence addresses adverse effects or safety, in relation to the number of the prior spontaneous preterm births.

Short Cervix as an Effect Modifier

Shortened cervical length has been studied and confirmed as an independent risk factor for preterm birth and is of interest as a modifier of treatment effectiveness when the primary goal is related to another indication. (The study of treatment for the specific indication of short cervix is reviewed with primary indications and outcomes in KQ1.) A consensus about cut-off for defining short cervix has not been established; data suggest that the shorter the cervical length, the greater the risk of subsequent preterm birth.

One RCT screened 24,620 women to identify 413 women and enroll 250 participants with cervical length of ≤ 1.5cm by ultrasound exam.[55] The intervention in this placebo-controlled trial was 200 mg micronized progesterone via vaginal suppository each evening with the primary outcome birth before 34 weeks gestation. Within this study of women who all had short cervical length were women with other risk factors: 15 percent had a prior spontaneous preterm birth and 10 percent had a current twin pregnancy. All estimates of effect of progesterone by subgroup (cervical length, one or more prior preterm births, or twin gestation) have overlapping confidence intervals meaning there was no evidence of modification of progesterone treatment outcomes by these characteristics. While effect estimates favor benefit of progesterone they were not statistically significant for more than half of the subgroups suggesting overall study power was lower than anticipated in the design of the trial.

A secondary analysis of a study of 620 women with a history of prior preterm birth and a current singleton pregnancy analyzed a subgroup of 547 participants with a cervix length > 3.0 cm at randomization compared to a subgroup of 104 participants with a cervix length of ≤ 3.0 cm at randomization. The intervention comparison was progesterone or placebo gel nightly. Of the 620 participants, 104 had a cervix length < 3.0 cm at randomization and received a second ultrasound measurement of cervix length at 28 weeks; 54 were in the progesterone group and 50 were in the placebo group. Cervical length at randomization was different between the two groups; the placebo group average length was 0.2 cm shorter. For the surrogate outcomes of 28 week cervical length less than 2.5 cm, or 28 week cervical length less than 1.5 cm, or more than 50 percent change in cervical length, no difference was found between the progesterone and placebo groups. After performing an adjustment for clinically relevant covariates for the subgroup of 110 participants with initial length of less than 3.0 cm, they found a small difference, with a very wide confidence interval, in cervical length change over the time from randomization to 28 weeks. The adjustment was performed by assigning a cervical length measurement of zero to all participants who delivered before the 28 week ultrasound study could be performed. Birth and neonatal outcomes were not statistically significant if expressed as

relative risk of the outcomes. This secondary analysis is downgraded for serious study limitations, risk of bias, imprecision, and selective outcome reporting.[52, 84]

Another study planned to report on women with a singleton pregnancy and without a history of prior spontaneous preterm birth, with a short cervix on ultrasound examination, but they had only nine women with short cervical length (1.3% of the study population), and reported that a separate analysis of these participants would not be meaningful.[82] Thus in total there is no evidence in the literature for either effect modification or differential risk of harms based on cervical length.

Order of Multiple Gestations

We sought evidence about whether the number of fetuses in a multiple gestation modifies outcomes, among women receiving progesterone for the indication of a current multiple pregnancy. No data were found for quadruplets or higher multiples.

All placebo-controlled randomized trials of progestogen for prevention of preterm birth before 35 weeks in twin pregnancies have found no significant difference between the progestogen and placebo groups.[35, 41, 48] One subgroup analysis of 67 twin pregnancies from a larger RCT of 150 women reported a benefit for prevention of preterm birth before 37 weeks for progestogen compared to placebo.[31] The effectiveness was not meaningfully different across twins versus singletons. These studies did not include triplets and as a result cannot contribute direct information about modification of effects of treatment by three compared to two fetuses. A single study enrolling exclusively triplet pregnancies found no benefit of 17OHP injections compared to placebo.[40]

Given lack of effectiveness for modifying critical outcomes in multiple gestations, it is probable but not proven that the effect estimates for twins and triplets both overlap the null and include the confidence intervals of the comparison subgroup indicating no expectation of effect modification. Of note as presented in KQ 1, expectations for singleton compared to twin gestation are substantively different with low strength of evidence suggesting benefit for singleton pregnancies while moderate strength of evidence suggests lack of benefit for multiple gestations. This is a tacit acknowledgement of potential effect modification by singleton versus twin/triplet status though studies have not been conducted with adequate numbers of both singleton and multiple gestations in the same study protocol to definitively reach this conclusion.

Preterm Labor in the Index Pregnancy

While a number of studies have information about the occurrence and treatment of preterm labor among their participants, these data were most often presented as descriptive or surrogate outcome data. No studies were designed to assess effect modification by preterm labor status. A small non-blinded quasi-randomized trial of participants with a mixture of risk factors, including 44 with threatened preterm labor, utilizing oral micronized progesterone as the intervention, reported no significant difference in prolongation of the pregnancy across risk groups. The risk of bias in this study was profound, and sample size was very small: 10 women had preterm births (seven in the placebo group and three in the progesterone group, after excluding participants with a multiple pregnancy).[65] There is insufficient evidence to determine whether the effect of progestogen treatment, either benefits or risks, is modified by occurrence of preterm labor.

Socioeconomic Risk Factors

Socioeconomic status and race have been candidates of interest as modifiers of response to progestogen treatment. A multi-center double-blind placebo-controlled randomized trial of 463 singleton gestation pregnancies with a history of spontaneous preterm birth, using weekly 17OHP injections as the intervention, showed a benefit for preventing preterm birth before 37 weeks in both subgroups assessed: Black, non-Hispanic women and all other women. Relative risk and absolute risk reduction are very similar:[60, 87]

- Black, non-Hispanic: RR=0.68 (95% CI: 0.51, 0.90); ARR=9.8 percent (95% CI: 1.19, 18.42%); Number needed to treat (NNT)=11 (95% CI: 5.4, 84)
- White, Hispanic, Asian, and Other: RR=0.64 (95% CI: 0.47, 0.87); ARR=8.8 percent (95% CI: 0.93, 16.7%); NNT=12 (95% CI: 6, 108)

Confidence bounds for estimates of effect overlap suggesting similar response to progesterone treatment in this trial. Information about response to treatment by race/ethnicity and socioeconomic factors is scant. As these are often characteristics identified in reproductive epidemiology studies as correlates of risk for preterm birth the paucity of information is surprising. Evidence from a single trial suggests race/ethnicity does not modify response to treatment; no data of sufficient power are available to estimate whether risk of harm varies.

Body Mass Index (BMI)

Speculation about the role of BMI in influencing treatment response includes concerns that the dose of progestogen may not be sufficient at the highest BMI, and that comorbidities cluster at the extremes of BMI; for instance eating disorders at below average levels and metabolic syndrome at the above average levels. A systematic review of the literature (39 studies: 1,788,633 women), including cohorts and case-control studies, published between 1968 and 2009, examined the association between BMI and preterm birth of all types.[88] The comparator group was BMI between 20 and 24.9. The overweight group (BMI=25-29.9) had a reduced adjusted OR=0.85 (95% CI: 0.80, 0.92) for preterm birth. The obese group (BMI=30-34.9) had a reduced adjusted OR=0.83 (95% CI: 0.75, 0.92) for preterm birth. The severely obese group (BMI=35-39.9) had an increased adjusted OR=1.33 (95% CI: 1.12, 1.57) for preterm birth. The morbidly obese group (BMI > 40) had an increased adjusted OR=2.27 (95% CI: 1.76, 2.94) for preterm birth.[88] The entanglement of BMI and its related morbidities with both risk of preterm birth and potentially with the biological activity or risk of treatment make it an important target for understanding modification of progestogen treatment outcomes.

Sub-analysis of a multi-center double-blind placebo-controlled randomized trial of 463 singleton gestation pregnancies with a history of spontaneous preterm birth, using weekly 17OHP injections as the intervention, showed a benefit for preventing preterm birth before 37 weeks in women with pre-pregnant BMI < 29, and no benefit for women with a pre-pregnant BMI > 29.[87] The p-value for the interaction term in multivariate models was < 0.001; however the confidence intervals for the effect itself by strata are not provided. Interaction terms may be significant in models while precision for confirming distinctive differences in treatment response at the relative and absolute level is insufficient.

The average prepregnant BMI in this study was 26.0 ± 7.0 in the placebo group, and 26.9 ± 7.9 in the treatment group, indicating that the average participant was overweight. The difference between treatment groups was most pronounced in the subgroup with a low pregravid BMI < 20

having increased risk of preterm birth whether treated (29% higher point estimate; 95% CI: 0.58, 2.88) or not, with threefold higher odds in the placebo group compared to women of normal weight (95% CI: 0.78, 19.19); however the study was underpowered for this factor with especially sparse data for low BMI participants (n=20). The authors suggested that weekly 17OHP injections are more effective in women with lower pregravid BMI and less effective in women with elevated pregravid BMI. Another interpretation could be that the effectiveness of progestogen is greater in women with a lower pregravid BMI. Another, that higher doses of progestogen may be needed in participants with a high pregravid BMI or that higher pregravid is protective for reduction of future preterm birth after prior preterm birth, and that progestogen does not confer additional benefit for this subgroup of participants. Last, in keeping with the broader literature about the relationship between obesity and preterm birth, it is possible that the placebo group of this RCT is atypical, and the trend seen in the subanalysis is reflective of the atypical placebo group, rather than a differential effect of progestogen in women with differing pregravid BMI.[87]

The evidence is insufficient to understand the influence of BMI on response to progestogens. Given a typical expectation that effective dose and BMI may be related, high prevalence of obesity in the United States, and need to assess risk of interaction with co-morbidities, this is an important lack of data that makes the literature less applicable than is desirable.

Cerclage

A planned secondary analysis[32] of the Eunice Kennedy Shriver National Institute of Child Health and Human Development-sponsored randomized trial evaluating cervical cerclage for women with singleton gestations, prior spontaneous preterm birth (17–33 6/7 weeks), and cervix length < 25 mm reported the impact of 17P usage on the primary outcome of preterm birth before 35 weeks. The study subjects were stratified at randomization by intent to use or not to use 17P. Intramuscular 17P had no additional benefit for prevention of preterm birth in women who had prior spontaneous preterm birth and received the randomized intervention of ultrasound-indicated cerclage for CL < 25 mm. The clinical trial was not powered for this secondary analysis. According the post hoc analysis in the publication, 14 times the number of subjects would have been needed to show a 4 percent decrease in the preterm birth < 35 weeks.

Other Candidate Modifiers

No analyses were identified that assessed modification of treatment effectiveness among women with these characteristics versus without:

- Fetal fibronectin testing results
- Prior PPROM
- Uterine malformation
- Conception using assisted reproductive technology (e.g., in vitro fertilization, intracytoplasmic sperm injection of eggs)
- Maternal age

Likewise, there were not related assessments of differences in adverse effects.

KQ4. Type of Progestogen as a Modifier of Outcomes

Randomized controlled trials making direct comparisons of one form of progestogen to another have not been conducted with currently available progestogens. A single 1979 study comparing intramuscular 17OHP and oral chlormadinone acetate is the only head-to-head comparison.[77] This means there are no high-quality data to determine superiority or equivalency of one formulation, dose, or route compared to another. As an extension of this lack of direct comparisons, it is not possible to determine with confidence whether acceptability, adherence, adverse effects, or safety of progestogens vary by formulation, dose, or interval of administration. Likewise no RCTs have investigated ideal timing for initiation or discontinuation of therapy.

Since the summary of the evidence for KQ1 is organized primarily by the risk group being treated with progestogens (prior preterm birth, preterm labor, multiple gestation), we reintroduce some of the related summary data in this section organized by type of progestogen.

First we present total yield of the literature search to convey the scope of the literature. Across all studies the most common progestogens and doses, by route, were: 250 mg of 17OHP injected intramuscularly weekly, 90 mg progesterone vaginal suppository or gel daily, and 200 to 1000 mg oral micronized progestogen daily. Next we present summary preterm birth outcomes in this order of prevalence in the literature, focusing on summaries of RCTS. Since data from separate RCTs cannot provide strong evidence for selecting one type of progestogen intervention over another, we have not provided detailed summaries of observational data which is even more prone to bias and less suitable to cross-study comparisons.

Injection of 17OHP

We identified 27 studies that administered injected 17OHP for prevention of preterm birth, 12 were RCTs;[30, 40-41, 46, 48, 56, 60, 68, 72, 77, 79, 83] three were clinical trials;[66, 71, 73] two, prospective cohorts;[74, 76] eight were retrospective cohorts;[33, 39, 44, 53-54, 59, 70, 80] one, a retrospective case series;[45] and one, a case-control study.[58] Four of these publications are ancillary publications from a single study population[60, 86-87, 89] and two share another population.[52, 82] We considered them as only two study populations. The majority of studies (19) were conducted in the United States,[30, 33, 39-41, 44-45, 48, 50, 53-54, 59-60, 70, 72, 76, 79-80, 83] seven in Europe,[46, 56, 58, 71, 73-74, 77] and one in Asia.[66] Exact combinations of dose, interval, and target window are provided in Table 3 under Results (above). The majority of 17OHP studies initiated treatment between 16-21 weeks gestation with a range of 15-36 weeks.

Table 18 summarizes the nine RCTs of 17OHP that reported prematurity outcomes at < 37 (singleton gestations) or < 35 (multiple gestations) weeks. Four different 17OHP doses were used and indications for treatment included prior preterm birth in one trial, preterm labor in two, multiple gestation in three, a variety of risk factors in one, and amniocentesis. Four of eight demonstrated effectiveness of 17OHP, four had nonsignificant findings, and none found significant advantage for the placebo group. Aggregate estimates indicated that 17OHP was not effective at reducing risk for neonatal mortality (OR=1.11, 95% BCI: 0.66, 1.73) but was effective at reducing risk of preterm birth (meta-estimate OR_{17OHP}=0.75, 95% BCI: 0.60, 0.90).

Table 18. Injection of 17OHP in RCTs reporting prematurity outcomes at < 35 or < 37 weeks

Author Year	Dose	Outcome	Favors 17OHP	NS	Favors Placebo
Caritis et al.[40] 2009	250 mg q 7d	< 35		RR=1.0 (0.9, 1.1)	
Combs et al.[30] 2010	250 mg q 7d	< 35		NR p=0.15	
Briery et al.[41] 2009	250 mg q 7d	< 35		NR p=0.117	
Facchinetti et al.[46] 2008	341 mg q 4d	< 37	NR p=0.049		
Rouse et al.[48] 2007	250 mg q 7d	< 35		RR=1.1 (0.09, 1.3)	
Facchinetti et al.[56] 2007	341 mg q 4d	< 37	NR p=0.004		
Meis et al.[60] 2003	250 mg q 7d	< 37	RR=0.66 (0.54, 0.81)		
Corrado et al.[62] 2002	340 mg twice a week until 2nd week after amniocentesis	< 37		NR p > 0.05	
Yemini et al.[68] 1985	250-12,500 mg over 36 wks (NR)	< 36	NR p < 0.05		

17OHP = 17 alpha-hydroxyprogesterone caproate; d = day; mg = milligrams; NR = not reported; NS = not significant; q = every; RR = relative risk; wks = weeks.

Vaginal Administration of Progestogens

We identified seven publications that report on either a vaginal gel, capsule, or suppository for administering progestogen treatment.[31, 35-36, 47, 52, 55, 61] Two studies[52, 82] are part of a single family of studies and are considered a single study population in this report. All studies[31, 35-36, 47, 52, 55, 61] were RCTs with four conducted outside of the United States. These include the United Kingdom,[35] Brazil,[61] India,[36] and Iran.[47] The remaining studies were either in the United States[31] or conducted at multiple sites. These include one study that included United States, South Africa, India, Czech Republic, Chile, and El Salvador[52] and another study that included the United Kingdom, Chile, Brazil, and Greece.[55] Exact combinations of dose, interval, and target window are provided in Table 3 under Results (above).

In the seven RCTs of vaginal administration, five different doses were used. The indication for treatment was history of preterm birth in two studies,[36, 52] multiple gestation in one,[35] varied risk factors in two,[31, 61], and shortened cervical length in one.[55] The gestational age at initiation of treatment was 24 weeks for three out of seven of these studies.[35, 55, 61] The remaining studies initiated treatment at 18-22+6 weeks,[52] 20–24 weeks,[36] 24–34 weeks,[31] and after tocolysis obtained.[47] Table 19 summarizes findings for prevention of preterm birth. Overall, four of six demonstrated effectiveness of vaginal progesterone, two had nonsignificant findings, and none found significant advantage for the placebo group. Of note neither trial of gel found benefit (combined n=1,109).[35, 52] Aggregate estimates indicated that vaginal progestogens were not effective at reducing risk for neonatal mortality (OR=0.77, 95% BCI: 0.39, 1.27) but were effective at reducing risk of preterm birth (meta-estimate $OR_{Vaginal}$=0.76, 95% BCI: 0.57, 0.98).

Table 19. Vaginal progestogens in RCTs reporting prematurity outcomes at < 35 or < 37 weeks*

Study Country	Form	Dose	Outcome	Favors Progestogen	NS	Favors Placebo
Cetingoz et al.[31] 2010 Turkey	Vaginal Supp	100 mg qd	< 37	OR=0.5 (0.26, 0.96)		
Norman et al.[35] 2009 UK	Vaginal Gel	90 mg qd	< 34		OR=0.74 (0.48, 1.12)	
Majhi et al.[36] 2009 India	Vaginal Cap	100 mg qd	< 37	RR=0.32 (0.14, 0.72)		
O'Brien et al.[52] 2007 Multinational	Vaginal Gel	90 mg qd	< 37		OR=0.93 (0.66, 1.32)	
Fonseca et al.[55] 2007 Multinational	Vaginal Cap	200 mg qd	< 34	RR=0.60 (0.35, 0.94)		
da Fonseca et al.[61] 2003 Brazil	Vaginal Supp	100 mg qd	< 37	NR p =0.03		

* One study was not included because they report at 34 weeks gestation.
Cap = capsule; mg = milligrams; NR = not reported; NS = not significant; OR = odds ratio; qd = every day; RR = relative risk; Supp=suppository, UK = United Kingdom.

Oral Administration of Progestogens

Five studies[34, 63-65, 67] used oral progestogens alone or in combination with Ritodrine in the treatment group. Three recruited participants in Europe (France),[63, 65, 67] one in the United States,[64] and one in Asia (India).[34] Four were RCTs [34, 64-65, 67] and one was a case-control study.[63]

Exact combinations of dose, interval, and target window are provided in Table 3 under Results (above). Two studies did not indicate gestational age at initiation[63, 65] and three reported ranges between 18–36 weeks.[35, 64, 67] One study required a previous history of preterm birth.[34] None enrolled multiple gestations as an indication for progestogen treatment.

Three RCTs reported prematurity outcomes at < 37 weeks and are summarized in Table 20. Each of the three RCTs use different doses and had different indications for treatment, including history of preterm birth, preterm labor, and a variety of risk factors. One of three demonstrated effectiveness of oral progestogens, two had nonsignificant findings, and none found significant advantage for the placebo group. Aggregate estimates indicated that oral progestogens were not effective at reducing risk for neonatal mortality (OR=0.68, 95% BCI: 0.04, 2.17) but were the most effective at reducing risk of preterm birth relative to the other meta-estimates for 17OHP and vaginal progestogens which were approximately 0.75 (meta-estimate $OR_{Oral=}$0.56, 95% BCI: 0.36, 0.79).

Table 20. Oral progestogens in RCTs reporting prematurity outcomes at < 37 weeks

Study Country	Progestogen	Dose	Outcome	Favors Progestogen	NS	Favors Placebo
Rai et al.[34] 2009 India	Progesterone†	100 mg b.i.d.	< 37	NR p=0.002		
Hobel et al.[64] 1994 U.S.	Provera	20 mg b.i.d.	< 37		NR p=0.98	
Noblot et al.[65] 1991 France	Progesterone†	4x 100 mg q6h for 24h; 4x 100 mg q8h for 24h; then 3 100 mg q8h	< 37		NR p=NS	

† Micronized progesterone.
b.i.d. = twice a day; h = hours; mg = milligrams; NR = not reported; NS = not significant; q = every.

Gestational Age at Initiation of Intervention

Gestational age at initiation has been a candidate of interest as a modifier of response to progestogens treatment. No direct comparator studies were found. Two clinical care cohorts in which timing of initiation varied, for reasons other than randomization, showed no significant difference in preterm birth rates based upon whether the progestogen was initiated before or after 21 weeks' gestation (combined n=1,181).[53-54] Two studies with intervention initiated before 20 weeks gestation in all participants have conflicting findings about prevention of preterm birth before 37 weeks:

- RR=0.66 (95% CI: 0.54, 0.81) with 17OHP and n=459[60]
- RR=1.03 (95% CI: 0.85, 1.24) with progesterone vaginal gel and n=611[52]

Initiation after 20 weeks gestation in all participants for birth before 37 weeks:

- RR=0.49 (95% CI: 0.25, 0.96) with progesterone vaginal suppository and n=142[61]

No RCTs directly address modification of effectiveness by timing of initiation. Given variation in pharmaceutical agents being studied, as outlined above, it is not possible to extrapolate from trends in study findings to determine an optimal time for initiation of treatment. There is no evidence available to determine if there are differences in adverse effects or safety, based upon gestational age at initiation of the intervention. Evidence is insufficient to define an ideal gestational age at which to start treatment.

Adherence

17OHP. Eight studies reported on adherence to 17OHP treatment.[33, 39-40, 45, 56, 59-60, 83] Two RCTs directly compared adherence among intervention and placebo groups. An RCT from Italy (n=38), reported 100 percent adherence in both the 17OHP intervention group and their control group,[56] and a large RCT in the United States (n=459) reported 8.5 percent of the17OHP intervention group was nonadherent, but not statistically different from the placebo group.[60] Another RCT in the United States (n=278), noted that 91.4 percent of the study participants were adherent with treatment but did not make statistical comparisons across groups. A prospective cohort from the United States (n=38), noted that 25 percent of the intervention group missed more than two doses.[59] A retrospective cohort in the United States (n=684), compared early discontinuation of treatment for reasons other than birth between a 17OHP intervention group (250 mg every seven to ten days) (9.4%) and daily perinatal nursing surveillance (7.3%) and did

not observe a significant difference.[33] Only one study,[45] a retrospective case series (n=208), directly assessed adherence in the context of frequency of injections; they observed that only 2.2 percent of participants missed a dose and all received less than five injections. None of the published studies directly compared adherence at varying gestational ages at initiation and discontinuation of treatment, or made comparisons across types of progestogens.

Vaginal progesterone. Adherence and/or compliance were only discussed in two studies of vaginal administration.[52, 55] One study[52] directly tested for differences in adherence between their treatment and intervention group and observed no significant difference between the two groups (96.2% compliance in treatment group versus 96.4% compliance in placebo group). The other[55] was less clear about how they assessed adherence, noting 7.2 percent had adherence < 80 percent but that this was not significantly different from controls.

Oral Progestogens. None of the studies directly assessed participant adherence to treatment.

Risk of Harms

Without direct comparisons of different formulations, doses and intervals it is not possible to know whether risk of harm varies for different formulations and routes of progestogens. Given lack of detailed reporting about harms and lack of consistent definitions, it is not meaningful to extrapolate among routes from available data. Overall, there is no evidence to help inform selection of the progestogen with the fewest side-effects and/or lowest risk of harms.

KQ5. Cointerventions as Modifiers of Outcomes

Ten studies reported using tocolytic treatments as a cointervention to prevent spontaneous preterm birth[31, 34, 50, 60-61, 64-65, 68, 74, 77] either alone or in combination with another cointervention. Eight studies used other forms of cointerventions for their intervention group including cortisol,[73] daily nursing surveillance,[43] nurses to administer drugs and availability to ask questions but not daily,[33] bed rest,[75] cervical cerclage,[32] estrogen,[78] omega-3 fatty acid supplements,[28] and DES.[13] 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. As a result, evidence is insufficient for understanding the role of cointerventions in either amplifying or undermining the potential benefits of progesterone treatment. It is not feasible to 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 choice of cointerventions.

KQ6. Effect of Health System and Provider Factors

Approach

We sought research that explicitly studied the knowledge, attitudes, and prescribing behaviors of care providers with regard to their clinical use of progestogens for women at risk of preterm birth, broadly defined. We also sought publications that included data about use of progestogens in well-circumscribed populations in which the proportion of eligible women who received progestogens could be estimated or in which authors present analyses focused on the

influence of health system factors like coverage for progestogens, formulary/availability, provider specialty, and institutional guidelines or policies.

Results

Using this approach, we identified 11 publications, from nine distinct study populations.[10, 33, 39, 49-50, 57, 59, 90-93] Three reports originate from a Matria Healthcare database, or databases, and present information from different but overlapping timeframes, likely resulting in some duplication of the clinical population studied.[33, 49-50] The other study populations were women enrolled in the high-risk clinic,[57] or a "prematurity prevention" clinic[39] of academic tertiary care centers, and an analysis of use within the Missouri Medicaid managed care component.[59]

Five studies directly surveyed providers about their practice patterns, knowledge, attitudes, and concerns. Three of these surveys were conducted in the United States,[10, 91, 93] with two directed to board-certified maternal-fetal medicine specialists (MFMS)[10, 93] and one directed to members of the American Congress of Obstetricians and Gynecologists (ACOG) Collaborative Ambulatory Research Network.[91] The remaining surveys were conducted in Canada (national registry of obstetricians)[92] and Australia and New Zealand (members of the Royal College).[90] In each of these surveys, information about progestogen use was collected from December 2003 and later; meaning all were conducted after the publication of the NICHD Maternal-Fetal Medicine Networks trial of 17OHP appeared in print.[60]

Among the six observational studies that provide data about use of progestogens in defined populations of participants, four publications had study objectives related to understanding prescribing practices or patterns of use;[33, 49, 57, 59] and two provide data that are informative for this KQ but were incidental to the aims of the publications.[39, 50] All reflect care for women in the United States from 1995 forward; the majority in 2003 and later.[49-50, 57, 59]

The provider survey studies reflect responses from 1,098 specialist practitioners (which includes an unknown but substantial amount of overlap given repeated survey of the same organization) and 345 generalist practitioners in the United States and 2,246 obstetricians in Australia, Canada and New Zealand, with survey response rates from 42 to 53 percent. The literature reflects increasing use in the United States from 38 percent of MFMS surveyed in 2003[93] to 74 percent of ACOG network members by 2007.[91] Ness and colleagues who surveyed MFMS twice, documented this was a statistically significant increase between 2003 with 38 percent prescribing for preterm birth prevention and 2005 with 67 percent prescribing ($p < 0.001$).[10] If the NICHD trial indication for prevention of preterm birth in singleton gestations for mothers who have had a prior spontaneous preterm birth is used as a general rubric for eligibility for treatment, then the self-reported prescribing progestogens beyond that specific indication is also rising, with 20 percent of MFMS reporting use for short cervix or preterm labor symptoms in the 2003 publication; 39 percent of MFMS by 2005; and 52 percent of ACOG network obstetricians in 2007. More than three-quarters of use has been intramuscular administration of weekly injections, with vaginal the next most common, and oral rare.

The list of barriers to use reported by those who do prescribe progestogens was topped by lack of availability and lack of insurance coverage, with other factors including lack of FDA approval for the indication and need for greater information about long-term effects.[10, 91] Nonprescribers identified similar ranking for barriers compared to prescribers in the MFMS survey but endorsed them as problems in higher proportions, with the exception of not being as likely to indicate that insurance coverage was an important barrier. Among generalists, the rank

order of barriers differed from prescribers with nonprescribers concerns being greatest to least in order from need for data, long-term effects, availability, efficacy, liability, to FDA approval.[91]

The survey of obstetricians participating in the ACOG research network was the only one to ask about patient demand. Overall, 63 percent of respondents reported that patients "never request"; 35 percent, "infrequently request"; and 2 percent "frequently request."[91] This was also the only study to examine patterns in responses about use, finding in multivariate models that those who trained more recently, who were specialists, and practiced in group or academic settings were most likely to prescribe treatment, and that regionally practitioners in the Western United States were least likely to use progestogens for preterm birth prevention.

In sharp contrast with trends in the United States, studies outside the United States, which happen also to be from countries with national health systems, found little use of progesterone—2 percent among Australian/New Zealand obstetricians and seven percent among Canadian obstetricians. Seventy-one percent of Canadian obstetricians cited "evidence not convincing" as the primary reason they do not prescribe routinely for prevention of preterm birth. 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. Given low reported use, neither report could provide data about use patterns or trends in indications.

Observational studies of progestogen use, suggest more than 40 percent of women who are eligible for treatment with progestogens, based on prior history of preterm birth and a current singleton gestation, do not receive treatment. Bailit and colleagues encompassed the earliest time period, investigating prescribing behavior from July 2003 through June 2004.[57] They explicitly choose a site that was part of the Maternal-Fetal Medicine Research Network 17OHP trial in order to examine uptake and use patterns in an environment in which the care providers and clinical staff had a high level of familiarity with providing the intervention. Among 500 high-risk participants, 57 percent of eligible women were offered progestogens; another two percent were offered treatment who would not have met trial criteria, most of the latter had multiple gestations and most of the prescribing beyond the trial evidence was done by a single provider. The pattern of progestogens prescribed was surprising—25.5 percent received injections; 55.8 percent vaginal suppositories, and 18.6 percent had missing information about dose and route. Even if all missing are assumed to be injection, the majority of women were given vaginal suppositories. The authors anecdotally relate this to drug availability and coverage.

Durnwald and colleagues' study at the other academic site encompassed 1999 to 2008 but did not relate the timing of care in secular time with the use of progestogens. Overall, 52.5 percent of eligible women received intramuscular 17OHP and analysis of predictors found older age, private insurance, earlier prior preterm birth, and earlier enrollment in prenatal care were associated with higher use.[39]

Missouri Medicaid managed care was an early adopter of coverage. This allowed comparison of 24 women who received 17OHP injections in 2004 to 14 who did not but would have been eligible. While the authors were focused on outcomes in their data analysis, they did offer the observation that later onset of care related to delays in establishing Medicaid eligibility could have contributed to lack of use when appropriate.[59]

Publications relying on Matria clinical care databases provide a different perspective. In order to be in the database a woman had to be referred for home health services that include a wide panel of options from home uterine activity monitoring, daily nurse calls, diabetes management, blood pressure monitoring, and home administration of 17OHP injections. Women

referred include both Medicaid and private pay patients. The database includes prior pregnancy history and can be used to assess eligibility for progesterone use in the index pregnancy. Processes of care also ensure that the provider indication for desiring to initiate progestogen treatment is indicated. In a matched study of 342 women who received 17OHP injections (with or without other services) and 342 who did not but received uterine monitoring and nurse calls, early enrollment in care was a determinant with 80.4 percent of those receiving entering care before 21 weeks (the percentage of women enrolling before this time among those that did not receive 17OHP injections is not reported).[33] Another analysis focused on gestational diabetes incidence among women receiving 17OHP injections, indirectly provides data that 557 women received progesterone treatment between April 2004 and January 2006, while another 1,524 women at similar risk of preterm birth based on prior preterm birth did not. Analysis of predictors of use whether provider or patient factors is not included.[50] The largest and most direct analysis of use in the Matria patient population includes 1,979 women, from April 2004 to January 2006, who did receive 17OHP and focuses on patterns of use. Among those women receiving progesterone, 79.5 percent had a prior preterm birth and 63.6 percent met the MFMU trial criteria. Of those appropriately offered treatment, 56.5 initiated between the target gestational ages of 16 and 20.9 weeks. Multiple gestations made up eight percent of nonstandard use, with current preterm labor treatment comprising 44.8 percent and 23.2 percent with cerclage, being the largest groups.

Overall this research provides intriguing glimpses that suggest that, as for most preventive interventions, individuals, care providers, care systems, access, and coverage influence practice. This evidence confirms that targets for progestogen use are evolving with indications at risk of evolving beyond evidence; and that uptake, at least in the United States, is likely rising. The limited spectrum and preliminary level of detail about influences is an invitation to more substantive investigation. Certain gating factors like coverage of costs and the necessity of enrolling in care in time to start treatment in the appropriate time window can be taken as tacit areas for improvement of access to progestogen treatment. However, most influences will be more complex. For example, at least one reputable national mail-order pharmacy dispenses progestogens, making literal "availability" possible anywhere in the United States. Yet, without information about this resource and others, demands on patient and provider time can make such a logistic barrier—knowing how and where to order and what the payment options are—into an absolute barrier that prevents treatment. As evidence about effectiveness and eligible populations advances, health services research will be needed to translate the evidence into practice.

Discussion

State of the Literature

We identified a total of 64 publications, representing 58 distinct study populations: 7 of good quality, 38 fair, and 19, poor. Forty-six percent of the studies identified were randomized clinical trials, a smaller proportion were clinical trials without clear evidence of randomization (7%), and the balance are observational research, a number of which are analyses of administrative databases. A complete description of study characteristics is listed in Table 3 under Results (above).

Strength of Evidence

Overall, the strength of evidence to answer the Key Questions (KQs) was insufficient to moderate, with a single exception in which evidence is moderate for lack of benefit (Table 21). Deficiencies in the strength of evidence most often related to a preponderance of study designs with high-risk of bias; inconsistent findings across studies and inconsistencies among outcomes that would be expected to show corresponding benefit; use of intermediate outcomes; and small studies with poor precision. In the summary below, we provide strength-of-evidence ratings by KQ.

Table 21. Strength of evidence for progestogens for prevention of preterm birth

Outcomes (n total RCTs; n total participants)	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Progestogen vs. placebo or no treatment for women with prior preterm birth					
PTB prevention < 37 weeks (4; 1,318)	Low	Inconsistent	Direct	Fair	Moderate; effect size in meta-estimate: OR=0.66; 95% BCI: 0.53, 0.82
Mean birth weight (3; 859)	Low	Consistent	Direct	Imprecise	Moderate; weighted mean difference=239 gm; 95% CI: -44.5, 523.3 gm
Fetal/neonatal death (4; 1,318)	Mod	Inconsistent	Direct	Imprecise	Insufficient: lack of precision to estimate
Progestogen vs. placebo or no treatment in participants with threatened preterm labor					
PTB prevention < 37 weeks (3; 149)	High*	Inconsistent	Direct	Imprecise	Insufficient
Mean birth weight (4; 385)	High*	Inconsistent	Direct	Imprecise	Insufficient; only two small trials reported birth weight
Fetal/neonatal death (1; 126)	High*	Inconsistent	Direct	Imprecise	Insufficient: lack of precision to estimate

Table 21. Strength of evidence for progestogens for prevention of preterm birth (continued)

Outcomes (n total RCTs; n total participants)	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Progestogen vs. placebo or no treatment in participants with multiple gestations					
PTB Prevention < 35 weeks (4; 900)	Low	Consistent	Direct	Imprecise	Moderate; effect in meta-estimate: OR=1.18; 95% BCI: 0.79, 1.39
Mean Birthweight (3; 698)	Low	Consistent	Direct	Imprecise	Moderate; no effect
Progestogen vs. placebo or no treatment in participants with multiple gestations					
Fetal/Neonatal Death (5; 2,966)	High	Consistent	Direct	Imprecise	Insufficient: lack of precision to estimate
Progestogen vs. placebo or no treatment in study populations with varied risk factors					
PTB prevention < 37 weeks (4; 1,194)	Mod-High	Inconsistent	Direct	Imprecise	Insufficient
Mean birth weight (2; 119)	Mod-High	Inconsistent	Direct	Imprecise	Insufficient
Fetal/neonatal death (3; 269)	High	Inconsistent	Direct	Imprecise	Insufficient: lack of precision to estimate
Progestogen vs. placebo or no treatment in studies with unique indications^					
PTB prevention < 37 weeks (1; 584)	High	NA	Direct	Imprecise	Insufficient; single study per unique indication
Mean birth weight (1; 584)	High	NA	Direct	Imprecise	Insufficient; single study per unique indication
Fetal/neonatal death (3; 1,080)	High	NA	Direct	Imprecise	Insufficient; single study per unique indication

*Average quality rating was Fair, additional deduction for sparse data, low event numbers, and non-placebo control – results in judgment of High Risk of Bias

^Unique indications include the following: post-operative management, treatment of active-duty military personnel, abdominal surgery unrelated to pregnancy, asymptomatic short cervix.

BCI = Bayesian credible interval; CI = confidence interval; gm = grams; Mod = moderate; NA = not applicable; OR = odds ratio; PTB = preterm birth; RCT = randomized control trial.

Principal Findings and Considerations

KQ1. Maternal, Fetal, and Neonatal Health Outcomes

Forty-six publications, six of good quality, 28 fair, and 12 poor, using 41 study populations examined outcomes of progestogen treatment to prevent preterm birth. These 41 studies include 26 RCTs, 4 clinical trials, and 11 observational studies. This literature contains 23 unique combinations of progestogen formulation, route, and dose, making comparison across studies challenging. Furthermore, the literature contains studies focused on five groups of candidates for

intervention: those with a prior preterm birth, those with symptoms of preterm labor, multiple gestations, populations with varied risk factors, and special circumstances (military service, non-obstetric abdominal surgery).

Interpretation of meta-analysis. In the Results chapter, we report the findings from meta-analysis as ORs from Bayesian models. It is important to note that when outcomes are common, such as preterm birth in these study populations, the odds ratio is not a direct surrogate for the RR. For instance, in KQ1 below consider these odds ratio and comparable approximate risk ratio 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 RR is somewhat smaller than it may appear from the ORs.

A total of four RCTs have focused on women with a history of preterm birth and the strength of evidence for progestogen use is low. Four RCTs provide data about gestational age at birth (< 37 weeks; for all other cutpoints fewer studies are available), three of the four demonstrate benefit (combined n=707), while a fourth (n=611) did not. In aggregate, these studies suggest reduction in risk of preterm birth (OR=0.66; 95% BCI: 0.53, 0.82) among those receiving progestogens (Figure 3). Differences in birth weight did not differ statistically across trial arms in the three studies that reported mean birth weight (239 gm; 95% CI: -44.5, 523.3 gm). Risk of neonatal death is reduced (OR=0.52; 95% BCI: 0.25, 0.96) in meta-estimates from the four trials providing data (Figure 4). All other maternal, fetal, or neonatal outcomes were reported by fewer studies or had incompatible definitions not appropriate for aggregate estimates. Findings from observational studies are inconsistent. In summary, the strength of evidence is low with documented benefit limited to reduction of births prior to 37 weeks and decreased neonatal mortality. A small number of trials have inconsistent findings; intermediate outcomes predominate; no long-term child development outcomes have been assessed; and precision for understanding rare outcomes (e.g. intraventricular hemorrhage, respiratory distress syndrome) is exceptionally poor.

Figure 3. Meta-estimate of effectiveness for preventing preterm birth (< 37 weeks) among women with prior preterm birth

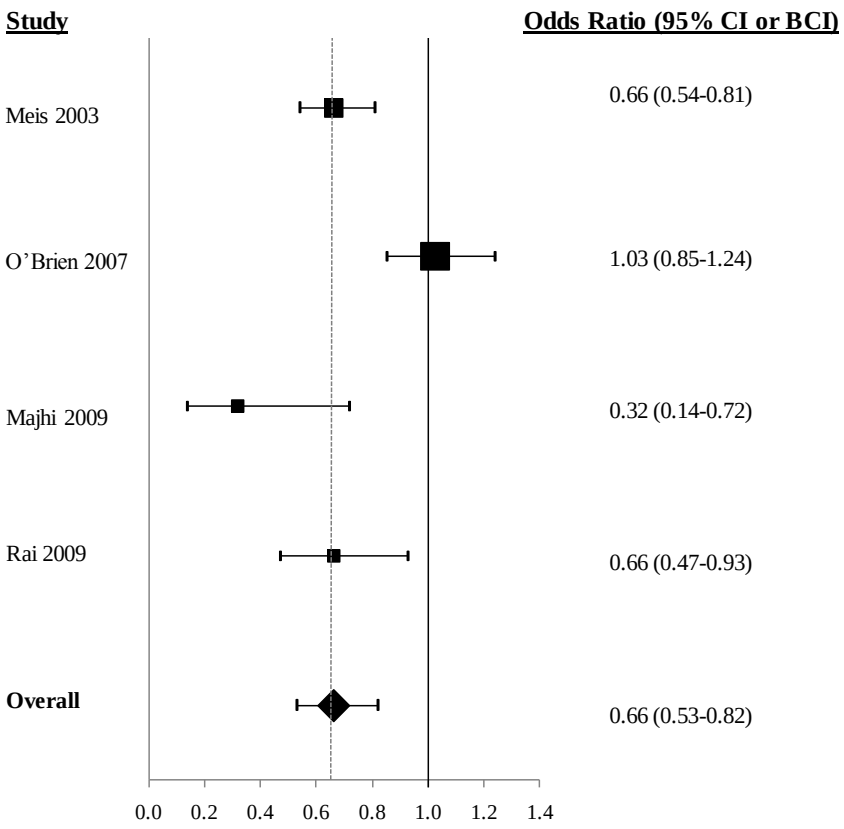
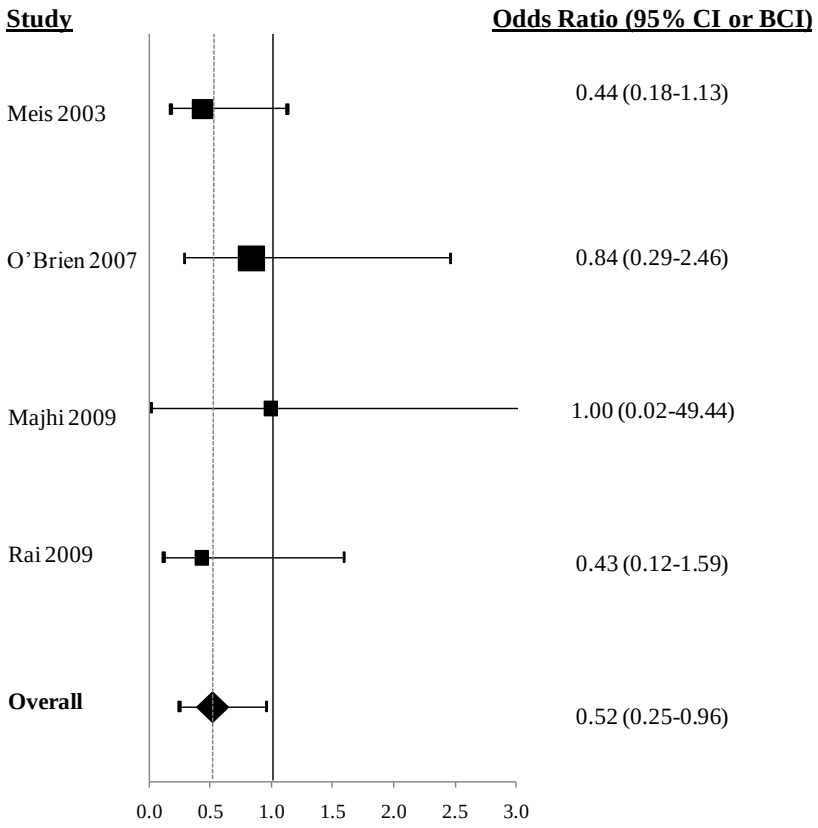


Figure 4. Meta-estimate of effectiveness for preventing neonatal death with maternal history of preterm birth

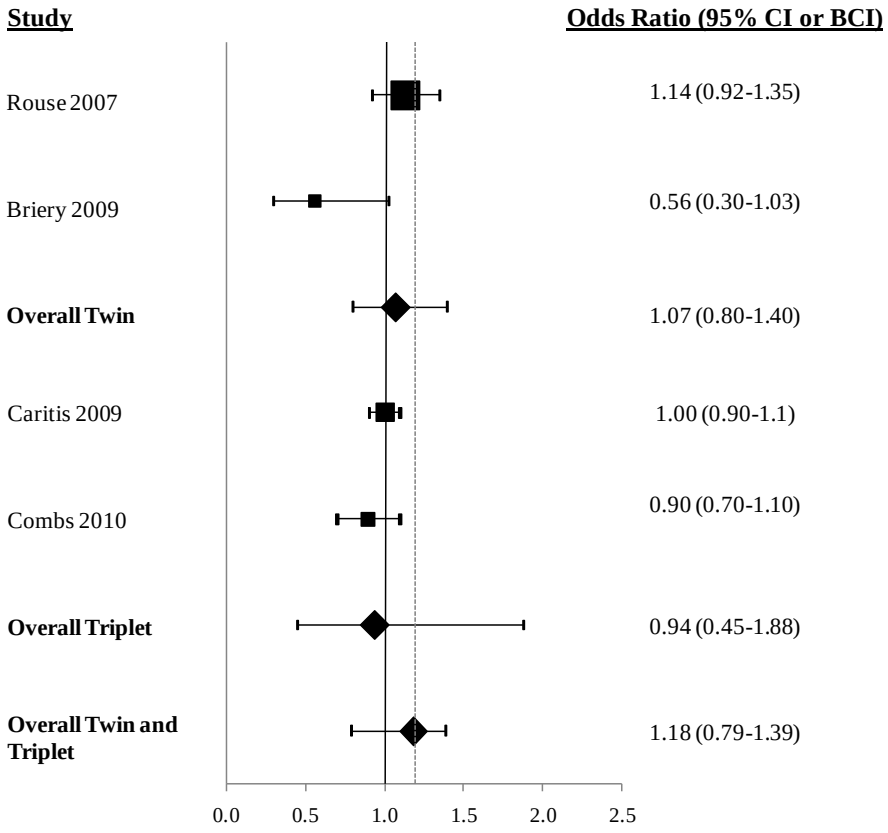


Five RCTs used progestogens in populations of women who presented with symptoms of preterm labor (n=511). The trials include both those with documented cervical change and those with threatened preterm labor. Strength of evidence for use in this group is insufficient. Three studies, with a total of 149 participants, contributed data about gestational age using a cutpoint of 37 weeks. The meta-estimate finds the odds of preterm birth among those treated is approximately a quarter of those among controls (OR=0.26; 95% BCI: 0.10, 0.49). These trials, and related nonrandomized trials, did not collect common maternal or neonatal outcomes, rather they emphasized uterine activity and elapsed time from presentation with preterm labor to birth. Results for latency were inconsistent with two RCTs finding significant benefit and another suggesting no prolongation of time to birth. Across studies of participants with preterm labor symptoms, risk of bias is moderate to high, with inconsistent findings of which few are direct, and which lack precision.

Progestogen treatment shows no clinically significant benefit in multiple gestations. Evidence of moderate strength supports this finding. A total of three RCTs and one nonrandomized trial focused on women with twins, with only two of the RCTs (n=685) reporting preterm birth at less than 35 weeks. Two RCTs enrolled triplets (n=215). The meta-estimate for odds of preterm birth at less than 35 weeks for twins and triplets combined was 1.18 compared to those receiving placebo (95% BCI: 0.79; 1.39; Figure 5). In aggregate neonatal deaths were not reduced by treatment with a meta-estimate of OR=1.75 (95% BCI: 0.93, 2.80).

Other outcomes also showed no benefit. Overall evidence related to multiple gestations draws on trials with low risk of bias, strong consistency, and a good grasp of neonatal outcomes, with fair precision for common outcomes like preterm birth and poor precision for more rare outcomes like neonatal death.

Figure 5. Meta-estimate of effectiveness for preventing preterm birth (< 35 weeks) in multiple gestations



Among nine studies that included populations with a variety of risk factors, aggregate estimates were not appropriate. The heterogeneity of these studies combined with the lack of reporting of outcomes by indication for progestogen treatment makes it impossible to interpret their significance for specific indications. Evidence is insufficient for use of progestogens in groups broadly defined to be at high-risk of preterm birth. Of note a number of these studies combined prior preterm birth and prior spontaneous abortion within their indications.

None of the four studies that examined unique indications (post-operative management, treatment of active-duty military personnel, abdominal surgery unrelated to pregnancy, and asymptomatic short cervix) for progestogen treatment demonstrated compelling findings; all provide insufficient evidence. However, this literature continues to progress. Additional research has potential to confirm or reject indications and to further refine knowledge. For example, since completion of our systematic review an additional multisite, international randomized clinical trial[94] added 458 women to the existing 250 with asymptomatic short cervix who have been studied.[55] Though small and focused on birth outcomes, both trials of vaginal progesterone gel for this indication find benefit for reducing preterm birth and neonatal mortality from prematurity. This opens the way for continued research about when to conduct ultrasound

screening and optimal cervical length at which to consider treatment of women with a short cervix, while also suggesting continued examination of optimal progestogens formulation[55, 94]

KQ2. Harms of Progestogen Treatments

Evidence about potential harms of progestogen treatment, other than anticipated injection site discomfort, is insufficient (Table 22). Risk of bias is high because uniform ascertainment methods and operational definitions of the adverse events sought are often not described. Those harms most frequently assessed are direct effects of medication administration (injection site reactions, vaginal irritation, nausea, headache), and studies were not typically designed to investigate potential consequences of exogenous hormone exposure. Followup is short, most frequently lasting only to birth or discharge of the infant from the hospital. Prospective followup of mothers and children over years has been reported only for a small number of participants. No registry data are available that explicitly track antenatal progestogen use. Because the most concerning outcomes are also likely to be rare, it is not possible with small study sizes to determine consistency of observed risk and risk estimates have very poor precision.

Table 22. Strength of evidence related to potential harms of progestogens*

Outcomes (n total RCTs)	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Complications during pregnancy					
Discomfort with injection (3)	Mod	Inconsistent	Direct	Fair (common)	Moderate evidence of injection site pain as common harm; risk similar for placebo injections; related to fact of injection.
Discomfort/irritation with vaginal route (3)	High	Inconsistent	Direct	Poor	Insufficient; wide range similar to placebo, highly variable.
Gestational diabetes (2)	High	Inconsistent	Direct	Poor	Insufficient; not consistently sought in studies; wide ranges overlap with placebo.
Hypertension/PIH (5)	High	Inconsistent	Direct	Poor	Insufficient; not consistently sought in studies; wide ranges overlap with placebo.
Mode of birth and complications at birth					
Cesarean (7)	High	Inconsistent	Direct	Fair	Insufficient; very wide ranges in placebo and treated; with high levels in both groups.
Chorioamnionitis (5)	High	Inconsistent	Direct	Fair	Insufficient; not consistently sought in studies; wide ranges overlap with placebo.
Postpartum bleeding complications (3)	High	Consistent	Direct	Poor	Insufficient; rare outcome; no power to assess
Neonatal complications					
Neonatal infections/sepsis (8)	Mod	Inconsistent	Direct	Fair	Insufficient; overlapping ranges in placebo and treated
Neonatal deaths (16)	High	Inconsistent	Direct	Poor	Insufficient; rare outcome; no power to assess

* See Table 17 for additional detail about range of risk estimates in RCTs and other studies.

Table 22. Strength of evidence related to potential harms of progestogens* (continued)

Outcomes (n total RCTs)	Risk of Bias	Consistency	Directness	Precision	Strength of Evidence
Longer term infant/child outcomes					
Congenital anomalies (8)	High	Inconsistent	Direct	Poor	Insufficient; rare outcome; no power to assess
Teratogenic effects/feminization of male infants (1)	High	NA	Direct	Poor	Insufficient; very rare outcome; no power to assess
Abnormal childhood development (1)	High	NA	Direct	Poor	Insufficient; rare outcome; no power to assess

* See Table 17 for additional detail about range of risk estimates in RCTs and other studies.
Mod = moderate; NA = not applicable; PIH = pregnancy-induced hypertension; RCT = randomized control trial.

KQ3, KQ4, and KQ5. Modifiers of Outcomes

We sought evidence about factors that might modify treatment response in all 64 included publications. Candidate modifiers were maternal characteristics (e.g., severity of prior preterm birth, number of prior preterm births, cervical length, twins versus singletons) in KQ3. KQ4 focused on whether the formulation, route, or dose of progestogen has been shown to modify outcomes compared to another formulation, route, or dose; and KQ5 examined evidence for synergy (or antagonism) between progestogen treatment and other cointerventions. In each case, we did not identify studies that were appropriately powered to estimate the joint and separate effects of the candidate modifiers. We sought stratified analyses or those that incorporated interaction terms in multivariate models in order to apportion the contributions of the candidate modifiers.

No studies of maternal characteristics had statistical precision to assert differential benefits based on maternal characteristics. Data were not suitable for aggregation across studies. Scant data, with insufficient power, address prior preterm birth history. No data inform whether effectiveness of progestogen treatment varies among women with prior PPROM, cerclage, uterine malformation, or conceptions via assisted reproductive technology, compared to other women.

No head-to-head trials of currently available progestogens have been conducted (one 1979 trial of poor quality is the only publication); and no dose finding studies focused on efficacy or effectiveness were identified in this review. No literature addresses whether adherence or acceptability to participants varies by formulation, dose, or route. Harms data are not uniformly collected so comparisons across studies cannot provide meaningful data to inform clinical decisions. The plethora of distinct indications, inclusion and exclusion criteria, drug, dose, and route combinations virtually eliminates the ability to make indirect outcomes comparisons across studies across strata of modifiers. Indirect evidence suggests, but cannot conclusively demonstrate, that vaginal suppositories (not vaginal gels) might be as effective as 17OHP, with oral routes appearing least effective.

Meta-analysis estimates were calculated for each progestogen formulation to assess the effectiveness of an individual formulation (17OHP, oral, and vaginal progestogen) at reducing the risk for preterm birth (< 37 weeks) and neonatal mortality. This included eight 17OHP, three oral progestogen, and four vaginal progestogen RCTs.

Meta-estimates indicate that no formulation was effective at reducing risk for neonatal mortality and that all formulations were effective at reducing the risk of preterm birth (meta-estimates: OR_{17OHP}=0.75, 95% BCI: 0.60 [Figure 6], $OR_{Vaginal}$=0.76, 95% BCI: 0.57, 0.98 [Figure 7], 0.90; OR_{Oral}=0.56, 95% BCI: 0.36, 0.79 [Figure 8]).

Figure 6. Meta-analysis results examining the effectiveness of intramuscular 17OHP for the prevention of preterm birth

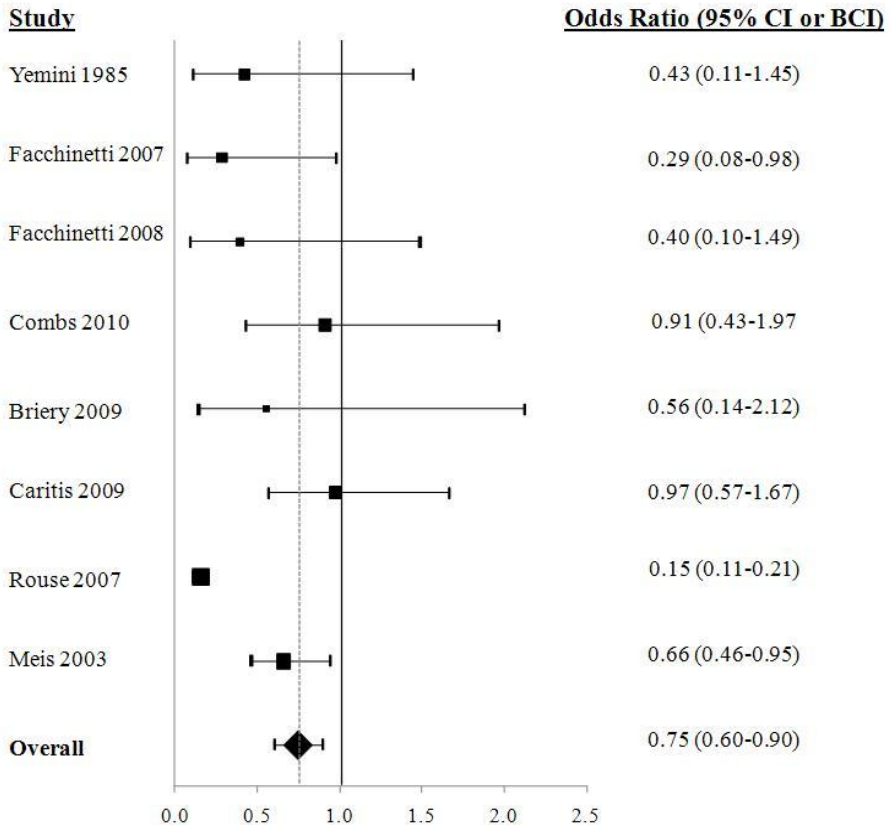


Figure 7. Meta-analysis results examining the effectiveness of vaginal 17OHP for the prevention of preterm birth

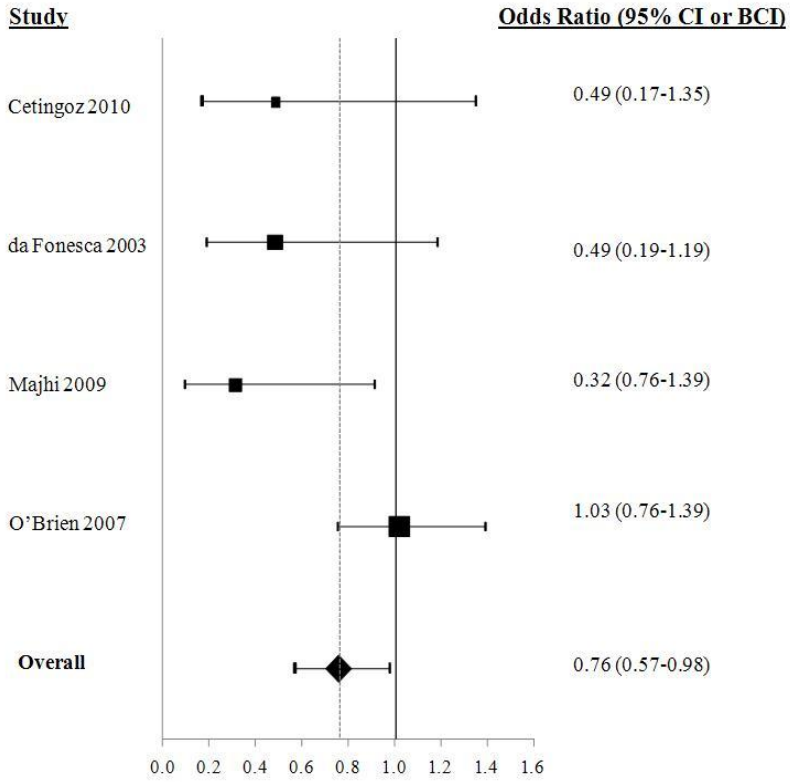
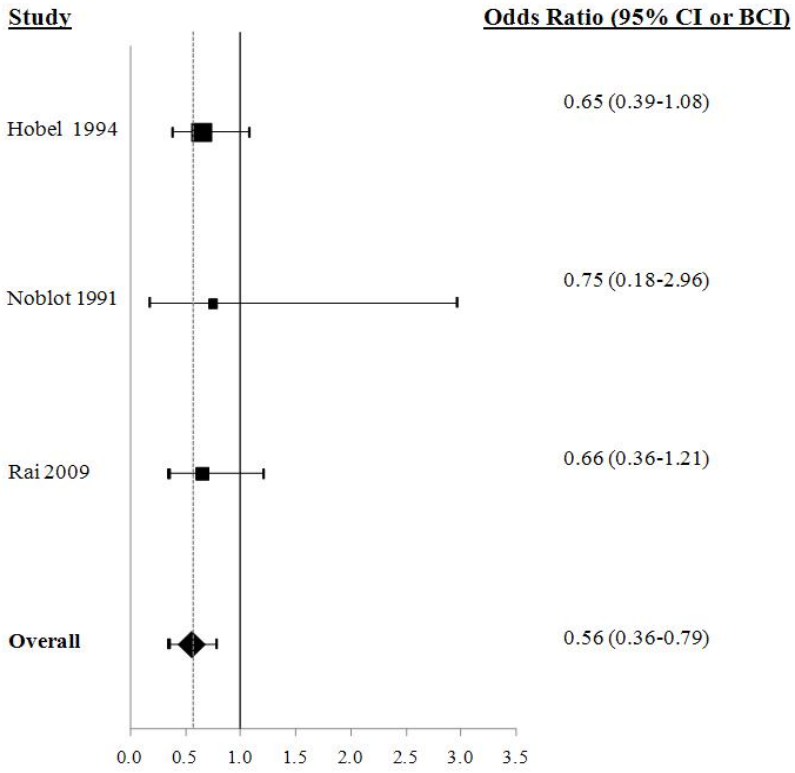


Figure 8. Meta-analysis results examining the effectiveness of oral 17OHP for the prevention of preterm birth



However without head-to-head comparisons it is possible that differences arise solely from populations studied or other biases. In order to make such comparisons other factors of study design would need to be fully comparable to allow isolation of the factor of interest such as formulations or cointervention and this is rarely strictly the case. The majority of the specific cointerventions were only represented once in the literature with tocolytics and tocolytics combined with another cointervention representing greater than 50 percent of the studies examining cointerventions.

Overall, no direct evidence with appropriate statistical power addresses differences in outcomes, adverse effects or safety, or adherence or acceptability based on the categories of modifiers studied in these KQs. For all modifiers evaluated evidence is insufficient to guide care. Risk of bias is high, consistency is poor or there are no relevant data, directness is lacking, and precision is poor.

KQ6. Health System and Provider Factors

Eleven studies, five based on surveys of care providers, provide some insight into knowledge, attitudes and prescribing behavior of providers. The evidence is largely cross-sectional, from administrative data, or incidentally available from studies with other primary aims. Two surveys provided repeated measures of the same professional groups, which is not strictly equivalent to followup of the same respondents; these provide some evidence about trends in increasing use within the U.S. while remaining flat in Canada. Quality of the evidence

about health system and provider factors is insufficient for understanding what factors drive decisions or modify access to intervention.

Applicability

We used inclusion criteria intended to identify studies with applicability to women receiving prenatal care in the United States, including research from international settings with comparably advanced prenatal and neonatal care. Study populations were generally selected based on characteristics that would be feasible to duplicate in clinical care. In order to study different risk indications for treatment, for instance prior preterm birth and multiple gestations, study populations have different but appropriate approaches to inclusion and exclusion of participants. Study populations are sufficiently well-described that it is possible to extrapolate how well they represent a clinical population of interest.

This literature includes a substantial proportion of RCTs, 26 of 57 publications (46%). As in practice, there is considerable variation in progestogen formulations, doses, and intervals used for treatment. Comparators were most often comparable forms of placebos. Heterogeneity of exact interventions, combined with lack of commonality in the outcomes reported, presents challenges to combining results to develop informative aggregate estimates of effectiveness of treatment. In general, studies have been too small to provide valid estimates of factors that may exert additional influence on treatment effects such as additional maternal risk factors or cointerventions intended to create synergy to further reduce risk of preterm birth. In practice such distinctions would have value in tailoring care.

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: observed rates of spontaneous preterm births among those who did not receive intervention exceed 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 proportion of preterm birth among those treated in practice may be greater in studies than practice. Overall the data that are available have fair to good applicability to prenatal care populations in settings within the United States and reflect interventions that could be used.

Update on Recently Completed Research

Research about progestogens for the prevention of preterm birth remains a highly active 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. Because clinical trials have the greatest potential to inform the state of the science, we restricted this update to randomized clinical trials. Eight additional trials of progestogens from prevention of preterm birth were identified (see Table 23, which supplements Table 3).

Table 23. Updated summary of progestogen interventions

Study Country Total N	Progestogen	Form	Dose & Interval	Target EGA, Start; End (weeks)	Indication
Glover et al.[95] 2011 U.S. N=33	Progesterone†	Oral	400 mg qd	16-19; 33.9	Prior PTB
Ibrahim et al.[96] 2010 Egypt N=50	17OHP	IM	250 mg q 7d	> 14; 36	PTL
Sharami et al.[97] 2010 Iran N=173	Progesterone	Vaginal Supp	200 mg qd	28-36; 36	PTL
Chawanpaiboon et al.[98] 2011 Thailand N=150	Proluton depot	IM	250 mg q 7d	≥ 28; 34	PTL
Combs et al.[81] 2011 U.S. N=240	17OHP	IM	250 mg q 7d	16-23; 34	Twins
Lim et al.[99] 2011 Netherlands N=671	17OHP	IM	250 mg q 7d	16-20; 36	Twins
Briery et al.[100] 2011 U.S. N=69	17OHP	IM	250 mg q 7d	≥ 24 (98.5%); 34	PPROM
Hassan et al.[94] 2011 U.S. N=458	Progesterone	Vaginal Gel	90 mg qd	20-23.9; 36.9	Short cervix

† Micronized progesterone

17OHP = 17 alpha-hydroxyprogesterone caproate; IM = intramuscular; mg = milligrams; PPROM = preterm premature rupture of membranes; PTB = preterm birth; PTL = preterm labor; qd = every day; Supp=suppository; U.S. = United States.

Four of the recently published trials were conducted outside the U.S. and four in U.S. populations. Intramuscular administration of 17OHP was studied in four trials;[81, 96, 99-100] one studied intramuscular administration of Proluton depot;[98] two studies used vaginal progestogens including one with gel[94] and one with suppositories;[97] and one trial used oral micronized progesterone.[95]

As organized in the table above, Table 24 below, and throughout the report, we summarize findings by the indication for use of progestogens:

Prior preterm birth. One new study enrolled a total of 33 women with a history of preterm birth.[95] The placebo group had a higher risk of preterm birth and lower gestational age compared to women in the 17OHP group. The trial was underpowered to document effectiveness. The findings are consistent with the overall literature for this indication, and this small study alone does not fundamentally change the strength of evidence for this indication which is moderate.

Preterm labor. Three trials enrolled women with preterm labor and randomly assigned participants to progesterone treatment or placebo.[96-98] The smallest of these trials (N=50) of intramuscular 17OHP, conducted in Egypt, had a statistically lower proportion of preterm birth at less than 37 weeks (32% vs. 52%) and a higher mean gestational age (37.5 ± 1.6 weeks vs. 34.7 ± 2.5 weeks) than women who received placebo.[96] The other two trials with 173 and 150 participants[97-98] did not demonstrate effectiveness. Prematurity outcomes were comparable in the study that compared Nifedipine treatment or bedrest to Proluton. Overall these additional studies do not substantively modify strength of evidence for this indication: risk of bias is high across studies with inconsistent findings and direct evidence. While these three studies add 373 women

to the total of 522 in all trials for the preterm labor indication, the inconsistency in findings suggest evidence remains insufficient with regard to whether progestogens reduce preterm birth in the context of preterm labor.

Multiple gestations. The two new trials of 17OHP in twin gestations find no benefit and observed marginally higher rates of prematurity among women receiving progestogens.[81, 99] This is consistent with the assessment that there is moderate evidence of lack of benefit in multiple gestations. Indeed the addition of 911 participants in studies with consistent and direct findings is in line with moderate evidence of lack of benefit for this indication.

Preterm premature rupture of membranes (PPROM). This trial of 17-OHP among a total of 69 study participants did not find benefit in mean gestational age. Findings from this single study provide insufficient evidence.[100]

Short cervix. Our update identified one additional study of 458 women who had a cervical length of 10 to 20mm identified by mid-pregnancy ultrasound.[94] Participants had no preterm labor symptoms and had not had cervical procedures such as conization. Those treated with vaginal progesterone gel had a significantly lower proportion of preterm birth at less than 35 weeks (14.5% vs. 23.3%) and ≤ 28 weeks (5.1% vs. 10.3%) than those in the placebo group.[94] The one prior trial, enrolling 250 women also reported benefit from progesterone administered as a vaginal capsule.[55] With a total of 708 participants in two trials that used different formulations, different cervical cut-points for treatment, and different outcome measures, evidence is of low strength in support of effectiveness for this indication.

Table 24. Preterm birth outcomes by indications for progestogens treatment

Author Year Study Type	Intervention (N)	Mean GA ± SD (weeks)	PTB < 37 wk (%)	PTB < 35 wk (%)	PTB ≤ 34 wk (%)	PTB ≤ 32 wk (%)	PTB ≤ 28 wk (%)
Prior Preterm Birth							
Glover et al.[95] 2011 RCT	Oral (19)	37.0 ± 2.7	26.3	NR	NR	NR	NR
	Placebo (14)	35.9 ± 3.8	57.1	NR	NR	NR	NR
Preterm Labor							
Ibrahim et al.[96] 2010 RCT	IM (25)	37.5 ± 1.6*	32.0*	NR	NR	NR	NR
	Placebo (25)	34.7 ± 2.5	52.0	NR	NR	NR	NR
Sharami et al.[97] 2010 RCT	Vaginal (86)	36.9 ± 2.3	41.2	NR	0.8	NR	NR
	Placebo (87)	36.3 ± 1.8	54.2	NR	10.0	NR	NR
Chawanpaiboon et al.[98] 2011 RCT	Proluton depot (50)	36.9 ± 2.1	NR	NR	NR	NR	NR
	Nifedipine (50)	37.1 ± 1.7	NR	NR	NR	NR	NR
	Bed rest (50)	36.3 ± 3.0	NR	NR	NR	NR	NR
Twin Gestation							
Combs et al.[81] 2011 RCT	IM (160)	35.3 ± 2.5	70.6	NR	19.4	9.4	1.9
	Placebo (78)	35.9 ± 2.3	58.9	NR	14.1	5.1	1.3
Lim et al.[99] 2011 RCT	IM (336)	35.4 ± 3.6	55.0	NR	NR	14.0	6.0
	Placebo (335)	35.7 ± 3.8	50.0	NR	NR	10.0	5.0

Table 24. Preterm birth outcomes by indications for progestogens treatment (continued)

Author Year Study Type	Intervention (N)	Mean GA ± SD (weeks)	PTB < 37 wk (%)	PTB < 35 wk (%)	PTB ≤ 34 wk (%)	PTB ≤ 32 wk (%)	PTB ≤ 28 wk (%)
Preterm Premature Rupture of Membranes							
Briery et al.[100] 2011 RCT	IM (33)	27.3 ± 6.9	NR	NR	NR	NR	NR
	Placebo (36)	29.5 ± 2.5	NR	NR	NR	NR	NR
Short Cervix by Ultrasound Screening							
Hassan et al.[94] 2011 RCT	Vaginal (235)	NR	30.2	14.5*	NR	NR	5.1*
	Placebo (223)	NR	34.1	23.3	NR	NR	10.3

*Findings are statistically significant
GA = gestational age <weeks>; IM = intramuscular; NR = not reported; PTB = preterm birth; RCT = randomized control trial; SD = standard deviation; wk = week.

Future Research

State of the Science

Progestogen treatment was made possible by synthesis of steroid hormones in the 1960s. The earliest trials appear in that decade, followed by relatively few contributions in the literature for the next three decades. More than half of the total body of evidence has appeared within the last decade. Observational studies have given way to RCTs, and initial data are accruing for an array of populations with different risk profiles.

Study quality is advancing, but the multiplicity of treatment targets and variations in combinations of drug, dose, and route mean that strength of evidence to inform particular clinical scenarios is limited and in many cases insufficient. Studies did not uniformly report the composition of the placebo. Use of castor oil as a placebo is a theoretical concern due to its use orally as an induction agent which causes uterine contractions. The literature contains speculative concerns[101] and rebuttals[102] with no definitive means of determining if castor oil as a vehicle for injected medications is itself a source of inflammatory response and harms. Direct evidence about the effects of intramuscular castor oil has not been examined in the preterm birth prevention literature.

Given continued emphasis on preventing preterm birth, and the lack of effective strategies, opportunities to expand the evidence base are likely to remain research and funding priorities. Progestogen treatment warrants continued research as a prevention strategy. Topics that would benefit from consideration include:

Methodologic Priorities

- Clear specifying of operational definitions for inclusion and exclusion criteria, for instance in definition of preterm labor.
- Documenting placebo formulation and biologic inactivity of the vehicle.
- Building consensus about critical maternal, fetal, neonatal, and childhood outcomes, developing a minimal core data set for future research.

- Unifying outcome definitions that facilitate aggregation of data across studies, for instance providing gestational age data for multiple cut-points or standardizing classification of neonatal morbidities like intraventricular hemorrhage.
- Ensuring adequate power to allow investigation of candidate modifiers, for instance severity of prior preterm birth and use of cointerventions, with reporting of outcomes by strata.
- Expanding use of models that allow estimation of independent and joint effects of individual risk factors and intervention.
- Developing registry or electronic medical record approaches to long-term surveillance for adverse effects.

Content Priorities

- Examining thresholds at which improvements in gestational age and birth weight translate to improve neonatal and childhood outcomes.
- Addressing maternal outcomes of treatment, for instance influence of hospitalization, tocolysis, and influence on risk of complications like gestational diabetes and pregnancy induced hypertension.
- Moving from surrogate outcomes closer to measures of critical health outcomes, for instance studies powered to examine neonatal survival and developmental milestones.
- Conducting comparative effectiveness trials that provide direct comparisons, for instance vaginal compared to intramuscular formulations, dose ranging studies to determine optimal effectiveness, and variation in timing of initiation and total treatment duration.
- Investigating the influence of candidate modifiers like BMI.
- Considering larger-scale studies for some indications in which there is a suggestion of potential benefit but scope of prior research is limited, for instance among women with short cervix and no evidence of preterm labor.
- Improving documentation of adherence and discontinuation of treatment with attention to reasons for discontinuation.
- Expanding the repertoire of hormonal effects that are uniformly obtained as part of surveillance for harms, for instance further investigating relationship to gestational diabetes and to teratogenic risk in infants.
- Exploring potential to identify non-responders or responders that may contribute to likelihood of benefit from progestogens.

These priorities are aligned with the research gaps identified in the 2007 Institute of Medicine report titled Preterm Birth: Causes, Consequences, and Prevention;[1] and the Biomedical Research Working group of the Surgeon General's Conference on the Prevention of Preterm Birth,[103] in 2008. Continued emphasis is ensured by the 2006 United States Congress Prematurity Research Expansion and Education for Mothers who deliver Infants Early (PREEMIE) Act (P.L. 109-450),[104] which includes prioritization of (1) reducing rates of preterm labor and delivery; (2) working toward an evidence-based standard of care for pregnant women at risk of preterm labor or other serious complications and for infants born preterm and at a low birthweight; and (3) reducing infant mortality and disabilities caused by prematurity.

Current and Future Research

Recently completed and ongoing research includes the following:

Completed (4 studies):

- Two studies in women with prior preterm birth and one study each in women pregnant with twins or women with shortened cervical length
- Two studies of vaginal progesterone; one study each of oral micronized progesterone and intramuscular 17OHP

Ongoing (14 studies):

- Six studies in women with prior preterm birth; five studies in women with multiple gestations; three studies in women with shortened cervical length
- Seven studies of vaginal progesterone and five studies of intramuscular 17OHP
- Two direct comparisons of 17OHP versus vaginal progesterone

Planned (3 studies):

- Two studies in women with prior premature rupture of the membranes and one study in women with threatened preterm labor
- Two studies of intramuscular 17OHP; one study of vaginal progesterone

Conclusions

Progestogens prevent preterm birth when used in singleton pregnancy in which the mother has had a prior spontaneous preterm birth or in which cervical length is short. The strength of the evidence supporting its use for these indications is moderate and low respectively. In contrast, moderate strength of evidence suggests *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 like 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 informed by consistent, high-quality evidence. In this gap, use is extending into groups that lack clear evidence of benefit. Pressure to intervene is amplified by the fact that no other prevention strategies are available. Lack of large-scale, systematic evidence about potential risks, including excess risk of fetal deaths, is concerning to providers and their concern is supported by the absence of high-quality data identified. Ultimately, providing data to support choice of an optimal form of progestogen, to determine if long-term outcomes are improved, and to rule out longer term risks, will require large scale comparative effectiveness and surveillance research.

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Acronyms/Abbreviations

17P, 17OHP	17 alpha-hydroxyprogesterone caproate
ARR	adjusted relative risk
ART	assisted reproductive techniques
BCI	Bayesian credible interval
b.i.d	two times a day
BMI	body mass index <kg/m^2>
CI	confidence interval
CT	clinical trial
DES	diethylstilbestrol
DM	Diabetes Mellitus
gm	grams
GA	gestational age <weeks>
HIV	Human Immunodeficiency Virus
hr(s)	hour(s)
IM	intramuscular (injection)
IUFD	intrauterine fetal death
IVH	intraventricular hemorrhage
LBW	low birth weight
mg(s)	milligram(s)
NA	not applicable
NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
NNT	Number needed to treat
NR	not reported
NS	not significant
OB	obstetrical
OR	odds ratio
P	progesterone
PPROM	preterm premature rupture of membranes
PTB	preterm birth
PTD	preterm delivery
PTL	preterm labor
q	every
qd	every day
RCT	randomized control trial
RDS	respiratory distress syndrome
ROP	retinopathy
RR	relative risk

SD	standard deviation
U.S.	United States of America
Vent	mechanical ventilator
wk(s)	week(s)

Appendix A. Exact Search Strings and Results

Table A-1: PubMed search strategies and results

Search terms		Preliminary search results
#1	obstetric labor, premature[mh] OR premature birth[mh] OR ((premature[tw] OR preterm[tw] OR pre-term[tw]) AND (labor[tw] OR labour[tw] OR birth[tw] OR births[tw] OR delivery[tiab] OR deliveries[tw]))	48,611
#2	"17-alpha-Hydroxyprogesterone"[mh] OR "17-OH progesterone"[tw] OR hydroxyprogesterone[tw] OR "17alpha-hydroxyprogesterone"[tw] OR 17-alpha-hydroxy-progesterone caproate [nm] OR 17-hydroxyprogesterone heptanoate [nm] OR progesterone[mh] OR progestins[pa] OR hydroxy-progesterone[tiab] OR hydroxyprogesterones[nm] OR progestogen[tiab] OR progestogens[tiab]	70,448
#3	#1 AND #2 AND eng[la] AND humans[mh]	438
#4	#3 AND editorial[pt]	10
#5	#3 AND letter[pt]	14
#6	#3 AND comment[pt]	21
#7	#3 AND case reports[pt]	17
#8	#3 AND review[pt]	101
#9	#3 AND practice guideline[pt]	1
#10	#3 AND news[pt]	3
#11	#3 NOT (#4 OR #5 OR #6 OR #7 OR #8 OR #9)	294*

*Numbers do not tally as some items were indexed with multiple publication types

Table A-2: EMBASE Drugs and Pharmacology search terms and results

Search terms		Search results
#1	exp "immature and premature labor"/ or ((premature or prematurity or pre-term or preterm) and (birth or births or delivery or deliveries or labor or labour)).af.	27,151
#2	exp gestagen/ or (progesterone or hydroxyprogesterone or hydroxy-progesterone or progestogen or progestogens or progestins or progestin).af.	95,571
#3	#1 and #2, limited to human and English language	820
#4	#3 and review.pt	281
#5	#3 and conference paper.pt	48
#6	#3 and editorial.pt	30
#6	#3 and letter.pt	27
#7	#3 and note.pt	19
#8	#3 and short survey.pt	14
#9	#3 and case report/	48
#10	#3 and practice guideline/	15
#11	#3 and “systematic review”/	44
#12	#3 and meta analysis/	44
#13	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	422
#14	#3 not #13	351*

Overlap with PubMed: 321 citations

*Numbers do not tally as some items were indexed with multiple publication types

Appendix B. Reference List of Excluded Studies

Article Exclusion Criteria Codes for Database
X-1: Not original research
X-2: Ineligible study size
X-3: Not related to the use of progestogens to prevent PTB
X-4: Did not address study questions

Arresting premature labour: orciprenaline and other drugs. Drug Ther Bull. 1973 Mar 30;11(7):25-7. X-1, X-2, X-4

Editorial: The initiation of labour. Lancet. 1974 Jan 26;1(7848):124-5. X-1

ACOG Committee Opinion. Use of progesterone to reduce preterm birth. Obstet Gynecol. 2003 Nov;102(5 Pt 1):1115-6. X-1

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Acs N, Banhidy F, Puho EH, et al. No association between vulvovaginitis-bacterial vaginosis, related drug treatments of pregnant women, and congenital abnormalities in their offspring - A population-based case-control study. Central European Journal of Medicine. 2008;3(3):332-340. X-3, X-4

al-Nuaim AR, Abdullah MA, Stevens B, et al. Effect of gender, birth weight and gestational age on serum 17-hydroxyprogesterone concentration and distribution among neonates in Saudi Arabia. Indian J Pediatr. 1995 Sep-Oct;62(5):605-9. X-3

Amory J, Lawler R and Shields L. Hydroxyprogesterone caproate and progesterone increase tumor necrosis factor-alpha production in lipopolysaccharide stimulated whole blood from non-pregnant women. J Perinat Med. 2005;33(6):506-9. X-2, X-3

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Anderson L, Martin W, Higgins C, et al. The effect of progesterone on myometrial contractility, potassium channels, and tocolytic efficacy. Reprod Sci. 2009 Nov;16(11):1052-61. X-3

Antinori S, Gholami GH, Versaci C, et al. Obstetric and prenatal outcome in menopausal women: a 12-year clinical study. Reprod Biomed Online. 2003 Mar;6(2):257-61. X-3

Anumba DO. Management of women with a previous preterm birth. Obstetrics, Gynaecology and Reproductive Medicine. 2007 Jun;17(6):188-191. X-1, X-2

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Aufdenblatten M, Baumann M, Raio L, et al. Prematurity is related to high placental cortisol in preeclampsia. Pediatr Res. 2009 Feb;65(2):198-202. X-3

Banhidy F, Acs N, Horvath-Puho E, et al. Pregnancy complications and delivery outcomes in pregnant women with severe migraine. European Journal of Obstetrics Gynecology and Reproductive Biology. 2007;134(2):157-163. X-3

Bauminger S, Atad J, Feuchtwanger S, et al. Hormonal profile during termination of midtrimester pregnancy by extraovular instillation of saline: plasma levels of prostaglandins, progesterone and human chorionic gonadotropin. Prostaglandins Leukot Med. 1982 Jan;8(1):83-92. X-2, X-3

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Behrman SJ. On reducing prematurity: the hospital's role. Hosp Pract (Hosp Ed). 1982 Jun;17(6):15-6. X-1

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Bengtsson LP and Siener H. Experiments on the inhibition of uterine motility in premature labour. Bibl Gynaecol. 1966;42:79-92. X-2

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Bolt RJ, Van Weissenbruch MM, Popp-Snijders C, et al. Maturity of the adrenal cortex in very preterm infants is related to gestational age. Pediatr Res. 2002 Sep;52(3):405-10. X-2, X-3

Borrero C, Remohi J, Ord T, et al. A program of oocyte donation and gamete intra-fallopian transfer. Hum Reprod. 1989 Apr;4(3):275-9. X-2, X-3

Boulot P, Hedon B, Pelliccia G, et al. Favourable outcome in 33 triplet pregnancies managed between 1985-1990. Eur J Obstet Gynecol Reprod Biol. 1992 Jan 31;43(2):123-9. X-4

Brancazio LR, Murtha AP and Heine RP. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Sep 11;349(11):1087-8; author reply 1087-8. X-1, X-2

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Buyukkayhan D, Ozturk MA, Kurtoglu S, et al. Effect of antenatal betamethasone use on adrenal gland size and endogenous cortisol and 17-hydroxyprogesterone in preterm neonates. J Pediatr Endocrinol Metab. 2009 Nov;22(11):1027-31. X-3

Cahill AG, Odibo AO, Caughey AB, et al. Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: a decision and economic analysis. Am J Obstet Gynecol. 2010 Jun;202(6):548 e1-8. X-3

Cakmak H, Schatz F, Huang ST, et al. Progestin suppresses thrombin- and interleukin-1beta-induced interleukin-11 production in term decidual cells: implications for preterm delivery. J Clin Endocrinol Metab. 2005 Sep;90(9):5279-86. X-3

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Appendix C. Sample Data Extraction Forms

17P for Prevention of Preterm Birth Systematic Evidence Review

Abstract Review Form

First Author, Year: _____ Endnote Reference ID #: _____

Abstractor Initials: ___ ___ ___

Primary Inclusion/Exclusion Criteria			
1. Original research (exclude reviews, editorials, commentaries, letters to editor, etc.)	Yes	No	Cannot Determine
2. Study size ≥ 20 pregnant women Record N if study size < 20 subjects enrolled: ____	Yes	No	Cannot Determine
3. Relevant to SER topic If "No", classify exclusion as related to (pick one): a. ___ Treatment for infertility/luteal phase defect b. ___ Treatment for recurrent miscarriage c. ___ Does not involve treatment with 17P d. ___ Basic science or anatomy only e. ___ Imaging/diagnostic study only f. ___ Other_____	Yes	No	Cannot Determine

Retain for:

_____BACKGROUND/DISCUSSION

_____REVIEW OF REFERENCES

_____Other_____

COMMENTS:

Systematic Review of Progestogens for Prevention of Preterm Birth

Full-text Review Form

First Author, Year: _____

REFID #: _____ Abstractor Initials:

__ __ __

Primary Inclusion/Exclusion Criteria		
	YES	**NO**
1. Original research (exclude editorials, commentaries, letters to editor, reviews, etc)		
2. Eligible study size of 20 pregnant females and/or infants Record N if < 20 relevant subjects enrolled: ____		
3. Does study apply to SER topic? (If No, select at least one of the following reasons): a. ___ Treatment for infertility/luteal phase defect b. ___ Treatment for recurrent miscarriage c. ___ Does not involve treatment with a progestogen d. ___ Basic science, anatomy or physiology only e. ___ Imaging/diagnostic study only f. ___ PTB prevention intervention without progestogens g. ___ Other _____		
4. Does study answer one of the following key questions? (check the box(es) next to the question(s) the study applies to)		

KQ1. In pregnant women who are at risk for preterm birth (<37 weeks EGA), does progestogen treatment compared with 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 IVH)
- 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 PTB such as: severity of prior PTB, degree of cervical shortening, order of multiple gestations, fetal fibronectin status, preterm premature rupture of membranes, threatened PTB, and socioeconomic predictors of prematurity including race/ethnicity?

Systematic Review of Progestogens for Prevention of Preterm Birth

Full-text Review Form

Primary Inclusion/Exclusion Criteria		
	YES	**NO**
4 (continued). Does study answer one of the following key questions? (check the box(es) next to the question(s) the study applies to)		
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 (GA) at initiation or discontinuation of therapy with the progestogen? KQ5. How do the effectiveness, adverse effects and safety of progestogen treatment differ based on co-interventions used to prevent PTB and its consequences, including antibiotics, corticosteroids, tocolysis, and surgical interventions such as cervical cerclage? KQ6. What is the effect of health systems 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?		
5. Did you answer yes to all 4 questions above? If YES, hand search references and record relevant reference numbers here:		

EXCLUDE IF AN ITEM IN A GRAY BOX IS SELECTED

If EXCLUDED, retain for:

_____**BACKGROUND/DISCUSSION**

_____**REVIEW OF REFERENCES**

_____**Other**_____

COMMENTS:

Appendix D. Evidence Tables

Tables are sorted by last name of first author.

Evidence Table D-1. Progestogens for Prevention of PTB

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Bacq et al., 1997 **Country:** France **Participant source:** Academic single site **Intervention setting:** Home **Enrollment period:** 1989 to 1995 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Case-control	**Intervention:** OMP 200 - 1,000 mg/d **Groups:** **G1:** Women treated w/ OMP for prevention of PTD **G1a:** Treated w/ OMP and developed ICP **G1b:** Treated w/ OMP and did not develop ICP **G2:** Control women **G2a:** Control women w/ ICP **G2**b: Control women w/o ICP **N at enrollment:** **G1:** 52 **G1a:** 34 **G1b:** 18 **G2:** 48 **G2a:** 16 **G2b:** 32 **N at birth:** **G1:** 52 **G1a:** 34 **G1b:** 18 **G2:** 48 **G2a:** 16 **G2b:** 32 **N at follow-up:** **G1:** 52 **G1a:** 34	**Inclusion criteria:** **G1a+G2a** • Diagnosed w/ ICP according to following criteria: • Pruritus and/or jaundice • Increased serum TBA and/or (ALT) concentration • Absence of current viral hepatitis, cytomegalovirus, EBV, biliary tract dilatation, and dermatological disease (except scratching lesions) • Normalization of routine LFTs after delivery **G1b+G2b** • Not diagnosed with ICP • Match w/ a woman in **G1** for parity, order of gestation, and yr of delivery **Exclusion criteria:** **G1a+G2a** • Signs of pre-eclampsia • Fever • Urinary or endocervical infection	**Prior PTB:** NR **Multiple gestation, n (%):** **G1**a+**G2**a: 9 (18) **G1**a: 8/32 **G2**a: 0/15 **G2***: NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Maximum dose, mean mg/d ± SD:** G: 548 ± 199 **Duration of treatment, mean ds ± SD:** **G1:** 68 ± 50 **G2:** 98 ± 196. **Treatment with OMP, n (%):** **G1**a+**G2**a: 32 (64) **G1**b+**G2**b: 18 (36) OR: 3.16 (95% CI: 1.29 to 7.80) ***P* < 0.01**	**Complications during pregnancy** **Timing of onset of pruritus, n:** Post-OMP initiation **G1**a: 32 Pre-OMP initiation **G1**a: 1 Initiation unclear **G1**a: 1 Onset of pruritus post-OMP initiation, mean ds ± SD (range): **G1**a: 55 ± 48 (-7 to 193) **Onset of pruritus, mean ds ± SD:** **G1**a: 217 ± 21 **G2**a: 240 ± 26 *P* < 0.01 **Prematurity** NR **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Bacq et al., 1997 (continued)	**Race/ethnicity:** NR **Parous, n:** **G1**a+**G2**a: 25 **G1**b+**G2**b*: NR **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance coverage:** NR	**Exclusion criteria (continued): G1b+G2b** • Pruritus or jaundice • Dermatological disease • Signs of pre-eclampsia or infection			

*Parity and order of gestation not reported for the control group; used as selection criteria to match tx group **G1**.

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Patient Risk Factors	Provider Characteristics	Findings
Author: Bailit et al., 2007 **Country:** US **Participant source:** Academic single site **Intervention setting:** NA (survey) **Enrollment period:** 07/2003 to 06/2004 **Funding:** NR **Author Industry Relationship Disclosure:** 0 of 6 **Design:** Retrospective cohort	**Assessment:** Appropriateness of progesterone use defined by MFMU trial criteria **Groups:** **G1:** All patients who sought care in high-risk clinic during study period **G1a:** appropriate offer **G1b:** appropriate non-offer **G1c:** inappropriate offer **G1d:** inappropriate non-offer **N physicians:** 7 **N pregnant participants:** **G1:** 502 **Participant age, mean yrs ± SD:** **G1**: 27 ± 9.5 **Participant race/ethnicity, n (%):** **Caucasian** **G1**: 195 (39) **African American** **G1:** 228 (45) **Asian** **G1:** 9 (1.8) **Hispanic** **G1:** 65 (13) **Other** **G1:** 5 (1) **Gravidity, mean pregnancies ± SD:** **G1**: 3.7 ± 2.6 **Medicaid, n (%):** **G1**: 457 (88.2)	**Physician inclusion:** Provided care in high risk prenatal clinic during study period **Participant inclusion:** All high risk clinic patients in study period **Definitions of appropriateness:** **Appropriate progesterone offer:** • Prior SPTB (after PTL or PPROM) • Presented to the high-risk clinic before 20 wks GA **Inappropriate offer:** • No prior SPTB between 20-37 wks • Seizure disorder • Multifetal gestation • Known fetal anomaly • HTN requiring medication • Allergy to progesterone • Planned cerclage • Heparin use	**Prior PTB, n (%):** **G1**: 143 (28.3) **Multiple gestation, n (%):** **G1:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length:** NR **Prior PPROM:** NR	**Provider specialty, n:** **Board certified maternal-fetal** **G1:** 4 of 7 **Fellowship trained and board eligible** **G1:** 4 of 7 **Doctor of osteopathy** **G1:** 1 of 7 **Doctor of medicine** **G1:** 6 of 7	**G1a:** 34 (appropriate offer) **G1b:** 433 (appropriate non-offer) **G1c:** 9 (inappropriate offer) **G1d:** 26 (inappropriate non-offer) **Progesterone prescribed, n:** **G1**a and **G1**c: 17OHP: 11 Prometrium vaginal suppositories: 24 Info missing: 8 **Received progesterone:** 25 of 34 received when offered; 9 of 34 did not **Patient barriers:** 4 of 9 who did not receive offered progesterone cited cost/lack of coverage **Inappropriate offers:** 1 provider of 7 responsible for 6 of 9 inappropropriate offers; all 6 for multiple gestations **Inappropriate non-offers:** "variety of physicians responsible"

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Berghella et al., 2010 **Country:** US **Participant source:** Community **Intervention setting:** Clinics **Enrollment period:** January 2003 to November 2007 **Funding:** NIH **Author Industry Relationship Disclosure:** NR **Design:** Prospective cohort	**Intervention:** 250mg IM 17P weekly, starting at 16 weeks and continued weekly until 36 weeks **Groups:** **G1:** 17P **G1a:** 17P and cerclage **G1b:** 17P without cerclage **G2:** No 17P **G2a:** No 17P with cerclage **G2b:** No 17P and no cerclage **N at enrollment*:** **G1**: 99 **G1a:** 47 **G1b:** 52 **G2**: 201 **G2a:** 101 **G2b:** 100 (+1 patient lost to follow-up and +1 patient who received vaginal progesterone instead of 17P; group allocation NR for these 2) **N at birth:** **G1**: 99 **G1a:** 47 **G1b:** 52 **G2**: 201 **G2a:** 101 **G2b:** 100 **N at follow-up:** **G1**: 99 **G1a:** 47 **G1b:** 52 **G2**: 201 **G2a:** 101 **G2b:** 100	**Inclusion criteria:** Singleton gestations Prior spontaneous PTB Short cervical length (<25mm) measured between 16-22 6/7 weeks **Exclusion criteria:** Fetal anomaly Planned history-indicated cerclage Clinically significant maternal-fetal complications	**Prior PTB, n (%):** 300 (100) **Multiple gestation, n (%):** 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** 152 (50.7) **Cervical length, baseline mm ± SD:** **G1a**: 19.0 ± 5.5 **G1b:** 19.5 ± 5.0 **G2a**: 18.5 ± 6.6 **G2b:** 19.4 ± 5.5 **GA of prior PTB, mean ± SD:** **G1a**: 23.2 ± 4.8 **G1b:** 24.0 ± 5.0 **G2a**: 24.7 ± 4.8 **G2b:** 24.7 ± 4.6 **Prior PPROM, n (%):** NR	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR	**Complications during pregnancy** NR **Prematurity** **Birth weight**: NR **GA at birth, weeks ± SD:** NR**PTB, <37 wks, n (%):** **G1:** 54 (54.5) **G1a:** 23 (49) **G1b:** 31 (60) **G2:** 102 (50.7) **G2a:** 43 (43) **G2b:** 59 (59) **G1a/G2a:** OR (95%CI) 1.29 (0.65 – 2.59) **G1b/G2b:** OR (95%CI) 1.03 (0.52 – 2.03) **PTB, <35 wks, n (%):** **G1a:** 14 (30) **G1b:** 20 (39) **G2a:** 34 (34) **G2b:** 44 (44) **G1a/G2a:** OR (95%CI) 0.84 (0.40 – 1.77) **G1b/G2b:** OR (95%CI) 0.80 (0.40 – 1.58) **PTB, <32 wks, n (%):** **G1a:** 8 (17) **G1b:** 11 (21) **G2a:** 25 (25) **G2b:** 34 (34) **G1a/G2a:** OR (95% CI) 0.62 (0.26 – 1.51) **G1b/G2b:** OR (95% CI) 0.52 (0.23 – 1.14)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Berghella et al., 2010 (continued)	**Age, yrs ± SD:** **G1a**: 26.9 ± 6.3 **G1b:** 26.3 ± 4.5 **G2a**: 26.1 ± 5.1 **G2b:** 26.8 ± 5.3 **Race/ethnicity, n (%):** Black (non-Hispanic) **G1**: 58 (58.6) **G1a:** 26 (55) **G1b:** 32 (61.5) **G2**: 114 (56.7) **G2a:** 54 (53) **G2b:** 60 (60) White (non-Hispanic) **G1:** 26 (26.3) **G1a:** 13 (28) **G1b:** 13 (25.0) **G2:** 27 (13.4) **G2a:** 12 (12) **G2b:** 15 (15) Hispanic **G1:** 6 (6.1) **G1a:** 2 (4) **G1b:** 4 (7.7) **G2:** 38 (18.9) **G2a:** 25 (25) **G2b:** 13 (13) Other **G1:** 9 (9.1) **G1a:** 6 (13) **G1b:** 3 (5.8) **G2:** 22 (10.9) **G2a:** 10 (10) **G2b:** 12 (12) **Parous, n (%):** 300 (100) **Maternal education, yrs ± SD:** **G1a**: 12.5 ± 2.1 **G1b:** 12.8 ± 1.8 **G2a**: 11.8 ± 3.0 **G2b:** 11.5 ± 2.6				**PTB, <28 wks, n (%):** **G1a:** 4 (9) **G1b:** 8 (15) **G2a:** 17 (17) **G2b:** 25 (25) **G1a/G1b:** OR (95% CI) 0.55 (0.23 – 1.31) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **Perinatal death:** **G1:** 5 (5.1) **G1a:** 3 (6) **G1b:** 10 (10) **G2:** 33 (16.4) **G2a:** 2 (4) **G2b:** 23 (23) **G1a/G2a:** OR (95% CI) 0.84 (0.40 – 1.77) **G1b/G2b:** OR (95% CI) 0.80 (0.40 – 1.58) **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Berghella et al., 2010 (continued)	**Maternal BMI, n (%):** NR **Maternal smoking, n (%):** **G1**: 24 (24.2) **G1a:** 12 (26) **G1b:** 12 (23) **G2**: 29 (14.4) **G2a:** 12 (12) **G2b:** 17 (17) **Medicaid:** NR **Private insurance coverage:** NR				

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Borna et al., 2008 **Country:** Iran **Participant source:** Academic single site **Intervention setting:** Home **Enrollment period:** 03/2004 to 12/2005 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT (computer generated number list with odds going to **G1** and evens to **G2**)	**Intervention:** Vaginal progesterone suppository (400 mg) daily **Groups:** **G1:** 400 mg progesterone suppository **G2:** No treatment **N at enrollment:** **G1**: 37 **G2**: 33 **N at birth:** **G1**: 37 **G2**: 33 **N at follow-up:** **G1**: 37 **G2**: 33 **Age, mean yrs ± SD:** **G1**: 26.1 ± 0.9 **G2**: 25.5 ± 0.9 **Race/ethnicity:** NR **Primiparous, n:** **G1**: 20 **G2**: 16 **Multiparous, n:** **G1**: 17 **G2**: 17 **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR	**Inclusion criteria:** Singleton pregnancy 24-34 wks of gestation Admitted for threatened PTL, defined as > 6 contractions in 30 min, shortening/softening or dilation by manual examination Intact membranes No cerclage Dilation ≤ 2 cm Dating confirmed by 1st trimester ultrasound **Exclusion criteria:** Intra-amniotic infection Pyelonephritis Medical contraindication to tocolysis Fetal growth retardation Congenital anomalies inconsistent w/ life	**Prior PTB, n (%):** **G1**: 5 (13.5) **G2**: 4 (12.1) **Multiple gestation:** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** **G1**: 0 (0) **G2: 0 (0)Cervical length, baseline:** NR **GA of prior PTB:** NR **PPROM:** NR **GA at admission, mean wks ± SD:** **G1**: 31.1 ± 2.9 **G2**: 32.4 ± 2.1	**Patient knowledge and attitudes:** NR **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR **History of infertility, n (%):** **G1**: 6 (16.2) **G2**: 7 (21.2) **Uterus abnormalities, n (%):** **G1**: 3 (8.1) **G2**: 2 (6)	**Complications during pregnancy** **Latency until delivery, mean days ± SD:** **G1**: 36.1±17.9 **G2**: 24.5±27.2 *P* = 0.037 **Recurrence of PTL, n (%):** **G1**: 13 (35.1) **G2**: 19 (57.6) *P* = 0.092 **Prematurity** **Birth weight mean g ± SD**: **G1**: 3101.54 ± 587.9 **G2**: 2609.39 ± 662.9 *P* = 0.041 **GA at birth, mean wks ± SD:** **G1**: 36.7 ± 1.5 **G2**: 34.5 ± 1.2 *P* = 0.002 **LBW, n (%):** **G1**: 10 (27) **G2**: 17 (51.5) *P* = 0.04 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **Need for mechanical ventilator, n (%):** **G1**: 2 (5.4) **G2**: 6 (18.2) *P* = 0.136

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Borna et al., 2008 (continued)					**NICU admission, n (%):** **G1**: 9 (24.3) **G2**: 13 (39.4) *P* = 0.205 **NICU LOS, mean days ± SD:** **G1**: 3.4 ± 7.6 **G2**: 3.8 ±8.2 *P* = 0.83 **Sepsis, n (%):** **G1**: 2 (5.4) **G2**: 6 (18.2) *P* = 0.136 **RDS, n (%):** **G1**: 4 (10.8) **G2**: 12 (36.4) *P* = 0.021 **Necrotizing entercolitis, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Congenital malformations, n (%):** **G1**: 0 (0) **G2**: 0 (0) **IVH, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Breart et al., 1979 **Country:** France **Participant source:** Academic multi-site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** Supported by a grant from the Institut National de la Sante et del la Recherche Medicale **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** 1,000 mg (2 500 mg injections) IM 17OHP weekly or Chlormadinone acetate 25 mg/d **Groups:** **G1:** IM 17OHP **G2:** Chlorma-dinone **N at enrollment:** G1: 105 G2: 106 **N at birth:** G1: 88 G2: 96 **N at follow-up:** G1: 88 G2: 96 **Age, mean yrs:** NR **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR	**Inclusion criteria:** Pregnant women between 20-34 wks of amenorrhea w/ signs of high risk PTL, such as presenting part that is too low, opening of the internal os and a shortened cervix w/ effacement. **Exclusion criteria:** Women needing β-mimetic agents because of painful regular contractions Cervical dilatation exceeding 3 cm PROM Premature separation of the placenta Placenta previa Dead fetus Any complication requiring immediate delivery	**Prior PTB:** NR **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR **Signs of PTL, n (%):** **Low presenting part** 7 (3) **Cervical dilatation of effacement** 191 (91) **Both** 13 (6)	**GA at start of treatment, n (%):** **<28 wks** 99 (47) **28-29 wks** 44 (21) **30-31 wks** 30 (14) **32-33 wks** 25 (12) **≥34 wks** 13 (6) **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**<u>Complications during pregnancy</u>** **Women receiving β-mimetics, (%):** G1: (37) G2: (35) **β-mimetic use at initiation of treatment, n (%):** **<28 wks** 83 (48) **28-29 wks** 39 (30) **30-31 wks** 26 (27) **32-33 wks** 25 (12) **≥34 wks** 11 (9) *P* < 0.005 **GA at start of β-mimetics, mean ds:** **<28 wks** 213 **28-29 wks** 223 **30-31 wks** 240 **32-33 wks** 246 **≥34** wks 256 **All** 220 *P* < 0.005 **Delay between start of treatment and start of β-mimetics, mean ds:** **<28 wks** 42 **28-29 wks** 21 **30-31 wks** 24

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Breart et al., 1979 (continued)					**32-33 wks** 18 **≥34wks** 14 **All** 32 *P* < 0.005 **Prematurity** **Time from start of treatment, mean ds:** To birth (no β-mimetics) G1: 77.1 G2: 78.4 **To start of β-mimetics** G1: 33.7 G2: 36.9 **To birth or start of beta-mimetics** G1: 60.6 G2: 63.7 **Birth weight, mean g**: G1: 3,156 G2: 3,099 **GA at birth, mean ds:** G1: 274.4 G2: 277.1 **Premature delivery, (%):** G1: (8.0) G2: (4.0) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Briery et al., 2009 **Country:** US **Participant source:** Academic single-site **Intervention setting:** Hospital, Clinic **Enrollment period:** NR **Funding:** 17OHP donated by PharmAmerica **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** Weekly injections of 250 mg 17OHP or placebo (castor oil injections) **Groups:** **G1:** Intervention **G2:** Placebo **N at enrollment:** **G1**: 16 **G2**: 14 **N at birth:** **G1**: 16 **G2**: 14 **N at follow-up:** **G1**: 16 **G2**: 14 **Age, mean yrs :** **G1**: 23.3 ± 5.8 **G2**: 25.4 ± 5.0 **Race/ethnicity, n African American/Caucasian:** **G1**: 15/1 **G2**: 13/1 **Gravidity, n ± SD:** **G1**: 2.9 ± 1.7 **G2**: 2.7 ± 1.9 **Maternal education, n (%):** NR **Maternal smoking, n (%):** NR **Maternal BMI, n (%):** NR **Medicaid, n (%):** 30 (100) **Private insurance, n (%):** 0 (0)	**Inclusion criteria:** Twin pregnancy between 20-30 weeks with intact membranes **Exclusion criteria:** Severe medical disorders such as: Sickle cell disease Insulin-dependent diabetes mellitus Chronic hypertension Cervical dilatation ≥ 1 cm Intrauterine grown restriction (<10th percentile) Growth discordancy between twins (≥20%) Cerclage Uterine abnormalities	**Prior PTB, n (%):** **G1**: 4 (33) **G2**: 4 (40) **Multiple gestation, n (%):** 30 (100) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NA **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR **Preterm labor, n (%):** **G1**: 7 (45) **G2**: 5 (35) (current pregnancy) P=0.980	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, $:** 0 (see Funding) **Drug availability, n (%):** NR **GA at randomization, wks:** **G1**: 24.7 ± 3.3 **G2**: 25.4 ± 3.9	**Complications during pregnancy** **Chorioamnionitis n (%):** NR **Antenatal hospitalizations, n (%):** NR **IUGR, n (%):** NR **Allergic reactions, n (%):** NR **GDM, n (%):** NR **PPROM, n (%):** **G1**: 1 (6) **G2**: 1 (7) (current pregnancy) P=0.525 **Prematurity** **Birth weight, g ± SD**: **G1**: 1968.8 ± 679 **G2**: 1934.7 ± 549 P = 0.641 **GA at birth:** **G1**: 33.9 ± 4 **G2**: 33.1 ± 2.9 P = 0.190 **GA by wks, n (%):** **G1**: <35: 7 (44) 34-37: 9 (56) 30-34: 2 (13) <30: 3 (19) **G2**: <35: 11 (79) 34-37: 5 (36) 30-34: 6 (43) <30: 2 (14)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Briery et al., 2009 (continued)					**Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **Postpartum hemorrhage,** n (%): NR **IVH**, **n (%):** **G1**: 3 (9) **G2**: 4 (14) P = 0.851 **Infections, n (%):** NR **Sepsis, n (%):** NR **Apgar score 5 min:** **G1**: 8.3 ± 1.5 **G2**: 8.9 ± 0.4 P = 0.338 **Respiratory distress syndrome, n (%):** **G1**: 10 (31) **G2**: 9 (32) P = 0.838 **Patent ductus arteriosus, n (%):** **G1**: 3 (9) **G2**: 1 (4) P = 0.704 **Necrotizing enterocolitis, n (%):** **G1**: 1 (3) **G2**: 0 (0) P = 0.946

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Briery et al., 2009 (continued)					**Neurologic handicap at NICU discharge, n (%):** **G1**: 1 (3) **G2**: 2 (7) P = 0.594 **NICU, days ± SD:** **G1**: 18.4 ± 65.8 **G2**: 17.3 ± 29.8 P = 0.155 **Neonatal deaths, n (%):** **G1**: 2 (6) **G2**: 0 (0) P = 0.359 **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Caritis et al., 2009 **Country:** US **Participant source:** Academic multi-site **Intervention setting:** Clinic **Enrollment period:** 04/2004 to 09/2006 **Funding:** NIH, MFMU **Author Industry Relationship Disclosure:** NR **Design:** RCT, sample urn method	**Intervention:** 250 mg of IM 17OHP in 1 mL castor oil weekly, begun at 16-20 +6 ds until wk 35 or delivery **Groups:** **G1:** 17OHP **G1a:** 17OHP infants **G2:** placebo (1 mL castor oil) **G2a:** placebo infants **N at enrollment:** **G1**: 71 **G2**: 63 **N at birth:** **G1**: 71 **G1a:** 213 **G2**: 63 **G2a:** 189 **N at follow-up:** **G1**: 71 **G1a:** 213 **G2**: 63 **G2a:** 189 **Age, median yrs (25th%, 75th%):** **G1**: 30 (28, 35) **G2**: 32 (28, 35) **Race/ethnicity, n (%):** African American **G1**: 6 (8) **G2**: 5 (8) White **G1**: 53 (75) **G2**: 56 (89) Hispanic **G1**: 12 (17) **G2**: 2 (3) *P* = 0.03	**Inclusion criteria:** GA 16 -20 wk Triplet pregnancy **Exclusion criteria:** Serious fetal anomalies ≥ 2 fetuses in one amniotic sac Suspected twin-to-twin transfusion syndrome Marked ultrasonographic growth discordance Planned non-study progesterone therapy after 16 weeks In-place or planned cervical cerclage Major uterine anomaly Unfractionated heparin therapy >10,000units/d Low molecular weight heparin therapy at any dose Major chronic medical diseases Triplet gestations resulting from quintuplet or higher order pregnancy	**Prior PTB, n (%):** **G1**: 0 (0) **G2**: 2 (3) **Multiple gestation, n (%): Twins** **G1**: 71 (100) **G2**: 63 (100) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at enrollment, median wks (25th%, 75th%):** **G1**: 19 (18, 20) **G2**: 19 (18, 20) †**Adverse effects, %:** **G1:** 69 **G2:** 65 **RR**: 1.1 (95%CI: 0.8 to 1.3) ‡**Severe adverse effects leading to termination of treatment, %:** **G1:** 2 **G2:** 1 *P = 0*.55 **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability, n (%):** **G1**: 71 (100) **G2**: 0 (0) **Adherence, (%):** **G1:** (95.6) **G2:** (97) *P* = 0.08	**Complications during pregnancy** **Chorioamnionitis, n (%):** **G1**: 1 (1) **G2**: 0 (0) **Tocolytic therapy, n (%):** **G1**: 33 (47) **G2**: 28 (44) **RR**: (95% CI: 0.7 to 1.5) **Corticosteroids for fetal maturation, n (%):** **G1:** 39 (55) **G2:** 32 (51) **RR**: 1.1 (95% CI: 0.8 to 1.5) **Cerclage placement, n (%):** **G1**: 3 (4) **G2**: 2 (3) **RR**: 1.3 (95% CI: 0.2 to 13.3) **PPROM, n (%):** **G1**: 6 (8) **G2**: 7 (11) **RR**: 0.8 (95% CI: 0.3 to 2.1) **Preeclampsia/ gestational HTN, n (%):** **G1**: 15 (21) **G2**: 18 (29) **RR**: 0.7 (95% CI: 0.4 to 1.3) **Prematurity** **Birth weight mean g ± SD**: **G1**: 1,650 ± 554 **G2**: 1,754 ± 494 *P* = 0.142

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)	**Nulliparous, n (%):** **G1**: 45 (63) **G2**: 33 (52) **Maternal education, median yrs of school (25th%, 75th%):** **G1**: 16 (12, 16) **G2**: 16 (14, 16) **Maternal smoking, n (%):** **G1**: 2 (3) **G2**: 4 (6) **Prepregnancy BMI, median (25th%, 75th%):** **G1**: 24.1 (22, 31) **G2**: 25.1 (22.1, 28.7) **Medicaid:** NR **Private insurance:** NR				**Birth weight, n (%)**: **< 2,500 g** **G1**: 191 (91) **G2**: 175 (96) **RR**: 0.9 (95% CI: 0.9 to 1.0) **< 1,500 g** **G1**: 91 (43) **G2**: 46 (25) **RR**: 1.7 (95% CI: 1.1 to 2.7) **GA at birth median wks (25th%, 75th%):** **G1**: 32.4 (30, 34.4) **G2**: 33 (31.6, 34.3) *P* = 0.527 **Delivery or fetal loss, n (%):** **< 35 wks** **G1:** 59 (83.1) **G2:** 53 (84.1) **RR**: 1.0 (95% CI: 0.9 to 1.1) **< 32 wks** **G1:** 29 (41) **G2:** 19 (30) **RR**: 1.4 (95% CI: 0.8 to 2.2) **< 28 wks** **G1:** 7 (10) **G2:** 7 (11) **RR**: 0.9 (95% CI: 0.3 to 2.4) **Fetal loss, n:** **< 35 wks** **G1:** 1 **G2:** 3 **>35 wks** **G1:** 0 **G2:** 0

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)					**Delivery or fetal loss < 35 wks, n/N:** **Spontaneously conceived** **G1:** 18/21 **G2:** 16/18 **ART conceived** **G1:** 41/50 **G2: 37/45** **<u>Mode of birth and complications during birth</u>** **Cesarean birth, n (%):** **G1**: 71 (100) **G2**: 62 (98) **RR:** 1.0 (95% CI: 1.0 to 1.1) **Spontaneous birth < 35 wks, n (%):** **G1**: 34 (48) **G2**: 27 (43) **RR:** 1.1 (95% CI: 0.8 to 1.6) **Indicated birth < 35 wks:** **G1**: 25 (35) **G2**: 26 (41) **RR:** 0.9 (95% CI: 0.6 to 1.3) **<u>Postpartum and neonatal complications</u>** **Composite adverse outcome, n (%)*:** **G1**a: 78 (37) **G2**a: 65 (34) **RR:** 1.1 (95% CI: 0.7 to 1.7)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)					**IVH grade III or IV, n (%):** **G1**a: 2 (0.9) **G2**a: 4 (2) **RR:** 0.4 (95% CI: 0.0 to 3.8) **Necrotizing enterocolitis stage II or III, n (%):** **G1**a: 2 (0.9) **G2**a: 5 (3) **RR:** 0.3 (95% CI: 0.0 to 3.1) **Culture-proven sepsis, n (%):** **G1**a: 20 (9) **G2**a: 13 (7) **RR:** 1.3 (95% CI: 0.6 to 3.0) **Neonatal death, n (%):** **G1**a: 5 (2) **G2**a: 2 (1) RR: 2.2 (95% CI: 0.4 to 12.4) **RDS, n (%):** **G1**a: 65 (31) **G2**a: 50 (27) **RR**: 1.1 (95%CI: 0.7 to 1.8) **Bronchopulmonary dysplasia, n (%):** **G1**a: 15 (7) **G2**a: 17 (9) **RR**: 0.8 (95% CI: 0.3 to 2.0) **Periventricular leukomalacia**, **n (%):** **G1**a: 0 (0) **G2**a: 1 (0.5) **RR**: 0 (95% CI: 0.0 to 12.8)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)					**Severe retinopathy of prematurity stage III or higher, n (%):** **G1**a: 0 (0) **G2**a: 0 (0) **Small for GA (< 10%)**, **n (%):** **G1**a: 48 (23) **G2**a: 30 (16) **RR**: 1.4 (95% CI: 0.9 to 2.2) **Apgar socre < 7**, **n (%):** 5 min **G1**a: 10 (5) **G2**a: 10 (6) **RR:** 0.9 (95% CI: 0.3 to 2.4) **Patent ductus arteriosus**, **n (%):** **G1**a: 34 (16) **G2**a: 16 (9) **RR**: 1.8 (95% CI: 0.8 to 4.1) **Pneumonia**, **n (%):** **G1**a: 4 (2) **G2**a: 1 (0.5) **RR**: 3.5 (95% CI: 0.4 to 30.1) **Mechanical ventilation**, **n (%):** **G1**a: **7**0 (33) **G2**a: 57 (31) **RR**: 1 (95% CI: 0.7 to 1.6) **Seizures**, **n (%):** **G1**a: 1 (0.5) **G2**a: 0 (0) **Longer term outcomes** NR

*includes all neonatal adverse outcomes below not necessarily due to 17OHP therapy
†AEs of 17OHP were mild majority (64%) were injection site reactions
‡Severe AEs included constitutional symptoms, elevated liver enzymes intense injection site reactions

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Cetingoz et al., 2010 **Country:** Turkey **Participant source:** Academic single-site **Intervention setting:** Clinic and home **Enrollment period:** December 2004 to February 2007 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT – allocation according to randomized number table, with computer-generated random number lists	**Intervention:** Micronized progesterone 100 mg (or placebo) vaginal suppositories given at night between 24 and 34 weeks gestation At weekly follow-up, patients received uterine contraction monitoring for preterm labor (PTL), defined as ≥6 contractions in 30 mins and cervical changes (shortening and/or softening and dilation). All women diagnosed with PTL, regardless of group, were treated in the hospital with nifedipine – 3 doses of 10 mg nifedipine given within 20 mins continuing with 10 mg nifedipine at 6 h, and 2 doses of 12 mg betametazone intramuscularly in 24 h. PTL treatment was in addition to randomized treatment.	**Inclusion criteria:** Pregnant women at high risk for preterm delivery High risk defined as twin pregnancies, pregnancies with at least 1 spontaneous preterm birth, and uterine malformation **Exclusion criteria:** 2 abortions, 7 deliveries, and 1 patient with prophylactic cervical cerclage were excluded before randomization	**Prior PTB, n (%):** **G1**a: 37 (46.2) **G2**a: 34 (40.6) **Multiple gestation, n (%):** **G1**b: 39 (48.7) **G2**b: 28 (40) given as twin gestation **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, mean baseline ± SD:** **G1**: 34.26 ± 6.06 **G1**a: 34.21 ± 6.12 **G1**b: 34.45 ± 6.29 **G2**: 34.61 ± 6.75 **G2**a: 33.66 ± 6.75 **G2**b: 34.96 ± 6.81 **GA of prior PTB:** NR **Prior PPROM, n (%):** NR **Uterine malformation, n (%):** **G1**: 4 (5) **G2**: 8 (11.4) **Assisted reproductive technology pregnancies, n (%):** **G1**: 9 (11.3) **G2**: 8 (11.4) **Positive urine culture, n (%):** **G1**: 6 (7.5) **G2**: 4 (5.7)	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR	**Complications during pregnancy** **Chorioamnionitis, n (%):** NR **Antenatal hospitalizations (admission due to PTL), n (%):** **G1**: 20 (25) **G1**a: 11 (29.7) **G1**b: 7 (17.9) **G2**: 32 (45.7) **G2**a: 19 (55.9) **G2**b: 11 (39.3) **G1 vs G2:** OR (95% CI) = 2.5 (1.27-5.04); P=0.008 **G1a vs G2a:** OR (95% CI) = 6.3 (1.25-31.7); P=0.033 **G1b vs G2b:** OR (95% CI) = 2.95 (0.96-9.02); P=NS **IUGR, n (%):** NR **Allergic reactions, n (%):** 0 **GDM, n (%):** NR **PPROM in current pregnancy, n (%):** **G1**: 3 (3.8) **G2**: 2 (2.9) **Prematurity** **Birth weight**: NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Cetingoz et al., 2010 (continued)	**Groups:** **G1:** women given progesterone suppositories **G1a:** women given progesterone suppositories with a history of PTB **G1b:** women given progesterone suppositories with twin gestation **G2:** women given placebo suppositories **G2a:** women given placebo suppositories with a history of PTB **G2b:** women given placebo suppositories with twin gestation **N at enrollment:** **G1**: 84 **G2**: 76 **N at birth:** **G1**: NR **G2**: NR **N at follow-up:** **G1**: 80 **G1**a: 37 **G1**b: 39 **G2**: 70 **G2**a: 34 **G2**b: 28 **Age, n (%):** 18-35 **G1**: 72 (90) **G2**: 64 (91.4) ≥35 **G1**: 8 (10) **G2**: 6 (9) **Race/ethnicity, n (%):** NR		**Positive cervicovaginal culture for bacterial vaginosis, n (%):** **G1**: 6 (7.5) **G2**: 6 (8.6)		**GA at birth, mean week/days (SD):** **G1**: 36w6d (2w3d) **G2**: 35w6d (3w2d) P<0.05 **Premature birth, %:** **G1**: 40 **G2**: 57.2 **Delivery <34 weeks, n (%):** **G1**: 7 (8.8) **G1**a: 2 (5.4) **G1**b: 4 (10.3) **G2**: 17 (24.3) **G2**a: 9 (26.5) **G2**b: 7 (25) **G1** vs **G2**: OR (95% CI) = 3.35 (1.3-8.63); P=0.010 **G1a vs G2a**: OR (95% CI) = 6.3 (1.25-31.7); P=0.033 **G1b vs G2b**: OR (95% CI) = 2.9 (0.76-11.2); P=NS **Delivery <37 weeks, n (%):** **G1**: 32 (40) **G1**a: 9 (24.3) **G1**b: 20 (51.3) **G2**: 40 (57.2) **G2**a: 17 (50) **G2**b: 22 (78.6) **G1** vs **G2**: OR (95% CI) = 2 (1.04-3.83); P=0.036 **G1a vs G2a:** OR (95% CI) = 3.11 (1.13-8.53); p=0.045

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Cetingoz et al., 2010 (continued)	**Parous, n (%):** 0 **G1**: 25 (31.2) **G2**: 29 (27.6) 1 **G1**: 31 (38.7) **G2**: 26 (37.1) ≥2 **G1**: 24 (30) **G2**: 5 (7.1) **Maternal education, n (%):** NR **Maternal BMI, n (%):** **<20** **G1:** 4 (5) **G2:** 3 (4.3) **20-29** **G1:** 59 (73.8) **G2:** 52 (74.7) **>29** **G1:** 17 (21.3) **G2:** 15 (21.4) **Maternal smoking, n (%):** NR **Medicaid:** NA **Private insurance coverage:** NR				**G1b vs G2b:** OR (95% CI) = 3.48 (1.16-10.46); P=0.043 **<u>Mode of birth and complications during birth</u>** NR **<u>Postpartum and neonatal complications</u>** **Postpartum hemorrhage,** n (%): NR **IVH, n (%):** NR **Infections, n (%):** NR **Sepsis, n (%):** NR **NICU admission, n (%):** **G1**: 13 (16.3) **G2**: 26 (37.1) OR (95% CI) = 3.04 (1.14-6.54) P=0.004 **Neonatal deaths, n (%):** **G1**: 3 (3.8) **G2**: 3 (4.3) OR (95% CI) = 1.15 (0.2-5.9); P=NS **<u>Longer term outcomes</u>** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Combs et al., 2010 **Country:** US **Participant source:** Community **Intervention setting:** Clinics **Enrollment period:** November 2004 to June 2008 **Funding:** NR **Author Industry Relationship Disclosure:** 5/5 Obstetrix Collaborative Research Network (5) **Design:** RCT	**Intervention:** 250mg IM 17P in 1mL castor oil injected weekly until 34 wks or delivery **Groups:** **G1:** 17P **G2:** Placebo (1mL castor oil) **N at enrollment:** 89 **N at birth:** **G1**: 56 **G2**: 25 **N at follow-up:** **G1**: 56 **G2**: 25 **Age, yrs ± SD:** **G1**: 33.4 ± 5.0 **G2**: 33.6 ± 5.4 **Race/ethnicity, n (%):** White: **G1**: 39 (70) **G2**: 17 (68) Hispanic: **G1**: 10 (18) **G2**: 7 (28) Asian/Pacific Islander: **G1**: 5 (9) **G2**: 0 African American: **G1**: 2 (4) **G2**: 1 (4) **Parous, n (%):** **G1**: 32 (57.1) **G2**: 12 (48.0) **G2**: 2 (8)	**Inclusion criteria:** 18yrs or older Gestational age of 15-23 wks at recruitment Trichorionic-triamniotic triplet pregnancy with normal amniotic fluid volume and no major fetal anomalies on detailed 2nd trimester ultrasound **Exclusion criteria:** Symptomatic uterine contractions Rupture of the fetal membranes Any contraindication to interventions intended to prolong the pregnancy (including amnionitis, preeclampsia, severe growth delay, or imminent fetal death Taken any progesterone-derivative medication after 15 weeks of gestation	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** 89 (100) **Fetal fibronectin, positive n (%):** **G1**: 5/46 (10.9) **G2**: 2/22 (9.1) *P* > 0.99 **Cerclage, n (%):** NR **Cervical length, <2.5 cm, n (%):** **G1**: 8/47 (17.0) **G2**: 8/23 (34.8) *P* = 0.13 **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR	**<u>Complications during pregnancy</u>** **Chorioamnionitis, n (%):** **G1**: 5 (8.9) **G2**: 2 (8.0) *P* > 0.99 **Antenatal hospitalizations, n (%):** NR **IUGR, n (%):** NR **Allergic reactions, n (%):** NR **GDM, n (%):** **G1**: 9/55 (16.4) **G2**: 3 (12.0) *P* = 0.77 **<u>Prematurity</u>** **Birth weight, mean g ± SD:** **G1**: 1719 ± 554 **G2**: 1609 ± 472 *P* = 0.36 **PTB <35 wks, n (%)** **G1:** 43 (76.8) **G2:** 21 (84.0) *P* = 0.56 **PTB <32 wks, n (%)** **G1:** 19 (33.9) **G2:** 13 (52.0) *P*=.15 **PTB <28 wks, n (%)** **G1:** 9 (16.1) **G2:** 2 (8.0) *P*=.49

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Combs et al., 2010 (continued)	**Maternal education, n (%):** College: **G1**: 39 (70) **G2**: 17 (68) High school or less: **G1**: 12 (21) **G2**: 6 (24) Unknown: **G1**: 5 (9) **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** **G1**: 0 **G2**: 0 **Medicaid:** NR **Private insurance coverage:** NR	**Exclusion criteria (continued):** Undergone placement of cervical cerclage for treatment of cervical change in the current pregnancy A preexisting medical condition that might be worsened by progesterone (including asthma requiring medications, impaired liver function, renal insufficiency, seizure disorder, ischemic heart disease, active cholecystitis, or history of breast cancer, thrombo-embolism, or depression requiring hospitalization) A preexisting medical condition carrying a high risk or preterm delivery (including refractory hypertension, diabetes with retinopathy or nephropathy, active lupus)			**GA at birth, week ± SD:** **G1**: 31.9 ± 4.1 **G2**: 31.8 ± 2.9 *P* = 0.36 **Mode of birth and complications during birth** **Cesarean birth, n (%):** **G1**: 52 (92.9) **G2**: 25 (100) *P* > 0.99 **Stillbirth/miscarriage, n (%)** **G1**: 13/168 (7.7) **G2**: 0 *P* = 0.01 **Maternal Harms, n (%):** Sepsis: **G1**: 1 (1.8) **G2**: 0 *P* > 0.99 Preeclampsia or gestational hypertension: **G1**: 8 (14.3) **G2**: 7 (28.0) *P* = 0.21 Postpartum endometritis, n (%): **G1**: 2 (3.6) **G2**: 0 *P* > 0.99 **Postpartum and neonatal complications** **Neonatal death, n (%):** **G1**: 6/155 (3.9) **G2**: 2/75 (2.7) *P* = 0.66

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Combs et al., 2010 (continued)		**Exclusion criteria (continued):** An allergy to 17P or the oil vehicle			**IVH, grade 3 or 4, n (%):** **G1**: 4/150 (2.7) **G2**: 3/75 (4.0) *P* = 0.63 **Sepsis, n (%):** **G1**: 4/154 (2.6) **G2**: 4/75 (5.0) *P* = 0.36 **RDS, n (%):** **G1**: 44/155 (28.4) **G2**: 28/75 (37.3) *P* = 0.38 **NICU, days ± SD:** **G1**: 16.0 ± 23.2 **G2**: 18.8 ± 30.1 **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Corrado et al., 2002 **Country:** Italy **Participant source:** Community **Intervention setting:** NA (doesn't specify where or by whom IM injections are given) **Enrollment period:** 03/1997 to 12/1999 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** IM natural progesterone 200 mg/d for 3 days post-procedure and 17OHP (340mg 2x/wk IM) until 2nd wk post-amniocentesis **Groups:** **G1:** Progesterone **G2:** No treatment **N at enrollment:** **G1**: 311 **G2**: 273 **N at birth:** **G1**: 311 **G2**: 273 **N at follow-up:** **G1**: 305 **G2**: 267 **Maternal age, mean yrs ± SD :** **G1**: 36.4 ± 3.6 **G2**: 36.5 ± 4.7 **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal BMI:** NR **Maternal smoking:** NR **Medicaid:** NR **Private insurance coverage:** NR	**Inclusion criteria:** Undergoing amniocentesis in midtrimester Singleton pregnancy **Exclusion criteria:** Chromosomal abnormality Failed amniocentesis cell culture; due to amniocentesis repeated Twin pregnancies Lost to follow up	**Prior PTB:** NR **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Provider knowledge/experience w/ amniocentesis (> 100 procedures performed prior to study), (%):** **G1**: (100) **G2**: (100) **Provider specialty, (%):** Ob/gyn **G1**: (100) **G2**: (100) **Amniocentesis, mean insertions ± SD:** **G1:** 1.04 ± 0.2 **G2:** 1.05 ± 0.2 *P* > 0.05 **Amount of AF, mean ml ± SD:** **G1:** 19.4 ± 0.9 **G2:** 19.2 ± 1.3 **Discolored AF, n:** **G1:** 23 **G2:** 20 **GA at enrollment, mean yrs ± SD:** **G1**: 16.7±0.8 **G2**: 16.5±0.8 *P* > 0.05	**Complications during pregnancy** **Miscarriages (pregnancy loss < 25 wks GA), n (%):** **G1**: 4 (1.3) **G2**: 3 (1.1) *P* > 0.05 **PPROM, n (%):** **G1**: 19 (6.1) **G2**: 17 (6.2) *P* > 0.05 **IUFD, n (%):** **G1**: 2 (0.6) **G2**: 3 (1.1) *P* > 0.05 **IUFD (> 25 wks) in diabetic women, n:** **G1:** 1 **G2:** 2 **Prematurity** **Birth weight mean g ± SD**: **G1**: 3,138.9 ± 665.9 **G2**: 3,073.6 ± 618.9 *P* > 0.05 **Premature delivery < 37 wks:** **G1**: 27 (8.7) **G2**: 20 (7.3) *P* > 0.05 **Apgar score, mean ± SD:** **1'** **G1**: 8.2 ± 1.9 **G2**: 7.9 ± 2.1 *P* > 0.05 **2'** **G1**: 9.6 ± 0.7 **G2**: 9.6 ± 0.7 *P* > 0.05

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Corrado et al., 2002 (continued)					**Mode of Birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Cortes-Prieto et al., 1980 **Country:** Spain **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Prospective cohort	**Intervention:** Allylestrenol (Gestanon) 10-40 mg/day begun at gestation for women who had aborted previously, 10 mg orally every 4 hs w/ complete bed-rest for women in TPTL – reduced to 10-15 mg/d w/ cessation of contractions. Drug continued until 1-2 wks before term. **Groups:** **G1:** Allylestrenol **G1a:** Threatened abortion, trimester 1 **G1b:** Threatened abortion, trimester 2 **G1c:** TPTL **G2:** Controls **N at enrollment:** **G1**: 375 **G1a:** 297 **G1b**: 37 **G1c:** 41 **G2**: 40 **N at birth:** **G1**: 283 **G1a:** 207 **G1b:** 37 **G1c:** 39 **G2**: 40 **N at follow-up:** **G1**: 283 **G1a:** 207 **G1b:** 37 **G1c:** 39 **G2**: 40 **Age, mean yrs :** NR	**Inclusion criteria:** Pregnant women w/o anatomical abnormalities of the genital tract with threatened abortion or preterm labor **Exclusion criteria:** See inclusion criteria	**Prior PTB:** NR **Multiple gestation, n:** **G1**: 1 **G1a:** 0 **G1b:** 1 **G1c:** 0 **G2**: NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**<u>Complications during pregnancy</u>** **PROM:** **G1b:** 37 **G1c:** 0 **Spontaneous abortions, n:** **G1**: 93 **G1a:** 90 **G1b:** 1 ***G1c:** 2 **G2**: 0 **<u>Prematurity</u>** **Birth weight, mean g**: **G1**†: 3,455 **G2**: 3,186 ∆ range (250 – 400) **GA at birth, n:** **39-41 wks** **G1b:** 36 **36 wks** **G1b:** 1 **Preterm** **G1c*:** 3 **<u>Mode of birth and complications during birth</u>** **Cesarean birth, n (%):** **G1**: 1 **G1a:** 0 **G1b:** 0 **G1c:** 1 **G2**: NR **<u>Postpartum and neonatal complications</u>** **Tetralogy of fallot, n:** **G1:** 1 **G2:** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Cortes-Prieto et al., 1980 (continued)	**Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR				**Evidence of masculinization, n:** **G1:** 0 **Longer term outcomes** NR

*Includes twins (aborted at 31 and 34 wks GA)
†Data from 25 treated mothers with known hormonal levels, text doesn't indicate what treatment group

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: da Fonseca et al., 2003 **Country:** Brazil **Participant source:** Academic single site **Intervention setting:** Home **Enrollment period:** 02/1996 to 03/2001 **Funding:** Foundation **Author Industry Relationship Disclosure:** NR **Design:** RCT – double blind, placebo controlled	**Intervention:** Progesterone 100 mg vaginal suppository daily between 24-34 wks GA **Groups:** **G1:** Progesterone vaginal suppository **G2:** Placebo **N at enrollment:** **G1**: 81 **G2**: 76 **N at birth:** **G1**: 72 **G2**: 70 **N at follow-up:** **G1**: 72 **G2**: 70 **Age, mean yrs:** **G1**: 27.6 **G2**: 26.8 **Race/ethnicity, (%):** **White** **G1:** (68.0) **G2:** (71.4) **Nonwhite** **G1:** (32.0) **G2:** (28.6) **Parous, %:** **G1**: (90.2) **G2**: **(**97.1) **Maternal education:** NR **Maternal BMI:** NR **Maternal smoking:** NR **Medicaid:** NR	**Inclusion criteria:** Asymptomatic singleton pregnancy High risk for PTD **Exclusion criteria (randomized but excluded from analysis):** PROM (N=10) Lost to follow-up (N=1) Therapeutic PTD (N=3) Allergic process (N=1) Fetal malformations	**Prior PTB, (%):** **G1:** (90.3) **G2:** (97.2) **Uterine malformation, (%):** **G1:** (5.6) **G2:** (1.4) **Incompetent cervix, (%):** **G1:** (4.1) **G2:** (1.4) **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB, mean wks ± SD:** **G1**: 33.3 ± 2.7 **G2**: 33.4 ± 2.6 **Prior PPROM:** NR	**GA at study admission, mean wks:** **G1:** 26.5 **G2:** 25.2	**Complications during pregnancy** **Admission for threatened PTL, n (%)**: **G1**: 14 (19.4) **G2:** 22 (31.4) *P* = NS **Admission for 2nd episode of PTL, n/N (%):** **G1**: 10/14 (71.4) **G2:** 12/22 (54.5) **Mean LOS of admissions for 2nd episode of PTL, mean days ± SD**: **G1**: 5.7 ± 2.3 **G2:** 3.9 ± 3.2 **B-mimetic use:** **G1:** significant benefit *P* = 0.031 **Delivery delay > 72 hrs, (%):** **G1**: (85.7) **G2**: (36.4) **Uterine contraction frequencies among groups, n (%):** **< 4 contractions** **G1**: 55 (76.4) **G2**: 32 (45.7) *P* = 0.0001 **4-5 contractions** **G1**: 3 (4.1) **G2**: 12 (17.1) *P* = 0.0118 **≥6 contractions** **G1**: 14 (19.4) **G2**: 26 (37.2) *P* = 0.0190

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
da Fonseca et al., 2003 (continued)	**Private insurance coverage:** NR				**Contraction frequency per gestational wk, mean ± SD:** Wk 28 **G1**: 1.0 ± 0.6 **G2**: 4.0 ± 3.0 *P* = 0.00001 Wk 29 **G1**: 1.0 ± 0.9 **G2**: 4.0 ± 2.1 *P* = 0.00001 Wk 30 **G1**: 2.8 ± 2.7 **G2**: 6.2 ± 3.0 *P* = 0.00001 Wk 31 **G1**: 3.2 ± 2.0 **G2**: 5.1 ± 2.5 *P* = 0.0001 Wk 32 **G1**: 2.5 ± 2.5 **G2**: 6.5 ± 3.1 *P* = 0.01 Wk 33 **G1**: 2.8 ± 2.4 **G2**: 7.0 ± 4.2 *P* = 0.0001 Wk 34 **G1**: 3.5 ± 2.0 **G2**: 6.5 ± 3.1 *P* = 0.0001 **Prematurity** **Birth weight**: NR **PTD, n (%)**: < 37 wks **G1**: 10 (13.8) **G2:** 20 (28.5) *P* = 0.03 **at 34 wks** **G1**: 2 (2.8) **G2:** 13 (18.6) *P* = 0.002 **GA for PTB incidences, mean wks ± SD**: **G1**: 33.5 ± 2.4 **G2:** 32.0 ± 0.7

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
da Fonseca et al., 2003 (continued)					**GA at birth, mean wks ± SD (range):** **G1:** 37 ± 2.8 (28-41) **G2:** 36 ± 3.3 (29-41) **Undelivered patients at 34 wks GA, (%):** **G1**: (97.2) **G2**: (81.4) *P* = 0.029 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Patient Risk Factors	Provider Characteristics	Findings
Author: Dodd et al., 2007 **Country:** Australia New Zealand **Participant source, physicians:** Membership Royal Australian and New Zealand College of Obstetricians and Gynaecologists **Participant source, patients:** Academic single site **Study period:** 06/2003 to 06/2005 **Funding:** Neil Hamilton Fairley Clinical Research Fellowship (JMD) **Author Industry Relationship Disclosure:** NR **Design:** Cross-sectional surveys	**Assessment measure:** Mail survey of physicians Mail survey of patients **Groups:** **G1a:** physicians **G1b:** patients who had preterm birth **N surveyed:** **G1a:** 1430 **G1b:** 207 **N respondents:** **G1a:** 738 (52%) **G1b**: 119 (57%) **Age, mean yrs :** NR **Patient race/ethnicity, n (%):** Caucasian **G1b**: 108 (91) Asian **G1b**: 7 (6) Aboriginal **G1b**: 4 (3) **Maternal education, n (%):** **Incomplete secondary education** **G1b**: 31 (26) **Completed secondary education** **G1b:** 36 (30) **Completed tertiary education** **G1b:** 29 (24) **Other qualifications**: **G1b**: 23 (19)	**Inclusion criteria:** **G1a**: membership in professional society **G1b**: women who gave birth to a liveborn singleton infant at < 34 wks gestation after spontaneous onset of labor (including after spontaneous rupture of membranes) **Exclusion criteria:** **G1a**: none **G1b**: women with multiple pregnancy, iatrogenic PTB (e.g. for preeclampsia or fetal growth restriction), fetal anomaly, or perinatal or neonatal death	**Prior PTB, n (%):** **G1b**: 119 (100) **Multiple gestation, n (%):** **G1b**: 0 (0) **Fetal fibronectin:** NR **Cerclage, n (%):** NR **Cervical length:** NR **GA of prior PTB, mean wks ± SD:** **G1b**: 31.5 ± 2.8 **Infant birth weight of PPTB, mean kg ± SD:** **G1b**: 1.7 ± 0.6 **Prior PPROM, n (%):** NR	**Provider specialty, n:** Currently practicing obstetrics: 490 Years in practice, n (%): <10yrs **G1a**: 161 (33) 11-20 yrs **G1a**: 148 (30) 21-30 yrs **G1a**: 115 (23) > 30 yrs **G1a**: 65 (13) Type of obstetric practice, n (%): Private only **G1a**: 108 (22) Public only **G1a**: 176 (36) Combined **G1a**: 207 (42)	**Physician-reported indications for progesterone, n (%):** **Previous SPTB at < 34 wks gestation** **G1a:** 12 (2) **Multiple gestation pregnancy** **G1a:**4 (1) **Ultrasound-diagnosed short cervix** **G1a:** 5 (1) **Positive fetal fibronectin** **G1a:** 4 (1) **History of previous miscarriage or conception following ART** **G1a:** 183 (37) Willing to participate in RCT of progesterone in women with prior PTB at < 34 wks gestation, n (%): **G1a**: 317 (65) **G1b**: 52 (44) Acceptability of start and stop timing among women willing to participate in RCT, n/N (%): Would initiate treatment at start of pregnancy **G1b**: 24/52 (46) Would continue medication until 36 wks gestation **G1b**: 39/52 (75)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Patient Risk Factors	Provider Characteristics	Findings
Dodd et al., 2007 (continued)					Patients not planning to become pregnant again: **G1b:** 9 (8)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Dudas et al., 2006 **Country:** Hungary **Participant source:** Database (Hungarian Case-Control Surveillance of Congenital Abnormalities, HCCSCA) **Intervention setting:** Clinic **Enrollment period:** 1980 to 1996 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Retrospective case control study	**Intervention:** Injection of IM 17OHP (usually 250 mg daily) **Groups:** **G1a:** Cases w/ congenital abnormalities whose mothers received 17OHP **G1b:** Cases w/ congenital abnormalities whose mothers did not receive 17OHP **G2a:** Controls w/ no congenital abnormalities whose mothers received 17OHP **G2b:** Controls w/ no congenital abnormalities whose mothers did not receive 17OHP **N at enrollment:** **G1**a: 318 **G1**b: 22,525 **G2**a: 433 **G2**b: 37,718 **N at birth:** **G1**a: 318 **G1**b: 22,525 **G2**a: 433 **G2**b: 37,718 **N at follow-up:** **G1**a: 318 **G1**b: 22,525 **G2**a: 433 **G2**b: 37,718 **Maternal age, mean yrs ± SD:** **G1**a: 25.8 ± 4.9 **G1**b: 25.5 ± 5.3 **G2**a: 26.1 ± 4.8 **G2**b: 25.4 ± 4.9	**Inclusion criteria:** Cases selected from births listed in the Hungarian Congenital Abnormality Registry (a population-based registry of cases w/ congenital abnormalities) data set Controls were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA, defined as newborn infants w/o congenital abnormalities **Exclusion criteria:** See inclusion criteria	**Prior PTB:** NR **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Duration of treatment, mean wks:** **G1a & G2a:** 6.2	**<u>Complications during pregnancy</u>** **Threatened abortion, n (%):** **G1**a: 266 (83.6) **G1**b: NR (15.3) **G2**a: 398 (92.0) **G2**b: NR (17.1) **Threatened PTB n (%):** **G1**a: 72 (22.7) **G1**b: NR (12.1) **G2**a: 135 (31.2) **G2**b: NR (15.7) **<u>Prematurity</u>** **Birth weight, mean g ± SD**: **G1**a: NR **G1**b: NR **G2**a: 3194 ± 555 **G2**b: 3277 ± 511 *P* = 0.002 (unadjusted) and 0.09 (adjusted) **GA at birth, mean wks ± SD:** **G1**a: NR **G1**b: NR **G2**a: 38.8 ± 2.4 **G2**b: 39.4 ± 2.0 *P* < 0.0001 (unadjusted and adjusted) **Low birthweight, n (%)**: **G1**a: NR **G1**b: NR **G2**a: 3435 (9.1) **G2**b: 61 (14.1) OR: 1.6 [95% CI: 1.2,2.2] (unadjusted) OR: 1.7 [95% CI: 1.3, 2.2] (adjusted)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Dudas et al., 2006 (continued)	**Race/ethnicity:** NR **Parous, n (%):** **G1**a: 1: 10,532 (46.8) >1: 11,993 (53.2) Mean ± SD: 1.9 ± 1.1 **G1**b: 1: 176 (55.4) >1: 142 (44.6) Mean ± SD: 1.6 ± 0.9 **G2**a: 1: 17,994 (47.7) >1: 19,724 (52.3) Mean ± SD: 1.7 ± 0.9 **G2**b: 1: 215 (49.7) >1: 218 (50.3) Mean ± SD: 1.7 ± 0.9 **Maternal education:** NR **Maternal BMI:** NR **Maternal smoking:** NR **Medicaid:** NR **Private insurance:** NR				**GA at birth, mean wks ± SD:** **G1**a: NR **G1**b: NR **G2**a: 2128(5.6) **G2**b: 39 (9.0) OR: 1.7 [95% CI: 1.2, 2.3] (unadjusted) OR: 1.4 [95% CI: 0.9,2.20] (adjusted) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **CAs, n (%):** **G1**a+b: 2nd/3rd months: 1 (0.4) Entire pregnancy: 3 (1.3) **Neural tube defects** **G1**a+b: $2^{nd}/3^{rd}$ months: 4 (0.3) Entire pregnancy: 15 (1.3) **Cleft lip ± palate** **G1**a+b: 2nd/3rd months: 7 (0.5) Entire pregnancy: 17 (1.2) **Posterior cleft palate** **G1**a+b: 2nd/3rd months: 2 (0.3) Entire pregnancy: 6 (1.0)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Dudas et al., 2006 (continued)					**Rectal/anal atresia/stenosis** **G1**a+b: 2nd/3rd months: 2 (0.9) Entire pregnancy: 5 (2.3) **Hypospadias** **G1**a+b: 2nd/3rd months: 17 (0.6) Entire pregnancy: 39 (1.3) **Undescended testis** **G1**a+b: 2nd/3rd months: 10 (0.5) Entire pregnancy: 27 (1.3) **Exomphalos/gastroschisis** **Microcephaly, primary** **G1**a+b: 2nd/3rd months: 2 (1.8) Entire pregnancy: 3 (2.8) **Congenital hydrocephaly** **G1**a+b: 2nd/3rd months: 2 (0.6) Entire pregnancy: 4 (1.3) **Ear CAs** **G1**a+b: 2nd/3rd months: 2 (0.6) Entire pregnancy: 3 (0.9) **Cardiovascular CAs** **G1**a+b: 2nd/3rd months: 25 (0.6) Entire pregnancy: 65 (1.5)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Dudas et al., 2006 (continued)					**CAs of gential organs** **G1**a+b: 2nd/3rd months: 1 (0.8) Entire pregnancy: 1 (0.8) **Clubfoot** **G1**a+b: 2nd/3rd months: 21 (0.9) Entire pregnancy: 45 (1.9) **Limb deficiencies** **G1**a+b: 2nd/3rd months: 7 (1.3) Entire pregnancy: 17 (3.1) **Poly/syndactyly** **G1**a+b: 2nd/3rd months: 6 (0.3) Entire pregnancy: 19 (1.1) **Diaphragmatic CAs** **G1**a+b: 2nd/3rd months: 2 (0.8) Entire pregnancy: 3 (1.2) **Other isolated CAs**: **G1**a+b: 2nd/3rd months: 11 (0.5) Entire pregnancy: 22 (0.9) **Multiple CAs** **G1**a+b: 2nd/3rd months: 7 (0.5) Entire pregnancy: 24 (1.8) **Total cases** **G1**a+b: 2nd/3rd months: 129 (0.6) Entire pregnancy: 318 (1.4)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Dudas et al., 2006 (continued)					**Total controls** **G1**a+b: NR **G2**a+b: 2nd/3rd months: 178 (0.5) Entire pregnancy: 433 (1.1) **<u>Longer term outcomes</u>** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Durnwald et al., 2009 **Country:** US **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** 1999 to 2008 **Funding:** Intramural **Author Industry Relationship Disclosure:** NR **Design:** Retrospective cohort	**Intervention:** IM 17OHP until wk 36 or birth **Groups:** **G1:** 17OHP **G2:** No 17OHP treatment **N at enrollment:** **G1**: 105 **G2**: 95 **N at birth:** **G1**: 105 **G2**: 95 **N at follow-up:** **G1**: 105 **G2**: 95 **Age, mean yrs ± SD:** **G1**: 26.5 ± 4.6 **G2**: 23.5 ± 3.7 *P* < 0.01 **Race/ethnicity, (%):** Non-black **G1**: (45.7) **G2**: (40) **Black** **G1:** (54.3) **G2:** (60) *P* = 0.42 **Gravidity, mean ± SD:** **G1:** 4.0 ± 2.0 **G2:** 3.8 ± 1.8 *P* = 0.61 **Maternal education:** NR **Maternal smoking, (%):** **G1**: (41.9) **G2**: (36.8) *P* = 0.47	**Inclusion criteria:** ≥1 PPTB between 18 - 36 + 6 wks gestation Underwent ≥ 2 cervical length measurements during the index pregnancy Singleton pregnancy **Exclusion criteria:** Known uterine anomalies Previous cervical surgery Cervical cerclage Multiple gestations	**Prior PTB, mean ± SD:** **G1**: 1.4 ± 0.5 **G2**: 1.4 ± 0.5 *P* = 0.40 **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1**: 0 (0) **G2**: 0 (0) ***Cervical length, baseline, mean mm ± SD:** **G1**: 34.3 ± 7.9 **G2**: 34.0 ± 7.1 *P* = 0.74 **GA of most recent PTB, mean wks ± SD:** **G1**: 28.6 ± 6.2 **G2**: 30.2 ± 5.7 *P* = 0.06 **Prior PPROM:** NR **GA of earliest PTB, mean wks ± SD:** **G1**: 26.0 ± 5.1 **G2**: 27.8 ± 5.0 *P* = 0.01	***GA at enrollment, mean wks ± SD:** **G1**: 15.0 ± 4.1 **G2**: 16.3 ± 3.5 *P* = 0.02 **Provider knowledge and attitudes, n (%):** Did not encourage 17OHP (pre NICHD 2003 trial) **G1**: NR †**G2**: 82 (86.3) **Encouraged (post NICHD 2003 report)** **G1:** NR **G2:** 13 (13.7) **Provider specialty, n (%):** Prematurity prevention **G1**: 105 (100) **G2**: 95 (100) **Cost of drug:** NR **Drug availability:** NR	**Complications during pregnancy** **Cervical shortening, mean mm/wk ± SD:** **G1:** 1.1 ± 1.2 **G2:** 0.7 ± 0.7 P = 0.02 ‡**Cervical shortening, mean mm/wk:** **G1:** 0.79 (95% CI: -1.18 to 2.76) **G2:** Referent *P* = 0.43 **Prematurity** **Birth weight:** NR **GA at birth < 37 wks, (%):** **G1**: (42.9) **G2**: (35.8) *P* = 0.31 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Durnwald et al., 2009 (continued)	**Maternal prepregnant BMI, kg/m^2, (%):** **Underweight** **G1:** (9.5) **G2:** (5.3) **Normal** **G1:** (37.1) **G2:** (42.1) **Overweight** **G1:** (20.0) **G2:** 30.5 () **Obese** **G1:** (33.3) **G2:** (22.1) *P* = 0.11 **Government, (%):** **G1**: (59.1) **G2**: (79) **Private insurance, (%):** **G1**: (35.2) **G2**: (17.9) **Self-pay, (%):** **G1**: (5.7) **G2**: (3.2) *P* = 0.01				

*Study table data (reported) does not match text in results section
†Women in G2 enrolled before positive 2003 NICHD trial not encouraged towards 17OHP; enrollees after release were
‡Protective effect of 17OHP seen against cervical shortening over time after adjusting for covariates

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Erny et al., 1986 **Country:** France **Participant source:** Academic multi-site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention, Paris group:** OMP (Utrogestan) 400mg (4 100mg capsules) or placebo given as single dose after 30 min bed rest; fetal cardiac rhythm and uterine contractility monitoring for 1 hr, followed by IV β-mimetics (ritodrine) given as required **Intervention, Marseilles group:** Same Utrogestan and monitoring treatment as Paris group (see above); for patients responding with a decrease in contractions at 1 hr (n = 23), 400mg Utrogestan every 4-8 hrs until discharge. Dose reduced from the 3rd day to mean 3 daily doses of 200 mg up to wk 36. Ritodrine used immediately when tocolytic effect of Utrogestan was insufficient.	**Inclusion criteria:** Admitted between week 30 and 36 of amenorrhea for risk of PTD to obstetric unit of two different hospitals in Marseilles and Paris, France **Exclusion criteria:** See inclusion criteria	**Prior PTB:** NR **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR		**Complications during pregnancy** **Frequency of contractions remained identical or increased as measured 1 hr after intervention, n:** **G1a:** 2 **G1b:** 5 **G2a:** 7 **G2b:** 9 **Frequency of contractions decreased as measured 1 hr after intervention, n:** **G1a:** 8 **G1b:** 14 **G2a:** 3 **G2b:** 9 **Frequency of contractions decreased as measured 1 hr after intervention, (%):** **G1:** (75.8) **G2:** (42.8) **Contractions improved as measured 1 hr after intervention, (%) pts:** **G1a:** (80) **G1b:** (73) **G2a:** (30) **G2b:** (50)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Erny et al., 1986 (continued)	**Groups:** **G1:** OMP **G1a:** Paris OMP **G1b:** Marseilles OMP **G2:** Placebo **G2a:** Paris placebo **G2b:** Marseilles placebo **N at enrollment:** G1: 29 G1a: 10 G1b: 19 G2: 28 G2a: 10 G2b: 18 **N at birth:** G1: 29 G1a: 10 G1b: 19 G2: 28 G2a: 10 G2b: 18 **N at follow-up:** G1: 29 G1a: 10 G1b: 19 G2: 28 G2a: 10 G2b: 18 **Age:** NR **Race/ethnicity:** NR **Parous:**NR **Maternal education:** NR **BMI:** NR **Smoking:** NR **Medicaid:** NR **Private insurance coverage:** NR				**Decrease in frequency of contractions as measured 1 hr after intervention, mean n/10 min (range):** **Baseline:** 3.67 (1.5-7) **G1:** 1.93 (0-4) **G2:** 2.91 (0-9) Baseline/G1: $P < 0.001$, baseline/G2: $P > 0.05$. **Prematurity** **Birth weight for Marseilles patients who continued OMP, n; mean kg (range):** 23; 3.07 (2.20-3.90) **Delay of delivery for those Marseilles patients who continued OMP, n; mean wks (range):** 23; 6.7 (2-14) **GA at birth:** NR **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Facchinetti et al., 2007 **Country:** Italy **Participant source:** Academic single site **Intervention setting:** Clinic and home **Enrollment period:** 09/2004 to 02/2006 **Funding:** Not sponsored **Author Industry Relationship Disclosure:** NR **Design:** RCT (longitudinal, not double blind) Randomization - # list – odds tx group Evens – Observational group	**Intervention:** 341 mg of IM 17OHP every 4 days, begun at 25-33 wks + 6 days, until gestational wk 36 **Groups:** **G1:** 17OHP **G2:** Observation, no placebo **N at enrollment:** **G1**: 30 **G2**: 30 **N at birth:** **G1**: 30 **G2**: 30 **N at follow-up:** **G1**: 30 **G2**: 30 **Age, mean yrs ± SD (range):** **G1**: 29.9±3.5 (20,35) **G2**: 29.8±2.7 (22,33) **Race/ethnicity:** NR/Italian ***Nulliparous, n (%):** **G1**: 16 (66.7) **G2**: 17 (73.9) **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR	**Inclusion criteria:** Admitted for threatened PTL, defined as simultaneous contractions (>6/30 min) and cervical changes including shortening and/or softening or dilation 25-33 + 6 wks gestation dated through 1st trimester ultrasound measuring singleton pregnancies intact membranes cervical dilation ≤2 cm negative vaginal culture for E coli, B strep and N gonorrhea **Exclusion criteria:** suspected intraamniotic infections large uterine myomas vascular complications of pregnancy placenta previa fetal distress chronic diseases such as diabetes mellitus, heart disease and/or autoimmune disorder	***Prior PTB, n (%):** **G1**: 1 (4.2) **G2**: 2 (8.7) *P* ≥ 0.05 Multiple **gestation, n (%):** **G1:** 0 (0) **G2:** 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline, mean mm ± SD (range):** **G1**: 24.5 ± 8.9 (5, 44) **G2**: 22.8 ± 9.6 (10, 38) *P* ≥ 0.05 **Cervical length, baseline ≤25 mm, n (%):** **G1**: 16 (53) **G2**: 17 (56) *P* ≥ 0.05 **Cervical dilation at threatened PTB, n (%):** 1 cm **G1**: 11 (37) **G2**: 10 (33) *P* ≥ 0.05 ≤2 cm **G1**: 1 (3) **G2**: 2 (7) *P* ≥ 0.05 **GA at prior PTB:** NR **Prior PPROM, n (%):** NR	**Adherence, n (%):** **G1**: 30 (100) **G2**: 30 (100) **GA at enrollment, mean days ± SD (range):** **G1**: 208.4 ± 22.1 (157, 238) **G2**: 212.3 ± 18.1 (171, 238) *P* ≥ 0.05	**<u>Complications during pregnancy</u>** **Tocolytic therapy (atosiban) for 48 hrs, n (%):** **G1**: 30 (100) **G2**: 30 (100) **IM betamethasone (12mg) therapy 2x/24 hrs, n (%):** **G1**: 30 (100) **G2**: 30 (100) **Adverse events linked to treatment, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Cervical shortening, mean mm ± SD:** Day 7 **G1**: 0.83 ± 1.74 **G2**: 2.37 ± 2.0 *P* = 0.002 **Day 21** **G1**: 2.40 ± 2.46 **G2**: 4.60 ± 2.73 *P* = 0.002 **≥4mm:** RR 0.175 (95% CI: 0.04 to 0.66) **Cervical shortening in patients w/ cervix baseline ≤25mm, mean mm ± SD:** Day 7 **G1**: 0.69 ± 1.71 **G2**: 2.35 ± 2.23 ***P* =** 0.024 **Day 21** **G1**: 1.38 ± 1.31 **G2**: 4.88 ± 3.14 ***P* <** 0.0001

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Facchinetti et al., 2007 (continued)	**Private insurance coverage:** NR				**Cervical lengthening > 2mm, n:** **G1**: 3 **G2**: 1 **<u>Prematurity</u>** **Birth weight, mean g ± SD**: **G1**: 3,103 ± 468 **G2**: 2,809 ± 317 **Preterm birth < 37 wks GA, n (%):** **G1**: 5 (16) **G2**: 17 (57) *P* = 0.004 RR: 0.15 (95%CI: 0.04 to 0.58) **PTB < 35 wks GA, n (%):** **G1**: 3 (10) **G2**: 7 (23.3) *P* ≥ 0.05 **Time from randomization to parturition, mean days ± SD:** **G1**: 35.3 ± 19 **G2**: 25.5 ± 15.1 *P* **=** 0.003 **<u>Mode of birth and complications during birth</u>** NR **<u>Postpartum and neonatal complications</u>** NR **<u>Longer term outcomes</u>** NR

* n/30 doesn't match percentages reported in Table – cannot determine if n or percentage is incorrect

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Facchinetti et al., 2008 **Country:** Italy **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** 01/2005 to 05/2006 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** 341 mg of IM 17OHP every 4 ds, until wk 36 **Groups:** **G1:** 17OHP **G2:** Usual care, no 17 P **N at enrollment:** **G1**: 23 **G2**: 22 **N at birth:** NA **N at follow-up, 7 ds:** **G1**: 21 **G2**: 19 **N at follow-up, 21 ds:** **G1**: 20 **G2**: 18 **Age, mean yrs ± SD:** **G1**: 30.3±2.0 **G2**: 28.6±4.8 **Race/ethnicity:** NR **Nulliparous, n (%):** **G1**: 16 (69.6) **G2**: 14 (63.6) **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR	**Inclusion criteria:** Singleton pregnancy GA of current pregnancy between 25-33+6 wks Admitted for threatened PTL, presence of contractions >6/30 min, and cervical changes (shortening and/ or softening or dilatation) by manual examination Intact membranes Cervical dilatation <2 cm Dating confirmed by 1st trimester ultrasound **Exclusion criteria:** Intra-amniotic infections >3 myomas > 8 cm myoma(s) HTN (gestational or chronic) Diabetes Heart disease Autoimmune disorder Positive vaginal/urine culture	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** **G1:** 0 (0) **G2:** 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline, mean mm ± SD:** **G1**: 24.7 ± 9.6 **G2**: 24.6 ± 10.2 **GA of prior PTB:** NR **PPROM, n (%):** NR **Cervical nitrites/nitrates, baseline, mean µM/mL ± SD:** **G1**: 0.48 ± 0.37 **G2**: 0.48 ± 0.44 **Cervical IL-1β, baseline, median µM/mL (IQR):** **G1**: 2.00 (0.86, 5.78) **G2**: 2.46 (1.19, 4.26) **Cervical IL-6, baseline, median µM/mL (IQR):** **G1**: 0.17 (0.09, 0.48) **G2**: 0.2 (0.16, 0.43)	**GA at inclusion, mean ds ± SD:** **G1**: 207.0 ± 24.0 **G2**: 211.5 ± 18.3	**Complications during pregnancy** **Antenatal hospitalizations, n (%):** **G1**: 23 (100) **G2**: 22 (100) **Cervical shortening, 21 ds, median mm (IQR):** **G1**: 2 (0, 4) **G2**: 4 (2, 6) *P* = 0.017 **Cervical nitrites/nitrates, 7 ds, mean µM/mL ± SD:** **G1**: 0.53 ± 0.44 **G2**: 0.35 ± 0.31 **Cervical IL-1β, 7 ds, median µM/mL (IQR):** **G1**: 1.18 (0.84, 2.34) **G2**: 3.16 (1.39, 4.3) **Cervical IL-6, 7 ds, median µM/mL (IQR):** **G1**: 0.32 (0.15, 0.68) **G2**: 0.36 (0.09, 0.64) **Cervical IL-8, 7 ds, median µM/mL (IQR):** **G1**: 16.2 (7.7, 43.4) **G2**: 9.6 (5.0, 42.3) **Cervical TNF-α, 7 ds, µM/mL (IQR):** **G1**: 16.3 (11.3, 19.9) **G2**: 11 (5.0, 16.4)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Facchinetti et al., 2008 (continued)	**Private insurance:** NR		**Cervical IL-8, baseline, median µM/mL (IQR):** **G1**: 22.3 (12.7, 38.1) **G2**: 28.9 (15.2, 42) **Cervical TNF-α, baseline, median µM/mL (IQR):** **G1**: 15.66 (8.8, 21.7) **G2**: 12.4 (0.6, 18.4)		**Cervical nitrites/nitrates, 21 ds, mean µM/mL ±SD:** **G1**: 0.40 ± 0.28 **G2:** 0.38 ± 0.32 **Cervical IL-1β, 21 ds, median µM/mL (IQR):** **G1**: 1.15 (0.64, 2.97) **G2**: 2.4 (1.74, 5.68) **Cervical IL-6, 21 ds, median µM/mL (IQR):** **G1**: 0.2 (0.05, 0.68) **G2**: 0.2 (0.08, 0.52) **Cervical IL-8, 21 ds, median µM/mL (IQR):** **G1**: 21.1 (8.5, 46.6) **G2**: 17.9 (4.0, 56.2) **Cervical TNF-α, 21 ds, median µM/mL (IQR):** **G1**: 14.1 (11.4, 23.9) **G2**: 11.8 (6.8, 17.1) **Prematurity** **Birth weight**: NR **GA at birth:** NR **Delivery <37+6 wks, n (%):** **G1**: 5 (22) **G2**: 12 (54) *P* = 0.049

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Facchinetti et al., 2008 (continued)					**Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Fonseca et al., 2007 **Country:** UK, Chile, Brazil, Greece **Participant source:** Academic multi-site **Intervention setting:** Home **Enrollment period:** 09/2003 to 05/2006 **Funding:** Foundation **Author Industry Relationship Disclosure:** 0 of 5 **Design:** RCT (computer generated random number lists with centralized randomization)	**Intervention:** Vaginal suppositories of 200 mg capsules of micronized progesterone every night before going to sleep from 24-33+6 wksof gestation **Groups:** **G1:** 200 mg vaginal suppositories **G2:** placebo suppositories containing safflower oil **N at enrollment:** **G1**: 125 **G2**: 125 **N at birth:** **G1**: 125, 136 infants **G2**: 125, 138 infants **N at follow-up:** **G1**: 125 **G2**: 125 **Age, median yrs (IQR) :** **G1**: 29 (24, 34) **G2**: 29 (24, 34) **Race/ethnicity, n (%):** White: **G1**: 46 (36.8) **G2**: 49 (39.2) Black: **G1**: 68 (54.4) **G2**: 69 (55.2) Other: **G1**: 11 (8.8) **G2**: 7 (5.6)	**Inclusion criteria:** Singleton or twin pregnancy Underwent routine ultrasound at 20-25 weeks for fetal anatomy and growth Cervical length of ≤15 mm by transvaginal ultrasound **Exclusion criteria:** Major fetal abnormalities Painful, regular uterine contractions Hx of ruptured membranes Cervical cerclage	**Prior PTB ≥ 1, n (%):** **G1**: 15 (12.0) **G2**: 23 (18.4) **Multiple gestation-dichorionic, n (%):** **G1**: 8 (6.4) **G2**: 9 (7.2) **Multiple gestation-monochorionic/ diamniotic, n (%):** **G1**: 3 (2.4) **G2**: 4 (3.2) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NA **Cervical length, baseline, median mm (IQR):** **G1**: 11.0 (9, 14) **G2**: 12.0 (9, 14) **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Adherence rate < 80%, n (%):** **G1**: 9 (7.2) **G2**: 7 (5.6) *P* = 0.80	**Complications during pregnancy** **Fetal death, n (%):** **G1**: 1 (0.7) **G2**: 1 (0.7) *P* = 0.98 **Prematurity** **Spontaneous delivery at <34 wk, n (%):** **G1**: 24 (19.2) **G2**: 43 (34.4) RR: 0.56 [95% CI : 0.36, 0.86] *P* = 0.007 ARR: 0.56 [95% CI: 0.32, 0.91] *P* = 0.02 **Any delivery at < 34 wk, n (%):** **G1**: 26 (20.8) **G2**: 45 (36.0) RR: 0.58 [95% CI: 0.38, 0.87] *P* = 0.008 ARR: 0.60 [95% CI: 0.35, 0.94] *P* = 0.02 **Spontaneous PTD in women without hx of delivery <34 wk, n (%):** **G1**: 20/112 (17.9) **G2**: 34/109 (31.2) RR: 0.57 [95% CI: 0.35, 0.93] *P* = 0.03

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fonseca et al., 2007 (continued)	**Nulliparous, n (%):** **G1**: 71 (56.8) **G2**: 69 (55.2) **Maternal education:** NR **Maternal smoking, n (%):** **G1**: 6 (4.8) **G2**: 10 (8.0) **Maternal BMI, median kg/m^2 (IQR):** **G1**: 23.8 (21.6, 27.7) **G2:** 25.4 (22.3, 28.4) **Medicaid:** NR **Private insurance:** NR				**SPTD, in singleton pregnancies, n (%):** **G1**: 20/114 (17.5) **G2**: 36/112 (32.1) RR: 0.54 [95% CI: 0.34, 0.88] P = 0.02 **Birth weight < 2500 g, n (%):** **G1**: 56 (41.2) **G2**: 59 (42.8) RR: 0.96 [95% CI: 0.69, 1.26] *P* = 0.81 ARR: 0.97 [95% CI: 0.68, 1.29] *P* = 0.85 **Birth weight < 1500 g, n (%):** **G1**: 18 (13.2) **G2**: 27 (19.6) RR: 0.68 [95% CI: 0.36, 1.21] *P* = 0.20 ARR: 0.74 [95% CI: 0.36, 1.37] *P* = 0.35 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **Composite adverse outcomes, n (%):** **G1**: 11 (8.1) **G2**: 19 (13.8) RR: 0.59 [95% CI: 0.26, 1.25] *P* = 0.17 ARR: 0.57 [95% CI: 0.23, 1.31] *P* = 0.19

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fonseca et al., 2007 (continued)					IVH (all grade 2), **n (%):** **G1**: 1 (0.7) **G2**: 2 (1.4) RR: 0.51 [95% CI: 0.05, 5.30] *P* = 0.58 ARR: 0.33 [95% CI: 0.01, 8.84] *P* = 0.52 **RDS, n (%):** **G1**: 11 (8.1) **G2**: 19 (13.8) RR: 0.59 [95% CI: 0.26, 1.25] *P* = 0.17 ARR: 0.57 [95% CI: 0.23, 1.31] *P* = 0.19 **Retinopathy of prematurity, n (%):** **G1**: 2 (1.5) **G2**: 0 (0) **Necrotizing entercolitis, n (%):** **G1**: 0 (0) **G2**: 1 (0.7) **Composite therapy, n (%):** **G1**: 34 (25.0) **G2**: 45 (32.6) RR: 0.77 [95% CI: 0.48, 1.15] *P* = 0.21 ARR: 0.75 [95% CI: 0.44, 1.16] *P* = 0.20 **NICU , n (%):** **G1**: 33 (24.3) **G2**: 42 (30.4) RR: 0.80 [95% CI: 0.49, 1.21] *P* = 0.30 ARR: 0.80 [95% CI: 0.47, 1.24] *P* = 0.34

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fonseca et al., 2007 (continued)					**Ventilation, n (%):** **G1**: 16 (11.8) **G2**: 25 (18.1) RR: 0.65 [95% CI: 0.33, 1.21] *P* = 0.18 ARR: 0.64 [95% CI: 0.30, 1.25] *P* = 0.20 **Phototherapy, n (%):** **G1**: 16 (11.8) **G2**: 14 (10.1) RR: 1.16 [95% CI: 0.56, 2.25) *P* = 0.68 ARR: 1.09 [95% CI: 0.50, 2.19] *P* = 0.82 **Tx for sepsis, n (%):** **G1**: 3 (2.2) **G2**: 11 (8.0) RR: 0.28 [95% CI: 0.07, 1.01] *P* = 0.05 ARR: 0.29 [95% CI: 0.07, 1.10] *P* = 0.07 **Blood transfusion, n (%):** **G1**: 4 (2.9) **G2**: 5 (3.6) RR: 0.81 [95% CI: 0.22, 2.86] *P* = 0.75 ARR: 0.79 [95% CI: 0.19, 3.10] *P* = 0.74

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fonseca et al., 2007 (continued)					**Neonatal death, n (%):** **G1**: 2 (1.5) **G2**: 7 (5.1) RR: 0.29 [95% CI: 0.06, 1.42] *P* = 0.13 ARR: 0.34 [95% CI: 0.06, 1.81] *P* = 0.22 **Longer term outcomes** NR

Spontaneous delivery <34 weeks was 489/23795 (2.1%)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Fuchs and Stakemann,1960 See Ovlisen and Iversen, 1963 **Country:** Denmark **Participant source:** Community **Intervention setting:** Community **Enrollment period:** 1956 to 1957 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** Parentally administered crystalline progesterone dissolved in vegetable oil with concentration of 25 mg/mL, 200 mg daily for 3 days (begun after observation period that ranged from 1 hour to >24 hours), then 150 mg for 2 days, then 100 mg/day. Treatment discontinued 1 week after symptoms subsided; only 50 mg given on last day Placebo group received vegetable oil only **Groups:** **G1:** progesterone **G1a:** G1 participants with vaginal hemorrhage as cause of admission **G1b:** G1 participants with rupture of the membranes as cause of admission **G1c:** G1 participants with rhythmic or constant pains as cause of admission **G2:** placebo	**Inclusion criteria:** Pregnant women with symptoms of threatened premature labor admitted to the hospital **Exclusion criteria:** Women in whom parturition seemed imminent Women discharge from hospital after symptoms subsided during initial treatment Women delivering at other sites Women undelivered at time of study analysis	**Prior PTB (one or more), n (%):** **G1**: 8 (12.7) **G2**: 11 (17.5) **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR **Placenta previa, n:** **G1:** 6 **G2:** 5 **Abruptio placentae, n:** **G1:** 3 **G2:** 6 **Bleeding and pains previously in present pregnancy, n:** **G1:** 23 **G2:** 10 **Previous treatment with progesterone for bleeding and pain in the current pregnancy, n:** **G1:** 4 **G2:** 1	**Provider knowledge and attitudes, n (%):** NA **Provider specialty, n (%):** NR **Cost of drug, n (%):** NA **Drug availability, n (%):** NA **Medicaid, n (%):** NA **Private insurance, n (%):** NR **Symptoms causing admission, n: Hemorrhage from the vagina** **G1:** 15 **G2:** 28 **Rupture of the membranes** **G1:** 21 **G2:** 19 **Rhythmic or constant pains or backache** **G1:** 19 **G2:** 16 **Symptoms found on admission, n: Hemorrhage from the vagina:** **G1:** 15 **G2:** 23 **Passage of amniotic fluid:** **G1:** 23 **G2:** 18	**Complications during pregnancy** **Chorioamnionitis, n (%):** NR Antenatal hospitalizations, n (%): NR **IUGR, n (%):** NR **Allergic reactions, n (%):** 0 **GDM, n (%):** NR **Prematurity** **Delivery during treatment, n: 1st or 2nd day** **G1a:** 4 **G1b:** 7 **G1c:** 2 **G2a:** 4 **G2b:** 6 **G2c:** 3 **3rd-7th day** **G1a:** 0 **G1b:** 1 **G1c:** 1 **G2a:** 2 **G2b:** 5 **G2c:** 0 **8th-14th day** **G1a:** 4 **G1b:** 6 **G1c:** 0 **G2a:** 2 **G2b:** 2 **G2c:** 0 **15th-28th day** **G1a:** 1 **G1b:** 2 **G1c:** 1 **G2a:** 0 **G2b:** 2 **G2c:** 0

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fuchs and Stakemann,1960 (continued)	**G2a:** G2 participants with vaginal hemorrhage as cause of admission **G2b:** G2 participants with rupture of the membranes as cause of admission **G2c:** G2 participants with rhythmic or constant pains as cause of admission **N at enrollment:** NR **N at birth:** **G1**: 63 **G1a:** 23 **G1b:** 21 **G1c:** 19 **G2**: 63 **G2a:** 28 **G2b:** 19 **G2c:** 16 **N at follow-up:** Same as birth Note: 2 **G2** participants withdrew but are included in results analysis **Age in years, n:** < 20 **G1**: 5 **G2**: 14 **20-29** **G1:** 43 **G2:** 36 **30-39** **G1:** 14 **G2:** 12			**Uterine contractions:** **G1:** 24 **G2:** 27 **No objective symptoms:** **G1:** 11 **G2:** 4 **Interval between onset of symptoms and 1st study injection, n:** **< 12 hours** **G1:** 11 **G2:** 10 **12-24 hours** **G1:** 22 **G2:** 15 **24-48 hours** **G1:** 13 **G2:** 11 **2-4 days** **G1:** 7 **G2:** 10 **> 4 days** **G1:** 10 **G2:** 17 **Duration of treatment when not interrupted by delivery, n:** **<1 week** **G1:** 1 **G2:** 4 **8-14 days** **G1:** 21 **G2:** 28 **15-21 days** **G1:** 8 **G2:** 2 **22-28 days** **G1:** 1 **G2:** 2	**After 28th day** **G1a:** 1 **G1b:** 1 **G1c:** 0 **G2a:** 1 **G2b:** 0 **G2c:** 0**Delivery after treatment, n:** **During 1st week** **G1a:** 3 **G1b:** 2 **G1c:** 1 **G2a:** 0 **G2b:** 0 **G2c:** 1 **During 2nd week** **G1a:** 2 **G1b:**0 **G1c:** 0 **G2a:** 2 **G2b:** 0 **G2c:** 1 **3rd or 4th week** **G1a:** 1 **G1b:** 0 **G1c:** 3 **G2a:** 3 **G2b:** 0 **G2c:** 4 **After 4th week** **G1a:** 7 **G1b:** 3 **G1c:** 12 **G2a:** 12 **G2b:** 4 **G2c:** 7 **Birth weight, n**: **<1000g** **G1:** 2 **G2:** 0 **1000-1450g** **G1:** 7 **G2:** 12 **1500-1950g** **G1:** 11 **G2:** 10

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fuchs and Stakemann,1960 (continued)	**>40** **G1:** 1 **G2:** 1 **Race/ethnicity, n (%):** NR **Parous, n (%):** **G1**: 44 (70) **G2**: 34 (54) **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NA **Private insurance coverage:** NR			**>4 weeks** **G1:** 1 **G2:** 0	**2000-2450g** **G1:** 15 **G2:** 13 **2500-2950g** **G1:** 9 **G2:** 15 **>3000g** **G1:** 19 **G2:** 13 **GA at birth:** NR **<u>Mode of birth and complications during birth</u>** **Cesarean birth, n (%):** NR **Surgical complications, n (%):** NR Maternal harms**:** No reactions requiring discontinuation of progesterone **Discontinuation for pain at injection site or other reasons, n:** **G1:** 2 **G2:** 1 Stillbirth, n: **G1**: 0 **G2:** 2 **<u>Postpartum and neonatal complications</u>** NR **<u>Longer term outcomes</u>** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Gonzalez-Quintero et al., 2007 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 04/ 2004 to 04/2005 **Funding:** NR **Author Industry Relationship Disclosure:** 3 of 6 Matria (3) **Design:** Retrospective cohort	**Intervention:** Weekly administration of IM 17OHP during home nursing visits w/ clinical assessment **Groups:** **G1a:** 17OHP initiated at 16-20 wks GA **G1b:** 17OHP initiated at 16-20 wks GA w/o cerclage **G1c:** 17OHP initiated at 21-26 wks GA **G1d:** 17OHP initiated at 21-26 wks GA w/o cerclage **N at enrollment:** **G1a**: 156 **G1b:** 131 **G1c**: 119 **G1d:** 109 **N at birth:** **G1a**: 156 **G1b:** 131 **G1c**: 119 **G1d:** 109 **N at follow-up:** **G1a**: 156 **G1b:** 131 **G1c**: 119 **G1d:** 109 **Age, mean yrs ± SD:** **G1a**: 30.2 ± 5.5 **G1b:** 30.4 ± 5.4 **G1c**: 29.1 ± 5.7 **G1d:** 28.9 ± 5.7 **Race/ethnicity:** NR **Parous:** NR	**Inclusion criteria:** Singleton gestations Hx of PPTD Without symptoms of PTL Between 16-26.9 wks GA at initiation of IM 17OHP **Exclusion criteria:** Women with pre-viable deliveries (<24 wks GA)	**Prior PTB, n (%):** **G1a**: 156 (100) **G1c**: 119 (100) **>1 PPTD, (%):** **G1a**: (32.1) **G1:** (26.7) **G1c**b: (37.8) **G1c:** (39.4) **Multiple gestation, n (%):** **G1:** 0 (0) **G2:** 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, (%):** **G1a**: (16.0) **G1c**: (8.4) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at initiation of 17OHP, mean wks ± SD:** **G1a:** 17.9±1.4 **G1b:** 17.9±1.5 **G1c:** 23.2±1.8 **G1d:** 23.2±1.8 **N of 17OHP injections, mean ± SD:** **G1a:** 16.4 ± 4.6 **G1b:** 16.2 ± 4.5 **G1c:** 12.4 ± 4.2 **G1d:** 12.4 ± 4.0	**Complications during pregnancy** NR **Prematurity** **Birth weight**: NR **GA at birth, mean wks ± SD:** **G1a**: 36.8 ± 3.0 **G1b:** 36.8 ± 2.9 **G1c**: 36.7 ± 2.5 **G1d:** 36.8 ± 2.3 **G1a/G1c**: *P* = 0.235 **G1b/G1d:** *P* = 0.258 **GA at delivery, < 37 wks, (%):** **G1a:** (40.4) **G1b:** (41.2) **G1c:** (48.7) **G1d:** (48.6) **G1a/G1c**: *P* = 0.215 **G1b/G1d:** *P* = 0.297 **GA at delivery < 37 wks, SPTL, %:** **G1a:** (26.3) **G1b:** (27.5) **G1c:** (37.0) **G1d:** (36.7) **G1a/G1c**: *P* = 0.065 **G1b/G1d:** *P* = 0.163 **GA at delivery < 35 wks, (%):** **G1a:** (16.7) **G1b:** (17.6) **G1c:** (16.8) **G1d:** (15.6) **G1a/G1c**: *P* = 1.000 **G1b/G1d:** *P* = 0.730

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Gonzalez-Quintero et al., 2007 (continued)	**Maternal education:** NR **Maternal BMI:** NR **Maternal smoking, (%):** **G1a**: (7.7) **G1b:** (9.2) **G1c**: (8.4) **G1d:** (8.3) **Medicaid:** NR **Private insurance coverage:** NR				**GA at delivery < 35 wks, SPTL, %:** **G1a:** (12.8) **G1b:** (13.0) **G1c:** (11.8) **G1d:** (11.0) **G1a/G1c**: *P* = 0.855 **G1b/G1d:** *P* = 0.694 **GA at delivery < 32 wks, (%):** **G1a:** (5.1) **G1b:** (4.6) **G1c:** (5.0) **G1d:** (3.7) **G1a/G1c**: *P* = 1.000 **G1b/G1d:** *P* = 1.000 **GA at delivery < 32 wks, SPTL, %:** **G1a:** (5.1) **G1b:** (4.6) **G1c:** (2.5) **G1d:** (1.8) **G1a/G1c**: *P* = 0.360 **G1b/G1d:** *P* = 0.298 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Gonzalez-Quintero et al., 2010 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Clinics **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Retrospective cohort	**Intervention:** 250mg IM 17P weekly until 36 completed weeks or preterm delivery **Groups:** **G1:** 17P **G2:** Outpatient services without 17P **N at enrollment:** **G1**: 2,978 **G2**: 1,260 **N at birth:** **G1**: 2,978 **G2**: 1,260 **N at follow-up:** NA **Age, mean yrs ± SD:** Prior PTB GA 20-27.9 wks (n=896): 29.9 ± 5.7 Prior PTB GA 28-33.9 wks (n=1,493) 30.5 ± 5.5 Prior PTB GA 34-36.9 wks (n=1,849) 30.5 ± 5.2 **Race/ethnicity, n (%):** Black: 936 (22.1) **Parous, n (%):** 4,238 (100) **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR	**Inclusion criteria:** Current singleton pregnancy History of at least one spontaneous PTB with a documented GA between 20-36.9 wks Documented pregnancy outcome of the current pregnancy **Exclusion criteria:** Use of progestational agents other than 17P in the current pregnancy 17P use initiated at ≥25 wks GA	**Prior PTB, n (%):** 4,238 (100) **Multiple gestation, n (%):** 0 **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** 20-36.9 wks for all participants **Prior PPROM, n (%):** NR	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR **Tocolytic use, %:** **G1:** 13.9 **G2:** 75.0	**Complications during pregnancy** NR **Prematurity** **PTB, %:** Prior PTB GA 20-27.9 wks (n=896): **G1:** 32.2 **G2:** 40.7 *P* = 0.025 OR (95% CI): 0.693 (0.503, 0.956) Prior PTB GA 28-33.9 wks (n=1,493) **G1:** 34.1 **G2:** 45.5 *P* < 0.001 OR (95% CI): 0.618 (0.484, 0.790) Prior PTB GA 34-36.9 wks (n=1,849) **G1:** 29.3 **G2:** 38.8 *P* < 0.001 OR (95% CI): 0.652 (0.535, 0.794) **Regression Analysis, PTB OR (95% CI)*:** Prior PTB GA 20-27.9 wks (n=896): 0.675 (0.487, 0.936 *P* = .018 Prior PTB GA 28-33.9 wks (n=1,493) 0.595 (0.463, 0.765) *P* <0.001

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Gonzalez-Quintero et al., 2010 (continued)	**Maternal smoking, n (%):** 241 (5.7) **Medicaid:** NR **Private insurance coverage:** NR				Prior PTB GA 34-36.9 wks (n=1,849) 0.647 (0.528, 0.792) *P* < 0.001 **GA at birth:** Prior PTB GA 20-27.9 wks (n=896): **G1:** 36.0 ± 3.6 **G2:** 35.7 ± 3.0 *P* = 0.025 Prior PTB GA 28-33.9 wks (n=1,493) **G1:** 36.4 ± 2.8 **G2:** 35.6 ± 2.9 *P* < 0.001 Prior PTB GA 34-36.9 wks (n=1,849) **G1:** 37.0 ± 2.2 **G2:** 36.3 ± 2.2 *P* < 0.001 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

*Regression analysis controlled for black race, maternal age, smoking, unmarried status, and >1 prior PTB

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Gyamfi et al., 2009 See Meis et al., 2003 and Rouse et al., 2007 **Country:** US **Participant source:** Academic multi-site **Intervention setting:** Clinic **Enrollment period:** **G1** and **G2**: 09/1999 to 02/2002 **G3 and G4:** 04/2004 to 02/2006 **Funding:** NIH **Author Industry Relationship Disclosure:** NR **Design:** Secondary analysis of pooled data from 2 RCTs	**Intervention:** 250 mg of IM 17OHP every week, begun at 16-20 + 6 wks until wk 34 (**G3** and **G4**) or 36 (**G1** and **G2**) or birth **Groups:** **G1:** IM 17OHP, singleton pregnancy **G2:** Placebo, singleton pregnancy **G3:** IM 17OHP, twin pregnancy **G4:** Placebo, twin pregnancy **N at enrollment:** **G1:** 293 **G2:** 148 **G3:** 323 **G4:** 330 **N at birth:** **G1:** 293 **G2:** 148 **G3:** 323 **G4:** 330 **N at follow-up:** **G1:** 293 **G2:** 148 **G3:** 323 **G4:** 330 **Age, mean yrs ± SD :** **G1:** 25.9 ± 5.6 **G2:** 26.4 ± 5.4 **G3:** 29.7 ± 7.0 **G4:** 29.6 ± 6.8 **Race, n (%): African American** **G1:** 175 (59.7) **G2:** 88 (59.5) **G3:** 73 (22.6) **G4:** 77 (23.3)	**Inclusion criteria:** Participant in primary trial (see inclusion and exclusion criteria in Meis et al., 2003 and Rouse et al., 2007) **Exclusion criteria:** Prepregnancy diagnosis of DM Unknown GDM status Lost to follow-up in primary trial	**Prior PTB, n (%):** **G1:** 293 (100) **G2:** 148 (100) **G3:** 20 (6.1) **G4:** 30 (9.0) **Multiple gestation, n (%):** **G1:** 0 (0) **G2:** 0 (0) **G3:** 323 (100) **G4:** 330 (100) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**Complications during pregnancy** **GDM, %:** **G1**: 5.8 **G2**: 4.7 RR: 1.23 (95% CI: 0.52 to 2.89) *P* = 0.64 **G3**: 7.4 **G4**: 7.6 RR: 0.98 (95% CI: 0.57 to 1.68) *P* = 0.94 **G1 and G3:** AOR: 1.04 (95% CI: 0.62 to 1.73) **Prematurity** **Birth weight:** NR **GA at birth:** NR **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Gyamfi et al., 2009 (continued)	**Parous, n (%):** **G1:** 293 (100) **G2:** 148 (100) **G3:** 176 (53.8) **G4:** 189 (56.6) **Maternal education, yrs:** **G1:** 11.7 ± 2.3 **G2:** 11.9 ± 2.4 **G3:** 13.7 ± 2.8 **G4:** 13.6 ± 2.9 **Maternal smoking, n (%):** **G1:** 67 (22.9) **G2:** 28 (18.9) **G3:** 38 (11.8) **G4:** 31 (9.4) **Maternal prepregnancy BMI, mean ± SD:** **G1**: 26.9 ± 7.9 **G2**: 26.0 ± 7.0 **G3:** 26.7 ± 6.5 **G4:** 27.1 ± 7.1 **Medicaid:** NR **Private insurance:** NR				

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Harper et al., 2010 **Country:** US **Participant source:** Academic multi-site **Intervention setting:** Clinics **Enrollment period:** 01/2005 to 10/2006 **Funding:** NIH **Author Industry Relationship Disclosure:** 0 of 0 **Design:** RCT (double masked; simple urn method of randomization; stratified according to clinical center)	**Intervention:** 250 mg IM 17OHP weekly supplement containing 1,200 mg of eicosapentaenoic acid (EPA, 20:5n-3) and 800 mg of docosahexaenoic acid (DHA, 22:6n-3), totaling 2,000 mg of omega-3 long-chain polyunsaturated fatty acids divided into 4 capsules, or matching placebo capsules (taken together or separately throughout day) **Groups:** **G1:** Omega-3 capsule and IM 17OHP **G2:** Placebo capsule and IM 17OHP **N at enrollment:** **G1**: 434 **G2**: 418 **N at birth:** **G1**: 434 **G2**: 418 **N at follow-up:** **G1**: 434 **G2**: 418 **Age, median yrs (IQR):** **G1**: 28 (23-32) **G2**: 27 (24-32)	**Inclusion criteria:** Women presenting for prenatal care with hx of ≥ 1 prior singleton PTD between 20 and 37 wks of gestation after SPTL or PPROM Current singleton pregnancy between 16 and 21+ 6 wks of gestation **Exclusion criteria:** Major fetal anomaly Intake of a fish oil supplement > 500 mg per week at any time during the preceding month Allergy to fish Anticoagulation therapy Hypertension White's classification D or higher diabetes Drug or alcohol abuse Seizure disorder Uncontrolled thyroid disease	**Prior PTB, n (%):** **G1**: 434 (100) **G2**: 418 (100) **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Cervical length, baseline:** NR **GA of prior PTB, median wks, (IQR):** **G1**: 32 (27-34) **G2**: 31 (26-34) **Prior PPROM, n (%):** NR	**Adherence for 17OHP, (%):** **G1**: **(**90.6) **G2**: (90.9) P=.78 **Adherence for omega-3 and placebo capsules, (%):** **G1**: (85.1) **G2**: (84.8) P=.33 **GA at initiation, median yrs (IQR):** **G1**: 19.6 (17.9-20.9) **G2**: 19.6 (18.0-21.0)	**Complications during pregnancy** **Preeclampsia or gestational hypertension, (%):** **G1**: **(**4.6) **G2**: (4.8) P=.9 **Injection site reactions, (%):** **G1**: **(**64.3) **G2**: (58.6) P=.09 **Burping, (%):** **G1**: **(**21.0) **G2**: (5.5) P<.001 **Vomiting, (%):** **G1**: **(**4.4) **G2**: (1.2) P=.005 **Bad taste, (%):** **G1**: **(**2.3) **G2**: (0) P=.002 **GDM, n (%):** **G1**: (7.4) **G2**: (5.5) P=.27 **Prematurity** **Birthweight median g (IQR)**: **G1**: 2990 (2585-333-) **G2**: 2923 (2389-3317) P=.13 **Birthweight < 2500g, n (%); RR (95%CI)**: **G1**: 94 (22.0) **G2**: 112 (27.3) 0.81 (0.64-1.02)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Harper et al., 2010 (continued)	**Race/ethnicity, n (%):** African American **G1**: 148 (34.1) **G2**: 145 (34.9) White **G1**: 245 (56.5) **G2**: 240 (57.7) Asian **G1**: 13 (3.0) **G2**: 5 (1.2) Other **G1**: 28 (6.5) **G2**: 26 (6.3) Hispanic/Latina **G1**: 64 (14.7) **G2**: 57 (13.6) **Parous, n (%):** **G1**: 434 (100) **G2**: 418 (100) **Maternal education, median yrs (IQR):** **G1**: 13 (12-16) **G2**: 13 (12-16) **Maternal BMI, median score (IQR):** **G1**: 25.1 (21.5-30.3) **G2**: 24.6 (21.5-30.3) **Maternal smoking, n (%):** **G1**: 64 (14.7) **G2**: 72 (17.2) **Medicaid:** NR **Private insurance coverage:** NR	**Exclusion criteria: (continued)** A plan to deliver either elsewhere or < 37 wks of gestation			**Birthweight < 1500g, n (%); RR (95%CI)**: **G1**: 26 (6.1) **G2**: 29 (7.1) 0.86 (0.52-1.44) **Small for GA < 10th percentile, n (%); RR (95%CI)**: **G1**: 35 (8.2) **G2**: 41 (10.0) 0.82 (0.53-1.23) **Large for GA > 90th percentile, n (%); RR (95%CI)**: **G1**: 21 (4.9) **G2**: 15 (3.7) 1.34 (0.70-2.57) **GA at birth median wks (IQR)**: **G1**: 37.7 (36.0-39.0) **G2**: 37.4 (35.7-38.7) P=.26 **GA at birth < 37 wks, n (%); RR (95% CI):** All **G1**: 164 (37.8) **G2**: 174 (41.6) 0.91 (0.77-1.07) Spontaneous **G1**: 143 (32.9) **G2**: 149 (35.6) 0.92 (0.77-1.11) Medically indicated **G1**: 21 (4.8) **G2**: 25 (6.0) 0.81 (0.46-1.42) **GA at birth < 35 wks, n (%); RR (95% CI):** **G1**: 82 (18.9) **G2**: 83 (19.9) 0.95 (0.72-1.25)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Harper et al., 2010 (continued)					**GA at birth < 32 wks, n (%); RR (95% CI):** **G1**: 43 (9.9) **G2**: 45 (10.8) 0.92 (0.62-1.37) **GA at birth > 40 wks, n (%); RR (95% CI):** **G1**: 11 (2.5) **G2**: 8 (1.9) 1.32 (0.54-3.25) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **Pregnancy loss or neonatal death, n (%); RR (95% CI)**: **G1**: 16 (3.7) **G2**: 17 (4.1) 0.90 (0.46-1.77) **NICU LOS, mean days±SD:** **G1**: 5.8±16.0 **G2**: 5.1±14.2 P=.82 **Postpartum hemorrhage, (%):** **G1**: **(**13.8) **G2**: (12.5) P=.56 ***Admission to ICN, n (%); RR (95%CI):** **G1**: 110 (25.9) **G2**: 99 (24.6) 1.05 (0.83-1.33)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Harper et al., 2010 (continued)					***Retinopathy of prematurity, n (%); RR (95%CI):** **G1**: 5 (1.2) **G2**: 4 (1.0) 1.18 (0.32-4.37) ***IVH, n (%); RR (95%CI):** **Any grade** **G1**: 10 (2.4) **G2**: 9 (2.2) 1.05 (0.43-2.57) **Grade 3-4** **G1**: 5 (1.2) **G2**: 3 (0.7) 1.58 (0.38-6.57) *** Patent ductus arteriosus, n (%); RR (95%CI):** **G1**: 11 (2.6) **G2**: 7 (1.7) 1.49 (0.58-3.81) ***Necrotizing enterocolitis, n (%); RR (95%CI):** **G1**: 3 (0.7) **G2**: 4 (1.0) 0.71 (0.16-3.16) ***Proven sepsis, n (%); RR (95%CI):** **G1**: 5 (1.2) **G2**: 3 (0.7) 1.58 (0.38-6.57) **†RDS, n (%):** **G1**: 59 (13.9) **G2**: 35 (8.7) 1.60 (1.08-2.37) P=.019 **†Received surfactant, n (%):** **G1**: 38 (8.9) **G2**: 29 (7.2) 1.24 (0.78-1.98)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Harper et al., 2010 (continued)					†**BPD, n (%):** **G1**: 9 (2.1) **G2**: 6 (1.5) 1.42 (0.51-3.96) †**Transient tachypnea, n (%):** **G1**: 31 (7.3) **G2**: 24 (6.0) 1.22 (0.73-2.05) †**Supplemental oxygen, mean±SD:** **G1**: 2.2±8.9 **G2**: 1.9±9.4 P=.16 †**Ventilator support, mean±SD:** **G1**: 0.8±5.6 **G2**: 0.5±4.0 P=.28 **Longer term outcomes** NR

*Outcomes for liveborn neonates according to maternal treatment assignment **G1** (n=425) **G2** (n=403)
† Respiratory outcomes for liveborn neonates according to maternal treatment assignment **G1** (n=425) **G2** (n=403)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Hartikainen-Sorri et al., 1980 **Country:** Finland **Participant source:** Academic single site **Intervention setting:** Home **Enrollment period:** NR **Funding:** Study drug provided by Schering AG **Author Industry Relationship Disclosure:** NR **Design:** Prospective cohort	**Intervention:** 250 mg of IM 17OHP administered weekly, begun at 28-33 weeks through 36 weeks or until delivery **Groups:** **G1:** intervention **G2:** placebo control **N at enrollment:** **G1**: 39 **G2**: 38 **N at birth:** **G1**: 39 **G2**: 38 **N at follow-up:** **G1**: 39 **G2**: 38 **Age, mean yrs±SD:** **G1**: 28.5±5.2 **G2**: 27.8±5.2 **Race/ethnicity, n (%):** NR **Parous, n:** **G1**: 29 **G2**: 24 **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NA **Private insurance coverage:** NR	**Inclusion criteria:** Women with twin pregnancy at 28-33 weeks gestation **Exclusion criteria:** Signs of premature labor	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** **G1**: 39 (100) **G2**: 38 (100) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Provider knowledge and attitudes, n (%):** NA **Provider specialty, n (%):** NR **Cost of drug, n (%):** NA **Drug availability, n (%):** NA **Gestational week at onset of medication, mean ± SD:** **G1:** 29.2±1.9 **G2:** 29.1±1.5	**<u>Complications during pregnancy</u>** **Chorioamnionitis, n (%):** NR **Antenatal hospitalizations, n**: **G1**: 37 **G2**: 34 **Length of hospital stay among hospitalized women, mean days ± SD:** **G1:** 23.5±10.9 **G2:** 30.8±2.7 **P<.01** **Use of beta-mimetics, n:** **Oral:** **G1:** 25 **G2:** 24 **Oral and parenteral:** **G1:** 5 **G2**: **5** **IUGR, n (%):** NR **Allergic reactions, n (%):** NR **GDM, n (%):** NR **Polyhydramnios, n:** **G1:** 2 **G2:** 2 **Premature rupture of membranes, n:** **G1:** 5 **G2:** 2

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hartikainen-Sorri et al., 1980 (continued)					**Perinatal mortality, n of fetuses/ neonates:** **G1:** 4 (5.2) **G2:** 2 (2.6) P=NS **<u>Prematurity</u>** **Birth weight**: NR **GA at birth, mean weeks ± SD:** **G1:** 36.9±2.6 **G2:** 37.3±2.4 **Spontaneous delivery before 37th gestational week, n (%):** **G1:** 12 (30.8) **G2:** 9 (23.7) **Induced delivery before 37th gestational week, n:** **G1:** 3 **G2:** 0 **<u>Mode of birth and complications during birth</u>** NR **<u>Postpartum and neonatal complications</u>** **Neonatal respiratory problems, n among surviving neonates:** **G1:** 7 **G2:** 3

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hartikainen-Sorri et al., 1980 (continued)					**Phototherapy for hyperbilirubinemia, n among surviving neonates::** **G1:** 8 **G2:** 8 **Omphalitis, n among surviving neonates:** **G1:** 1 **G2:** 2 **Accessory thumb, n among surviving neonates:**: **G1:** 1 **G2:** 0 **Testicular hydrocele, n among surviving neonates:** **G1:** 1 **G2:** 0 **Minimal ventricular septal defect in the heart, n among surviving neonates:** **G1:** 0 **G2:** 1 **Postpartum hemorrhage,** n (%): NR **IVH, n (%):** NR **Pulmonary infections, n among surviving neonates:**: **G1:** 0 **G2:** 2 **<u>Longer term outcomes</u>** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Hauth et al., 1983 **Country:** US **Participant source:** Community (military) **Intervention setting:** Clinic **Enrollment period:** July 1977 to March 1981 **Funding:** Industry **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** 1,000 mg/wk of IM 17OHP (Delalutin), from 16-20 wks until 36 wks GA **Groups:** **G1:** 17OHP **G2:** Placebo (castor oil, benzyl benzoate 46%, benzyl alcohol 2%) **G3:** Offered but declined protocol **N at enrollment:** **G1**: 80 **G2**: 88 **G3:** 78 **N at birth:** **G1**: 80 **G2**: 88 **G3:** 78 **N at follow-up:** **G1**: 80 **G2**: 88 **G3:** 78 **Age, mean yrs :** NR **Race/ethnicity, (%):** **Black** **G1**: (20) **G2**: (17) **G3:** (24) **Multiparity, (%):** **G1**: (29) **G2**: (22) **G3:** (28) **Maternal education:** NR	**Inclusion criteria:** Active military-duty pregnant female between 16 - 20 wks gestation Gave informed consent to protocol **Exclusion criteria:** See Inclusion criteria	**Prior PTB, (%):** **G1**: (2.5) **G2**: (3.4) **G3:** (3.8) **Prior therapeutic abortion, (%):** **G1**: (14) **G2**: (13) **G3:** (14) **Prior abortion, (%):** **G1**: (13) **G2**: (13) **G3:** (14) **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Provider knowledge and attitudes:** NR **Provider specialty, n (%):** Ob/Gyn **G1**: 80 (100) **G2**: 88 (100) **G3:** 78 (100) **Cost of drug:** NR **Drug availability, n (%):** **G1**: 80 (100) **G2**: NA **G3:** NA	**Complications during pregnancy** **Pregnancy-induced HTN, (%):** **G1:** (12.5) **G2:** (13.6) **G3:** (3.0) *P* = 0.01 **Prematurity** **Premature labor, (%):** **G1:** (6.3) **G2:** (5.7) **G3:** (10.2) **Post-term pregnancy, (%):** **G1:** (16) **G2:** (10) **G3:** (18) **Birth weight < 2,500 g, (%):** **G1**: (7.5) **G2**: (9.0) **G3**: (11.5) **†Incidence of birth weight < 2,500 g, (%):** **All active-duty women:** (9.1) **Nonactive-duty dependents:** (5.6) *P* = 0.001 **Active-duty women in study analysis:** (9.3) **Nonactive-duty dependents:** (5.6) *P* = 0.009

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hauth et al., 1983 (continued)	**Maternal smoking, (%):** **G1**: (28) **G2**: (25) **G3:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR				**Mode of birth and complications during birth** **Stillbirth, n:** **G1:** 1 **G2:** 3 **G3:** 0 **Postpartum and neonatal complications** **Neonatal death, n:** **G1:** 2 **G2:** 0 **G3:** 2 **Major congenital defects, (%):** **G1:** (3.8) **G2:** (2.3) **G3:** (2.6) **Perinatal mortality/1,000 births*:** **G1:** 38 **G2:** 34 **G3:** 26 **Perinatal mortality/1,000 births†*:** **All active-duty women:** 21.6 **Nonactive-duty dependents:** 9.8 *P* = 0.02 **Active-duty women in study analysis:** 32.5 **Nonactive-duty dependents:** 9.8 *P* = 0.001 **Longer term outcomes** NR

*Perinatal mortality included all stillbirths ≥ 500 g and deaths of infants ≥ 500 g through day 28 post-delivery.
†Comparisons to non-active duty dependents given w/o description of that patient population or % treated with 17OHP

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Author: Henderson et al., 2009 **Country:** US **Participant source:** Members of the ACOG Collaborative Ambulatory Research Network (CARN). Network members are ACOG Fellows or Junior Fellows in Practice who have volunteered to participate in ACOG Surveys. **Intervention setting:** NA (survey) **Enrollment period:** 03/2007 to 06/2007 **Funding:** CDC CARN is supported by the Maternal and Child Health Bureau **Author Industry Relationship Disclosure:** NR **Design:** Cross-sectional	**Assessment:** Mail survey **Groups:** **G1:** Total respondents **G1a:** Progesterone users (recommend or offer progesterone to prevent PTB) **G1b:** Nonusers **G2:** Nonrespondents who completed 6 demographic questions **N sampled:** 787 **Survey response rate, n (%)** **G1:** 469 (59.6) **G1a:** 254 (32.3) **G1b:** 91 (11.6) **G2:** 105 (33.0 of 318 total nonrespondents) **Age >45 yrs, n (%):** **G1:** 179 (51.9) **G1a:** 119 (46.8) **G1b:** 60 (65.9) P=0.002 NS when controlled for association between age and gender **Age, median years (range):** **All:** 46 (31-74) **Female:** 40 **Male:** 52	**Inclusion criteria:** CARN member Currently in obstetrics practice in the US **Exclusion criteria:** See inclusion criteria	**Factors routinely used to screen for patients at risk for PTB, n (%):** Prior PTB **G1**: 344 (99.7) Multiple gestation **G1**: 338 (98.0) Prematurely dilated/effaced cervix **G1**: 319 (92.5) > 1 prior PTB **G1**: 310 (89.9) Short cervix on ultrasound **G1**: 306 (88.7) Maternal substance abuse **G1**: 284 (82.3) Low socioeconomic status **G1**: 279 (80.9) Maternal tobacco use **G1**: 246 (71.3) Fetal fibronectin test **G1**: 241 (69.9) Maternal age < 17 y **G1**: 240 (69.6)	**Years in clinical practice, n (%):** ≤ 10 yrs **G1:** 146 (42.3) **G1a:** 109 (42.9) **G1b:** 37 (40.6) > 10 yrs **G1:** 196 (56.8) **G1a:** 143 (56.3) **G1b:** 53 (58.2) P=0.72 **Specialty, n (%):** MFM **G1:** 28 (9.1) **G1a:** 33 (13.0) **G1b:** 1 (1.1) Non-MFM **G1:** 316 (91.9) **G1a:** 22 (87.0) **G1b:** 90 (98.9) P=0.001 **Specialty, %:** **General obstetrics and gynecology:** 89 **MFM:** 8 **Obstetrics only:** 2 **Practice type, n (%):** Solo practice **G1:** 56 (16.2) **G1a:** 29 (11.4) **G1b:** 27 (29.7) Multispecialty group **G1:** 38 (11.0) **G1a:** 26 (10.2) **G1b:** 12 (13.2) University-based **G1:** 48 (13.9) **G1a:** 40 (15.7) **G1b**: 8 (8.8)	**Survey results:** **Report use of progesterone in practice, %:** **G1:** 74 **G2:** 86 P=0.01 **Patients receive Medicaid, mean %:** **G1**: 30 **Patients' race is white, mean %:** **G1**: 59 **Patient population is at higher than average risk for PTB, %:** **G1**: 28 **Patients request progesterone to prevent PTB, %:** Frequently **G1a**: 2 Infrequently **G1a**: 35 Never **G1a**: 65 **When physician began recommending progesterone, %:** Within past 3 years **G1a**: 92 Within year prior to survey **G1a**: 49

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Henderson et al., 2009 (continued)	**Female gender, n (%):** **G1:** 172 (49.9) **G1a:** 136 (53.5) **G1b:** 36 (39.6) P=0.02 NS when controlled for association between age and gender			Obstetrics-gynecology group **G1:** 174 (50.4) **G1a:** 139 (54.7) **G1b:** 35 (38.5) Other (includes HMO-based and military practice types) **G1:** 29 (8.3) **G1a:** 20 (7.9) **G1b:** 9 (9.9) P=0.001 **Geographic region, n (%):** West **G1:** 81 (23.5) **G1a:** 45 (17.7) **G1b:** 36 (39.5) Midwest **G1:** 80 (23.2) **G1a:** 66 (26.0) **G1b:** 14 (15.4) South **G1:** 127 (36.8) **G1a:** 99 (39.0) **G1b:** 28 (30.8) Northeast **G1:** 57 (16.5) **G1a:** 44 (17.3) **G1b:** 13 (14.3) P=0.001 **Confident or very confident in ability to screen for patients who are high risk for PTB, %:** **G1**: 95 **Manage patients at high risk for PTB, %:** **G1:** 57	**Physician's preferred route for administration of progesterone, %:** Intramuscular **G1a**: 83 Vaginal **G1a**: 9 **How many patients decline progesterone, %:** ≤ 50% **G1a**: 86 None **G1a**: 35 **Where patients or physicians obtain progesterone, %:** Local compounding pharmacy **G1a**: 37 Home health care services **G1a**: 16 Mail order **G1a**: 14 **Physicians offer progesterone for women with prior PTB by gestational age of prior PTB, %:** <37 weeks **G1a**: 42.6 <36 weeks **G1a**: 14.6 <34 weeks **G1a**: 15.4 <32 weeks **G1a**: 6.3 Only if additional risk factors **G1a**: 14.5

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Henderson et al., 2009 (continued)					**Most frequent indication = prior spontaneous PTB<37 wks, n (%):** **G1:** 137 (42) Indications for recommending or offering progesterone, %: Prior PTB **G1a**: 93 No prior PTB but other conditions in current pregnancy **G1a**: 52 No prior PTB, dilated/effaced cervix in current pregnancy **G1a**: 36.6 No prior PTB, short cervix on ultrasound in current pregnancy **G1a**: 33.9 No prior PTB, cerclage in current pregnancy **G1a**: 26.0 No prior PTB, positive FFN in current pregnancy **G1a**: 22.4 No prior PTB, PTL symptoms in current pregnancy **G1a**: 21.3 No prior PTB, multiple gestation in current pregnancy **G1a**: 19.3

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Henderson et al., 2009 (continued)					No prior PTB, uterine anomalies **G1a:**18.5 Recommend progesterone to women without a prior PTB, %: Age >45 years **G1a**: 60 Age <45 years **G1a**: 45 P=0.021 Not MFM specialist **G1a**: 55 MFM specialist **G1a**: 30 P=0.008 Midwest and South **G1a**: 50 and 49 West and Northeast **G1a**: 25 and 25 P < 0.001 Physicians who are very concerned about various aspects of progesterone to prevent PTB, %: Not easily available **G1**: 36 Not covered by insurance* **G1**: 31 More data are needed* **G1**: 28 May be long-term fetal or neonatal effects* **G1**: 27 *P <0.05 for **G1a** vs. **G1b**

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Henderson et al., 2009 (continued)					Concerns of non-users (n=91), %: Need for more data: 87 Efficacy: 82 Long-term effects: 72 **Safety:** 53 Consider prophylactic progesterone for high-risk patients an effective treatment to reduce PTB, %: **G1**: 55 How convinced clinical trial evidence demonstrates prophylactic progesterone effective for patients at high of PTB, %: Convinced **G1**: 26 Somewhat convinced **G1:** 51

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Hill et al., 1975 **Country:** US **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** 1955 - 1971 **Funding:** Intramural **Author Industry Relationship Disclosure:** NR **Design:** Retrospective cohort	**Intervention:** Various doses (250-7,500 mg) of hydroxyprogesterone caproate prior to and/or after abdominal surgery or 200 - 600 mg of IM progesterone **Groups:** **G1**: Hydroxyprogesterone caproate or IM progesterone **G2:** Controls **N at enrollment:** **G1**: 38 **G2**: 35 **N at birth:** **G1**: 35 **G2**: 35 **N at follow-up:** **G1**: 35 **G2**: 35 **Age, mean yrs :** **G1**: 26.6 **G2**: 25.4 **Race/ethnicity:** NR **Parity, n:** **0** **G1**: 8 **G2:** 13 **1** **G1:** 6 **G2:** 10 **2** **G1:** 9 **G2:** 3 **3** **G1:** 6 **G2:** 4 **≥4** **G1:** 7 **G2**: 6	**Inclusion criteria:** Pregnant women who underwent abdominal surgery (unrelated to delivery) who received various doses of hydroxyprogesterone caproate or IM progesterone **Controls matched to tx group for age, parity, abortion history, GA at surgery, and type of surgery** **Exclusion criteria:** See inclusion criteria Therapeutic and spontaneous abortions Vaginal bleeding Irregular contractions before tx start	**Prior PTB, n (%):** NR **Previous abortions, n:** 1 **G1**: **7** **G2**: 6 2 **G1:** 2 **G2:** 1 **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Received IM progesterone, n:** **G1:** 5 **GA at surgery, wks:** **G1**: 13.6 **G2**: 13.1 **Type of abdominal surgery, n:** **Cholecystectomy** **G1**: 1 **G2:** 2 **Abdominoperineal** **G1:** 1 **G2:** 0 **Fulguration for recal carcinoma** **G1:** 0 **G2:** 1 **Lysis of adhesions** **G1:** 1 **G2:** 1 **Laparotomy** **G1:** 3 **G2:** 2 **Acute appendectomy** **G1:** 9 **G2:** 7 **Ruptured appendectomy** **G1:** 2 **G2:** 3 **Excision of ovarian cyst** **G1:** 15 **G2:** 16 **Myomectomy** **G1:** 1 **G2:** 1 **Salpingo-oophorectomy** **G1:** 2 **G2**: 2	**Complications during pregnancy** **Stillbirth, n:** **G1**: 1 **G2**: 0 **Abortion, n:** **G1**: 3 **G2:** 3 **Prematurity** **Premature labor w/ fetal death, n:** **G1**: 1 **G2**: 3 **Birth weight**: NR **GA at birth:** NR **Mode of birth and complications during birth** **Normal delivery, n:** **G1**: 30 **G2:** 29 **Total fetal loss, n:** **G1**: 5 **G2:** 6 **Fetal mortality, (%):** **G1**: (14.3) **G2:** (17.1) **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hill et al., 1975 (continued)	**Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR			**Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Hobel et al., 1994 **Country:** US **Participant source:** Community **Intervention setting:** Clinic and home **Enrollment period:** 1983-1988 **Funding:** CA dept of Health Services, Maternal and Child Health branch; Upjohn Company **Author Industry Relationship Disclosure:** NR **Design:** RCT (randomized for primary intervention at clinic level; randomized by participant within intervention clinics to additional secondary intervention)	**Intervention:** PTB prevention education and increased clinic visits with selected prophylactic interventions including: bed rest, social work, Provera (Oral progestin 20mg BID after 20 wks gestation), and oral placebo. **Groups:** **G1:** Experimental **G1a**: No secondary intervention **G1b:** Bed rest **G1c:** Social work **G1d:** Placebo **G1e:** Provera **G2:** Routine care **N at enrollment:** **G1:** 2,335 **G2:** 1,124 **N at birth:** **G1:** 1,774 **G2:** 880 **N at follow-up:** **G1:** 1,774 **G2:** 880 **Age, mean yrs ± SD :** G1: 25.9 ± 5.6 G2: 26.3 ± 5.7 **Race/ethnicity, (%):** **Hispanic** **G1:** 71.2 **G2:** 78.9 **White** **G1:** 15.9 **G2:** 11.2	**Inclusion criteria:** Pregnant women classified as high risk at 2nd clinic visit (≥ 1 risk factor: induced abortion, ≥ 3 SA, PPTB, previous neonatal death, uterine cervical abnormality, previous cesarean or myomectomy, HTN, renal disease, psychiatric hospitalization, ≥ 10 cigarettes/day within past year, marijuana use, narcotics use, size/date discrepancy (>3 cm size from dates), unknown last menstrual period, severe anemia, threatened abortion, bleeding, incompetent cervix, multiple pregnancy, hospitalized for surgery or PTL, cervical status (length < 1 cm or dilatation > 2 cm) GA < 31 wks at 1st visit	**Prior PTB:** NR **Multiple births, n (excluded from outcomes analysis):** **G1:** 7 **G2:** 12 **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**N of high risk problems, mean n ± SD:** **G1:** 1.53 ± 0.8 G2: 1.46 ± 0.7 **GA at 1st clinic visit, mean wks ± SD:** **G1:** 19.1 ± 7.1 **G2:** 19.7 ± 7.1 *P* = 0.06 **Adherence, n:** **Positive** **G1e:** 228 **Non** **G1e:** 182 **Incidence of PTB, (%):** **Compliant** **G1e:** 6.1 **Noncompliant** **G1e:** 17.6 **Loss to Follow up, n: (Excluded)** **G1:** 307 **G2:** 132	**Complications during pregnancy** NR **Prematurity** Gestational Age at 1st Clinic Visit (wk), n (mean ± s.d.); p-value: **G1:** Preterm: 121 (19.1 ± 6.7) **Term:** 1538 (19.1 ± 7.1) **p-value:** 0.91 **G2:** Preterm: 72 (19.9 ± 7.3) **Term:** 707 (19.7 ± 7.1) **p-value:** 0.78 Gravidity, n (mean ± s.d.); p-value: **G1:** Preterm: 131 (2.6 ± 2.2) **Term:** 1641 (2.4 ± 2.0) **p-value:** 0.38 **G2:** Preterm: 80 (3.1 ± 2.1) **Term:** 800 (2.6 ± 2.1) **p-value:** 0.03

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hobel et al., 1994 (continued)	**Black** **G1:** 8.1 **G2:** 8.5 **Asian** **G1:** 4.8 **G2:** 1.4 **Parity, mean ± SD:** **G1:** 1.5 ± 1.7 **G2:** 1.7 ± 1.8 **Gravidity, mean ± SD:** **G1:** 2.4 ± 2.0 **G2:** 2.6 ± 2.1 **Maternal education, %:** **Less than high school** **G1:** 65.2 **G2:** 73.5 **High school or more** **G1:** 34.8 **G2:** 26.5 **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** < 10%* **Private insurance:** < 10%*	**Inclusion criteria: (continued)** English or Spanish speaking **Exclusion criteria:** Cardiac disease Hyperthyroidism Diabetes Asthma (on medication) Seizures or epilepsy Drug sensitivity to Provera Hx of deep vein thrombosis or thromboembolic disorders Liver disease Malignancy of breast or genital organs Disability impeding one to follow directions Attempted suicide (during current pregnancy) **Excluded from randomized analysis:** Pregnancies after 1986 Pregnancies aborted at < 20 wks gestation Pregnancies that resulted in stillbirths or major congenital anomalies Multiple gestations			Parity, n (mean ± s.d.); p-value: **G1:** Preterm: 131 (1.6 ± 1.7) **Term:** 1642 (1.5 ± 1.6) **p-value:** 0.41 **G2:** Preterm: 80 (2.0 ± 1.7) **Term:** 800 (1.7 ± 1.8) **p-value:** 0.10 High-risk problems (No.), n (mean ± s.d.); p-value: **G1:** Preterm: 131 (1.8 ± 1.0) **Term:** 1642 (1.5 ± 0.8) **p-value:** 0.003 **G2:** Preterm: 80 (1.6 ± 0.8) **Term:** 800 (1.4 ± 0.7) **p-value:** 0.10 Race, N (n); p-value: **G1:** Hispanic: 1242 (6.7) **White:** 277(7.2) Black: 141 (14.9) **Asian:** 84 (6.0) **p-value:** 0.01 **G2:** Hispanic: 678 (7.7) **White:** 96 (7.3) Black: 73 (21.9) **Asian:** 12 (16.7) **p-value:** 0.001

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hobel et al., 1994 (continued)					Education, N (n); p-value: **G1:** Less than high school: 1016 (5.8) **High School or More:** 543 (9.6) **p-value:** 0.01 **G2:** Less than high school: 559 (7.0) **High School or More:** 201 (11.9) **p-value:** 0.03 **Program impact on risk of PTB:** SE = 0.15 OR: 0.78 (95% CI: 0.58 to 1.04) *P* = 0.045 **Incidence of PTB among secondary prophylaxis groups, n (%):** **G1a:** 422 (9.7) **G1b:** 432 (7.9) *G1a/b:P* = 0.20 **G1c:** 407 (9.1) *G1a/c: P* = 0.42 **G1d:** 412 (7.3) **G1e:** 411 (11.2) *G1a/e: P* = 0.98 **Birth weight**: NR **GA at birth:** NR **Mode of birth and Complications during birth** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: How et al., 2007 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 02/2004 to 03/2006 **Funding:** NR **Author Industry Relationship Disclosure:** 3 of 5 Matria (3) **Design:** Retrospective cohort	**Intervention:** Weekly IM 17OHP injections w/ nursing assessment **Groups:** **G1:** 17OHP initiated at GA wk 16-20.9 **G1a:** 17OHP initiated at GA wk 16-20.9 w/ 1 PPTB **G1b:** 17OHP initiated at GA wk 16-20.9 w/ 2 PPTB **G1c:** 17OHP initiated at GA wk 16-20.9 w/ >2 PPTB **G2:** 17OHP initiated at GA wk 21-26.9 **G2a:** 17OHP initiated at GA wk 21-26.9 w/ 1 PPTB **G2b:** 17OHP initiated at GA wk 21-26.9 w/ 2 PPTB **G2c:** 17OHP initiated at GA wk 21-26.9 w/ >2 PPTB **N at enrollment:** **G1**: 599 **G2**: 307 **N at birth:** **G1**: 599 **G1a:** 440 **G1b:** 113 **G1**c: 46 **G2**: 307 **G2a:** 192 **G2b:** 82 **G2c:** 33	**Inclusion criteria:** Single gestation history of ≥ 1 PPTB No PTL symptoms or diagnosis at 16.0-26.9 wks gestation **Exclusion criteria:** Cervical cerclage Withdrawal from the program after receiving only the initial test injection	**Prior PTB, n (%):** **G1**: 599 (100) **G2**: 307 (100) **>1 PPTB, %:** **G1:** 26.5 **G2:** 37.5 Previous term delivery, %: **G1**a: 24.9 **G1b:** 27.4 **Multiple gestation:** NA **Fetal fibronectin, baseline:** NR **Cerclage:** NA **Cervical length, baseline:** NR **GA of prior PTB:** NR **PPROM:** NR	**GA at start of 17OHP, mean wks ± SD:** **G1:** 17.9 ± 1.5 **G2:** 23.4 ± 1.7 **N of 17OHP injections, mean ± SD:** **G1:** 16.0 ± 4.4 **G2:** 10.8 ± 3.3	**Complications during pregnancy** **Tocolysis, %:** **G1:** 11.7 **G2:** 10.1 *P* = 0.543 **Prematurity** **Birth weight**: NR **Delivery < 37 wk, %:** **G1**: 41.9 **G1a:** 37.0 **G1b:** 51.3 **G1**c: 65.2 **G2**: 42.0 **G2a:** 41.1 **G2b:** 43.9 **G2c:** 42.4 **G1/ G2:** *P* = 0.973 **G1a/ G2a:** *P* = 0.329 **G1b/ G2b:** *P* = 0.314 **G1c/G2c:** *P* = 0.066 **SPTB< 32 wk, %:** **G1**: 5.8 **G1a:** 4.8 **G1b:** 9.7 **G1**c: 6.5 **G2**: 4.2 **G2a:** 2.6 **G2b:** 2.4 **G2c:** 18.2 **G1/ G2:** *P* = 0.306 **G1a/ G2a:** *P* = 0.296 **G1b/ G2b:** *P* = 0.077 **G1c/G2c:** *P* = 0.154 **G2**a/**G2**b/**G2**c: *P* < 0.05

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
How et al., 2007 (continued)	**N at follow-up:** **G1**: 599 **G1a:** 440 **G1b:** 113 **G1**c: 46 **G2: 307** **G2a:** 192 **G2b:** 82 **G2c:** 33 **Age, mean yrs ± SD:** **G1**a: 29.6 ± 5.5 **G1**b: 29.1 ± 5.7 **Age, median years (range):** **G1a:** 29 (16, 44) **G1b:** 29 (17, 43) **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal smoking, %:** **G1a**: 6.7 **G1b**: 11.4 **Maternal BMI <20, %:** **G1a**: 14.5 **G1b:** 16.0 **Maternal BMI ≥30, % :** **G1a:** 26.2 **G1b:** 17.8 **Medicaid, n (%):** NR **Private insurance, n (%):** NR				**SPTB< 35 wk, %:** **G1**: 15.7 **G1a:** 12.3 **G1b:** 26.5 **G1**c: 21.7 **G2**: 16.6 **G2a:** 15.1 **G2b:** 14.6 **G2c:** 30.3 **G1/ G2:** *P* = 0.721 **G1a/ G2a:** *P* = 0.332 **G1b/ G2b:** *P* = 0.053 **G1c/G2c:** *P* = 0.438 **G1**a/**G1**b/**G1**c: *P* < 0.05 **G2**a/**G2**b/**G2**c: *P* < 0.05 **SPTB< 37 wk, %:** **G1**: 32.7 **G1a:** 27.0 **G1b:** 244.2 **G1**c: 58.7 **G2**: 35.8 **G2a:** 33.9 **G2b:** 39.0 **G2c:** 39.4 **G1/ G2:** *P* = 0.349 **G1a/ G2a:** *P* = 0.083 **G1b/ G2b:** *P* = 0.557 **G1c/G2c:** *P* = 0.113 **Mode of birth and complications during birth** **Stillbirths, n (%):** **G1:** 3 (0.5) **G2:** 2 (0.65)*

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
How et al., 2007 (continued)					**Postpartum and neonatal complications** **Neonatal deaths, n:** **G1:** 3 (0.5)* **G2:** 1 (0.33)* **Longer term outcomes** NR

*Calculated by the reviewer

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Health Services	Outcomes
Author: Hui et al., 2007 **Country:** Canada **Participant source:** Community **Intervention setting:** NA (survey) **Enrollment period:** 12/1997 to 05/1998 and 05/2004 to 07/2004 **Funding:** Intramural **Author Industry Relationship Disclosure:** NR **Design:** Retrospective case series stratified by survey response date	**Intervention:** Cross-sectional survey **Groups:** **G1:** First survey **G2:** Second survey **N with complete survey:** **G1**: 458 **G2**: 502 **N at follow-up:** NA **Gender, n (%):** **Male** **G1**: 308 (67.5) **G2:** 275 (55.7) **Female** **G1:** 148 (32.5) **G2**: 219 (44.3) **Age:** NR **Race/ethnicity:** NR **Parity:** NA **Maternal education:** NA **Maternal smoking:** NA **Maternal BMI:** NA **Medicaid:** NR **Private insurance:** NR	**Inclusion criteria:** Practicing ob/gyns from the Canadian Medical Directory Completed full survey **Exclusion criteria:** ○ Duplicate questionnaires • Respondents not practicing obstetrics	**Prior PTB:** NA **Multiple gestation:** NA **Fetal fibronectin, baseline:** NA **Cerclage:** NA **Cervical length, baseline:** NA **Severity of PTB:** NA **Prior PPROM::** NA	**Provider knowledge and attitudes** **Offered drug to woman at high risk, (%):** **G1**: NR **G2**: (7) Refrain from prescribing 17OHP because not convinced by evidence, (%): **G1**: NR **G2**: (70.6) **Willing to participate in large multicenter RCT, (%):** **G1:** NR **G2:** (83.9) **Provider specialty, n (%):** Ob/gyn **G1**: 458 (100) **G2**: 502 (100) **Type of practice, n (%):** **Teaching (community) hospital** **G1:** 220 (48) **G2:** 233 (46.4) **Community hospital only** **G1:** 230 (50.2) **G2:** 257 (51.2)	**Complications during pregnancy** NR **Prematurity** **Birth weight:** NR **GA at birth:** NR **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Health Services	Outcomes
Hui et al., 2007 (continued)				**Residency completion yr range, n (%):** **1995-2005** **G1:** 66 (14.5) **G2:** 182 (36.7) **1980-1994** **G1:** 243 (53.3) **G2:** 212 (42.7) **Before 1980** **G1:** 147 (32.2) **G2:** 102 (20.6)	

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Johnson et al., 1975 **Country:** US **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** Industry **Author Industry Relationship Disclosure:** NR **Design:** RCT, double blind assignment of medication	**Intervention:** 250 mg/wk of IM 17OHP, begun < 24 wks until wk 37 or birth **Groups:** **G1:** 17OHP **G2:** Placebo (castor oil & 46% benzyl benzoate) **N at enrollment:** **G1**: 23 **G2**: 27 **N at birth:** **G1**: 18 **G2**: 25 **N at follow-up:** **G1**: 18 **G2**: 25 **Age, mean yrs ± SD:** **G1**: 24.7 ± 5.4 **G2**: 24.3 ± 6.0 **Race/ethnicity, n %:** Black **G1:** 13 (72) **G2:** 21 (84) **Parous, living infant, mean ± SD:** **G1**: 1.5 ± 1.4 **G2**: 1.4 ± 1.3 **Maternal education:** NR	**Inclusion criteria:** 2 spontaneous abortions immediately preceding present pregnancy or 1 *premature birth and 1 spontaneous abortion immediately preceding present pregnancy or ≥ 2 premature births **Exclusion criteria:** Received < 3 doses of medication Received medication < 50% of prescribed time Did not have viable intrauterine pregnancy Failure to enter the study prior to 24 wks gestation	**Prior premature birth, mean ± SD*:** **G1**: 1.9 ± 1.3 **G2**: 1.7 ± 1.5 **Prior abortion, mean ± SD:** **G1**: 0.9 ± 0.9 **G2**: 1.7 ± 2.0 **Multiple gestation, n (%):** Twins **G1**: 0 (0) **G2**†: 1 (4) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1****: 4 (22) **G2**: 3 (12) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at initiation, mean wks ± SD:** **G1:** 16.7 ± 4.4 **G2:** 14.0 ± 3.8 *P* < 0.025 **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug, n (%):** **Free** **G1**: 0 (0) **G2**: 0 (0) **Drug availability, n (%):** **G1**: 23 (100) **G2**: 0 (0)	**Complications during pregnancy** **Tocolytic (Isoxsuprine) administration, n (%):** **G1:** 2 (11) **G2:** 2 (8) **IUFD, n (%):** **G1:** 0 (0) **G2‡:** 5 (19.2) *P* < 0.05 **Prematurity** **Premature infants, n (%)*:** **G1:** 0 (0) **G2:** 11 **(**44) *P* < 0.01 **Birth weight >2501g, n (%)**: **G1**: 14 (77.8) **G2**: 15 (57.7) **Birth weight, mean g ± SD:** **G1:** 2,836 ± 412 **G2:** 2,361 ± 1,085 *P* < 0.025 **GA at birth >35 wks, n (%):** **G1**: 18 (100) **G2**: 16 (64) **GA at birth, mean wks ± SD:** **G1:** 38.6 ± 1.4 **G2:** 35.2 ± 6.2 *P* < 0.025 **Mode of birth and complications during birth** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Johnson et al., 1975 (continued)	**Maternal smoking, %:** **Nonsmoker** **G1**: 28 **G2**: 59 **<1 package/d** **G1:** 36 **G2:** 27 **1-2 packages/d** **G1:** 21 **G2:** 14 **>2 packages/d** **G1:** 15 **G2:** 0 **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR				**Postpartum and neonatal complications**‡ **Perinatal mortality, n (%)** **G1:** 0 (0) **G2:** 7 (27) *P* < 0.05 **Neonatal death, n (%):** **G1:** 0 (0) **G2:** 2 (7.7) **Longer term outcomes** NR

*Premature birth defined as birth weight < 2,501g or GA at birth < 36wks
†G2 twin deaths excluded from analysis; ‡perinatal and neonatal data includes twins in total infant count, G2: 26
**Reported in text as G1: 27%

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Johnson et al., 1979 **Country:** US **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** NIH **Author Industry Relationship Disclosure:** NR **Design:** Prospective cohort	**Intervention:** 250 mg/week of IM 17OHP begun at 16 wks gestation until 36 wks or spontaneous labor, whichever occurs first **Groups:** **G1:** Controls **G2**:Treated; birth > 36 wks **G3:** Treated; birth occurred < 36 wks **N at enrollment:** **G1**: 5 **G2**: 6 **G3**: 10 **N at birth*:** **G1**: 5 **G2**: 6 **G3**: 10 **N at follow-up*:** **G1**: 5 **G2**: 6 **G3**: 10 **Age, mean yrs :** NR **Race/ethnicity, n (%):** NR **Parous, n (%):** **G1**: 5 (100) **G2**: 6 (100 **G3**: 10 (100) **Maternal education, n (%):** NR **Maternal smoking, n (%):** NR **Maternal BMI:** NR	**Inclusion criteria:** Treatment (high risk): ≥2 PPTB or ≥2 previous spontaneous miscarriages, or 1 miscarriage and 1 PTB directly preceding existing pregnancy Control (low risk): ≥2 previous term pregnancies without any preceding PTB or spontaneous miscarriages **Exclusion criteria:** See Inclusion criteria	**Prior PTB:** NR **Multiple gestation:** **G1**: 0 (0) **G2**: 0 (0) **G3**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Provider knowledge and attitudes:** NR **Provider specialty, n (%):** Ob/Gyn **G1**: 5 (100) **G2**: 6 (100 **G3**: 10 (100) **Cost of drug:** NR **Drug availability, n (%):** **G1**: 0 (0) **G2**: 6 (100 **G3**: 10 (100)	**Complications during pregnancy** NR **Prematurity** **Birth weight, mean g ± SD**: **G1**: 2950±221 **G2**: 2937±63 **G3:** 1056±203 **GA at birth, mean wks ± SD:** **G1**: 38.8±0.7 **G2**: 38.5±0.4 **G3:** 26.1±1.7 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **Congential Anomalies, n (%)**: **G1**: 0 (0) **G2**: 0 (0) **G3:** 0 (0) **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Johnson et al., 1979 (continued)	**Medicaid:** NR **Private insurance:** NR				

*Perinatal mortality data was not used because of unclear group association

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Joy et al., 2010 **Country:** US **Participant source:** Database (Alera, formerly Matria) **Intervention setting:** Clinics **Enrollment period:** April 2004 to January 2007 **Funding:** NA **Author Industry Relationship Disclosure:** NR **Design:** Retrospective cohort	**Intervention:** 250mg of IM 17P weekly until 36 completed weeks or preterm delivery **Groups:** **G1a:** 17P and PTL diagnosed at <34 wks **G1b:** 17P and no PTL **N at enrollment:** 1,177 **N at birth:** **G1a**: 270 **G1b**: 660 (additional 257 with preterm labor at 34 – 36 weeks excluded from analysis) **N at follow-up:** NA **Age, yrs ± SD:** **G1a**: 29.6 ± 5.6 **G1b**: 29.9 ± 5.3 **Race/ethnicity, %:** Black: **G1a**: 19.6 **G1b**: 22.0 **Parous, n (%):** 1,177 (100) **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, %:** **G1a**: 10.0 **G1b**: 9.2	**Inclusion criteria:** Current singleton pregnancy enrolled in an outpatient 17P administration program between 16.0 and 26.9 wks of gestation At least one prior spontaneous preterm delivery at <37 wks gestation **Exclusion criteria:** A diagnosis of preterm labor or suspected preterm labor at initiation of 17P	**Prior PTB, n (%):** 1 Prior PTB: **G1a**: 175 (64.8(**G1b**: 489 (74.1) >1 Prior PTB: **G1a:** 95 (35.2) **G1b:** 171 (25.9) **Multiple gestation, n (%):** 0 **Fetal fibronectin, baseline:** NR **Cerclage, %:** **G1a**: 18.9 **G1b**: 16.1 **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**GA at onset of 17P treatment, wks ± SD:** **G1a:** 19.4 ± 2.9 **G1b:** 19.5 ± 3.1 **17P treatment started between wks 21-26.9, %:** **G1a:** 28.5 **G1b:** 31.8 **Compliance with treatment, % :** **G1a:** 90.0 **G1b:** 90.9 **No. weekly 17P injections, mean ± SD:** **G1a:** 12.2 ± 2.0 **G1b:** 15.3 ± 4.6 **Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR	**Complications during pregnancy** NR **Prematurity** **PTB, n (%):** **G1a:** 170 (63.0) **G1b:** NR 17P initiated between 16-20.9 wks, %: 18.7 (n = 643) 17P initiated between 21-26.9 wks, %: 17.4 (n = 287) **Birth weight**: NR **GA at birth, wks ± SD:** **G1a**: 33.9 ± 4.4 **G1b**: 39.0 ± 4.6 *P* < 0.001 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Joy et al., 2010 (continued)	**Medicaid, %:** **G1a**: 27.4 **G1b**: 24.8 **Private insurance coverage:** NR				

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Kauppila et al., 1980 **Country:** Finland **Participant source:** Academic single-site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Non-randomized control trial	**Intervention:** 250mg of IM 17OHP + 100 mg IV bolus cortisol, followed immediately by 150 mg cortisol in 500 ml of 5% glucose over 2hrs; 100 mg IV bolus cortisol on 2nd and 3rd ds at 8AM; 250mg IM 17OHP at 8AM on 3rd d until 37 wks GA **Groups:** **G1:** 17OHP + Cortisol **G2:** Control: Ritodrine (50mg in 500ml of 5% glucose infused at 50 µg/min for 10 min; 50 µg/min at 10 min intervals until uterine relaxation and BP maintained. Lowest effective dose maintained for 48 hrs, followed by IM Ritodrine 20 mg 3x/d for 2 ds) **N at enrollment:** **G1**: 24 **G2**: 24 **N at birth:** **G1**: 24 **G2**: 24 **N at follow-up:** **G1**: 24 **G2**: 24 **Age, mean yrs ± SEM:** **G1**: 25.5 ± 1.1 **G2**: 25.9 ± 1.0	**Inclusion criteria:** Admitted for TPTB at 27 – 36 wks GA **Exclusion criteria:** See inclusion criteria	**Prior PTB:** NR **Multiple gestation, n:** **G1**: 1 **G2**: 0 **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at initiation, mean wks ± SEM*:** **G1**: 33.8 ± 0.4 **G2**: 32.8 ± 0.6 Δ = NS **Co-intervention (Cortisol), n (%):** **G1**: 24 (100) **G2**: 0 (0) **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**Complications during pregnancy** **Tocolysis index, mean±SEM:** **G1**: 3.2 ± 0.3 **G2**: 3.1 ± 0.3 **Pyelonephritis, n:** **G1**: 0 **G2**: 1 **GDM, n:** **G1**: 1 **G2**: 1 **PROM, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Uterine bleeding, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Pre-eclampsia, n:** **G1**: 0 **G2**: 1 **Bronchial asthma, n:** **G1**: 0 **G2**: 1 **Prematurity** ***Birth weight, mean g ± SEM**: **G1**: 3,460 ± 119 **G2**: 3,106 ± 118 *P* < 0.05 **Birth weight, n:** **< 2,500 g** **G1**: 2 **G2:** 3 **2,500 - 2,999 g** **G1**: 4 **G2**: 7 **≥3,000 g** **G1**: 19 **G2**: 14

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kauppila et al., 1980 (continued)	**Race/ethnicity:** NR **Parity, mean ± SEM:** **G1**: 1.8 ± 0.2 **G2**: 1.8 ± 0.2 **Maternal education:** NR **Maternal BMI:** NR **Maternal smoking:** NR **Medicaid:** NR **Private insurance:** NR				***GA at birth, mean wks ± SEM:** **G1**: 39.1 ± 0.3 **G2**: 37.7 ± 0.4 *P* < 0.01 **Prolongation after therapy, mean days ± SEM:** **G1**: 38.1 ± 4.3 **G2**: 35.9 ± 5.7 Δ **=** NS **Prolongation of pregnancy post-admission, n (success rate %):** > 7 days **G1**: 21 (87.5) **G2**: 18 (75) **≤ 7 days** **G1**: 3 **G2**: 6 **≤ 3 days** **G1**: 3 **G2**: 5 **Mode of birth and complications during birth** **Duration of premature labor, mean hrs ± SEM:** **G1**: 5.1 ± 0.4 **G2**: 2.2 ± 0.3 *P* < 0.001 **Apgar score > 7, n:** **G1**: 22 **G2**: 23

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kauppila et al., 1980 (continued)					**Postpartum and neonatal complications** **Transient postpartum asphyxia, n:** **G1**: 0 **G2**: 2 **Mild cerebral lesions, n:** **G1**: 0 **G2**: 1 **Aspiration syndrome, n:** **G1**: 0 **G2**: 1 **Death due to RDS, n:** **G1**: 1 **G2**: 0 **Neonatal neurological disorder, n:** **G1**: 1 **G2**: 0 **Longer term outcomes** NR

*Only analyzed for women with single fetus, G1 = 23 women

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Keeler et al., 2009 **Country:** US **Participant source:** Community **Intervention setting:** Clinic **Enrollment period:** November 2003 to December 2006 **Funding:** Lehigh Valley Hospital **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** 250mg IM 17P weekly until 36 weeks gestation; cerclage removed at 36 weeks or on an emergent basis for those with rupture of membra,s preterm labor placing tension on the cerclage and refractory to tocolytics, PTL with contraindications to tocolytics, clinical diagnosis of chorioamniotis or abruption placentae **Groups:** **G1:** 17P **G2:** McDonald cerclage **N at enrollment:** 91 (79 randomized) **N at birth:** **G1**: 37 **G2**: 42 **N at follow-up:** **G1**: 37 **G2**: 42 **Age, yrs ± SD:** **G1**: 27.6 ± 6.6 **G2**: 29.6 ± 7.2 **Race/ethnicity, n (%):** Caucasian: **G1**: 16 (43.2) **G2**: 18 (42.9) Hispanic: **G1**: 11 (29.7) **G2**: 16 (38.1)	**Inclusion criteria:** Singleton pregnancy with risk factors for spontaneous PTB (history of spontaneous PTB, second-trimester pregnancy loss, previous cervical surgery, documented uterine anomaly) Low-risk, asymptomatic singleton pregnancy between 16 and 24 wks gestation Short cervix (transvaginal CL ≤25mm) **Exclusion criteria:** Any known fetal chromosomal or structural anomaly Multiple gestation Known allergy to progesterone Ruptured membranes Vagina l bleeding Evidence of an active intra-amniotic infection (diagnosed clinically or by amniocentesis)	**Prior PTB, n (%):** 16-23 wks: **G1**: 6 (16.2) **G2**: 9 (21.4) 24-26 wks: **G1:** 11 (29.7) **G2:** 16 (38.1) **Multiple gestation, n (%):** 0 **Positive fetal fibronectin, n (%):** **G1**: 8 (25.0) **G2**: 11 (29.7) n = 69 **Cerclage, n (%):** **G1**: 0 **G2**: 42 (100) **Cervical length, mm ± SD:** **G1**: 16.8 ± 5.1 **G2**: 14.5 ± 6.6 **GA of prior PTB:** Earliest PTB, wks ± SD: **G1:** 25.7 ± 5.4 **G2:** 25.3 ± 5.9 **Prior PPROM, n (%):** NR	**GA at entry, wks ± SD:** **G1:** 20.9 ± 5.9 **G2:** 20.0 ± 6.4 **Days from enrollment to birth, mean ± SD:** **G1**: 84.8 ± 38.6 **G2**: 92.2 ± 40.9 *P*=.41 **Cost of drug, n (%):** NR **Drug availability, n (%):** NR	**Complications during pregnancy** **Chorioamnionitis, n (%):** **G1**: 8 (21.6) **G2**: 12. (28.6) RR G2/G1 (95% CI): 0.76 (0.35, 1.65) **Abruptio placentae, n (%):** **G1**: 6 (17.1) **G2**: 3 (7.5) RR G2/G1 (95% CI): 2.27 (0.61, 8.44) **PPROM, n (%):** **G1**: 13 (37.1) **G2**: 13 (32.5) RR G2/G1 (95% CI): 1.14 (0.61, 2.12) **Prematurity** **PTB <37 wks, cervical length (CL)≤ 25 mm, n (%):** **G1:** 22 (59.4) **G2:** 22 (52.4) RR G2/G1 (95% CI): 1.14 (0.77, 1.68) **PTB <35 wks, CL≤ 25 mm, n (%):** **G1:** 16 (43.2) **G2:** 16 (38.1) RR G2/G1 (95% CI): 1.14 (0.67, 1.93) **PTB <32 wks, CL≤ 25 mm, n (%):** **G1:** 13 (35.1) **G2:** 15 (35.7) RR G2/G1 (95% CI) 0.98 (0.54, 1.79)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Keeler et al., 2009 (continued)	African American: **G1**: 9 (24.3) **G2**: 7 (16.7) Other: **G1**: 1 (2.7) **G2**: 1 (2.4) **Parous, n (%):** **G1**: 22 (59.5) **G2**: 29 (69.0) **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NR **Private insurance coverage, n (%):** **G1**: 15 (40.5) **G2**: 16 (38.1)	**Exclusion criteria (continued):** Prolapse of endocervical membranes beyond the external cervical os Persistent uterine activity accompanied by cervical change An obstetrically indicated delivery			**PTB <28 wks, CL≤ 25 mm, n (%):** **G1:** 7 (18.9) **G2:** 10 (23.8) RR G2/G1 (95% CI) 0.79 (0.34, 1.88) **PTB <24 wks, CL≤ 25 mm, n (%):** **G1:** 3 (8.1) **G2:** 5 (11.9) RR G2/G1 (95% CI) 0.68 (0.17, 2.66) **PTB <37 weeks, CL≤15mm, n (%):** **G1:** 13 (86.7) **G2:** 10 (45.5) RR G2/G1 (95% CI) 0.52 (0.32, 0.86) **PTB <35 weeks, CL≤15mm, n (%):** **G1:** 10 (66.7) **G2:** 7 (31.8) RR G2/G1 (95% CI) 0.48 (0.24, 0.97) **PTB <32 weeks, CL≤15mm, n (%):** **G1:** 8 (53.3) **G2:** 7 (31.8) RR G2/G1 (95% CI) 0.60 (0.27, 1.29) **PTB <28 weeks, CL<15mm, n (%):** **G1: 5 (33.3)** **G2:** 5 (22.7) RR G2/G1 (95% CI) 0.68 (0.24, 1.95)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Keeler et al., 2009 (continued)					**PTB <24 weeks, CL≤15mm, n (%):** **G1:** 3 (20.0) **G2:** 3 (13.6) RR G2/G1 (95% CI): 0.68 (0.17, 2.75) **GA at birth, wks ± SD:** **G1**: 33.0 ± 5.9 **G2**: 32.9 ± 6.4 *P*=.96 **Mode of birth and complications during birth** **Rescue procedure, n (%):** **G1**: 5 (13.5) **G2**: 4 (9.5) RR G2/G1 (95% CI): 1.42 (0.41, 4.89) **Postpartum and neonatal complications** **Neonatal morbidities, n (%):** None: **G1**: 21 (56.8) **G2**: 28 (66.7) Mild: **G1:** 5 (13.5) **G2:** 1 (2.3) Severe: **G1:** 7 (18.9) **G2:** 9 (21.4) **Neonatal death, n (%):** **G1:** 4 (10.8) **G2:** 5 (11.9) **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Kester et al., 1980 See Kester et al., 1984 **Country:** US **Participant source:** Academic single site **Intervention setting:** NA (participants were located from records via private clinic) **Enrollment period:** NR **Funding:** NIH **Author Industry Relationship Disclosure:** NR **Design:** Retrospective case series	**Intervention:** DES, Natural progesterone, synthetic progesterone **Groups:** **G1:** DES **G2:** DES & Natural progesterone **G3:** Natural progesterone **G4:** Synthetic progesterone **G5:** Matched controls not exposed to exogenous pregnancy hormones in utero **N at enrollment:** **G1**: 17 **G2**: 22 **G3:** 10 **G4:** 13 **G5:** NR **N at birth:** NR **N at follow-up:** NR **Age, mean yrs :** 18-30 **G1**: 25.6 **G5:** 26 **24-29** **G2:** 25.8 **G5:** 26 **19-24** **G3:** 20.5 **G5:** 20.9 **19-24** **G4:** 21.5 **G5:** 21.8 **Race/ethnicity:** NR **Parous:** NR	**Inclusion criteria:** Males exposed in utero to stilbestrol and/or a progestational compound between 1945 and 1957 **Exclusion criteria:** See inclusion criteria	**Prior PTB:** NR **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Treatment dosage, mean mg (range;median):** **DES** 3,979 (50-14,000; 1,055) **DES & natural progesterone** (DES) 1,075 (56 - 14,315; 366) (Natural progesterone) 761 (100-1,890; 370) **Natural progesterone dosage** 713 (25-1,955; 423) **Synthetic progesterone dosage** 865 (125-2,198; 822) **Treatment duration, mean wks (range; median):** **DES** 13.5 (0.5-29.0; 10.0) **DES and natural progesterone** 20.0 (2.0-32.0; 23.5) **Natural progesterone** 16.0 (0.5-34.0; 12.5) **Synthetic progesterone** 16.0 (2.0-28.0; 14.5) **Provider knowledge and attitudes:** NR	**Complications during pregnancy** NR **Prematurity** **Birth weight**: NR **GA at birth:** NR **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** **Subjects' educational achievement, (%):** High school **G1**: (0) **G5:** (0) **G2:** (5) **G5:** (0) **G3:** (10) **G5:** (0) **G4:** (0) **G5:** (0) **High school graduate:** **G1**: 7 **G5:** 21 **G2:** 5 **G5:** 10

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)	**Maternal education:** NR **Maternal smoking:** NR Maternal BMI: NR **Medicaid:** NR **Private insurance:** NR			**Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**G3:** 0 **G5:** 10 **G4:** 23 **G5:** 23 **Some college:** **G1**: 21 **G5**: 28 **G2**: 21 **G5**: 42 **G3**: 60 **G5:** 70 **G4:** 54 **G5:** 46 **College graduate:** **G1**: 50 **G5:** 14 **G2:** 47 **G5:** 21 **G3:** 10 **G5:** 20 **G4:** 15 **G5:** 23 **Professional training:** **G1**: 21 **G5:** 36 **G2:** 21 **G5:** 26 **G3:** 20 **G5:** 0 **G4:** 8 **G5:** 8 **Subjects' occupation, (%):** Professional/ managerial **G1**: **(**50**)** **G5:** (43)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**G2:** (61) **G5:** (39) **G3:** (10) **G5:** (10) **G4:** (0) **G5:** (25) **Clerical/sales** **G1**: (7) **G5:** (7) **G2:** (11) **G5:** (28) **G3:** (0) **G5:** (10) **G4:** (33) **G5:** (17) **Skilled labor** **G1**: (28) **G5:** (43) **G2:** (22) **G5:** (17) **G3:** (20) **G5:** (10) **G4:** (33) **G5:** (42) **Unskilled labor** **G1**: (0) **G5:** (0) **G2:** (0) **G5:** (0) **G3:** (0) **G5:** (0) **G4:** (0) **G5:** (0) **Student** **G1**: (14) **G5:** (7)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**G2:** (5) **G5:** (17) **G3:** (70) **G5:** (70) **G4:** (33) **G5:** (17) **P-values:** **G1: DES** **Bem Sex-Role Inventory Feminine Scale:** Subjects exposed in first trimester having higher scores vs. those not exposed in first trimester: p < 0.1 Subjects exposed in first trimester having higher scores vs. those initially exposed later: p < 0.1 **Strong Vocational Interest Blank:** Subjects exposed in first trimester having higher scores on technical supervisor: p<0.01 Subjects exposed in first trimester having higher scores on social service: p <0.01 Subjects exposed in first trimester having higher scores on writing: p <0.01

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Subjects exposed in first trimester having higher scores on academic achievement: p <0.05 Subjects exposed to drug being more extroverted: p <0.05Subjects exposed in first trimester being more extroverted: p <0.01 **Boyhood:** Drug-exposed subjects dressing in girl's clothes less often vs. controls: p <0.05 Drug-exposed in first trimester subjects dressing in girl's clothes less often vs. controls: p < 0.05 Drug-exposed subjects having more boys as friends than girls vs. controls: p < 0.10 Drug-exposed in first trimester subjects having more boys as friends than girls vs. controls: p < 0.05 Drug-exposed subjects more often reading books with male main characters vs. controls: p < 0.1

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Drug-exposed subjects fighting less vs. controls: $p < 0.05$ Drug-exposed subjects having less interest in 'girl-type' toys and activities vs. controls: $p < 0.05$ **Adolescence:** Hormone-exposed in first trimester subjects more interested in sports vs. controls: $p < 0.05$ Drug-exposed subject's recalling first nocturnal emission earlier vs. controls: $p < 0.1$ **Adulthood:** Drug-exposed subjects reading material with male main characters vs. controls: $p < 0.1$ Drug-exposed subjects preferring TV shows with more aggressive themes vs. controls: $p < 0.1$

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**G2: DES & natural progesterone Bem Sex-Role Inventory Feminine Scale:** Hormone exposed subjects having higher scores vs. those not exposed in first trimester: $p < 0.1$ Hormone exposed in first trimester subjects having higher scores vs. those not exposed in first trimester: $p < 0.1$ **Guilford-Zimmerman Temperament Survey:** Drug-exposed subjects scoring higher reflective vs. unreflective scale: $p < 0.05$ Drug-exposed not in first trimester subjects scoring higher reflective vs. unreflective scale: $p < 0.05$ Drug-exposed subjects scoring more on masculinity-femininity scale: $p < 0.1$ Drug-exposed not in second trimester subjects scoring more on masculinity-femininity scale: $p < 0.05$

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**Strong Vocational Interest Blank:** Drug-exposed subjects scoring higher on mathematics scale: p <0.05 Drug-exposed after first trimester subjects scoring higher on office practice scale: p <0.1 Not drug-exposed in first trimester subjects scoring higher on military activities vs. those exposed in first trimester and controls: p < 0.01 **Boyhood:** Drug-exposed subjects tending to have favorite games that are non-contact in nature: p < 0.1 Drug-exposed not in first trimester more interested in competitive non-contact sports vs. controls or those exposed in first trimester: p < 0.1 Drug-exposed subjects more interested in individual competitive non-contact sports: p < 0.05

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Drug-exposed not in first trimester more interested individual competitive non-contact sports: p <0.01 Drug-exposed not in first trimester more interested in sedentary games vs. those exposed in first trimester and controls: p < 0.01 Drug-exposed subjects participating less in sports: p < 0.01 Drug-exposed subjects often being spectators of sports vs. controls: p < 0.05 **Adolescence:** Drug-exposed after first trimester more interested in sports vs. other subjects and controls: p < 0.1 Drug-exposed after first trimester more interested in team competitive, non-contact sports vs. subjects and controls: p < 0.1 Drug-exposed after first trimester more interested in non-athletic games vs. subjects and controls: p < 0.01

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Drug-exposed after first trimester subject's recalling earlier onset of nocturnal emission vs. controls: p <0.1 Drug-exposed in first trimester subjects younger at initial intercourse experience: p <0.05 **Adulthood:** Drug-exposed in first trimester tending to participate less in sports: p < 0.1 Drug-exposed in first trimester tending to watch individual, competitive, contact sports more: p < 0.1 Drug-exposed subjects having higher sex drive vs. controls: p < 0.01 Drug-exposed in first trimester subjects in having higher sex drive vs. controls: p < 0.01 **G3: Natural progesterone** **Bem Sex-Role Inventory Masculine Scale:** Hormone-exposed subjects scoring lower: p < 0.1

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Hormone-exposed subjects with higher dosages scoring lower: p < 0.005 **Bem Sex-Role Inventory Feminine Scale:** Subjects exposed to higher dosages of hormones scoring lower: p < 0.05 **Guilford-Zimmerman Temperament Survey:** Subjects exposed in second trimester scoring lower on activity than other hormone exposed or control subjects: p <0.01 **Masculinity-Femininity Scale:** Subjects exposed in third trimester scoring more feminine vs. other hormone exposed or control subjects: p < 0.05 **Strong Vocational Interest Blank** Hormone exposed subjects scoring higher on law and politics: p < 0.1 Hormone exposed subjects scoring lower on technical supervisor: p < 0.05

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Hormone exposed after first trimester scoring lower on science scale: p < 0.1 Hormone exposed in second trimester scoring lower on mechanical scale vs. other hormone exposed or control subjects: p <0.05 Hormone exposed subjects scoring lower on medical service: p < 0.1 **Boyhood:** Hormone exposed in second trimester subjects tending to be more sports spectators vs. other hormone exposed or control subjects: p < 0.1 Hormone exposed in first trimester tending to prefer stories with male main characters vs. other hormone exposed or control subjects: p < 0.1 Hormone exposed subjects preferring stores with more aggressive themes: p < 0.05 Hormone exposed in first trimester subjects preferring stores with more aggressive themes: p < 0.05

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**Adolescence:** Hormone exposed subjects recalling later onset of nocturnal emissions: $p < 0.1$ Hormone exposed in first trimester subjects recalling later onset of nocturnal emissions: $p < 0.1$ **Adulthood:** Hormone exposed subjects participating more in sports: $p < 0.1$ Hormone exposed subjects being less interested in team competitive contact sports: $p < 0.1$ Hormone exposed subjects watching individual competitive contact sports less: $p < 0.01$ Hormone exposed after first trimester subjects watching individual competitive contact sports less: $p < 0.05$ Hormone exposed subjects tending to prefer stories with female main characters: $p < 0.1$ Hormone-exposed subjects tending to report more frequent nocturnal emissions: $p < 0.1$

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Higher dosage Hormone-exposed subjects tending to report higher frequency of more frequent nocturnal emissions: $p < 0.001$ Higher dosage hormone-exposed subjects reporting difficulty to keep and erection: $p < 0.05$ **G4: Synthetic progesterone** **Bem Sex-Role Inventory Masculine Scale:** Subjects with later initial drug administration have higher scores on Masculine scale vs. subjects exposed to hormone in first trimester: $p < 0.1$ **Bem Sex-Role Inventory Feminine Scale:** Hormone-exposed subjects score higher: $p < 0.1$ Hormone-exposed after first trimester score higher: $p < 0.05$) Hormone-exposed after third trimester subjects scored most feminine: $p < 0.05$

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**Strong Vocational Interest Blank:** Drug-exposed subjects score high on technical supervisor scale: $p < 0.05$ Drug-exposed subjects score high on social scale: $p < 0.05$ Drug-exposed after first trimester subjects score high on social scale: $p < 0.1$ **Boyhood:** Drug-exposed subjects after first trimester have more girls as best friends vs. other drug exposed or control subjects: $p < 0.01$ Drug-exposed after third trimester prefer girls as playmates more than other drug-exposed or control subjects: $p < 0.05$ Drug-exposed subjects have more girls as friends vs. controls: $p < 0.1$ **Adolescence:** Drug-exposed subjects were more interested in team, competitive, contact sports: $p < 0.05$

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Drug-exposed after first trimester subjects were more interested in team, competitive, contact sports: p< 0.05 Higher dosage subjects had increasing interest in individual, competitive, non-contact sports: p <0.05 Drug-exposed subjects had a greater interest in participating in sports: p < 0.05 Drug-exposed after third trimester subjects had a greater interest in participating in sports: p < 0.01 Drug-exposed subjects learn about masturbation later: p < 0.05 Drug-exposed after third trimester subjects learn about masturbation later: p < 0.05 Drug-exposed subjects tended to masturbate less often: p <0.1 Drug-exposed after first trimester subjects tended to masturbate less often: p <0.05

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					Drug-exposed subjects tend to recall being older when first learning about nocturnal emissions: $p < 0.1$ Drug-exposed after first trimester subjects tend to have more nocturnal emissions: $p < 0.1$ **Adulthood:** Hormone-exposed subjects like watching team competitive contact sports: $p < 0.05$ Hormone-exposed after first trimester subjects watch sports vs. other drug exposed or control subjects: $p < 0.05$ Drug-exposed subjects report fewer disappointments when asked to rate sex life: $p < 0.05$ Drug-exposed after first trimester subjects rate sex drive as lower vs. other drug-exposed or control subjects: $p < 0.05$

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**Sexual Orientation and Drug Regimen, n:** **Fantasy** **Exclusively heterosexual** **G1:** 13 **G5:** 13 **G2:** 15 **G5:** 14 **G3:** 6 **G5:** 3 **G4:** 10 **G5:** 11 **Predominately heterosexual** **G1:** 3 **G5:** 2 **G2:** 4 **G5:** 2 **G3:** 1 **G5:** 1 **G4:** 1 **G5:** 1 **Ambisexual** **G1:** 1 **G5:** 1 **G2:** 1 **G5:** 5 **G3:** 3 **G5:** 1 **G4:** 1 **G5:** NR **Predominantly homosexual** **G1:** NR **G5:** NR **G2:** NR **G5:** NR **G3:** NR **G5:** NR **G4:** 1 **G5:** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**Exclusively homosexual** **G1:** NR **G5:** NR **G2:** 1 **G5:** NR **G3:** NR **G5:** NR **G4:** NR **G5:** 1 **Behavior: Exclusively heterosexual** **G1:** 15 **G5:** 16 **G2:** 20 **G5:** 16 **G3:** 8 **G5:** 9 **G4:** 12 **G5:** 12 **Predominately heterosexual** **G1:** NR **G5:** NR **G2:** NR **G5:** 3 **G3:** 2 **G5:** 1 **G4:** NR **G5:** NR **Ambisexual** **G1:** 1 **G5:** NR **G2:** NR **G5:** 1 **G3:** NR **G5:** NR **G4:** NR **G5:** NR **Predominantly homosexual** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**Exclusively heterosexual** **G1:** NR **G5:** NR **G2:** 1 **G5:** NR **G3:** NR **G5:** NR **G4:** 1 **G5:** 1

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Kester et al., 1984 See Kester et al., 1980 **Country:** US **Participant source:** Community **Intervention setting:** Home **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Retrospective cohort	**Intervention:** Delalutin (17-alpha-hydroxyprogesterone caproate), usually administered at 250 mg IM once weekly; adjustments included extra dose or doses at beginning of treatment, break in regime for 4-6 weeks, and administration every 2 weeks. **Groups:** **G1:** Males whose mothers took Delalutin and no other exogenous sex hormones during pregnancy **G2:** Matched control males whose mothers did not receive exogenous sex hormones during pregnancy **N at enrollment:** **G1**: 25 **G2**: 25 **N at birth:** **G1**: 25 **G2**: 25 **N at follow-up:** **G1**: 25 **G2**: 25 **Age of child at study, mean yrs (range):** **G1**: 15.3 (12-18) **G2**: 15.4 (12-18)	**Inclusion criteria:** **G1** Males with prenatal exposure to Delalutin and no other exogenous sex hormone between 1957 and 1963 **G2** Males not exposed to exogenous sex steroids *in utero*, matched to **G1** males by race, date of birth, age of mother at son's birth; 14 controls also matched by number of siblings in family. When possible, also matched for problems during pregnancy (e.g. breakthrough bleeding, prior abortions) **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR **Duration of Delalutin therapy, mean weeks (range; median)** **G1:** 21.48 (1-36; 16) **G2:** NA **Total dosage of Delalutin, mean mg (range; median):** **G1**: 4098.00 (250-12,500; 3750) **G2**: NA **Gestation period at Delalutin initiation, mean months (range; median)**: **G1**: 2.84 (1-6; 2) **G2**: NA	**<u>Complications during pregnancy</u>** **Acute appendicitis, n:** **G1:** 0 **G2:** 1 **Prenatal bleeding, n:** **G1:** 9 **G2:** 4 **<u>Prematurity</u>** **Birth weight, mean ounces ± SD (range)**: **G1**: 108.4±15.0 (78-122) **G2**: 124.6±15.4 (100-164) P<.001 **GA at birth:** NR **<u>Mode of birth and complications during birth</u>** **Cesarean birth, n:** **G1**: 3 **G2**: 1 **Artificial rupture of membranes, n:** **G1:** 0 **G2:** 2 **Breech, n:** **G1:** 1 **G2:** 2 **Induced labor, n:** **G1:** 1 **G2:** 1 **Premature delivery, n:** **G1:** 0 **G2:** 1

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1984 (continued)	**Race/ethnicity, n (%):** Caucasion: 50 (100) **Parous, n (%):** NR **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Mother overweight during pregnancy, n:** **G1:** 1 **G2:** 1 **Maternal smoking, n (%):** NR **Medicaid:** NR **Private insurance coverage:** NR				**Surgical complications, n (%): NR** **Maternal harms, n (%):** NR **Postpartum and neonatal complications** **Postpartum hemorrhage, n (%):** NR IVH, **n (%):** NR **Infections, n (%):** NR **Sepsis, n (%):** NR **Birth abnormalities, n:** **Lop ears:** **G1:** 1 **G2:** 0 **Accessory digit on the hand:** **G1:** 1 **G2:** 0 **Hydrocele:** **G1:** 1 **G2:** 0 **Inguinal hernia:** **G1:** 0 **G2:** 1 **Hypospadias:** **G1:** 0 **G2:** 1 **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Majhi et al., 2009 **Country:** India **Participant source:** Academic single site **Intervention setting:** Home **Enrollment period:** December 2004 to February 2006 **Funding:** NR **Author Industry Relationship Disclosure:** None **Design:** RCT	**Intervention:** 100 mg capsule of micronized natural progesterone intravaginally once daily starting at 20-24 weeks until 36 weeks gestation or delivery, whichever earlier **Groups:** **G1:** intervention **G1**a: intervention; previous PTB GA 20-29 wks **G1**b: intervention; previous PTB GA 30-33 wks **G1**c: intervention; previous PTB GA 34-36 wks **G1**d: intervention; 1 previous PTB **G1**e: intervention; >1 previous PTB **G2:** no intervention **G2**a: no intervention; previous PTB GA 20-29 wks **G2**b: no intervention; previous PTB GA 30-33 wks **G2**c: no intervention; previous PTB GA 34-36 wks **G2**d: no intervention; 1 previous PTB **G2**e: no intervention; >1 previous PTB	**Inclusion criteria:** Women at high risk for preterm birth (≥1 spontaneous PTB of singleton infant > 20 and < 37 weeks due to spontaneous labor or preterm rupture of fetal membranes) Singleton pregnancy Current gestation of 16-24 weeks **Exclusion criteria:** Multifetal gestation Congenital malformation in the fetus Current or planned cervical cerclage Any associated medical disorder	**Prior PTL and PTB, n (%):** **G1**: 25 (50) **G2**: 32 (64) **Multiple gestation, n (%):** 0 **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** 0 **Cervical length, baseline:** NR **GA of prior PTB, mean weeks±SD:** **G1**: 30.52±3.3 **G2**: 30.70±3.01 **Prior PPROM and PTB, n (%):** **G1**: 25 (50) **G2**: 18 (36) **GA at enrollment, mean weeks±SD:** **G1**: 20.72±2.1 **G2**: 20.52±2.4	**Provider knowledge and attitudes, n (%):** NA **Provider specialty, n (%):** NA **Cost of drug, n (%):** NA **Drug availability, n (%):** NA	**Complications during pregnancy** **Chorioamnionitis, n (%):** NR **Antenatal hospitalizations, n (%):** **G1**: 1 (2) **G2**: 3 (6) **IUGR, n (%):** NR **Allergic reactions, n (%):** NR **GDM, n (%):** NR **Prematurity** **Birth weight in grams, mean ±SD**: **G1**: 2813±501 **G2**: 2599±421 **GA at birth:** PTB at < 37 weeks, n (%): **G1**: 6 (12) **G2**: 19 (38) P=.00027 **G1**a: 3 (10.7) **G2**a: 13 (48.1) P=.002 **G1**b: 3 (18.7) **G2**b: 4 (22.2) P=.80 **G1**c: 0 **G2**c: 2 (40) P=.08 **G1**d: 5 (11.1) **G2**d: 14 (35.0) P=.008 **G1**e: 1 (20) **G2**e: 5 (50) P=.29

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Majhi et al., 2009 (continued)	**N at enrollment:** **G1**: 50 **G1**a: 28 **G1**b: 16 **G1**c: 6 **G1**d: 45 **G1**e: 5 **G2**: 50 **G2**a: 27 **G2**b: 18 **G2**c: 5 **G2**d: 40 **G2**e: 10 **N at birth:** **G1**: 50 **G1**a: 28 **G1**b: 16 **G1**c: 6 **G1**d: 45 **G1**e: 5 **G2**: 50 **G2**a: 27 **G2**b: 18 **G2**c: 5 **G2**d: 40 **G2**e: 10 **N at follow-up:** **G1**: 50 **G1**a: 28 **G1**b: 16 **G1**c: 6 **G1**d: 45 **G1**e: 5 **G2**: 50 **G2**a: 27 **G2**b: 18 **G2**c: 5 **G2**d: 40 **G2**e: 10 **Age, mean yrs±SD:** **G1**: 26.56±3.5 **G2**: 26.42±3.2 **Race/ethnicity, n (%):** NR				PTB at ≤34 weeks, n (%): **G1**: 2 (4) **G2**: 3 (6) P=.64 **Mode of birth and complications during birth** **Cesarean birth, n (%):** **G1**: 4 (8) **G2**: 7 (14) P=.33 **Surgical complications, n (%):** NR **Maternal harms, n (%):** Mild vaginal discharge and occasional irritation: **G1**: 28% **G2**: NR **Postpartum and neonatal complications** **Postpartum hemorrhage, n (%):** NR **IVH, n (%):** NR **Infections, n (%):** NR **Sepsis, n (%):** **G1**: 0 **G2**: 3 (6) P=.16 **NICU, n (%):** **G1**: 0 **G2**: 4 (8) P=.12

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Majhi et al., 2009 (continued)	**Parity, mean±SD:** **G1**: 2.2±1.2 **G2**: 2.3±1.2 **Maternal education, n (%):** NR **Maternal BMI<19.8 mg/kG2, n (%):** **G1**: 3 (6) **G2**: 2 (4) **Maternal smoking, n (%):** **G1**: 1 (2) **G2**: 0 **Medicaid:** NA **Private insurance coverage:** NR				**Hyperbilirubinemia, n (%):** **G1**: 1 (2) **G2**: 3 (6) P=.30 **Necrotizing enterocolitis, n (%):** **G1**: 0 **G2**: 1 (2) P=.31 **Cord pH, mean±SD:** **G1:** 7.257±0.047 **G2:** 7.262±0.045 P=.57 **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Mason et al., 2005 **Country:** US **Participant source:** Database (Medicaid) **Intervention setting:** Home or Clinic **Enrollment period:** 2004 to 2005 **Funding:** Industry **Author Industry Relationship Disclosure:** 6 of 6 HealthCare USA (6) **Design:** Retrospective cohort study	**Intervention:** 250 mg IM 17OHP administered weekly via guidelines of NICHD 2003 trial by Meis et. al between 16 to 21 wks GA through 36 wks GA or delivery **Groups:** **G1:** 17OHP **G2:** Control **N at enrollment:** **G1**: 24 **G2**: 14 **N at birth:** **G1**: 24 **G2**: 14 **N at follow-up:** **G1**: 23 **G2**: 14 **Age:** NR **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR Maternal BMI: NR **Maternal smoking:** NR **Medicaid, (%):** **G1**: (100) **G2**: (100)	**Inclusion criteria:** **Tx** History of PTD or PTL **Control** Hx of PTB within last 36 ms **Exclusion criteria:** Multi-fetal gestation Known fetal anomaly Progesterone or heparin treatment Current or planned cervical cerclage HTN necessitating medication Seizure disorder	**Prior PTB, (%):** **G1**: (100) **G2**: (100) **Multiple gestation, n:** **G1**: 1 **G2**: NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1:** 0 (0) **G2:** 0 (0) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Adherence, n (%):** **0 doses missed** **G1**: 10 (41.60) **1 dose missed** **G1:** 4 (16.70) **2 doses missed** **G1:** 4 (16.70) **5 doses missed** **G1:** 3 (12.50) **6 doses missed** **G1:** 2 (8.33) **>6 doses missed** **G1:** 1 (4.17) **GA at initiation, wks:** **G1**: 15-33 **Administration timing of 17OHP, n (%):** **16-21 wks GA** **G1**: 15 (62.5) **>20 wks** **G1**: 10 (41.67) **Financial Impact, $ cost:** **G1**: 165,486.75 **G2**: 586,461.78 *P* **=** 0.000 **NICU/SCN delivery adherence, n (%):** **100%** **G1:** 1/5 (20) **NICU/SCN delivery GA at 17OHP initiation, n (%):** **> 20 wks** **G1:** 2/5 (40) **16 wks** **G1:** 2/5 (40)	**Complications during pregnancy** **Allergic reaction at injection site, n (%):** **G1**: 2 **Prematurity** **PTB, n:** **G1**: 5 **G2:** NR **GA at 17OHP initiation for PTB, n (%):** **16-21 wks** **G1**: 3/5 (60) **> 20 wks** †**G1**: 2/5 (20) **Birth weight:** NR **GA at birth:** NR **Mode of birth and complications during birth** **Well delivery at full term, n (%):** **G1**: 19 (79.1) **G2:** 11 (78.6) Δ = NS **NICU/SCN delivery, n:** **G1:** 5 (27.7) **G2:** 3 (21.4) **Postpartum and neonatal complications** **NICU admissions, n (%):** **G1**: 2 (8.33) **G2**: 2 (14.3) Δ **=** NS

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Mason et al., 2005 (continued)	**Private insurance coverage, (%):** **G1**: 0 (0) **G2**: 0 (0)			***Well delivery adherence, n (%):** **90% adherence** **G1:** 13 (72.2) **<90% adherence** **G1:** 5 (27.7) ***Well delivery GA at 17OHP initiation, n (%):** **> 20 wks** **G1:** 9 (50) **< 20 wks** **G1:** 9 (50) **16-20 wks** **G1**: 13 (72.2) **< 16 wks** **G1:** 3 (16.67)	**NICU LOS, ds :** **G1**: 149 **G2**: 231 *P* < 0.000 **SCN, n (%):** **G1**: 3 (12.5) **G2**: 1 (7.1) Δ **=** NS **<u>Longer term outcomes</u>** NR

*Reported in text as 18 well deliveries; shown in outcomes table and outcomes column here as 19 well deliveries
†Twin births included

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Mason et al., 2008 **Country:** US **Participant source:** Database (Medicaid) **Intervention setting:** Clinic and Home **Enrollment period:** 2004 to 2007 **Funding:** NR **Author Industry Relationship Disclosure:** 6 of 6 Centene Corp (5) Quest Alliance Inc (1) **Design:** Retrospective case series	**Intervention:** IM 17OHP every week, begun at 16-21 or 22-34 wks GA **Groups:** **G1a:** IM 17OHP begun 16-21 wks **G1b:** IM 17OHP begun 22-34 wks **G1c:** <5 17OHP injections **G1d:** ≥5 17OHP injections **N at enrollment:** **G1a:** 47 **G1b:** 57 **G1c:** 13 **G1d:** 91 **N at birth:** **G1a:** 47 **G1b:** 57 **G1c:** 13 **G1d:** 91 **N at follow-up:** **G1a:** 47 **G1b:** 57 **G1c:** 13 **G1d:** 91 **Age:** NR **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal BMI:** NR **Maternal smoking:** NR **Medicaid, n (%):** 104 (100)	**Inclusion criteria:** Received 17OHP during pregnancy; History of PTB; Participant in managed Medicaid plan administered by Centene **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** 104 (100) **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cervical length:** NR **Cerclage, n (%):** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Missed doses, n (%):** 24 (2.2) **Members missing doses, n:** 12	**Complications during pregnancy** **Complications associated with drug, n (%):** 0 (0) **Prematurity** **Delivery < 32 wks, n (%):** **G1a:** 12 (25.5) **G1b:** 8 (14) **G1c:** 8 (61.5) **G1d:** 12 (13.1) **G1**a/**G1**b: *P* = NS **G1**c/**G1**d: *P* = 0.000 **Delivery < 37 wks GA, n (%):** **G1a:** 22 (46.8) **G1b:** 27 (47.3) **G1c:** 10 (76.9) **G1d:** 39 (42.8) **G1**a/**G1**b: *P* = NS **G1**c/**G1**d: *P* = 0.021 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **NICU admission, n (%):** **G1a:** 18 (38.2) **G1b:** 18 (31.5) **G1c:** 8 (61.5) **G1d:** 28 (30.7) **G1**a/**G1**b: *P* = NS **G1**c/**G1**d: *P* = 0.029

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Mason et al., 2008 (continued)	**Private insurance:** NA				**Fetal demise, n:** 1 in each category (<32, <37 wks), not reported by group **<u>Longer term outcomes</u>** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Mason et al., 2010 **Country:** US **Participant source:** Database (Medicaid) **Intervention setting:** Clinics **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** 5 of 5 Centene Corp. (5) **Design:** Retrospective cohort	**Intervention:** 17P (dosage NR) **Groups:** **G1:** 17P **G2:** No 17P **N at enrollment:** **G1**: 193 **G2**: 60 **N at birth:** **G1**: 193 **G2**: 60 **N at follow-up:** NA **Age, mean yrs :** NR **Race/ethnicity, n (%):** NR **Parous, n (%):** NR **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid, n (%):** 253 (100) **Private insurance, n (%):** NR	**Inclusion criteria*:** History of spontaneous singleton PTB in a previous pregnancy Current pregnancy between 15 wks and 20 + 3 wks GA **Exclusion criteria*:** Multifetal gestation Known fetal anomaly Progesterone or heparin treatment during the current pregnancy Current or planned cervical cerclage HTN requiring medication Seizure disorder	**Prior PTB, mean (range):** **G1**: 1.43 (1-4) **G2:** Unknown >1 PTB, % **G1:** 32.6 **G2:** Unknown **Multiple gestation, n (%):** 0 **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB, mean wks:** **G1**: 30.0 **G2**: 30.3 **Prior PPROM, n (%):** NR	**GA at 17P initiation, wks:** **G1**: 14-28 **G2**: NA **Case management, %:** **G1**: 93.8 **G2**: 25.0 **Confirmed hospital stay, n (%):** **G1**: 54 (28.0) **G2**: 60 (100) **Confirmed hospital stay duration, mean days:** **G1**: 28.3 **G2**: 29.3	**Complications during pregnancy** NR **Prematurity** **Birth weight data available, n (%):** **G1**: 191 (99.0) **G2**: 60 (100) <2500g, %: **G1:** 37.7 **G2:** 48.3 <1500g, %: **G1:** 12.6 **G2:** 13.3 <1000g, %: **G1:** 4.7 **G2:** 5.0 **GA at birth,%:** <37 wks: **G1:** 46.6 **G2:** 51.7 <35 wks: **G1:** 26.4 **G2:** 41.7 *P* = 0.024 <32 wks: **G1:** 13.5 **G2:** 21.7 **% delivered < 37 weeks and < 2500 g** **G1:** 34.0 **G2:** 45.0 **Mode of birth and complications during birth** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Mason et al., 2010 (continued)					**Postpartum and neonatal complications** **NICU, %:** **G1:** 33.7 **G2:** 45.0 *P* = 0.095 **Data available for length of hospital stay, n:** **G1:** 54 **G2:** 60 **Length of hospital stay, mean days:** **G1:** 28.35 **G2:** 29.30 **Longer term outcomes** NR

*Inclusion and exclusion criteria taken from Meis et al., 2003

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Meis et al., 2003 Meis et al., 2005 Klebanoff et al., 2008 Spong et al., 2005 **Country:** US **Participant source:** Academic multi-site **Intervention setting:** Clinic **Enrollment period:** 09/1999 to 02/2002 **Funding:** NIH (NICHD) **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** 250 mg of IM 17OHP weekly, begun at 16-20 + 6 wks gestation, until wk 36 or birth **Groups:** **G1:** IM 17OHP **G1a:** GA of earliest prior birth 20-27.9 wks **G1b:** GA of earliest prior birth 28-33.9 wks **G1c:** GA of earliest prior birth 34-36.9 wks **G2:** Placebo **G2a:** GA of earliest prior birth 20-27.9 wk **G2b:** GA of earliest prior birth 28-33.9 wks **G2c:** GA of earliest prior birth 34-36.9 wks **N at enrollment:** **G1**: 310 **G2**: 153 **N at birth:** **G1**: 306 **G1a:** 98 **G1b:** 105 **G1c:** 103 **G2**: 153 **G2a:** 38 **G2b:** 68 **G2c:** 47 **N at follow-up:** *__G1__: 301-306 **G1a:** 98 **G1b:** 105 **G1c:** 103 *__G2__: 151-153 **G2a:** 38 **G2b:** 68 **G2c:** 47	**Inclusion criteria:** History of spontaneous singleton PTB in a previous pregnancy Current pregnancy between 15 wks and 20 + 3 wks GA **Exclusion criteria:** Multifetal gestation Known fetal anomaly Progesterone or heparin treatment during the current pregnancy Current or planned cervical cerclage HTN requiring medication Seizure disorder Plan to deliver elsewhere	**Prior PTB, n (%):** **G1**: 306 (100) **G2**: 153 (100) **Prior PTB, mean n ± SD:** **G1**: 1.4 ± 0.7 **G2**: 1.6 ± 0.9 *P* = 0.007 **Prior PTB, > 1, n (%):** **G1**: 86 (27.7) **G2**: 63 (41.2) **G1a+G2a:** (41.2) **G1b+G2b:** (33.5) **G1c+G2c:** (14.0) **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Cervical length, baseline:** NR **GA of prior PTB, mean wks ±SD:** **G1**: 30.6 ± 4.6 **G2**: 31.3 ± 4.2 **Prior PPROM:** NR	**Noncompliance (gap of ≥ 10 ds between any 2 injections), (%):** **G1:** (8.5) ***G1/G2**: P* = NS **GA at randomization, mean wks ± SD:** **G1:**18.4 ± 1.4 **G2:** 18.4 ± 1.4 **G1a+G2a:** 18.8 ± 1.5 **G1b+G2b:** 18.8 ± 1.5 **G1c+G2c:** 19.0 ± 1.4 **Logistic regression analysis of risk factors for PTB in women receiving intervention vs. placebo** **> 1 PPTB:** **G1:** OR: 1.54 (95% CI: 0.85 to 2.79) *P* = 0.153 **G2:** OR: 3.38 (95% CI: 1.36 to 8.40) *P* = 0.009 **Last birth preterm:** **G1:** OR: 2.81 (95% CI: 1.36 to 5.82) *P* = 0.005 **G2:** OR: 3.07 (95% CI: 1.03-9.13) *P* = 0.043	**Complications during pregnancy** **Chorioamnionitis, n (%):** **G1**: 11 (3.6) **G2**: 5 (3.3) RR: 1.09 (95% CI: 0.39 to 3.09) Antenatal hospital visit for PTL, n (%): **G1**: 49 (16.0) **G2**: 21 (13.8) RR: 1.15 (95% CI: 0.72 to 1.86) **Adverse effects in total study population, (%):** ≥ 1: **(**50) Soreness: (34.2) Itching: (11.3) Bruising: (6.7) **Swelling at the injection site, (%):** **G1**: (17.2) **G2**: (7.8) *P* = 0.007 **Lump at the injection site, (%):** **G1**: (5.5) **G2**: (1.3) *P* = 0.03 Miscarriage at < 20 wks, n (%): **G1**: 5 (1.6) **G2**: 0 (0) Fetal death, antepartum or intrapartum, n/N (%): **G1**: 6/306 (2.0) **G2**: 2/153 (1.3) RR: 1.50 (95% CI: 0.31 to 7.34)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Meis et al., 2003 Meis et al., 2005 Klebanoff et al., 2008 Spong et al., 2005 (continued)	**Age, mean yrs ± SD:** **G1**: 26.0 ± 5.6 **G2**: 26.5 ± 5.4 **G1a+G2a:** 25.9 ± 5.7 **G1b+G2b:** 26.3 ± 5.5 **G1c+G2c:** 26.5 ± 5.5 **Race/ethnicity, n (%):** **Non-Hispanic black** **G1:** 183 (59.0) **G2:** 90 (58.8) **G1a+G2a:** NR (63.2) **G1b+G2b:** NR (59.0) **G1c+G2c:** NR (55.3) **Non-Hispanic white** **G1:** 79 (25.5) **G2:** 34 (22.2) **Hispanic** **G1:** 43 (13.9) **G2:** 26 (17.0) **G1a+G2a:** (18.4) **G1b+G2b:** (16.2) **G1c+G2c:** (9.3) **Asian** **G1:** 2 (0.6) **G2:** 1 (0.7) **Other** **G1:** 3 (1.0) **G2:** 2 (1.3) **Parous, n (%):** **G1**: 310 (100) **G2**: 153 (100) **Maternal education, mean yrs ± SD:** **G1**: 11.7 ± 2.3 **G2**: 11.9 ± 2.3			**BMI < 20:** **G1:** OR: 1.29 (95% CI: 0.58 to 2.88) *P* = 0.535 **G2:** OR: 3.92 (95% CI: 0.78 to 19.79) *P* = 0.098 **BMI > 29:** **G1:** OR: 1.75 (95% CI: 0.94 to 3.24) *P* = 0.077 **G2:** OR: 0.14 (95% CI: 0.05 to 0.38) *P* < 0.001 **Tobacco:** **G1:** OR: 0.72 (95% CI: 0.35 to 1.45) *P* = 0.354 **G2:** OR: 1.48 (95% CI: 0.49 to 4.54) *P* = 0.49 **NNT:** 5-6 women (95%CI: 3.6 to 11.1) w/ level of risk of PTD similar to women in this study would need to be treated with IM 17OHP to prevent 1 PTD < 37 wks GA 12 women (95% CI 6.3-74.6) w/ similar level of risk would need to be treated to prevent 1 PTD < 32 wks GA	Tocolytic therapy, n (%): **G1**: 53 (17.3) **G2**: 24 (15.9) RR: 1.09 (95% CI: 0.70 to 1.69) Corticosteroids for fetal lung maturity, n (%): **G1**: 52 (17.8) **G2**: 30 (19.7) RR: 0.91 (95% CI: 0.60 to 1.35) **Prematurity** **Birth weight < 2500g, n/N (%)**: **G1**: 82/301 (27.2) **G2**: 62/151 (41.1) RR: 0.66 (95% CI: 0.51 to 0.87) *P* = 0.003 **Birth weight < 1500 g, n/N (%)**: **G1**: 26/301 (8.6) **G2**: 21/151 (13.9) RR: 0.62 (95% CI: 0.36 to 1.07) *P* = 0.08 **GA at birth < 37 wks, n (%):** **G1**: 111 (36.3) **G2**: 84 (54.9) RR: 0.66 (95% CI: 0.54 to 0.81) *P* < 0.001 Adjusted RR: 0.70 (95% CI: 0.57 to 0.85) **Spontaneous delivery at GA < 37 wks, n (%):** **G1:** 90 (29.4) **G2:** 69 (45.1) RR: 0.65 (95% CI: 0.51 to 0.83)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Meis et al., 2003 Meis et al., 2005 Klebanoff et al., 2008 Spong et al., 2005 (continued)	**BMI, mean ± SD:** **G1**: 26.9 ± 7.9 **G2**: 26.0 ± 7.0 **Maternal smoking, n (%):** **G1**: 70 (22.6) **G2**: 30 (19.6) **G1a+G2a:** (22.1) **G1b+G2b:**(19.6) **G1c+G2c:** (24.0) **Medicaid:** NR **Private insurance:** NR			4.7 women w/ level of risk similar to **G1**a and **G2**a would need to be treated to prevent 1 PTD. 4.6 women w/ level of risk similar to **G1**b and **G2**b would need to be treated to prevent 1 PTD.	**Delivery at GA < 37 wks indicated due to complications, n (%):** **G1:** 21 (6.9) **G2:** 15 (9.8) RR: 0.70 (95% CI: 0.37 to 1.32) **Delivery at GA < 37 wks, black women, n (%):** **G1:** 64 (35.4) **G2:** 47 (52.2) RR: 0.68 (95% CI: 0.51 to 0.90) **Delivery at GA < 37 wks, nonblack women, n (%):** **G1:** 47 (37.6) **G2:** 37 (58.7) RR: 0.64 (95% CI: 0.47 to 0.87) **GA at birth < 35 wks, n (%):** **G1**: 63 (20.6) **G2**: 47 (30.7) RR: 0.67 (95% CI: 0.48 to 0.93) *P* = 0.02 **GA at birth < 32 wks, n (%):** **G1**: 35 (11.4) **G2**: 30 (19.6) RR: 0.58 (95% CI: 0.37 to 0.91) *P* = 0.02 **GA at birth, median wks:** **G1a:** 37.3 **G2a:** 35.4 *P* = 0.046 **G1b:** 38.0 **G2b:** 36.7 *P* = 0.004 **G1c:** 37.7 **G2c:** 37.3 *P* = 0.73

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Meis et al., 2003 Meis et al., 2005 Klebanoff et al., 2008 Spong et al., 2005 (continued)					**Recurrence of PTB, (%):** **G1a:** (42) **G2a:** (63) *P* = 0.026 **G1b:** (34) **G2b:** (56) *P* = 0.005 **G1c:** (33) **G2c:** (57) *P* = 0.11 **Odds ratios for GA at birth < 37 wks w/ 17OHP (logistic regression model):** **G1a vs. G2a:** 0.43 (0.19-0.98) *P* = 0.44 **G1b vs. G2b:** 0.44 (0.23-0.85) *P* = 0.014 **G1c vs. G2c:** 0.62 (0.29-1.32) *P* = 0.215 **17OHP reduction in occurrence of PTB associated w/baseline salivary progesterone or estriol:** (progesterone) *P* = 0.77 (estriol) *P* = 0.72. **Mode of birth and complications during birth** **Cesarean birth, n (%):** **G1**: 77 (25.2) **G2**: 41 (26.8) RR: 0.94 (95% CI: 0.68 to 1.30)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Meis et al., 2003 Meis et al., 2005 Klebanoff et al., 2008 Spong et al., 2005 (continued)					**<u>Postpartum and neonatal complications</u>** IVH, **n/N (%):** Grade 3 or 4 **G1**: 2/305 (0.7) **G2**: 0/153 (0) Any grade **G1**: 4/305 (1.3) **G2**: 8/153 (5.2) RR**: 0.25 (95% CI: 0.8 to 0.82)** **Necrotizing enterocolitis, n /N (%):** **G1**: 0/305 (0) **G2**: 4/152 (2.6) *P* = 0.01 **Proven sepsis, n/N (%):** **G1**: 9/305 (3.0) **G2**: 4/152 (2.6) RR: 1.12 (95% CI: 0.35 to 3.58) **Neonatal death, n/N (%):** **G1**: 8/306 (2.6) **G2**: 9/153 (5.9) RR: 0.44 (95% CI: 0.17 to 1.13) **Transient tachypnea, n/N (%):** **G1**: 11/305 (3.6) **G2**: 11/152 (7.2) RR: 0.50 (95% CI: 0.22 to 1.12) **Respiratory distress syndrome, n (%):** **G1**: 29/305 (9.5) **G2**: 23/152 (15.1) RR: 0.63 (95% CI: 0.38 to 1.05)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Meis et al., 2003 Meis et al., 2005 Klebanoff et al., 2008 Spong et al., 2005 (continued)					**Bronchopulmonary dysplasia, n/N (%):** **G1**: 4/305 (1.3) **G2**: 5/152 (3.3) RR: 0.40 (95%CI: 0.11 to 1.46) **Ventilatory support, n (%):** **G1**: 26/303 (8.6) **G2**: 22/151 (14.6) RR: 0.59 (95% CI: 0.35 to 1.00) **Supplemental oxygen, n/N (%):** **G1**: 45/303 (14.9) **G2**: 36/151 (23.8) RR: 0.62 (95% CI: 0.42 to 0.92) **Patent ductus arteriosus, n/N (%):** **G1**: 7/305 (2.3) **G2**: 8/151 (5.3) RR 0.43 (0.16-1.17) **Retinopathy, n (%):** **G1**: 5/305 (1.6) **G2**: 5/152 (3.3) RR: 0.50 (95% CI: 0.15 to 1.70) **Congenital malformations, (%):** **G1**: (2.0) **G2**: (2.0) RR 0.50 (0.15-1.70) **Longer term outcomes** NR

*N at follow-up is a range because the number with data varied by outcome

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Meyer-Bahlburg et al., 1977 Ehrhardt et al., 1977 **Country:** US **Participant source:** Community **Intervention setting:** Community **Enrollment period:** NR **Funding:** Supported by a grant from the Spencer Foundation **Author Industry Relationship Disclosure:** NR **Design:** Case control	**Intervention*:** In utero exposure to exogenous progestogens, estrogens and/or thyroid hormone for more than one week during the 2nd-8th month after last menstrual period **Groups:** **G1:** children exposed to progestogens, estrogens and/or thyroid hormone in utero **G1a:** males exposed to medroxyprogesterone acetate (MPA) **G1b:** females exposed to MPA **G2:** matched controls with documented lack of hormonal exposure **G2a:** matched male controls **G2b:** matched female controls **N at enrollment:** **G1**: 74: 40 males, 34 females **G1**a: 13 **G1**b: 15 **G2**: 74: 40 males, 34 females **G2**a: 13 **G2**b: 15	**Inclusion criteria:** Children exposed to exogenous progestogens, estrogens and/or thyroid hormone in utero for more than one week during the 2nd-8th month after last menstrual period **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR **Duration of MPA exposure, mean wks (range):** **G1**a: 18.3 (2-31) **G1**b: NA **G2**a: 17.1 (2-34) **G2**b: NA **Total dosage MPA, mean mg (range):** **G1**a: 1478 (140-3900) **G1**b: NA **G2**a: 1086 (140-2020) **G2b:** NA	**Complications during pregnancy** NR **Prematurity** **Birth weight - lbs, ozs (range)**: **G1**a: 7,0 (5,6 – 9,4) **G1**b: 6,9 (3,10 – 8,10) **G2**a: 7,2 (5,9 – 8,10) **G2**b: 6,15 (4,14 – 8,8) 1 premature (<2500 kg) birth each in **G1**a and **G2**a. **GA at birth, mean wks, days (range):** **G1**a: 38,3 (34,4 – 40,2) **G1**b: 38,3 (30,5 – 42,3) **G2**a: 39,4 (35,3 – 45,1) **G2**b: 39,2 (33,6 – 41,4) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** **Neurodevelopmental delay, n (%):** **G1**: 123 **G2**: 123

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Meyer-Bahlburg et al., 1977 Ehrhardt et al., 1977	**N at birth:** **G1**: 74: 40 males, 34 females **G1**a: 13 **G1**b: 15 **G2**: 74: 40 males, 34 females **G2**a: 13 **G2**b: 15 **N at follow-up:** **G1**: 74: 40 males, 34 females **G1**a: 13 **G1**b: 15 **G2**: 74: 40 males, 34 females **G2**a: 13 **G2**b: 15 **Age at time of study, mean yrs, mos (range):** **G1**: NR **G1**a: 11,3 (9,1 – 12,8) **G1**b: 10,8 (8,7 – 12,1) **G2**: NR **G2**a: 11,10 (9,8 – 14,0) **G2**b: 11,4 (9,3 – 12,11) **Race/ethnicity, n (%):** **G1**: NR **G1**a: Caucasian 13 (100) **G1**b: Caucasian 15 (100) **G2**: NR **G2**a: Caucasian 13 (100) **G2**b: Caucasian 15 (100) **Parous, n (%):** NA **Maternal education, n (%):** NR				**Future fertility, n (%):** NR **Full IQ (WISC-R), mean (range):** **G1**a: 108.2 (74-133) **G1**b: 114.6 (96-132) **G2**a: 109.9 (81-131) **G2**b: 112.1 (90-141) **G1a v G2a:** NS in energy expenditures, athletic skills, sex of playmates, being teased for effeminacy, gender preference, toy preference, interest in marriage and having children, or in infant care. **G1**b v **G2**b: Statistical significance was seen in tomboyism (p=0.062) and in clothing preference (feminine style clearly preferred, p=0.035). NS in energy expenditures, athletic skills, sex of playmates, gender preference, toy preference, interest in marriage and having children, or in infant care.

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Meyer-Bahlburg et al., 1977 Ehrhardt et al., 1977	**Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NR **Private insurance coverage:** NR				

*Exposure duration and dose, behavioral category results shown graphically for both studies

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Author: Ness and Baxter et al., 2006 (a) Ness and Dias et al., 2006 (b) **Country:** US **Participant source:** Community **Intervention setting:** NA (survey) **Enrollment period:** Survey a: 12/2003 to 01/2004 Survey b: 02/2005 to 03/2005 **Funding:** NR **Author Industry Relationship Disclosure:** 0 of 7 **Design:** Survey	**Assessment method:** Mail survey **Groups:** **Ga:** Progestogens users **Gb:** Progestogens nonusers **G1a:** Progestogens users from survey 6 mos following NICHD publication, 2003 **G1b:** Progestogens users from follow up survey, 2005 **G2a** Nonusers of progestogens from survey 6 mos following NICHD publication, 2003 **G2b:** Nonusers of progestogens from follow-up survey, 2005 **N sampled:** a: 1264 b: 1264 N respondents (%): a: 526 b: 572 **Age, mean yrs :** < 40 **G1b**: 41 (10.7) G2b: 15 (8.0) 40-49 **G1b**: 193 (50.3) G2b: 87 (46.3) 50-59 **G1b**: 111 (28.9) G2b: 70 (37.2) ≥ 60 **G1b**: 37 (9.6) G2b: 16 (8.5)	**Inclusion criteria:** Board certified MFM specialists in the US Listed in the SMFM mailing list **Exclusion criteria:** Incomplete survey	**Most frequent indication for use w/ hx of prior SPTB, (%):** **Prior SPTB <32 wks** **G1a**: (53) **Prior SPTB <34 wks** **G1b**: (41) *P* = 0.002 **Most frequent indication for use, n (%):** **PPTB** **G1a:** 159 (83) **PPTB at <32wks** **G1a:** (66) **PPTB at <37 wks** **G1a:** (34) **Current symptom indications, (%):** **Combined** **G1a:** (20) **PTL symptoms** **G1a:** (5) **Short cervix** **G1a:** (7) **PTL and short cervix** **G1a:** (8) **Coindications with hx of prior SPTB, (%):** **Additional risk factors** **G1b:** (10) **Indication for use w/o hx of SPTB, n/N (%):** **Total** **G1a**: 73/198 (37) **G1b**: 148/384 (39) *P* = 0.73	**Progestogen use by region, n (%)*:** Southeast **G1b**: 94 (79.0) G2b: 25 (21.0) Midwest **G1b**: 95 (72.0) G2b: 37 (28.0) Northeast **G1b**: 107 (64.5) G2b: 59 (35.5) Southwest **G1b**: 68 (63.0) G2b: 40 (37.0) Northwest **G1b**: 16 (45.7) G2b: 19 (52.3) *SE vs. NW-* Highest and lowest use, respectively *P* = 0.008 **Progestogen users within practice type, (%):** **Academics:** (70) **Non-academics:** (65) *P* = 0.2 **Initiation of progestogen prescribing, n (%):** **Within 6 mos** **G1a**: 102 (52) **Within previous yr** **G1a**: 161 (81) **G1b**: (56) **Within the past 3 yrs** **G1b:** (91)	**<u>Survey comparisons</u>** **Survey response rate, n (%):** **Ga:** 526/1264 (42) **Gb:** 572/1264 (45) **G1a**: 198 (38) **G1b:** 384 (67) G2a: 324 (62) G2b: 188 (33) **Progestogen use trend, n (%)** **G1a:** 198 (38) **G1b:** 384 (67) *P* < 0.001 **Concerns of nonusers, %^:** **Long-term effects** **G2a:** 80.0 **G2b:** 77.0 *P* < 0.001 **Efficacy** **G2a:** 18.0 **G2b:** 86.0 *P* < 0.001 **Need for more data** **G2a:** 39.0 **G2b**: 97.0 *P* < 0.001 **Safety** **G2a:** 12.0 **G2b:** 56.0 *P* < 0.001

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Ness and Baxter et al., 2006 (a) Ness and Dias et al., 2006 (b) (continued)	**Geographic Region, n (%)*:** Southeast **G1b**: 94 (24.5) G2b: 25 (13.3) Midwest **G1b**: 95 (24.7) G2b: 37 (19.7) Northeast **G1b**: 107 (27.9) G2b: 59 (31.4) Southwest **G1b**: 68 (17.7) G2b: 40 (21.3) Northwest **G1b**: 16 (4.2) G2b: 19 (10.1) **Gender, n (%):** Male **G1b**: 253 (65.9) G2b: 121 (64.4) Female **G1b**: 130 (33.9) G2b: 66 (35.1) **Years in clinical practice, n (%):** 0-9 **G1b**: 463 (16.4) G2b: 25 (13.3) 10-19 **G1b**: 190 (49.5) G2b: 87 (6.3) ≥20 **G1b**: 129 (33.6) G2b: 70 (37.2) **Years as MFM specialists, n (%):** 0-9 **G1b**: 157 (40.9) G2b: 72 (38.3) 10-19 **G1b**: 158 (41.1) G2b: 89 (47.3) ≥20 **G1b**: 69 (18.0) G2b: 27 (14.4)		**Premature dilatation or effacement of the cervix** **G1b**: 85/148 (57)	**Administration preference, n (%):** **Weekly IM** **G1a**: 147 (74) **G1b**: (87) *P* = 0.023 **Vaginal** **G1a**: 51 (26) **G1b**: (13) **Location progestogens obtained, (%):** **Local compounding pharmacy** **G1b:** (49) **Home health care service** **G1b:** (23) **Mail order pharmacy** **G1b:** (21) **Patients declining progestogens, n (%):** ****> 0% decline** **G1b:** 211 (55) **≤ 50% decline** **G1b:** (90) **0% decline** **G1b:** 173(45) **Reasons for patient decline of progestogen therapy, (%)†:** **Lack of insurance coverage** **G1b:** (62) **Need for IM injection** **G1b:** (54) **Concerns about risk** **G1b:** (42)	

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Ness and Baxter et al., 2006 (a) Ness and Dias et al., 2006 (b) (continued)	**Type of medicine, (%):** **Academic** **Gb:** (54) **Clinical practice** **Gb:** (99)			**Concern regarding progestogen, level, n (%):** **Safety** *P* < 0.0005 **Very** **G1b:** 31 (7.1) **G2b:** 31 (17.9) **Somewhat** **G1b:** 120 (32.6) **G2b:** 66 (38.2) **Not** **G1b:** 222 (60.3) **G2b:** 76 (43.9) **Efficacy** *P* < 0.0005 **Very** **G1b:** 53 (14.4) **G2b:** 79 (44.6) **Somewhat** **G1b:** 188 (51.1) **G2b:** 74 (41.8) **Not** **G1b:** 127 (34.5) **G2b:** 24 (13.6) **No insurance coverage** P<.0005 **Very** **G1b:** 111 (30.1) **G2b:** 27 (16.9) **Somewhat** **G1b:** 148 (40.1) **G2b:** 57 (35.6) **Not** **G1b:** 110 (29.8) **G2b:** 76 (47.5) **Lack of availability** *P* = 0.21 **Very** **G1b:** 121 (32.6) **G2b:** 67 (40.1) **Somewhat** **G1b:** 163 (43.9) **G2b:** 68 (40.7)	

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Ness and Baxter et al., 2006 (a) Ness and Dias et al., 2006 (b) (continued)				**Not** **G1b:** 87 (23.5) **G2b:** 32 (19.2) **No FDA approval** *P* < 0.0005 **Very** **G1b:** 30 (8.2) **G2b:** 41 (24.7) **Somewhat** **G1b:** 128 (34.9) **G2b:** 60 (36.0) **Not** **G1b:** 209 (56.9) **G2b:** 65 (39.2) **Liability** P < 0.0005 **Very** **G1b:** 21 (5.7) **G2b:** 25 (14.8) **Somewhat** **G1b:** 113 (30.7) **G2b:** 67 (39.6) **Not** **G1b:** 234 (63.6) **G2b:** 77 (45.6) **Need for more data** *P* < 0.0005 **Very** **G1b:** 105 (28.2) **G2b:** 137 (77.0) **Somewhat** **G1b:** 185 (49.7) **G2b:** 36 (20.2) **Not** **G1b:** 82 (22.0) **G2b:** 5 (2.8) **G2a:** (30) **G2b:** 78 (44.6) Geographical region NW had greatest concern(Gb): *P* = 0.04	

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Ness and Baxter et al., 2006 (a) Ness and Dias et al., 2006 (b) (continued)				**Long-term neonatal effects** Ga: (*P* < 0.0001) Gb: (*P* < 0.0005) **Very** **G1a:** (0) **G1b:** 60 (16) **G2a:** (10) **G2b:** 56 (32) **Somewhat** **G1a:** (8) **G1b:** 175 (46.8) **Minimally** **G1a:** (64) **G2a:** (40) **Not** **G1a:** (28) **G1b:** 139 (37.2) **G2a:** (20) **G2b:** 41 (23.4)	

* % of total user and non-user populations calculated; extrapolated nonusers and calculated the % from each geographic region. Original data reported in Aspects of Care using extrapolated % for nonusers.
†Extrapolated % of 'subscribers' w/ >0 progestogen-declining patients is denominator for % of reasons declined.
^Concerns of nonusers in comparison Table IV of survey b (reported here) does not match text of survey a; text states concerns of nonusers in GA as 81% need more data, 25% (84/324) efficacy, 12% (38/324) safety.

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Noblot et al., 1991 **Country:** France **Participant source:** Academic multi-site **Intervention setting:** Clinic **Enrollment period:** 02/1987 to 10/1987 **Funding:** Intramural **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** Ritodrine (Prepar) 0.2 mg/min for 1 hr (2 ampules of 50 mg of Ritodrine in 500 ml of isotonic glucose serum, at 20 drops/min) and thereafter tailored individually Natural OMP (Utrogestan) 4 caps/ 6h during 1st 24h, then 4caps/8h for 2nd 24h and then 3caps/8h from 3rd 24h onwards **Groups:** **G1:** Ritodrine and OMP **G2:** Ritodrine and placebo **N at enrollment:** **G1**: 22 **G2:** 22 **N at birth:** **G1:** 22 **G2:** 22 **N at follow-up:** **G1:** 22 **G2:** 22 **Age, mean yrs :** **G1:** 28.6 **G2:** 22.6 **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal smoking:** NR	**Inclusion criteria:** Undergoing tocolytic treatment before 35th wk of gestation for menace of PTL Presenting change in uterine cervix or regular uterine contractions at least every 10' and persisting after 1 hr rest **Exclusion criteria:** Cardiopathy Fever Abnormality in fetal cardiac rhythm PROM prior to 32 wks GA Previously treated w/ β-mimetics	**Prior PTB, n (%):** NR **Multiple gestation, n:** G1: 3 G2: 1 **Single pregnancies, n‡:** **G1:** 19 **G2:** 21 **Fetal fibronectin, baseline:** NR **Cerclage, n:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Provider specialty, (%):** Ob/gyn G1: (100) G2: (100) **GA at enrollment, wks:** **G1:** 32.2 **G2:** 30.8 *P* = 0.05	**Complications during pregnancy** †Antenatal LOS, n days: **G1:** 13.6 **G2:** 17.8 *P* < 0.05 **PPROM, n:** **G1:** 1 **G2:** 3 *P* > 0.05 **Tocolytic therapy (Ritodrine), n (%):** **G1:** 22 (100) **G2:** 22 (100) **Ritodrine, total mg:** **IV** **G1:** 345 **G2:** 875 *P* < 0.01 Oral **G1:** 863 **G2:** 1370 *P* < 0.05 Ritodrine, mean duration of infusion†: **G1:** 2.95 **G2:** 5.63 *P* < 0.01

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Noblot et al., 1991 (continued)	**Maternal weight, mean kg*:** **G1:** 61.5 **G2:** 58.9 **Maternal height, mean cm*:** **G1:** 162 **G2:** 161 **Medicaid:** NR **Private insurance coverage:** NR				**Prematurity** **Frequency of uterine contractions, mean ± SD:** **day 0 on admission** **G1:** 3.95 ± 2.68 **G2:** 3.41 ± 2.48 **day 0 after 1st hr** **G1:** 0.70 ± 1.26 **G2:** 0.22 ± 0.77 *P* < 0.05 **day 1 after 24th hr of treatment** **G1:** 0.045 ± 0.2 **G2:** 0.28 ± 0.6 *P* < 0.05 **Pregnancy prolonged, wks:** **G1:** 6.0 **G2:** 6.4 *P* = NS **Index of prolongation:**: **G1:** 15.7 **G2:** 17.2 *P* = NS **Delivery < 37 wks:**: All: **G1:** 6 **G2:** 8 *P* = NS ‡**Birth weight, mean g:** **G1:** 3,077 **G2:** 2,832 *P* = NS

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Noblot et al., 1991 (continued)					**‡Apgar, score:** **1 min:** **G1:** 8.7 **G2:** 7.7 *P* = NS **5 min:** **G1:** 9.7 **G2:** 9.3 *P* = NS **10 min:** **G1:** 9.7 **G2:** 9.8 *P* = NS **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

*Maternal weight and height included because BMI was not specifically indicated
†Excluding patients with ruptured membranes
‡Single pregnancies only

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Norman et. al, 2009 **Country:** UK **Participant source:** Academic multi-site **Intervention setting:** Home **Enrollment period:** 12/2004 to 04/2008 **Funding:** Scottish Government Health Directorate **Author Industry Relationship Disclosure:** 3 of 17 Government and charitable grants (2) Pharmaceutical consultant (2) Data Safety and Monitoring Board (1) PTL prevention therapy patent (1) **Design:** RCT,permuted blocks of mixed sizes	**Intervention:** Progesterone gel, 90 mg (Crinone) or placebo gel daily from 24 + 0 wks gestation until 34 wks or delivery **Groups:** **G1:**Vaginal progesterone gel **G2:** Vaginal placebo gel **N at enrollment:** **G1**: 250 **G2**: 250 **N at birth:** **G1**: 247 **G2**: 247 **N at follow-up:** **G1**: 247 **G2**: 247 **Age, mean yrs ± SD (range) :** **G1**: 33 ± 5 (18-44) **G2**: 33 ± 6 (19-50) **Race/ethnicity:** NR **Parous, n (%):** **G1**: 119 (48) **G2**: 122 (49) **Maternal education:** NR **Maternal smoking, n (%):** **G1**: 44 (18) **G2**: 31 (12) **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR	**Inclusion criteria:** Twin pregnancy Gestation and chorionicity established by scan before 20 wks gestation Attending antenatal clinic **Exclusion criteria:** Pregnancy complicated by structural or chromosomal fetal abnormality Contraindications to progesterone Planned cervical suture Planned elective delivery before 34 wks GA Planned intervention for twin-to-twin transfusion before 22 wks Higher multiple pregnancies	**Prior PTB:** NR **Prior miscarriage, n (%):** **G1:** 3 (1) **G2**: 1 (<1) **Multiple gestation, n (%): Twins** **G1:** 250 (100) **G2:** 250 (100) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Patient attitudes regarding treatment, mean score ± SD:** Satisfaction (1=very satifsfied to 10=completely dissatisfied): **G1**: 2.8 ± 2.1 **G2**: 2.8 ± 1.9 OR: 0.0 (95% CI: 0.5 to 0.4) *P* = 0.89 Perception of efficacy (1=worked perfectly to 10=did not work at all): **G1**: 3.8 ± 2.3 **G2**: 3.9 ± 2.5 OR: -0.1 (95% CI: 0.6 to 0.4) *P* = 0.73 Ease of use overall (1=very easy to 10=very difficult): **G1**: 2.6 ± 1.9 **G2**: 2.5 ±1.7 OR: 0.2 (95%CI: -0.2 to 0.6) *P* = 0.38 Ease of insertion (1=very easy to 10=very difficult): **G1**: 2.6 ± 1.9 **G2**: 2.4 ± 1.7 OR: 0.2 (95% CI: -0.2 to 0.6) *P* = 0.30 Easy to remember (1=very easy;10-very difficult): **G1**: 2.6 ± 1.7 **G2**: 2.9 ± 1.7 OR: -0.2 (95% CI: -0.6 to 0.2) *P* = 0.26	**<u>Complications during pregnancy</u>** **Chorioamnionitis or intrauterine infection, n (%):** **G1**: 0 (0) **G2**: 0 (0) *P* = 1.0 Prolonged inpatient maternal hospital admission, n (%): **G1**: 87 (103) **G2**: 72 (87) *P* = 0.16 Persistent/Significant maternal disability or incapacity, n: **G1**: 1 **G2**: 0 *P* = 0.32 Life threatening, n: **G1**: 1 **G2**: 2 *P* = 0.56 **Bloating, n (%):** **G1**: 6 (3) **G2**: 5 (3) OR: 1.23 (95% CI: 0.37 to 4.11) *P* = 0.73 **Fluid retention, n (%):** **G1**: 20 (11) **G2**: 22 (12) OR: 0.92 (95% CI: 0.48 to 1.75) *P* = 0.80 **Breast tenderness, n (%):** **G1**: 14 (7) **G2**: 12 (6) OR: 1.20 (95% CI: 0.54 to 2.68) *P* = 0.64

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)				Pleasantness (1=very pleasant to 10=very unpleasant): **G1**: 4.8 ± 2.0 **G2**: 4.9 ± 1.8 OR: -0.1 (95% CI: -0.5 to 0.3) *P* = 0.60 Messyness (1=very messy to 10=not messy at all): **G1**: 5.5 ± 2.5 **G2**: 6.1 ± 2.4 OR: -0.6 (95% CI: -1.1 to 0.1) *P* = 0.026 Uncomfortable (1=very uncomfortable to 10=very comfortable): **G1**: 6.4 ± 2.5 **G2**: 6.5 ± 2.3 OR: -0.1 (95% CI: -0.6 to 0.4) *P* = 0.65 Rate of side-effects overall(1=a lot to 10=none): **G1**: 8.2 ± 2.3 **G2**: 8.4 ± 1.9 OR: -0.2 (95% CI: -0.7 to 0.2) *P* = 0.32 Preference of weekly IM injection (bit uncomfortable) to vaginal gel (1=daily vaginal gel to 10=IM weekly injection): **G1**: 4.3 ± 3.6 **G2**: 4.2 ± 3.6 OR: 0.2 (95% CI: -0.6 to 0.9) *P* = 0.70	**Excessive weight gain, n (%):** **G1**: 2 (1) **G2**: 2 (1) OR: 1.02 (95% CI: 0.14 to 7.33) *P* = 0.98 **Nausea, n (%):** **G1**: 10 (5) **G2**: 22 (12) OR: 0.43 (95% CI: 0.20 to 0.94) *P* = 0.035 **Headache, n (%):** **G1**: 8 (4) **G2**: 17 (9) OR: 0.45 (95% CI: 0.19 to 1.09) *P* = 0.077 **Dizziness, n (%):** **G1**: 8 (4) **G2**: 9 (5) OR: 0.90 (95% CI: 0.34 to 2.40) *P* = 0.84 **Difficulty sleeping, n (%):** **G1**: 31 (17) **G2**: 40 (21) OR: 0.75 (95% CI: 0.45 to 1.26) *P* = 0.28 **Drowsiness, n (%):** **G1**: 8 (4) **G2**: 4 (2) OR: 2.09 (95% CI: 0.62 to 7.06) *P* = 0.24 **Depression, n (%):** **G1**: 6 (3) **G2**: 5 (3) OR: 1.23 (95% CI: 0.37 to 4.11) *P* = 0.73

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)				Preference of weekly IM (quite uncomfortable) to vaginal gel (1=daily vaginal gel to 10=IM weekly injection): **G1**: 3.3 ± 3.0 **G2**: 3.1 ± 2.9 0.2 (95% CI: -0.4 to 0.9) *P* = 0.50	**Itching, n (%):** **G1**: 19 (10) **G2**: 21 (11) OR: 0.92 (95% CI: 0.48 to 1.77) *P* = 0.79 **Rash, n (%):** **G1**: 7 (4) **G2**: 4 (2) OR: 1.82 (95% CI: 0.52 to 6.32) *P* = 0.35 **Acne, n (%):** **G1**: 4 (2) **G2**: 2 (1) OR: 2.07 (95% CI: 0.37 to 11.42) *P* = 0.41 **Excessive hair growth, n (%):** **G1**: 3 (2) **G2**: 4 (2) OR: 0.76 (95% CI: 0.17 to 3.45) *P* = 0.73 Hair loss, n (%): **G1**: 1 (1) **G2**: 1 (1) OR: 1.02 (95% CI: 0.06 to 16.45) *P* = 0.99 **Allergic reactions, n (%):** **G1**: 1 (1) **G2**: 1 (1) OR: 1.02 (95% CI: 0.06-16.45) *Pb*0.99 **Vaginal irritation, n (%):** **G1**: 20 (11) **G2**: 15 (8) OR: 1.45 (95% CI: 0.70 to 2.83) *P* = 0.34

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)					**Vaginal itching, n (%):** **G1**: 19 (10) **G2**: 18 (9) OR: 1.09 (95% CI: 0.55 to 2.14) *P* = 0.81 **Vaginal discharge, n (%):** **G1**: 59 (32) **G2**: 46 (24) OR: 1.45 (95% CI: 0.92 to 2.29) *P* = 0.11 **Vaginal discomfort, n (%):** **G1**: 24 (13) **G2**: 17 (9) OR: 1.51 (95% CI: 0.78 to 2.91) *P* = 0.22 **Jaundice, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Joint pain, n/N (%):** **G1**: 11/173 (6) **G2**: 13/176 (7) OR: 0.85 (95% CI: 0.37 to 1.96) *P* = 0.71 **Pubic pain, n (%):** **G1**: 6 (3) **G2**: 5 (3) OR: 1.23 (95% CI: 0.37 to 4.11) *P* = 0.73 **Prematurity** **GA at birth mean wks ± SD:** **G1**: 35.4 ± 3.5 **G2**: 35.7 ± 3 Δ: -0.3(95% CI: -0.9 to 0.3) *P* = 0.31

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)					**Longer term outcomes** NR **Delivery or IUFD < 34 wks gestation, n/N (%):** **All** **G1**: 61/247 (24.7) **G2**: 48/247 (19.4) OR: 1.36 (95% CI: 0.89 to 2.09) *P* = 0.16 **Monochorionic** **G1**: 10/46 (21.7) **G2**: 14/45 (31.1) OR: 0.62 (95% CI: 0.24 to 1.58) **Dichorionic** **G1**: 51/201 (25.4) **G2**: 34/202 (16.8) OR: 1.73 (95% CI: 1.06 to 2.83) *P* = 0.056 **IUFD, n:** **G1:** 6 **G2:** 4 *P* = 0.52 **Mode of birth and complications during birth** **Cesarean birth (lower section), n (%)[†]:** **G1**: 148 (59.2) **G2**: 161 (64.4) OR: 0.53 (95% CI: 0.34 to 0.84) *P* = 0.006 **Forceps or ventouse, n (%)[†]:** **G1**: 22 (8.8) **G2**: 30 (12.0) OR: 0.42 (95% CI: 0.21 to 0.83) *P* = 0.013

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)					**Spontaneous vertex delivery or vaginal breech, n (%)[†]:** **G1**: 66 (26.4) **G2**: 38 (15.2) *P* = 1.00 **Mode of delivery NR, n (%)[†]:** **G1**: 14 (5.6) **G2**: 21 (8.4) **Maternal death, n:** **G1**: 0 **G2**: 0 *P* = 1.0 **<u>Postpartum and neonatal complications</u>** **NICU admission, n (%):** **G1**: 167 (33.8) **G2**: 158 (32) OR: 1.08 (95% CI: 0.76 to 1.54) *P* = 0.65 **NICU LOS mean days ± SD:** N all **G1**: 7.5 ± 19.9 **G2**: 8.7 ± 23.1 ∆: 1.5 (95% CI: -1.9 to 5.0) *P* = 0.38 **N admitted 167** **G1:** 26.9 ± 33.5 **G2:** 23.6 ± 29.5 ∆: 3.3 (95% CI: -5.3 to 11.9) *P* = 0.45 **Neonatal death, n:** **G1:** 8 **G2:** 6 *P* = 0.59

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)					**Congenital anomaly or birth defect, n:** **G1:** 0 **G2:** 0 *P* = 1.0

*Delivery and death outcomes based on first infant
†Uses groups at enrollment (**G1**: 250 and **G2**: 250)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Northen et al., 2007 See Meis et al., 2003; Meis et al., 2005; Klebanoff et al., 2008; Spong et al., 2005) **Country:** US **Participant source:** Academic multi-site **Intervention setting:** Clinic and home **Enrollment period:** November 2004 – November 2005 **Funding:** NIH (NICHD) **Author Industry Relationship Disclosure:** No potential conflicts of interest to disclose. **Design:** RCT – original study, now comparing long term outcomes from groups	**Intervention:** 250 mg of IM 17OHP every week, begun at 16-20 weeks + 6 days, until week 36 or birth Children were evaluated using the Ages and Stages Questionnaire (ASQ), Preschool Activities Inventory (PAI), survey assessment from caregivers, and physical examination by study personnel or chart abstraction. **Groups:** **G1:** children of mothers from 17OHP group **G2:** children of mothers from placebo group **N at enrollment:** **G1**: 194 **G2**: 84 **N at birth:** NR **N at follow-up:** **G1**: 194 **G2**: 84 **Age, mean yrs±SD:** **G1**: 26.4±5.8 **G2**: 26.1±5.5	**Inclusion criteria:** Parent or guardian of all surviving offspring of the mothers enrolled in the Maternal-Fetal Medicine Units (MFMU) Network study of 17OHP Conducted only at MFMU clinical centers active in the network in 2004 **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Age at which ASQ performed, n (%):** ≤36 months **G1**: 40 (20.7) **G2**: 11 (13.4) 42 months **G1**: 49 (25.4) **G2**: 25 (30.5) 48 months **G1**: 32 (16.6) **G2**: 12 (14.6) 54 months **G1**: 38 (19.7) **G2**: 17 (20.7) 60 months **G1**: 34 (17.6) **G2**: 17 (20.7) Median: 48 months (41.8-55.0, 25th-75th percentile) **Compliance, %±SD:** **G1**: 91.4±23.5 **G2:** 94.0±15.1 Defined as ratio of study visits attended to the number expected. **ASQ completed by mother or primary caregiver, n (%):** **G1**: 121 (62.7) **G2**: 57 (69.5) **ASQ completed by study nurse, n (%):** **G1**: 72 (37.3) **G2**: 25 (30.5)	**Complications during pregnancy** NR **Prematurity** **Birth weight, n (%)**: <2500 g **G1**: 42 (21.8) **G2**: 29 (34.5) <1500 g **G1**: 9 (4.7) **G2**: 7 (8.3) **GA at birth, n (%):** Delivery before 37 weeks **G1**: 59 (30.4) **G2**: 44 (52.4) Delivery before 35 weeks **G1**: 29 (14.9) **G2**: 21 (25.0) Delivery before 32 weeks **G1**: 14 (7.2) **G2**: 11 (13.1) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **Postpartum hemorrhage,** n (%): NR IVH, **n (%):** Any grade **G1**: 3 (1.6) **G2**: 5 (6.0) Grade 3 or 4 **G1**: 1 (0.5) **G2**: 0

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)	**Race/ethnicity, n (%):** African American **G1**: 105 (54.1) **G2**: 47 (56.0) White **G1**: 55 (28.4) **G2**: 20 (23.8) Hispanic **G1**: 29 (14.9) **G2**: 15 (17.9) Asian **G1**: 2 (1.0) **G2**: 1 (1.2) Other **G1**: 3 (1.5) **G2**: 1 (1.2) **Parous, n (%):** NR **Maternal education, mean yrs±SD:** **G1**: 11.9±2.1 **G2**: 12.2±2.4 **Maternal BMI, mean ±SD:** **G1:** 26.9±8.0 **G2:** 25.8±6.7 **Maternal smoking, n (%):** **G1**: 43 (22.2) **G2**: 13 (15.5) **Medicaid:** NR **Private insurance coverage:** NR			**ASQ performance site, n (%):** Home **G1**: 84 (43.5) **G2**: 40 (48.8) Clinical center **G1**: 94 (48.7) **G2**: 34 (41.5) Combination **G1**: 15 (7.8) **G2:** 8 (9.8)	**Infections, n (%):** NR **Sepsis (proven), n (%):** **G1**: 4 (2.1) **G2**: 2 (2.4) **Respiratory distress syndrome, n (%):** **G1**: 18 (9.3) **G2**: 9 (10.7) **Mechanical ventilation, n (%):** **G1**: 16 (8.3) **G2**: 9 (10.7) **Patent ductus arteriosus, n (%):** **G1**: 6 (3.1) **G2**: 3 (3.6) **Necrotizing enterocolitis, n (%):** **G1**: 0 **G2**: 1 (1.2) **Retinopathy, n (%):** **G1**: 4 (2.1) **G2**: 3 (3.6) **Bronchopulmonary dysplasia, n (%):** **G1**: 3 (1.6) **G2**: 3 (3.6) **Genital or reproductive anomalies, % (types):** **G1**: 2.1 (2 males with micropenis, 1 male with undescended testicle, 1 female with early puberty) **G2**: 1.2 (1 female with pubic hair)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**Longer term outcomes** **Neurodevelopmental delay, n (%):** NR **Future fertility, n (%):** NR **PAI mean score:** **G1**: Male: 66.5 Female: 32 **G2**: Male: 67.3 Female: 33 **ASQ scored below cutoff on, n (%)*:** ≥1 area **G1**: 53 (27.5) **G2**: 23 (28.0) Communication **G1**: 22 (11.4) **G2**: 9 (11.0) Gross motor **G1**: 5 (2.6) **G2**: 3 (3.7) Fine motor **G1**: 40 (20.7) **G2**: 15 (18.3) Problem solving **G1**: 20 (10.4) **G2**: 9 (11.0) Personal-social **G1**: 7 (3.6) **G2**: 1 (1.2) All P=NS **Medical diagnoses*:** **Anemia, n (%):** **G1**: 5 (2.6) **G2**: 4 (4.9) **Arthritis, n (%):** **G1**: 1 (0.5) **G2**: 0

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**Asthma, n (%):** **G1**: 39 (20.3) **G2**: 20 (24.4) **Cerebral palsy, n (%):** **G1**: 0 **G2**: 1 (1.2) **Diabetes, n (%):** **G1**: 1 (0.5) **G2**: 0 **Diarrhea or colitis, n (%):** **G1**: 5 (2.6) **G2**: 1 (1.2) **Ear infections (≥3), n (%):** **G1**: 20 (10.4) **G2**: 7 (8.5) **Eczema, n (%):** **G1**: 35 (18.2) **G2**: 12 (14.6) **Food or digestive allergy, n (%):** **G1**: 3 (1.6) **G2**: 3 (3.7) **Respiratory allergy, n (%):** **G1**: 16 (8.3) **G2**: 9 (11.0) **Seizures, with fever, n (%):** **G1**: 3 (1.6) **G2**: 1 (1.2) **Seizures, without fever, n (%):** **G1**: 0 **G2**: 1 (1.2) **Severe headaches or migraines, n (%):** **G1**: 1 (0.6) **G2**: 2 (2.6)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**Hay fever, n (%):** **G1**: 19 (9.9) **G2**: 5 (6.1) **Sickle cell, n (%):** **G1**: 0 **G2**: 1 (1.2) **Stuttering or stammering, n (%):** **G1**: 11 (6.4) **G2**: 5 (6.6) **Communication problems, n (%):** **G1**: 9 (4.7) **G2**: 7 (8.5) **Attention or learning problems, n (%):** **G1**: 16 (8.3) **G2**: 8 (9.8) **ADHD or ADD, n (%):** **G1**: 1 (0.5) **G2**: 2 (2.4) **Developmental delay, n (%):** **G1**: 14 (7.2) **G2**: 7 (8.3) **Autism, n (%):** **G1**: 1 (0.5) **G2**: 0 **Mental retardation, n (%):** **G1**: 1 (0.5) **G2**: 0 **Overall activity problems, n (%):** **G1**: 2 (1.0) **G2**: 1 (1.2) **Coordination problems, n (%):** **G1**: 1 (0.5) **G2**: 1 (1.2)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					Caregiver's assessment*: **Overall health, n (%):** Excellent **G1**: 117 (60.9) **G2**: 46 (56.1) Very good **G1**: 43 (22.4) **G2**: 22 (26.8) Good **G1**: 28 (14.6) **G2**: 10 (12.2) Fair **G1**: 4 (2.1) **G2:** 4 (4.9) **Health compared with 12 months ago, n (%):** Better **G1**: 64 (33.3) **G2**: 26 (31.7) Worse **G1**: 2 (1.0) **G2**: 2 (2.4) About the same **G1**: 126 (65.6) **G2**: 54 (65.9) **Required medications in last 3 months, n (%):** **G1**: 21 (10.9) **G2**: 16 (19.5) **Hearing, n (%):** Good **G1**: 188 (97.9) **G2**: 77 (93.9) Little trouble **G1**: 4 (2.1) **G2**: 5 (6.1) **Vision, n (%):** No trouble **G1**: 188 (97.9) **G2**: 80 (97.6)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					Trouble – glasses **G1**: 3 (1.6) **G2**: 1 (1.2) Trouble – no glasses **G1**: 1 (0.5) **G2**: 1 (1.2) **Use of special equipment, n (%)*:** None **G1**: 191 (99.5) **G2**: 81 (98.8) Wheelchair **G1**: 0 **G2**: 1 (1.2) Brace **G1**: 1 (0.1) **G2:** 0 **Impairment limiting walk, run, or play, n (%):** **G1**: 5 (2.6) **G2**: 5 (6.1) **Physical examinations performed by study personnel, n (%)†:** **G1**+**G2**: 256 of 270 (95) **Height percentile, n (%):** **G1**: 54 (29.0) **G2**: 57 (29.0) **Height less than 5th percentile, n (%):** **G1**: 7 (4.0) **G2**: 4 (5.0) **Weight percentile, n (%):** **G1**: 55 (30.0) **G2**: 57 (30.0)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**Weight less than 5th percentile, n (%):** **G1**: 11 (6.0) **G2**: 6 (8.0) **Head circumference percentile, n (%):** **G1**: 50 (31.0) **G2:** 54 (31.0) **Blood pressure mmHg, n (%):** **G1**: Systolic: 92 (11.0) Diastolic: 56 (9.0) **G2**: Systolic: 93 (10.0) Diastolic: 58 (9.0)

*192 children of mothers from 17OHP group in survey data and 82 children of mothers from placebo group in survey data
†189 children of mothers from 17OHP group in physical examination data and 81 children of mothers from placebo group in physical examination data

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: O'Brien et al., 2007 DeFranco et al., 2007 See O'Brien et al., 2009 **Country:** US, South Africa, India, Czech Republic, Chile, El Salvador **Participant source:** Academic multi-site **Intervention setting:** Home **Enrollment period:** 04/2004 to 01/2007 **Funding:** Industry (Columbia Laboratories, Inc.) **Author Industry Relationship Disclosure:** 2 of 25 Cook Biotech (1) Columbia Laboratories (1) **Design:** RCT (1:1 randomization scheme provided by Quintiles, Inc.)	**Intervention:** Vaginal progesterone gel (Prochieve® 8%/ Crinone® 8%) in pre-filled single use applicators of 1.125 g of gel with 90 mg of progesterone, self-administered daily, until 37 wks gestation, PROM, or PTD **Groups:** **G1:** Vaginal progesterone gel **G1a:** Vaginal progesterone gel and short cervix <28 mm **G1b:** Vaginal progesterone gel and short cervix ≤32 mm **G1c:** Vaginal progesterone gel and short cervix ≤30 mm **G2:** Placebo gel (Replens®) **G2a:** Placebo gel (Replens®) and short cervix <28 mm **G2b:** Placebo gel (Replens®) and short cervix ≤32 mm **G2c:** Placebo gel (Replens®) and short cervix ≤ 30 mm **N at enrollment:** 669	**Inclusion criteria:** Pregnant women aged 18-45 yrs Estimated GA 16 to 22 + 6 wks Hx of singleton PTB, 20-35 wks GA in the immediate preceding pregnancy Short cervix, <28 mm^ Understand English or common local language Provide written informed consent Demonstrate understand of the purpose of study Adhere to study protocol **Exclusion criteria:** Hx of adverse reaction to progesterone or any component of formulation Progesterone tx w/in 4 wks of enrollment Tx for seizure disorder, psychiatric illness, chronic HTN at enrollment	**Prior PTB, mean ± SD:** **G1**: 1.3 ± 0.6 **G1a:** 1.2 ± 0.5 **G2**: 1.4 ± 0.7 **G2a:** 1.4 ± 0.8 **> 1 PPTB, n (%):** **G1:** 73 (23.6) **G1a:** 7 (37) **G2:** 77 (25.5) **G2a:** 5 (19) **1 previous SPTB, (%):** **G1:** (74.5) **G2:** (76.4) **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length ≤ 32 mm, baseline, n:** 172 **Cervical length > 32 mm, baseline, n:** 437 **Cervical baseline, mean length ± SD:** **G1:** 3.7 cm ± 0.7 **G1a:** 24 mm ± 0.2 **G2:** 3.7cm ± 0.7 **G2a:** 22 mm ± 0.5 **GA of prior PTB:** NR **Prior PPROM:** NR	**Intervention adherence, mean % ± SD:** **G1:** 96.2 ± 9.4 **G1a:** 93.9 ± 9.77 **G2:** 96.4 ± 7.8 **G2a:** 94.7 ±13.03 Mean diff (**G1** v **G2**): −0.2 (95% CI: −1.5 to 1.2) **Discontinuation due to AE, (%):** **G1**: (1.6) **G2**: (0.9) **Country of study site, n (%):** **US** **G1**: 200 (64.7) **G2**: 195 (64.6) **India** **G1**: 54 (17.5) **G2**: 57 (18.9) **South Africa** **G1**: 44 (14.2) **G2**: 40 (13.2) **Czech Republic** **G1**: 7 (2.3) **G2**: 6 (2.0) **Chile/El Salvador** **G1**: 4 (1.3) **G2**: 4 (1.3) **GA at randomization, mean wks ± SD:** **G1**: 19.9 ± 2.1 **G1a:** 20.4 ± 1.3 **G2**: 20.1 ± 3.3 **G2a:** 20.4 ± 1.6	**<u>Complications during pregnancy</u>** **Adverse events, (%):** **G1**: (81.3) **G2**: (83.2) **Serious adverse events, (%):** **G1**: (39.6) **G2**: (42.7) **Proportion of serious AEs due to complications of pregnancy, (%):** **G1**: (85) **G2**: (91) **Complaints about vaginal discharge, (%):** **G1**: (8.4) **G2**: (9.2) **Vaginal discharge due to study medication, (%):** **G1**: (4.0) **G2**: (4.4) **Serious vaginal discharge, n/N (%):** **G1**: 4/321 (1.2) **G2**: 3/316 (0.9) **IUFD, n (%):** **< 20 wks** **G1**: 0 (0) **G2**: 0 (0) **>20 wks** **G1**: 5 (1.6) **G2**: 4 (1.3) OR: 1.22 (95% CI: 0.33 to 4.61)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
O'Brien et al., 2007 DeFranco et al., 2007 (continued)	**N at birth:** **G1**: 309 **G1a:** 19 **G1b:** 83 **G2**: 302 **G2a:** 27 **G2b:** 89 **N at follow-up:** **G1**: 309 **G1a:** 19 **G2**: 302 **G2a:** 27 **Age, mean yrs (SD) :** **G1**: 27.1 (5.8) **G1a:** 27.4 (4.9) **G2**: 27.3 (5.6) **G2a:** 25.4 (4.8) **Race/ethnicity, n (%):** **Caucasian** **G1**: 111 (35.9) **G1a:** 9 (47.4) **G2**: 99 (32.8) **G2a:** 10 (37) **African American** **G1**: 76 (24.6) **G1a:** 3 (15.8) **G2**: 85 (28.1) **G2a:** 11 (40.7) **Hispanic** **G1**: 22 (7.1) **G1a:** 1 (5.3) **G2**: 14 (4.6) **G2a:** 0 **Asian/Pacific Islander** **G1**: 55 (17.8) **G1a:** 0 **G2**: 60 (32.8) **G2a:** 4 (14.8) **Native American** **G1**: 0 **G1a:** NR **G2**: 1 (0.3) **G2a:** NR	Hx of acute or chronic CHF, renal failure, uncontrolled DM, active liver disorder HIV infection w/CD4 < 350 cells/mm^3 and multiple antiviral meds Placenta previa Hx or suspicion of breast or GU cancer Hx or suspicion of thromboembolic disease Müllerian duct anomaly Enrollment in another study in last month Major fetal anomaly by ultrasound or chromosomal disorder Cervical cerclage or planned cerclage placement PTL PPROM Clinical chorioamnionitis Vaginal bleeding Hx of previous PTD w/out spontaneous PTL			**PPROM, n (%):** **G1**: 37 (12.0) **G2**: 38 (12.6) OR: 0.95 (95% CI: 0.58 to 1.53) Admitted for PTB, n (%): **G1**: 79 (25.6) **G1a:** 6 (31.6) **G2**: 75 (24.8) **G2a:** 7 (25.9) **G1 v G2:** OR: 1.14 (95% CI: 0.38 to 3.37) **G1a v G2a:** *P* = 1.0 **Tocolytic therapy, n (%):** **G1**: 35 (11.3) **G2**: 31 (10.3) OR: 1.12 (95% CI: 0.67 to1.86) **Antepartum corticosteroid use, n (%):** **G1**: 72 (23.3) **G2**: 74 (24.5) OR: 0.94 (95% CI: 0.65 to 1.36) **Latency period to delivery after tocolysis for PTB, mean ds ± SD:** **G1**: 30.0 ± 30.0 **G1a:** 42.7 ± 52.3 **G2**: 19.6 ± 19.8 **G2a:** 10.0 ± 18.0 **G1 v G2:** Δ: 10.3 (95% CI: −2.4 to 23.0) **G1a v G2a:** *P* = 0.287 **Cervical length, at 28 wks, mean mm ± SD:** **G1a:** 25 ± 0.8 **G2a:** 22 ± 0.8 *P* = 0.27

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
O'Brien et al., 2007 DeFranco et al., 2007 (continued)	**Other** **G1**: 45 (14.6) **G1a:** 6 (31.6) **G2**: 43 (14.2) **G2a:** 2 (7.4) **Parity, mean ± SD:** **G1**: 1.5 ± 1.1 **G2**: 1.5 ± 1.1 **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI, mean kg/m^2 ± SD:** **G1**: 26.6 ± 6.5 **G1a:** 28.5 ± 8.3 **G2**: 26.4 ± 7.1 **G2a:** 26.9 ± 6.7 **Medicaid:** NR **Private insurance:** NR				**Change in cervical length, mean mm ± SD:** **G1a:** 2 ± 0.9 **G2a:** 0 ± 0.9 *P* = 0.70 **<u>Prematurity</u>** **Birth weight, mean g ± SD:** **G1**: 2,680 ± 710 **G1a:** 2,726 ± 645 **G2**: 2,661 ± 738 **G2**a: 2,290 ± 937 **G1 v G2:** Δ: 19 (95% CI: -96 to 135) **G1a v G2a:** *P* = 0.1 **GA at birth, mean wks ± SD:** **G1**: 36.6 ± 3.8 **G1a:** 36.3 ± 2.4 **G2**: 36.6 ±4.2 **G2a:** 34.6 ± 4.6 **G1 v G2:** Δ: 0.0 (95% CI: -0.64 to 0.64) **G1a v G2a:** *P* = 0.16 **PTB, (%):** **< 28 wks** **G1**b: (1.2) **G2b:** (6.7) **G1b v G2b:** *P* = 0.12 **< 35 wks** **G1**b: (22.9) **G2b:** (30.3) **G1b v G2b:** *P* = 0.3 **< 37 wks** **G1**b: (44.6) **G2b:** (51.7) **G1b v G2b:** *P* = 0.36

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
O'Brien et al., 2007 DeFranco et al., 2007 (continued)					**PTB, n (%):** **≤ 28 wks** **G1**: 10 (3.2) **G1a:** 0 (0) **G2**: 9 (3.0) **G2a:** 3 (11.1) **G1 v G2:** OR: 1.07 (95% CI: 0.38 to 2.96) **G1a v G2a:** *P* = 0.257 **≤ 32 wks** **G1**: 31 (10.0) **G1a:** 0 (0) **G2**: 34 (11.3) **G2a:** 8 (29.6) **G1 v G2:** OR: 0.9 (95% CI: 0.52 to 1.56) **G1a v G2a:** *P* = 0.014 **≤ 35 wks** **G1**: 70 (22.7) **G1a:** 7 (36.8) **G2**: 80 (26.5) **G2a:** 13 (48.1) **G1 v G2:** OR: 0.9 (95% CI: 0.61 to 1.34) **G1a v G2a:** *P* = 0.551 **< 37 wks** **G1**: 129 (41.7) **G1a:** 8 (42.1) **G2**: 123 (40.7) **G2a:** 16 (59.3) **G1 v G2:** OR: 1.08 (95% CI: 0.76 to 1.52) **G1a v G2a:** *P* = 0.370 **Mode of birth and complications during birth** **Cesarean section, n (%):** **G1**: 89 (29) **G2**: 83 (27.8)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
O'Brien et al., 2007 DeFranco et al., 2007 (continued)					**<u>Postpartum and neonatal complications</u>** **NICU admission, n (%):** **G1**: 54 (17.5) **G1a:** 3 (15.8) **G1**b: 13 **G1**c: 16 **G2**: 65 (21.5) **G2a:** 14 (51.9) **G2b:** 21 **G2c:** 32 **G1 v G2:** OR: 0.75 (95% CI: 0.51 to 1.11) **G1a v G2a:** *P* = 0.016 **G1b v G2b:** *P* = 0.25 **G1c v G2c:** *P* = 0.077 NICU LOS, mean ds ± SD**:** **G1**: 14.2 ±16.6 **G1a:** 1.1 ± 2.7 **G2**: 20.5 ± 30.7 **G2a:** 16.5 ± 24.9 **G1 v G2:** Δ: -6.2 (95% CI: -15.2 to 2.8) **G1a v G2a:** *P* = 0.013 NICU LOS, mean ds ± SD: **G1a:** 5.8 ± 9 **G1**b: 13 **G1**c: 7 **G2a:** 18.2 ± 25.5 **G2b:** 32.7 **G2c:** 14 **G1a v G2a:** *P* = 0.055 **G1b v G2b:** *P* = 0.14 **G1c v G2c:** *P* = 0.095

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
O'Brien et al., 2007 DeFranco et al., 2007 (continued)					**IVH, n (%):** **Grade 1** **G1**: 4 (1.3) **G1a:** 0 (0) **G2**: 4 (1.3) **G2a:** 2 (7.4) **G1a v G2a:** *P* = 0.5 **Grade 2** **G1**: 1 (0.3) **G1a:** 0 (0) **G2**: 0 (0) **G2a:** 0 (0) **Grade 3** **G1**: 1 (0.3) **G1a:** 0 (0) **G2**: 0 (0) **G2a:** 0 (0) **Grade 4** **G1**: 0 (0) **G1a:** 0 (0) **G2**: 1 (0.3) **G2a:** 0 (0) **IVH, (%):** **G1**b: (1.2) **G2b:** (2.4) **G1b v G2b:** *P* = 1.0 **RDS, n (%):** **G1**: 34 (11) **G1a:** 1 (5.3) **G1**b: (7.2) **G1c:** (7) **G2**: 36 (11.9) **G2a:** 8 (29.6) **G2b:** (13.5) **G2c:** (19) **G1 v G2:** OR: 0.91 (95% CI:0.56 to 1.5) **G1a v G2a:** *P* = 0.06 **G1b v G2b:** *P* = 0.21 **G1c v G2c:** *P* = 0.09

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
O'Brien et al., 2007 DeFranco et al., 2007 (continued)					**Proven sepsis, n (%):** **G1**a: 1 (5.3) **G2**a: 3 (11.1) *P* = 1.0 **Necrotizing enterocolitis, n (%):** **G1**: 3 (1.0) (3 clinical) **G1a:** 0 **G1**b: (1.2) **G2**: 5 (1.7) (2 clinical, 3 surgical) **G2a:** 1 (3.7) (1 clinical) **G2b:** (1.1) **G1 v G2:** OR: 0.58 (95% CI: 0.14 to 2.46) **G1a v G2a:** *P* = 1.0 **G1b v G2b:** *P* = 1.0 **Neonatal death, n (%):** **G1**: 6 (1.9) **G1a:** 0 (0) **G2**: 7 (2.3) **G2a:** 1 (3.7) **G1 v G2:** OR: 0.87 (95% CI: 0.29 to 2.60) **G1a v G2a:** *P* = 1.0 **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: O'Brien et al., 2009 See O'Brien et al., 2007 and DeFranco et al., 2007 **Country:** US, South Africa, India, Czech Republic, Chile, El Salvador **Participant source:** Academic multi-site **Intervention setting:** Home **Enrollment period:** 04/2004 to 01/2007 **Funding:** Industry (Columbia Laboratories, Inc.) **Author Industry Relationship Disclosure:** 2 of 25 Cook Biotech (1) Columbia Laboratories (1) **Design:** RCT (1:1 randomization scheme provided by Quintiles, Inc.)	**Intervention:** Vaginal progesterone gel (Prochieve® 8%/ Crinone® 8%) in pre-filled single use applicators of 1.125 g of gel with 90 mg of progesterone, self-administered daily, until 37 wks gestation, PROM, or PTD **Groups:** **G1:** Progesterone **G1a.** History of PTB **G1b:** Prematurely shortened cervix ≤30mm **G2:** Placebo **G2a:** History of PTB **G2b:** Prematurely shortened cervix ≤30mm **N at enrollment*:** **G1a**: 273 **G1b:** 55 **G2a:** 274 **G2b:** 50 **N at birth:** Birth outcomes NR **N at follow-up*:** **G1a**: 269 **G1b:** 53 **G2a:** 272 **G2b:** 45 **Age, yrs ± SD:** **G1a**: 27.3 ± 5.8 **G1b:** 27.0 ± 5.3 **G2a:** 27.4 ± 5.6 **G2b:** 26.1 ± 5.0	**Inclusion criteria:** Pregnant women aged 18-45 yrs Estimated GA 16 to 22 + 6 wks Hx of singleton PTB, 20-35 wks GA in the immediate preceding pregnancy Short cervix, ≤25 mm Understand English or common local language Provide written informed consent Demonstrate understand of the purpose of study Adhere to study protocol **Exclusion criteria:** Hx of adverse reaction to progesterone or any component of formulation Progesterone tx w/in 4 wks of enrollment Tx for seizure disorder, psychiatric illness, chronic HTN at enrollment	**Prior PTB, n (%):** 620 (100) Prior PTB, mean ± SD: **G1a**: 1.3 ± 0.7 **G1b:** 1.3 ± 0.5 **G2a:** 1.3 ± 0.7 **G2b:** 1.5 ± 0.8 **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline mm ± SD:** **G1a**: 37.0 ± 7.0 **G1b:** 28.0 ± 3.0 **G2a:** 37.0 ± 8.0 **G2b:** 26.0 ± 5.0 **GA of prior PTB:** 20-35 wks **Previous cervical surgery, n (%):** **G1a**: 19 (7.0) **G1b:** 7 (13.0) **G2a:** 25 (9.1) **G2b:** 4 (8.0) **Prior PPROM, n (%):** NR	**GA at randomization, wks ±SD:** **G1a**: 20.0 ± 2.2 **G1b:** 20.2 ± 1.6 **G2a:** 20.2 ± 3.5 **G2b:** 20.1 ± 1.9 **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR	**Complications during pregnancy** **Change in cervical length at 28wks GA, mm ± SD:** **G1a:** -5 ± 9 **G2a:** -6 ± 9 *P* = 0.02 More cervical length was preserved on average in **G1b** participants than in **G2b** (*P* = 0.03; mean values NR) **Cervical length ≤25 mm at 28wks GA, n (%):** **G1a**: 46 (16.8) **G1b:** 14 (25.9) **G2a:** 63 (23.0) **G2b:** 21 (42.0) *P* values: **G1a/G2a:** 0.087 **G1b/G2b:** 0.1 **Cervical length ≤15 mm at 28wks GA, n (%):** **G1a**: 9 (3.3) **G1b:** 3 (5.6) **G2a:** 19 (6.9) **G2b:** 7 (14.0) *P* values: **G1a/G2a:** 0.079 **G1b/G2b:** 0.19 **≥ 50% decrease in cervical length at 28wks GA, n (%):** **G1a**: 27 (9.9) **G1b:** 1 (1.9) **G2a:** 35 (12.8) **G2b:** 5 (10.0) *P* values: **G1a/G2a:** 0.35 **G1b/G2b:** 0.10

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
O'Brien et al., 2009 (continued)	**Race/ethnicity, n (%):** African or African-American: **G1a**: 100 (36.6) **G1b:** 20 (37.0) **G2a:** 107 (39.0) **G2b:** 25 (50.0) Caucasian: **G1a**: 101 (37.0) **G1b:** 14 (26.0) **G2a:** 94 (34.3) **G2b:** 10 (20.0) Asian/Pacific Islander: **G1a**: 53 (19.4) **G1b:** 15 (28.0) **G2a:** 58 (21.2) **G2b:** 15 (30.0) **Parous, n (%):** 620 (100) **Maternal education, n (%):** NR **Maternal BMI, kg/m^2 ± SD:** **G1a**: 26.6 ± 6.3 **G1b:** 26.3 ± 7.1 **G2a:** 26.3 ± 6.9 **G2b:** 25.1 ± 7.1 **Maternal smoking, n (%):** NR **Medicaid:** NR **Private insurance coverage:** NR	Hx of acute or chronic CHF, renal failure, uncontrolled DM, active liver disorder HIV infection w/CD4 < 350 cells/mm^3 and multiple antiviral meds Placenta previa Hx or suspicion of breast or GU cancer Hx or suspicion of thromboembolic disease Müllerian duct anomaly Enrollment in another study in last month Major fetal anomaly by ultrasound or chromosomal disorder Cervical cerclage or planned cerclage placement PTL PPROM Clinical chorioamnionitis Vaginal bleeding Hx of previous PTD w/out spontaneous PTL			**Prematurity** **PTB <28wks GA, n:** **G1:** 5 **G2**: 7 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

*Participants may be included in both the history of PTB and short cervix subgroups, resulting in a total greater than the population at enrollment

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: O'Brien et al., 2010 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** April 2004 to July 2006 **Funding:** NR **Author Industry Relationship Disclosure:** 1 of 6 Alere/Matria (1) **Design:** Retrospective cohort	**Intervention:** 250mg IM 17P injected weekly until 36wks GA or delivery along with uterine activity monitoring **Groups:** Participants receiving 17P with uterine activity monitoring **N at enrollment:** 388 **N at birth:** 388 **N at follow-up:** NA **Age, yrs ± SD:** 30.1 ± 5.2 **Race/ethnicity, n (%):** NR **Parous, n (%):** 287 (74.0) **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, %:** 4.9 **Medicaid:** NR **Private insurance coverage:** NR	**Inclusion criteria:** Enrolled in Matria Healthcare outpatient administration program Uterine contraction frequency data Singleton pregnancy **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** 287 (74.0) >1 Prior PTB: 97 (25.0) **Multiple gestation, n (%):** 0 **Fetal fibronectin, baseline:** NR **Cerclage, %:** 23.7 **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**GA at 17p initiation, wks ± SD:** 22.2 ± 4.9 **GA at uterine monitoring initiation, wks ± SD:** 26.4 ± 3.4 **Prescribed tocolytic medications, n (%):** 290 (74.7) **Drug availability, n (%):** NR	**Complications during pregnancy** **Hourly contraction frequency, median (range):** PTD: 1.5 (0, 14.5) Term delivery: 1.2 (0, 21.0) *P* < 0.001 **Prematurity** **Spontaneous PTD, n (%):** 234 (60.3) **GA at birth, wks ± SD:** 36.1 ± 2.3 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Ovlisen and Iversen, 1963 See Fuchs and Stakemann, 1960 **Country:** Denmark **Participant source:** Community **Intervention setting:** Clinic **Enrollment period:** January 1961 to January 1962 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Prospective case series with historical comparison	**Intervention:** 6-alpha-methyl-17-alpha-acetoxy-progesterone (Perlutex) started within 4-8 hours after admission, 60 mg 3 times daily for first 3 days; 20 mg 3 times daily for next 4 days; patients then confined to bed for a few days after medication withdrawal. **Groups:** **G1:** intervention **G1a**: women with hemorrhage **G1b**: women with passage of amniotic fluid **G1c**: women with rhythmic or constant pains **N at enrollment:** **G1**: 63 **G1a**: 22 **G1b**: 23 **G1c**: 31 **N at birth:** **G1**: 63 **G1a**: 22 **G1b**: 23 **G1c**: 31 **N at follow-up:** **G1**: 63 **G1a**: 22 **G1b**: 23 **G1c**: 31 **Age, n:** <20 years: 10 20-29 years: 38 30-39 years: 14 ≥ 40 years: 1	**Inclusion criteria:** Patients with signs of threatened premature labor **Exclusion criteria:** See inclusion criteria	**Prior PTB, n:** 1 PTB: 8 2 prior PTB: 1 ≥3 prior PTB: 1 **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR Cervical length, baseline: NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR **Symptoms causing admission, n:** Hemorrhage from the vagina: 28 Rupture of the membranes: 20 Rhythmic or constant pains or backache: 15 **Symptoms found on admission, n:** Hemorrhage from vagina: 22 Passage of amniotic fluid: 23 Uterine contractions: 31 No objective symptoms: 4	**Provider knowledge and attitudes, n (%):** NA **Provider specialty, n (%):** NA **Cost of drug, n (%):** NA **Drug availability, n (%):** NA **Duration of treatment, n:** <1 day: 8 1-2 days: 4 3-4 days: 6 5-7 days: 10 7 days: 35	**Complications during pregnancy** **Chorioamnionitis, n (%):** NR **Antenatal hospitalizations, n (%):** NR **IUGR, n (%):** NR **Allergic reactions, n (%):** 0 **GDM, n (%):** NR Delivery after treatment, n: During 1st week: **G1a**: 3 **G1b**: 1 **G1c**: 0 During 2nd week: **G1a**: 2 **G1b**: 1 **G1c**: 0 During 3rd and 4th week: **G1a**: 1 **G1b**: 1 **G1c**: 1 >28 days: **G1a**: 10 **G1b**: 3 **G1c**: 13 **Prematurity** Delivery during treatment, n: 1st day: **G1a**: 3 **G1b**: 1 **G1c**: 12nd day: **G1a**: 2 **G1b**: 2 **G1c**: 0

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Ovlisen and Iversen, 1963 (continued)	**Race/ethnicity, n (%):** NR **Parous:** NR **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NA **Private insurance coverage:** NR				3rd day: **G1a**: 2 **G1b**: 1 **G1c**: 0 4th day: **G1a**: 0 **G1b**: 2 **G1c**: 0 5th day: **G1a**: 2 **G1b**: 0 **G1c**: 0 6th day: **G1a**: 3 **G1b**: 5 **G1c**: 0 7th day: **G1a**: 0 **G1b**: 3 **G1c**: 0 **Birth weight in grams, n:** <1,000: 8 1000-1450: 12 1500-1950: 10 2000-2450: 9 2500-2950: 5 ≥ 3000: 19 **GA at birth:** NR **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Rai et al., 2009 **Country:** India **Participant source:** Academic single site **Intervention setting:** Home **Enrollment period:** 01/2005 to 12/2006 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT	**Intervention:** 100 mg of OMP 2x/day, begun at 18-24 wks until wk 36 or birth **Groups:** **G1:** OMP **G2:** Placebo **N at enrollment:** **G1**: 75 **G2**: 75 **N at birth:** **G1**: 74 **G2**: 74 **N at follow-up:** **G1**: 74 **G2**: 74 **Age, mean yrs :** **G1**: 26.07 ± 3.24 **G2**: 25.72 ± 3.42 **Race/ethnicity:** NR **Parous, n (%):** **G1**: 74 (100) **G2**: 74 (100) **Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR	**Inclusion criteria:** Asymptomatic 18-35 yrs in age 18-24 wks pregnant History of at least 1 SPTB (between 20 and 30 + 6 wks) Singleton pregnancy **Exclusion criteria:** First trimester bleeding PROM Multiple pregnancy Fetal anomalies Acute liver disease	**Prior PTB, n (%):** **G1**: 74 (100) **G2**: 74 (100) **Prior PTB, mean n ± SD:** **G1**: 1.21 ± 0.53 **G2**: 1.31 ± 0.52 **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at study entry, mean ± SD:** **G1**: 20.69 ± 2.83 **G2**: 20.73 ± 1.78 **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**Complications during pregnancy** **Tocolysis, n (%):** **G1**: 15 (20) **G2**: 20 (27) *P* = 0.686 (95% CI: 0.32 to 1.47) Tocolysis-to-delivery interval, mean hrs (range): **G1**: 49.7 (8-216) **G2**: 26.84 (17-70) *P* = 0.058 **Adverse effects, n:** **Acne** **G1**: 2 **G2**: 1 **Esophageal reflux** **G1**: 2 **G2**: 0 **Somnolence** **G1**: 1 **G2**: 1 **Headache** **G1**: 0 **G2**: 1 **Depression** **G1**: 0 **G2**: 4 **Prematurity** **Birth weight, mean g ±SD**: **G1**: 2,400 ± 650 **G2**: 1,890 ± 560 *P* < 0.001 **GA at birth, mean wks ± SD:** **G1**: 36.1 ± 2.66 **G2**: 34.0 ± 3.25 *P* < 0.001

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rai et al., 2009 (continued)					**GA at birth <37 wks, n (%):** **G1**: 29 (39.2) **G2**: 44 (59.5) *P* = 0.002 **< 28 wks** **G1**: 0 **G2**: 3 (4.0) *P* = 0.25 **28-31+6 wks** **G1**: 2 (2.7) **G2**: 15 (20.3) RR: 0.20 (95% CI: 0.05 to 0.73) *P* = 0.001 **32-33 + 6 wks** **G1**: 20 (27.0) **G2**: 19 (25.7) RR: 0.86 (95% CI: 0.60 to 1.22) *P* = 0.85 **34-36+6 wks** **G1**: 7 (9.5) **G2**: 7 (9.5) RR: 0.83 (95% CI: 0.48-1.45) *P* = 1.000 **Duration pregnancy prolonged, mean wks ± SD:** **G1**: 15.57 $\pm$ 7.38 **G2**: 11.10 $\pm$ 7.01 *P* < 0.001 **Duration index pregnancy prolonged compared w/ previous births, mean wks ± SD:** **G1**: 14.68 $\pm$ 3.53 **G2**: 12.23 $\pm$ 3.17 P<0.001 Neonatal age at birth, mean wks ± SD (Ballard Score)**:** **G1**: 34.26 $\pm$ 2.88 **G2**: 32.95 $\pm$ 3.20 *P* < 0.001

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rai et al., 2009 (continued)					**Mode of birth and complications during birth** NR **Postpartum and neonatal complications** **NICU stay duration, n:** **< 24 h** **G1**: 7 **G2**: 7 **24 h – 1 wk** **G1**: 1 **G2**: 20 **> 1 wk** **G1**: 2 **G2**: 11 *P* < 0.001 **Total NICU admissions, n (%):** **G1**: 10 (13.5) **G2**: 38 (51.3) **Indication for NICU stay, n:** **RDS with septicemia** **G1**: NR **G2**: 16 **RDS with hyperbilirubinemia** **G1**: NR **G2**: 9 **RDS with hyperbilirubinemia and septicemia** **G1**: NR **G2**: 6

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rai et al., 2009 (continued)					**Apgar score at 1 min:** **<6** **G1**: 10 **G2**: 42 **>6** **G1**: 64 **G2**: 32 *P* < 0.001 **Apgar score at 10 min:** **<6** **G1**: 8 **G2**: 29 **>6** **G1**: 66 **G2**: 45 *P* < 0.001 **Neonatal deaths, n:** **G1**: 3 **G2**: 7 *P* = 0.190 **Cause of neonatal death, n:** **RDS** **G1**: 1 **G2**: 0 **RDS with hyperbilirubinemia** **G1**: 0 **G2**: 5 **RDS with septicemia** **G1**: 0 **G2**: 2 b **G1**: 2 **G2**: 0 **<u>Longer term outcomes</u>** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Rebarber and Ferrara et al., 2007 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 01/2004 to 05/2006 **Funding:** NR **Author Industry Relationship Disclosure:** 4 of 7 Matria (4) **Design:** Retrospective cohort study	**Intervention:** 250 mg of IM17OHP administered by perinatal nurse using Z-track method at 7-10 day intervals, begun at 16-20+6 wks **Groups:** **G1a:** 17OHP treatment; elective early cessation of 17OHP (excluding hospitalization for imminent delivery or an acute condition that led to delivery within 10 days at < 32 wks GA, w/ delivery occurring > 10 days from last injection) **G1b:** 17OHP taken weekly until 36+6 wks GA or delivery **N at enrollment:** **G1a**: 81 **G1b**: 400 **N at birth:** **G1a**: 81 **G1b**: 400 **N at follow-up:** **G1a**: 71 **G1b**: 364 **Age, mean yrs ± SD :** **G1a**: 28.1 ± 6.3 **G1b**: 29.7 ± 5.3 **Median age, mean yrs (range):** **G1a:** 28 (16, 43) **G1b:** 30 (16, 42)	**Inclusion criteria:** Singleton pregnancy Hx of PPTB GA of 16-20+6 wks at initiation Analysis inclusion required height, prepregnancy weight, and outcome data **Exclusion criteria:** Women w/ cervical cerclage No documented delivery date	**Prior PTB, n (%):** **G1a**: 81 (100) **G1b**: 400 (100) **> 1 PPTB, n (%):** **G1a**: 28 (34.6) **G1b**: 94 (23.5) **Multiple gestation, n (%):** **G1a:** 0 (0) **G1b:** 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1a:** 0 (0) **G1b:** 0 (0) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**N of 17OHP injections, mean ± SD:** **G1a**: 8.1 ± 3.9 **G1b**: 17.3 ± 3.9 *P* < 0.001 **GA at initiation, mean wks ± SD:** **G1a**: 17.9 ± 1.5 **G1b**: 17.8 ± 1.5 *P* = 0.440 **GA at cessation, mean wks ± SD:** **G1a**: 25.4 ± 4.2 **G1b**: 34.4 ± 3.5 *P* < 0.001	**Complications during pregnancy** NR **Prematurity** **Birth weight for live born infants**: **G1a**: 2,640±862 **G1b**: 2,989±635 *P* = 0.001 **GA at birth, mean wks ± SD:** **G1a**: 35.1±4.2 **G1b**: 36.4±4.1 *P* < 0.001 **GA at birth, median wks (range):** **G1a**: 35.6 (19.4, 41.3) **G1b**: 37.4(16.1, 43.3) **SPTB, n (%):** **Overall** **G1a**: 51 (63.0) **G1b**: 164 (41.0) *P* < 0.001 **at <37 wks GA** **G1a**: 39 (48.1) **G1b**: 133 (33.3) *P* = 0.011 **at <35 wks GA** **G1a**: 25 (30.9) **G1b**: 56 (14.0) *P* < 0.001 **at <32 wks GA** **G1a**: 13 (16.0) **G1b**: 28 (7.0) *P* = 0.020

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rebarber and Ferrara et al., 2007 (continued)	**Race/ethnicity:** NR **Parous, n (%):** **G1a**: 81 (100) **G1b**: 400 (100) **Maternal education:** NR **Maternal BMI:** NR **Maternal smoking, n (%):** **G1a**: 10 (12.3) **G1b**: 23 (5.8) **Medicaid, n (%):** **G1a**: 81 (100) **G1b**: 400 (100) **Private insurance coverage:** NR				**Association of maternal age < 20 yrs w/ SPTB outcome at 37 wks, mean (min, max):** 0.24 (0.05, 1.18) *P* = 0.079 **Association of maternal smoking w/ SPTB outcome at 37 wks, mean (min, max):** 0.66 (0.29, 1.51) *P* = 0.330 **Association of >1 previous PTB w/ SPTB outcome at 37 wks, mean (min, max):** 2.96 (1.83, 4.79) *P* < 0.001 **Association of early cessation of IM 17OHP w/ SPTB outcome at 37 wks, mean (min, max):** 2.11 (1.13, 3.94) *P* = 0.019 **Association of >1 previous PTB and early cessation of IM 17OHP w/ SPTB outcome at 37 wks, mean (min, max):** 0.62 (0.22, 1.82) *P* < 0.387

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rebarber and Ferrara et al., 2007 (continued)					**Mode of birth and complications during birth** ***Infant loss (stillbirths, miscarriages and PTB at 21 wks GA), n:** **G1a**: 1 **G1b**: 13 **Postpartum and neonatal complications** **Nursery LOS, mean days ± SD:** **G1a**: 13.8±26.2 **G1b**: 4.7±9.5 *P* < 0.001 **Median days (range):** **G1a:** 3.0 (1,157) **G1b:** 2.0 (1,103) **NICU admission, (%):** **G1a**: (45.7) **G1b**: (16.8) *P* < 0.001 **Longer term outcomes** NR

*G1a is out of 71 and G1b is out of 364

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Rebarber et al., 2007 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 04/2004 to 01/2006 **Funding:** ADA (article is listed as advertisement) **Author Industry Relationship Disclosure:** 3 of 7 Matria (3) **Design:** Retrospective cohort study	**Intervention:** 250 mg of IM17OHP weekly, begun at 16-20.9 wks gestation **Groups:** **G1:** 17OHP **G2:** control **N at enrollment:** **G1**: 557 **G2**: 1,524 **N at birth:** **G1**: 557 **G2**: 1,524 **N at follow-up:** **G1**: 557 **G2**: 1,524 **Age, median yrs (range) :** **G1**: 29 (16-44) **G2**: 30 (16-45) **Age > 37 years, n (%):** **G1**: 53 (9.5) **G2**: 125 (8.2) **Race/ethnicity:** NR **Parous, n (%):** **G1**: 557 (100) **G2**: 1,524 (100) **Maternal education:** NR **Maternal BMI, mean kg/m^2±SD :** **G1**: 26.2 ± 6.6 **G2**: 26.2 ± 6.7 **Obese BMI, n (%):** **G1:** 140 (25.1) **G2:** 340 (22.3)	**Inclusion criteria:** Singleton pregnancy Hx of prior PTB Enrolled in outpatient services at <27 wks GA Analysis inclusion required height, pre-pregnancy weight, and outcome data **Exclusion criteria:** Preexisting diagnosis of diabetes at admission for outpatient services Medical history of diabetes before current pregnancy Those who had "unknown" designated for GDM in antepartum outcome record Women experiencing recurrent PTB <28 wks in the current pregnancy	**Prior PTB, n (%):** **G1**: 557 (100) **G2**: 1,524 (100) **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Nursing support available, (%):** **G1**: (100) **G2**: (100) **Received daily PTB surveillance, (%):** **G1**: NR **G2**: (62.1) **Received specialized counseling and education from perinatal nurse, %:** **G1**: (100) **G2**: (100) **N of 17OHP injections, mean±SD:** **G1**: 14.9 ± 4.5 **G2**: 0 **GA at initiation, median (range):** **G1**: 19.0 (16.0-26.9) **G2**: 21.6 (4.7-25.9) *P* <0.001	**<u>Complications during pregnancy</u>** **Betamimetic tocolysis, n (%)**: **G1**: 101 (18.1) **G2**: 375 (24.6) *P* **=** 0.002 **GDM, n (%):** **G1**: 12.9 **G2**: 4.9 *P* < 0.001 OR: 2.9 (95% CI: 2.1 to 4.1) **Association of Betamimetic tocolysis w/ GDM outcome:** *P* = 0.852 OR: 1.04 (95% CI: 0.67 to 1.64) **Association of GA at start of outpatient care w/ GDM outcome:** *P* = 0.05 OR: 0.97 (95% CI: 0.933 to 1.000) **Association of 17OHP prophylaxis w/ GDM outcome:** *P* < 0.001 OR: 3.09 (95% CI: 2.17 to 4.40) **Association of Obese BMI (≥30 kg/m^2) w/ GDM outcome:** *P* < 0.001 OR: 6.91 (95% CI: 2.93 to 16.28)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rebarber et al., 2007 (continued)	**Maternal tobacco use, n (%):** **G1**: 54 (9.7) **G2**: 87 (5.7) **Medicaid:** NR **Private insurance coverage:** NR				**Association of Overweight BMI (25.0-29.9 kg/m^2) w/ GDM outcome:** *P* = 0.004 OR: 3.70 (95% CI: 1.53-8.92) **Association of Normal BMI (20.0-24.9 kg/m^2) w/ GDM outcome:** *P* = 0.192 OR: 1.80 (95% CI: 0.74-4.38) **Association of Tobacco use w/ GDM outcome:** *P* = 0.193 OR: 0.57 (95% CI: 0.24-1.33) **Prematurity** **Recurrent spontaneous PTB rate (GA at birth < 35 wks), %**: **G1**: 12.4 **G2**: 9.6 *P* **=** 0.062 **GA at birth:** **G1**: 36.9±2.3 **G2**: 37.1±2.4 *P* **=** 0.080 **Mode of birth and complications during birth** NR **Postpartum and neonatal outcomes** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Rebarber et al., 2008 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 01/2004 to 05/2006 **Funding:** NR **Author Industry Relationship Disclosure:** 3 of 7 Matria (3) **Design:** Retrospective cohort	**Intervention:** 250 mg of IM17OHP weekly, nurse-administered in home , along with 1 in-home education session including PTL materials and 24/7 nurse and pharmacist support Control: ONS including daily telephonic nursing assessment of HUAM and patient-reported symptoms of PTL **Groups:** **G1:** 17OHP **G1a:** 17OHP w/ hx of 1 PPTB **G1b:**17OHP w/ hx of >1 PPTB **G2**: control (ONS) **G2a:** ONS w/ hx of 1 PPTB **G2b:** ONS w/ hx of >1 PPTB **N at enrollment:** **G1**: 232 **G2**: 1650 **N at birth:** **G1**: 232 **G2**: 1650 **N at follow-up:** **G1**: 232 **G2**: 1650 **Age, mean yrs ± SD:** **G1**: 30.6 ± 5.5 **G2**: 29.5 ± 5.7 **Race/ethnicity:** NR	**Inclusion criteria:** History of SPTD Cervical cerclage in current pregnancy Current singleton gestation ready for treatment or service at 16.0-28.9 wks GA **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** **G1**: 232 (100) **G2**: 1650 (100) **>1 Prior PTB, (%):** **G1**: (39.2) **G2**: (31.8) *P* = 0.030 **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1**: 232 (100) **G2**: 1650 (100) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**Total IM 17OHP administrations, mean n ± SD:** **G1:** 13.5 ± 5 **G2:** NA **GA at initiation, mean wks ± SD:** **G1**: 20.3 ± 3.6 **G2**: 24.6 ± 3.2	**Complications during pregnancy** *Antenatal hospitalizations (≥ 24 h stay for symptoms of PTL, w/ or w/o PTB), (%): **G1**: (45.7) **G2**: (70.8) *P* < 0.001 **G1**a: (44.0) **G2**a: (70.3) *P* < 0.001 **G1**b: (48.4) **G2**b: (72.0) *P* < 0.001 PPROM, **(**%): **G1**: (8.6) **G2**: (8.1) *P* = 0.770 **G1**a: (9.9) **G2**a: (8.4) *P* = 0.522 **G1**b: (6.6) **G2**b: (7.4) *P* = 0.949 **Prematurity** **Birth weight**: NR **GA at birth, mean wks ± SD:** **G1**: 35.4 ± 4.7 **G2**: 36.0 ± 3.0 *P* = 0.388 **G1**a: 35.6 ± 4.6 **G2**a: 36.1 ± 3.0 *P* = 0.608 **G1**b: 35.2 ± 4.9 **G2**b: 35.7 ± 3.0 *P* = 0.273

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rebarber et al., 2008 (continued)	**Parous, n (%):** **G1**: 232 (100) **G2**: 1650 (100) **Maternal education:** NR **Maternal smoking, (%):** **G1**: **(**3.0) **G2**: (5.8) **Medicaid:** NR **Private insurance coverage:** NR				**SPTD < 37 wks, %**: **G1**: 40.5 **G2**: 46.2 *P* = 0.121 **G1**a: 39.7 **G2**a: 44.7 *P* = 0.300 **G1**b: 41.8 **G2**b: 49.3 *P* = 0.222 **SPTD <35 wks, %**: **G1**: 25.9 **G2**: 21.5 *P* = 0.152 **G1**a: 24.8 **G2**a: 20.1 *P* = 0.187 **G1**b: 27.5 **G2**b: 24.4 *P* = 0.618 **SPTD <32 wks, %**: **G1**: 13.4 **G2**: 7.9 *P* = 0.008 **G1**a: 12.8 **G2**a: 7.7 *P* = 0.060 **G1**b: 14.3 **G2**b: 8.4 *P* = 0.110 **SPTD 24-32 wks, %**: **G1**: 8.2 **G2**: 7.5 ***P* = 0.792** **Mode of birth and complications during birth** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rebarber et al., 2008 (continued)					**Postpartum and neonatal complications** NR **Longer term outcomes** NR

*AP hospitalizations defined the same as PTL diagnosis and are combined here

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Reinisch and Karrow, 1977 **Country:** US **Participant source:** Community **Intervention setting:** Home **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Case control	**Intervention:** In utero exposure to exogenous progestin and estrogen **Groups:** **G1:** children exposed to hormones in utero **G1a:** children exposed to highest amounts of estrogenic hormones and the lowest dosages of progestin **G1b:** children exposed to intermediate dosages of progestin and the lowest amounts of estrogen **G1c:** children exposed to maximum dosages of progestin and intermediate amounts of estrogen **G2:** siblings with same parents not exposed to hormones **G2a:** unexposed children matched to those exposed to highest amounts of estrogenic hormones and the lowest dosages of progestin	**Inclusion criteria:** Mother had been treated during at least one pregnancy with synthetic progestin and estrogen Treatment during pregnancy had to conform to a minimum of 4 weeks of hormone administration during the first two trimesters Family included one sibling from the same parents whose gestation was not at risk and not treated for hormones for comparison Subjects at least 4 years old for Wechsler IQ test **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR **Retroverted uterus, n:** **G1**: 1 **G2**: 0 **Incompetent cervix, n:** **G1**: 3 **G2**: 0	**Mean total dose hormone, mg (range):** **G1**: progestin: 2779.75 (478 – 10,650) estrogen: 1495.36 (0 – 13,925) **G2**: NA **Duration of hormone exposure, mean wks (range):** **G1**: progestin: 17.03 (3.97 – 36.08) estrogen: 13.36 (0 – 34.22) **G2**: NA **Range total dose progestin, mg:** **G1**a: 478-5611 **G1**b: 525-9890 **G1**c: 490-10,650 **G2**: NA **Range total dose estrogen, mg:** **G1**a: 3500-13,905 **G1**b: 4-40 (17 of 26 recieved no estrogen) **G1**c: 6-1390 **G2**: NA **Ratio progestin to estrogen, mg (range):** **G1**a: >1:1.5 (1:9 – 1:1.5) **G1**b: >100-1 (100:1 – 358:1) **G1**c: <100-1 (3:1 – 82:1) **G2**: NA	**<u>Complications during pregnancy</u>** **Chorioamnionitis, n (%):** NR Antenatal hospitalizations, n (%): NR **IUGR, n (%):** NR **Allergic reactions, n (%):** NR **GDM, n (%):** NR **Anemia, n:** **G1**: 0 **G2**: 1 **Bed rest, n:** **G1**: 9 **G2**: 0 **Bleeding, n:** **G1**: 43 **G2**: 12 **Bloody urine, n:** **G1**: 0 **G2**: 1 **Cramps (serious), n:** **G1**: 8 **G2**: 1 **Edema, n:** **G1**: 9 **G2**: 2 **Hypertension, n:** **G1**: 1 **G2**: 0 **Nausea (severe), n:** **G1**: 1 **G2**: 0 **Premature labor, n:** **G1**: 2 **G2**: 1

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)	**G1b:** unexposed children matched to those exposed to intermediate dosages of progestin and the lowest amounts of estrogen **G1c:** unexposed children matched to those exposed to maximum dosages of progestin and intermediate amounts of estrogen **N at enrollment (males, females):** **G1** + **G2**: 141 in 56 families **G1**: 71 (26, 45) **G1**a: 16 (5, 11) **G1**b: 26 (10, 16) **G1**c: 29 (11, 18) **G2**: 70 (27, 43) **G2**a: 13 (2, 11) **G2**b: 29 (16, 13) **G2**c: 33 (14, 19) **N at birth:** NA **N at follow-up:** **G1** + **G2**: 141 in 56 families **G1**: 71 **G1**a: 16 (5, 11) **G1**b: 26 (10, 16) **G1**c: 29 (11, 18) **G2**: 70 **G2**a: 13 (2, 11) **G2**b: 29 (16, 13) **G2**c: 33 (14, 19) **Age at time of testing, mean yrs, (range):** **G1**: 11.23 (5 – 17) **G1**a: 12.06 (6 – 15)				**Toxemia, n:** **G1**: 0 **G2**: 2 **Weight gain (excessive), n:** **G1**: 2 **G2**: 2 **Viral meningitis, n:** **G1**: 0 **G2**: 1 **Placenta issues, n:** **G1**: 5 (1 focal sclerosis, 1 man y infarcts, 1 large placenta, 2 twin births) **G2**: 2 (1 foamy placenta, 1 placenta previa) **<u>Prematurity</u>** **Birth weight - lbs, ozs (range)**: **G1**a: 7,0 (5,6 – 9,4) **G1**b: 6,9 (3,10 – 8,10) **G2**a: 7,2 (5,9 – 8,10) **G2**b: 6,15 (4,14 – 8,8) 1 premature (<2500 kg) birth each in **G1**a and **G2**a. **GA at birth, mean wks, days (range):** **G1**a: 38,3 (34,4 – 40,2) **G1**b: 38,3 (30,5 – 42,3) **G2**a: 39,4 (35,3 – 45,1) **G2**b: 39,2 (33,6 – 41,4)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)	**G1**b: 12.46 (5 – 17) **G1**c: 10.61 (6 – 18) **G2**: 11.29 (4 – 21) **G2**a: 11.81 (8 – 16) **G2**b: 111.81 (6 – 18) **G2**c: 12.12 (4 – 21) **Race/ethnicity, n (%):** NR **Parous, n (%):** NA **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NR **Private insurance coverage:** NR **Other prenatal medication exposures reported for G1, n:** Thyroid: 4 Cytomel: 7 Methergine: 2 Prednisone: 2 Proloid: 1 Sterane: 5 Synthroid: 5				**Premature birth, n:** **G1**: 6 **G2:** 1 **<u>Mode of birth and complications during birth</u>** **Cesarean birth, n (%):** **G1**: 5 **G2**: 0 **Surgical complications, n (%):** NR **Maternal Harms, n (%):** NR **Artificial rupture of membranes, n:** **G1**: 4 **G2**: 8 **Breech , n:** **G1**: 5 **G2**: 1 **Cord around neck, n:** **G1**: 2 **G2**: 1 **Fetal heart tone slowed, n:** **G1**: 2 **G2**: 0 **Induced labor, n:** **G1**: 4 **G2**: 6 **Premature rupture, n:** **G1**: 2 **G2**: 2 **Prolapsed cord, n:** **G1**: 1 **G2**: 1

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)					**Prolonged labor, n:** **G1**: 2 **G2**: 1 **Placenta issues, n:** **G1**: 2 (1 abruptio/ablatio, 1 adherent) **G2**: 4 (2 adherent, 2 retained) **Postpartum and neonatal complications** NR **Longer term outcomes** **Neurodevelopmental delay, n (%):** NR **Future fertility, n (%):** NR **Full IQ, mean score:** **G1**: 121.85 **G2**: 119.92 The Wechsler Preschool and Primary Scale of Intelligence (WPPSI) was given to subjects 4 years of age (N = 2), the Wechsler Intelligence Scale for Children (WISC) to subjects between 5 years and 15 years 11 months (n= 124), and the Wechsler Adult Intelligence Scale (WAIS) to subjects who were over 16 years of age (n=15).

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)					**Personality factors [range 1-9, norm set at 5], mean score (group mean difference):** Dry cognitive style vs dependence on feeling **G1**a: 4.98 (-0.60) **G1**b: 5.84 (+0.64) **G1**c: 6.26 (+0.28) **G2**: NR Independent vs subdued **G1**a: 7.30 (+1.19) **G1**b: 5.13 (-0.05) **G1**c: 5.49 (-0.17) **G2**: NR Sensitive vs tough minded **G1**a: 6.75 (+0.37) **G1**b: 5.28 (-0.65) **G1**c: 4.54 (-1.13) **G2**: NR Individuallistic vs group oriented **G1**a: 7.82 (+1.39) **G1**b: 4.04 (-1.40) **G1**c: 5.24 (+0.03) **G2**: NR Insecure vs self assured **G1**a: 2.54 (-1.03) **G1**b: 5.07 (-0.06) **G1**c: 4.66 (-0.16) **G2**: NR Self-sufficient vs group dependent **G1**a: 6.70 (+2.93) **G1**b: 3.11 (-3.67) **G1**c: 6.14 (-0.16) **G2**: NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)					The Early School Personality Questionnaire (ESQP) was administered to subjects 5 years 11 months through 7 years of age (N = 22), the Children's Personality Questionnaire (CPQ) to subjects 8-11 years of age (n = 50), the High School Personality Questionnaire (HSPQ) to subjects 12-17 years of age (n = 61), and the 16 Personality Factors (16 PF) to subjects 18 years and older (N = 6). The two children who were under 5 years of age were not tested.

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Resseguie et al., 1985 **Country:** US **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** January 1, 1936 to December 31, 1974 **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Retrospective cohort	**Intervention:** Progestin exposure during pregnancy, including 17-alpha-hydroxyprogesterone caproate (n=649), progesterone (n=244), medroxyprogesterone (n=60), ethisterone (n=45), algesterone acetophenide (n=24), norethindrone (n=11), dydrogesterone (n=1) **Groups:** **G1*:** exogenous progesterone exposure *in utero* **G1a:** 17-alpha hydroxyprogesterone caproate exposure *in utero* **G2:** no exogenous progesterone exposure *in utero* **G2a:** no exogenous progestin exposure *in utero*, matched to **G1**a **N at enrollment:** **G1:** 988 **G1a:** 609 **G2:** 1976 **G2a:** 1218 **N at birth:** **G1:** 988 **G1a:** 609 **G2:** 1976 **G2a:** 1218	**Inclusion criteria:** Children born to women receiving prenatal care at Mayo Clinic Exposed group: exposure *in utero* to any exogenous progestin but not exposed to any other sex hormone or gonadotropin Unexposed group: children not exposed *in utero* to an exogenous progestin **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** NR **Multiple gestation, n (%):** NR **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM, n (%):** NR	**Provider knowledge and attitudes, n (%):** NR **Provider specialty, n (%):** NR **Cost of drug, n (%):** NR **Drug availability, n (%):** NR **Medicaid, n (%):** NR **Private insurance, n (%):** NR **Day of gestation at 1st exposure to progestins, median (25th centile – 75th centile) (earliest – latest):** Any progestin **G1**: 60 (46-84) (0-266) 17-alpha-hydroxyprogesterone caproate: **G1**: 60 (47-82) (4-249) Progesterone: **G1**: 59.5 (43-93.5) (0-266)	**<u>Complications during pregnancy</u>** **Chorioamnionitis n (%):** NR **Antenatal hospitalizations, n (%):** NR **IUGR, n (%):** NR **Allergic reactions, n (%):** NR **GDM, n (%):** NR **<u>Prematurity</u>** **Birth weight<2500 g, n (%)**: **G1**: 89 (9.0) **G1a:** 59 (9.7) **G2**: 92 (4.7) **G2a:** 55 (4.5) **GA at birth:** NR **<u>Mode of birth and complications during birth</u>** **Stillbirth, n (%):** **G1:** 11 (1.1) **G1a:** 9 (1.5) **G2:** 20 (1.0) **G2a:** 14 (1.2) **Cesarean birth, n (%):** NR **Surgical complications, n (%):** NR **Maternal harms, n (%):** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Resseguie et al., 1985 (continued)	**N at follow-up:** **G1:** 988 **G1a:** 609 **G2:** 1976 **G2a:** 1218 **Age, mean yrs±SD (median):** **G1:** 27.6±5.0 (27) **G2:** 27.3±4.7 (27) **Race/ethnicity, n (%):** NR **Prior live births, mean±SD (median):** **G1:** 1.3±1.3 (1) **G2:** 1.3±1.3 (1) **Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NR **Private insurance coverage:** NR			**Total dose of 17-alpha-hydroxyprogesterone caproate (among those not receiving other exogenous progestins, n=501), median (25th centile – 75th centile) (min-max):** 1625 (500-3000) (125-11250)	**<u>Postpartum and neonatal complications</u>** **Neonatal death, n (%):** **G1:** 26 (2.6) **G1a:** 18 (3.0) **G2:** 20 (1.0) **G2a:** 12 (1.0) **<u>Longer term outcomes</u>** **Neurodevelopmental delay, n (%):** NR **Future fertility, n (%):** NR **Any major anomaly, n (%):** **G1:** 54 (5.5) **G1a:** 38 (6.2) **G2:** 88 (4.5) **G2a:** 52 (4.3) **Any anomaly, including hydrocele, n (%):** **G1:** 280 (28.3) **G1a:** 166 (27.3) **G2:** 478 (24.2) **G2a:** 294 (24.1) **Any anomaly, excluding hydrocele, n (%):** **G1:** 254 (25.7) **G1a:** 151 (24.8) **G2:** 431 (21.8) **G2a:** 265 (21.8) **Genitourinary anomaly, including hydrocele, n (%):** **G1**: 88 (8.9) **G1**a: 57 (9.4) **G2**: 151 (7.6) **G2**a: 94 (7.7)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Resseguie et al., 1985 (continued)					**Genitourinary anomaly, excluding hydrocele, n (%):** **G1**: 36 (3.6) **G1**a: 22 (3.6) **G2**: 53 (2.7) **G2**a: 28 (2.3) **Anomaly of female genitalia, n (%):** **G1**: 12 (2.5) **G1**a: 7 (2.3) **G2**: 18 (1.9) **G2**a: 10 (1.7) **Anomaly of male genitalia, n (%):** **G1**: 16 (3.1) **G1**a: 14 (4.5) **G2**: 25 (2.4) **G2**a: 16 (2.6) **Hypospadias, n (%):** **G1**: 5 (1.0) **G1**a: 5 (1.6) **G2**: 15 (1.5) **G2**a: 11 (1.8) **Abnormal testis, n (%):** **G1**: 9 (1.8) **G1**a: 7 (2.3) **G2**: 12 (1.2) **G2**a: 6 (1.0) **CNS anomaly, n (%):** **G1**: 25 (2.5) **G1**a: 13 (2.1) **G2**: 46 (2.3) **G2**a: 25 (2.1) **Major CNS anomaly, n (%):** **G1**: 4 (0.4) **G1**a: 4 (0.7) **G2**: 9 (0.5) **G2**a: 7 (0.6)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Resseguie et al., 1985 (continued)					**Major cardiovascular anomaly, n (%):** **G1**: 9 (0.9) **G1**a: 5 (0.8) **G2**: 18 (0.9) **G2**a: 12 (1.0) **Inguinal hernia, n (%):** **G1**: 52 (5.3) **G1**a: 32 (5.3) **G2**: 83 (4.2) **G2**a: 54 (4.4) **Limb reduction defect, n (%):** **G1**: 1 (0.1) **G1**a: NR **G2**: 4 (0.2) **G2**a: NR **Malignancy, n (%):** **G1**: 4 (0.4) **G1**a: NR **G2**: 6 (0.3) **G2**a: NR

*742 of 988 exposed children (75%): 1st in utero exposure to exogenous progestin occurred during 1st trimester

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion/ Exclusion Criteria	Clinical Indicators	Aspects of Care	Outcomes
Author: Rittenberg et al., 2007 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 04/2004 to 01/2006 **Funding:** NR **Author Industry Relationship Disclosure:** 3 of 6 Matria (3) **Design:** Retrospective case series	**Intervention:** 250 mg IM 17OHP administered during weekly skilled nursing visits **Groups:** **G1:** Pregnant women receiving outpatient 17OHP tx **G1a:** Singletons with PPTD **G1b:** singletons without PPTD **G1c:** Multiple gestation with PPTD **G1d:** Multiple gestation without PPTD **N at enrollment:** **G1**: 2159 **N at birth:** **G1**: 1979 **G1a:** 1517 **G1b:** 297 **G1c:** 56 **G1d:** 109 **N at follow-up:** **G1**: 1979 **G1a:** 1517 **G1b:** 297 **G1c:** 56 **G1d:** 109 **Age, mean yrs ± SD:** **G1**a: 29.6 ± 5.6 **G1**b: 30.0 ± 5.5 **G1**c: 31.9 ± 5.8 **G1**d: 31.6 ± 5.9 **Race/ethnicity:** NR **Parous, :** NR	**Inclusion criteria:** Pregnant women enrolled in an outpatient 17OHP administration program provided by Matria Healthcare Documented pregnancy outcomes **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** **G1**: 1573 (79.5) **G1b:** 95 (32) **Multiple gestation, n (%):** **G1**: 165 (8.3) **Fetal fibronectin, baseline:** NR **Cervical length, baseline:** NR **Cerclage, n (%)** **G1a:** 259 (17.1) **G1b:** 69 (23.2) **G1c:** 14 (25.0) **G1d:** 22 (20.2) **GA of PTB:** NR **PPROM, n (%):** NR	**Discontinued after 1 injection, n (%):** **G1:** 59 (3) **G1a:** 37 (2.4) **G1b:** 10 (3.4) **G1c:** 3 (5.4) **G1d:** 9 (8.3) **Discontinued injections prior to 34 wks (elective and PTD), n (%):** **G1:** 474/1979 (24.0) **Injections, mean ± SD:** **G1a: 12.6 ± 5.6** **G1b: 10.5 ±5.5** **G1c: 9.4 ± 5.1** **G1d: 8.0 ± 4.8** **GA at start of 17OHP, mean wks ± SD:** **G1**a: 21 ± 4.4 **G1b:** 23.1 ± 4.7 **G1c:** 21.6 ± 4.3 **G1d:** 23.2 ± 4.2 **≥ 21 wks gestation at 17OHP initiation, n (%):** **G1**a: 665 (43.8) **G1b:** 190 (64.0) **G1c:** 23 (41.1) **G1d:** 76 (69.7) **GA at discontinuation, mean wks ± SD:** **G1:** 28.9 ± 4.7 **Receiving care at community hospitals, (%):** **G1:** (88.3)	**Complications during pregnancy** **Experienced PTL with or without PTD, n (%):** **G1:** 877 (44.3) **Prematurity** **Birth weight**: NR **GA at birth mean weeks ± SD:** **G1**a: 36.4 ± 3.5 **G1**b: 36.6 ± 3.5 **G1**c: 32.5 ± 3.8 **G1**d: 33.3 ± 3.5 Delivery at <32 wks, (%): **G1**: (9.0) Delivery at <35 wks,(%): **G1**a: (22.1) Delivery at <37 wks, n (%): **G1**a: 681 (44.9) **G1**b: 120 (40.4) **G1**c: 51 (91.1) **G1**d: 102 (93.6) SPTD at < 32 wks, n (%): **G1**a: 91 (6.0) **G1**b: 19 (6.4) **G1**c: 13 (23.2) **G1**d: 19 (17.4) SPTD at < 35 wks, n (%): **G1**a: 225 (14.8) **G1**b: 39 (13.1) **G1**c: 29 (51.8) **G1**d: 44 (40.4)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion/ Exclusion Criteria	Clinical Indicators	Aspects of Care	Outcomes
Rittenberg et al., 2007 (continued)	**Maternal education, n (%):** NR **Maternal smoking, n (%):** **G1a:** 102 (6.7) **G1b:** 14 (4.7) **G1c:** 4 (7.1) **G1d:** 3 (2.8) **Maternal BMI:** NR **Medicaid, n (%):** **G1:** 414 (21) **Private insurance coverage or self-pay, n (%)** **G1:** 1565 (79)				SPTD at < 37 wks, n (%): **G1**a: 549 (36.2) **G1**b: 93 (31.3) **G1**c: 36 (64.3) **G1**d: 60 (55.0) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Rittenberg et al., 2008 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 04/2004 to 03/2007 **Funding:** NR **Author Industry Relationship Disclosure:** 3 of 6 Matria (3) **Design:** Retrospective cohort, matched by Medicaid status and GA at hospitalization for PTL	**Intervention:** 250 mg of IM 17OHP weekly **Groups:** **G1:** 17OHP w/ dPNS, including HUAM and telephonic perinatal nursing assessment **G2:** 17OHP w/ weekly home nursing visits for 17OHP administration **N at enrollment:** **G1**: 99 **G2**: 280 **N at birth:** **G1**: 83 **G2**: 83 **N at follow-up:** NA **Age, mean yrs ± SD:** **G1**: 30.2 ± 5.5 **G2**: 30.9 ± 5.4 **Race/ethnicity, (%):** **Black** **G1**: (16.9) **G2:** (18.1) **Parous:** NR **Maternal education:** NR **Maternal smoking, (%):** **G1**: (7.2) **G2**: (4.8) **Maternal BMI:** NR	**Inclusion criteria:** Enrolled in outpatient 17OHP administration program between 16 and 26 wks gestation Singleton pregnancy Hx of prior SPTD < 37 wks gestation Hospitalized for PTL at <34 wks gestation, successfully treated and remained undelivered for ≥ 3 ds **Exclusion criteria:** See inclusion criteria	**Prior PTB, n (%):** **G1**: 83 (100) **G2**: 83 (100) **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage,(%):** **G1**: (18.1) **G2**: (16.9) **Cervical length, baseline:** NR **GA of prior PTB:** NR **PPROM:** NR **> 1 previous SPTD, (%):** **G1:** (30.1) **G2:** (30.1)	**GA at diagnosis of PTL, mean wks ± SD:** **G1:** 28.2 ± 3.9 **G2:** 28.2 ± 4.0 **GA at initiation of 17OHP, mean wks ± SD:** **G1:** 20.0 ± 3.3 **G2:** 19.7 ± 3.1 **GA of 21-26 wks at 17OHP initiation, (%):** **G1:** (36.1) **G2:** (34.9) **N of IM 17OHP administrations, mean ± SD:** **G1:** 12.8 ± 4.9 **G2:** 11.9 ± 5.0	**Complications during pregnancy** NR **Prematurity** **Birth weight**: NR **GA at birth, mean wks ± SD:** **G1**: 35.2 ± 3.3 **G2**: 33.9 ± 4.5 *P*=0.027 Δ: +1.3 [95% CI: +0.16, +2.5] **SPTD < 37 wks, (%):** **G1:** (59.0) **G2:** (61.5) *P*=0.86 **SPTD<35 wks, (%):** **G1:** (24.1) **G2:** (49.4) *P*=0.001 OR: 0.25 [95% CI: 0.17, 0.33] **SPTD<32 wks, (%)** **G1:** (9.6) **G2:** (24.1) *P*=0.017 OR: 0.29 [95% CI: 0.21, 0.38] **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rittenberg et al., 2008 (continued)	**Medicaid, (%):** **G1**: (15.7) **G2**: (15.7) **Private insurance coverage:** NR				

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Rittenberg et al., 2009 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 1995 to 2005 **Funding:** South Carolina Department of Health and Human Services (Matria noted as vendor for many of the services provided in this grant) **Author Industry Relationship Disclosure:** 4 of 5 Matria (4) **Design:** Retrospective cohort, matched on maternal race, marital status, tobacco use, and number of PTD	**Intervention:** 250 mg of IM 17OHP every 7-10 ds, until wk 36 gestation vs. dPNS, including education on signs and symptoms of PTL, with ≥ 2x daily HUAM **Groups:** **G1:** 17OHP **G2:** dPNS **N at enrollment:** **G1**: 385 **G2**: 385 **N at birth:** **G1**: 342 **G2**: 342 **N at follow-up:** **G1**: 342 **G2**: 342 **Age, mean yrs ± SD (median):** **G1**: 29.1 ± 5.2 (29) **G2**: 29.3 ± 5.6 (30) **Race/ethnicity, n (%):** African American: **G1**: 78 (22.8) **G2**: 78 (22.8) **Parous:** NR **Maternal education:** NR **Maternal smoking, n (%):** **G1**: 37 (10.8) **G2**: 37 (10.8)	**Inclusion criteria:** Singleton pregnancy History of prior SPTD Referred for weekly 17OHP administration or dPNS Enrolled at < 27 wks gestation **Exclusion criteria:** Simultaneously receiving 17OHP and dPNS Diagnosis of PTL Cervical erclage Vaginal bleeding at enrollment	**Prior PTB, n (%):** **G1**: 385 (100) **G2**: 385 (100) Previous PTD, n (%): >1 **G1**: 119 (34.8) **G2:** 119 (34.8) 1 (65.2) 2 (27.8) **3** (6.4) **4** (0.6) **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage, n (%):** **G1**: 0 (0) **G2**: 0 (0) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at initation of 17OHP or HUAM, mean wks ± SD (median):** **G1:** 19.3 ± 2.9 (18.7) **G2:** 23.7 ± 2.1 (24.1) **17OHP injections started at < 21 wks gestation, (%):** **G1:** (80.4) **Mean 17OHP injections:** **G1:** 15.5 **Mean interval of 17OHP injections, ds:** **G1:** 7.1 **Discontinued x at < 34 wks for reasons other than delivery, n (%):** **G1**: 32 (9.4) **G2**: 25 (7.3) *P*= 0.333 **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**Complications during pregnancy** **PPROM, n (%):** **G1**: 25 (7.3) **G2**: 29 (8.5) *P* = 0.677 Antenatal hospitalizations, n (%): **G1**: 43 (12.6) **G2**: 147 (43.0) *P* < 0.001 **Diagnosis of PTL w/ or w/o PTD, n (%):** **G1:** 134 (39.2) **G2:** 208 (60.8) *P* < 0.001 **Tocolysis, n (%):** **G1:** 44 (12.9) **G2:** 170 (49.7) *P* < 0.001 **Prematurity** **Birth weight**: NR **GA at birth, mean wks ± SD (median):** **G1**: 36.6 ± 3.0 (37.1) **G2**: 36.7 ± 2.9 (37.1) *P* = 0.842 **GA at birth < 37 wks, n (%)** **G1:** 157 (45.9) **G2:** 146 (42.7) *P* = 0.436

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rittenberg et al., 2009 (continued)	**Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR				**SPTD, n (%):** **< 37 wks** **G1:** correct data NR* **G2:** 102 (29.8) *P* = 0.245 **< 35 wks** **G1:** 41 (12.0) **G2:** 37 (10.8) *P* = 0.712 **< 32 wks** **G1:** 13 (3.8) **G2:** 17 (5.0) **Medically indicated preterm delivery, n (%):** **G1:** 40 (11.7) **G2:** 44 (12.9) **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

*Correct data not reported, 17/342 as 24.2%

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Rouse et al., 2007 **Country:** US **Participant source:** Academic multi-site **Intervention setting:** Clinic **Enrollment period:** 04/2004 to 02/2006 **Funding:** NIH **Author Industry Relationship Disclosure:** NR **Design:** RCT, double-blind, placebo controlled	**Intervention:** 250 mg of IM 17OHP weekly, begun at 16-20 wks until 35 + 6 wks gestation **Groups:** **G1:** 17OHP **G1a:** 17OHP infants/fetuses **G2:** Placebo (Castor Oil) **G2a:** Placebo infant/fetuses **N at enrollment:** **G1**: 327 **G2**: 334 **N at birth:** **G1**: 325 **G1a:** 650 **G2**: 330 **G2a:** 660 **N at follow-up:** **G1**: 325 **G1a:** 632 **G2**: 330 **G2a:** 648 **Age, mean yrs ± SD:** **G1**: 29.7 ± 7.0 **G2**: 29.6 ± 6.8 **Race/ethnicity, n (%):** **White:** **G1**: 218 (66.7) **G2**: 218 (65.3) **Black:** **G1**: 75 (22.9) **G2**: 80 (24.0) **Asian:** **G1**: 8 (2.4) **G2**: 5 (1.5) **Hispanic or Latino:** **G1**: 51 (15.6) **G2**: 54 (16.2)	**Inclusion criteria:** Twin gestations GA 16 wks to 20 wks + 3 days **Exclusion criteria:** Serious fetal anomalies Spontaneous death of fetus after 12 wks Monoamnionic placenta Suspected TTTS Marked ultra-sonographic growth discordance (difference of ≥3 wks GA) Planned nonstudy progesterone therapy after 16 wks In-place or planned cerclage Major uterine anomaly Tx with ≥10,000 units of unfractionated heparin per day, Tx with low-molecular-weight heparin Major chronic medical diseases Twin gestations that were the result of intentional fetal reduction	**Prior PTB, n (%):** **G1**: 20 (6.1) **G2**: 30 (9.0) **Multiple gestation,(%):** **G1**: (100) **G2**: (100) **Fetal fibronectin, baseline:** NR **Dichorionic Placenta, n (%):** **G1**: 268 (82.0) **G2**: 277 (82.9) **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **PPROM:** NR	**Proportion of protocol-specified injections, (%):** **G1:** (94.5) **G2:** (95.0) **GA at randomization, mean wks** ± SD **:** **G1**: 19.2 ± 1.5 **G2**: 19.2 ± 1.4 **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**<u>Complications during pregnancy</u>** **Chorioamnionitis, n (%):** **G1**: 6 (1.9)* **G2**: 6 (1.8) **Hypertensive disorder, n (%):** **G1**: 66 (20.3) **G2**: 55 (16.7) Cerclage placement, n (%): **G1**: 6 (1.9)* **G2**: 4 (1.2) **Corticosteroids for fetal maturation, n (%):** **G1**: 80 (24.7)* **G2**: 90 (27.3) **Tocolytic Therapy, n (%)*:** **G1**: 71 (21.9) **G2**: 97 (29.4) **Any side effects, n (%)†:** **G1**: 211 (65.9) **G2**: 210 (64.4) **Injection site, n (%)†:** **G1**: 197 (61.6) **G2**: 203 (62.3) **Urticaria, n (%)†:** **G1**: 11 (3.4) **G2**: 4 (1.2) **Nausea, n (%)†:** **G1**: 5 (1.6) **G2**: 10 (7.1) **Other side effects, n (%)†:** **G1**: 24 (7.5) **G2**: 23 (7.1)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)	**Other:** **G1**: 26 (8.0) **G2**: 31 (9.3) **Nulliparous, n (%):** **G1**: 151 (46.2) **G2**: 145 (43.4) **Maternal educational level, mean yrs ± SD:** **G1**: 13.6 ± 2.8 **G2**: 13.6 ± 2.9 **Maternal smoking, n (%):** **G1**: 38 (11.6) **G2**: 31 (9.3) **Maternal BMI (pre-pregnancy), mean kg/m^2 ± SD:** **G1:** 26.7 ± 6.5 **G2:** 27.1 ± 7.1 **Medicaid:** NR **Private insurance coverage:** NR				**Side effect leading to discontinuation , n (%)[†]:** **G1**: 2 (0.6) **G2**: 1 (0.3) **Prematurity** **GA at Delivery, wk ± sd:** **G1**: 34.6 ± 3.9 **G2**: 34.9 ± 3.6 **Delivery or fetal death at < 35 wk, n (%):** **G1**: 135 (41.5) **G2:** 123(37.3) RR: 1.1 (95% CI: 0.9 to 1.3) **GA at delivery or fetal death, < 37 wks, n (%):** **G1**: 226 (69.5) **G2**: 232 (70.3) RR: 1.0 (95% CI: 0.9 to 1.1) **GA at delivery or fetal death, <32 wks, n (%):** **G1**: 55 (16.9) **G2**: 48 (14.5) RR: 1.2 (95% CI: 0.8, 1.7) **G1**: 26 (8.0) **G2:** 20 (6.1) RR: 1.3 (95% CI: 0.8 to 2.3) Birth weight < 2500 g**, n (%):G1**: 377 (60.0) **G2**: 415 (64.0) RR: 0.9 (95% CI: 0.8 to 1.0)Birth weight < 1500 g**, n (%):< G1:** 81 (12.9) **G2:** 64 (9.9) RR: 2.0 (95% CI: 1.0 to 3.9)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)					**Mode of birth and complications during birth** **Cesarean birth, n/N (%):** **G1**: 200 (61.7)* **G2:** 204 (62.2)‡ RR: 1.0 (95% CI: 0.9 to1.1) **2 live births, n (%):** **G1**: 125 (38.5) **G2**: 115 (34.8) RR: 1.1 (95% CI: 0.9 to 1.4) **≥ 1 fetal death, n (%):** **G1**: 10 (3.1) **G2**: 8 (2.4) RR: 1.3 (95% CI: 0.9 to 1.5) **Spontaneous delivery, n (%):** **G1**: 101 (31.2)* **G2**: 86 (26.1) RR: 1.2 (95% CI: 0.9 to 1.5) **Medically indicated delivery, n (%):** **G1**: 33 (10.2)* **G2**: 37 (11.2) RR: 0.9 (95% CI: 0.6 to 1.4) **Postpartum and neonatal complications** **Major malformation, n (%):** **G1**: 3 (0.5) **G2:** 4 (0.6) RR: 0.5 (95% CI: 0.1 to 2.4)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)					**5-Minute Apgar score < 7, n (%):** **G1**: 27 (4.3) **G2**: 33 (5.1) RR: 0.9 (95% CI: 0.5 to1.6) **Patent ductus arteriosus, n (%):** **G1**: 18 (2.8) **G2**: 31 (4.8) RR: 0.7 (95% CI: 0.4 to 1.3) **Pneumonia, n (%):** **G1**: 8 (1.3) **G2**: 10 (1.5) RR: 1.0 (95% CI: 0.4 to 2.7) **Mechanical ventilation, n (%):** **G1**: 70 (11.1) **G2**: 77 (11.9) RR: 1.0 (95% CI: 0.7 to 1.5) **Seizures, n (%):** **G1**: 5 (0.8) **G2**: 5 (0.8) RR: 1.3 (95% CI: 0.5 to 5.0) **Severe retinopathy of prematurity, n:** **G1**: 0 **G2:** 0 **RDS, n (%):** **G1**: 96 (15.2) **G2**: 87 (13.4) RR: 1.2 (95% CI: 0.8 to 1.6) **Early-onset, culture-proven sepsis, n (%):** **G1**: 24 (3.8) **G2**: 26 (4.0) RR: 1.0 (95% CI: 0.6 to 1.9)

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)					**Stage 2 or 3 necrotizing enterocolitis , n (%):** **G1**: 3 (0.5) **G2**: 4 (0.6) RR: 0.8 (95% CI: 0.1 to 3.0) **Bronchopulmonary dysplasia, n (%):** **G1**: 19 (3.0) **G2**: 17 (2.6) RR: 1.2 (95% CI: 0.6 to 2.7) **Grade 3 or 4 IVH, n (%):** **G1**: 7 (1.1) **G2**: 6 (0.9) RR: 1.0 (95% CI: 0.3 to 3.1) **Periventricular leukomalacia, n (%):** **G1**: 5 (0.8) **G2**: 6 (0.9) RR: 0.9 (95% CI: 0.3 to 2.8) **Longer term outcomes** NR

*G1 out of 324 participants
†G1 out of 320 and G2 out of 326 participants
‡G2 out of 328 participants

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Suvonnakote, 1986 **Country:** Thailand **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Non-randomized clinical trial	**Intervention:** 250 mg of IM 17OHP weekly,initiated at 16 -20 wks GA and continued until 37+6 wks GA or until patient chooses to stop **Groups:** **G1:** IM 17OHP **G2:** Control **N at enrollment:** **G1**: 36 **G2**: 39 **N at birth:** **G1***: 35 **G2**: 39 **N at follow-up:** **G1***: 35 **G2**: 39 **Age, mean yrs ± SD:** **G1**: 25.25 ± 4.6 **G2**: 24.77 ± 4.9 **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR Maternal BMI: NR **Maternal smoking:** NR **Medicaid:** NR **Private insurance coverage:** NR	**Inclusion criteria:** Hx of unsuccessful pregnancy ≥ 1 PPTB, ≥ 2 mid-trimester abortions, or mix of term births, PTBs and mid-trimester abortions **Exclusion criteria:** Underlying disease that may contribute to PTL Cervical incompetence	**Prior PTB, n: (2)** **G1:** 7 **G2**: 6 **(3)** **G1:** 0 **G2:** 1 **Prior term and PTB, n:** **G1:** 1 **G2**: 2 **Prior mid-trimester abortion, n:** (2) **G1:** 7 **G2:** 11 **(3)** **G1:** 3 **G2**: 2 **(4)** **G1:** 2 **G2:** 3 **Prior PTB and mid-trimester abortion, n:** **G1**: 7 **G2**: 8 **Prior term birth, PTB, and mid-trimester abortion:** **G1**: 9 **G2**: 6 **Multiple gestation:** NR **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR	**Drug availability, (%):** **G1**: **(**100) **G2**: (100)	**Complications during pregnancy** ***Anencephalic fetus, n (%):** **G1:** 1 (2.78) **G2:** 0 (0) **Prematurity** **GA at birth, n (%):** **< 28 wks** **G1:** 0 (0) **G2:** 2 (5.13) **28-30 wks** **G1:** 3 (8.57) **G2:** 2 (5.13) **31-33 wks** **G1:** 1 (2.86) **G2:** 3 (7.69) **34-36 wks** **G1:** 1 (2.86) **G2:** 12 (30.77) **≥37 wks** **G1:** 30 (85.71) **G2:** 20 (51.28) **≥37 wks:** *P* = 0.0036 **Birth weight, n (%):** **600 g - 999 g** **G1:** 0 (0) **G2:** 2 (5.13) **1,000 g - 1,499 g** **G1:** 1 (8.57) **G2:** 4 (10.26) **1,500g - 1,999 g** **G1:** 3 (8.57) **G2:** 12 (30.77) **2,000 g - 2,499 g** **G1:** 5 (14.29) **G2:** 1 (2.56) **≥ 2500 g** **G1:** 24 (68.57) **G2:** 20 (51.28) **≥ 2500 g** *P* = 0.2022

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Suvonnakote, 1986 (continued)			**GA of prior PTB:** NR **Prior PPROM:** NR		**Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

*1 patient had anencephalic fetus and was excluded from the analysis

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Szekeres-Bartho et al., 1983 **Country:** Hungary **Participant source:** Academic single-site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** Non-randomized control trial	**Intervention:** β -mimetic + 250 mg of IM 17OHP weekly, begun at 27-30 wks or acetylsalicylic acid 2.7 g/d alternate wks until 34wks **Groups:** **G1:** 17OHP **G2:** Acetyl-salicylic acid **G3:** Control: β -mimetic treatment alone **N at enrollment:** **G1**: 11 **G2**: 9 **G3**: 13 **N at birth:** **G1**: 11 **G2**: 9 **G3**: 13 **N at follow-up:** **G1**: 11 **G2**: 9 **G3**: 13 **Age:** NR **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal BMI:** NR **Maternal smoking:** NR	**Inclusion criteria:** Clinical diagnosis of TPTL on the basis of high cytotoxic activity and low progesterone binding capacity of lymphocytes Presenting either: vaginal bleeding, regular uterine contractions and/or progressing cervical dilatation GA 27 to 30 wks **Exclusion criteria:** See inclusion criteria	**Prior PTB:** NR **Multiple gestation, n (%)*:** **G1**: 1 (9.1) **G2**: 0 (0) **G3**: 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at initiation, mean wks ± SD**: **G1**: 28.5 ± 1.00 **G2**: 28.8 ± 0.83 **G3**: 29.2 ± 0.927 **Tocolytic as co-intervention (β-mimetic) n, (%):** **G1**: 11 (100) **G2**: 9 (100)	**Complications during pregnancy** **Progesterone binding capacity of lymphocytes increase in G1&G2 vs.G3:** *P* < 0.001 **Cytotoxic activity of lymphocytes decrease in G1&G2 vs. G3:** *P* < 0.001 **Prematurity** **PTB, n (%)**: **G1**[†]: 3 (27.3) **G2**: 1 (11.1) **G3**: 9 (69.2) **G1 vs. G3:** *P* < 0.05 **G2 vs. G3:** *P* < 0.01 **GA at birth, mean wks ± SD**: **G1**: 36.6 ± 4.17 **G2**: 38.2 ± 2.11 **G3**: 36.2 ± 2.45 **Birth weight, mean g ± SD**: **G1**: 2,595 ± 736.4 **G2**: 3,077 ± 506.5 **G3**: 2,776 ± 659.8 **Mode of birth and complications during birth** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Szekeres-Bartho et al., 1983 (continued)	**Medicaid:** NR **Private insurance:** NR				**Postpartum and neonatal complications** NR **Longer term outcomes** NR

All mean ± SD data extracted from raw data presented in Tables 1-3
*Assumed twin birth from row 1 of Table 2 (2 birth weights given for same entry)
†Twin births count as 1 of the 3 PTBs reported for G1

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Ventolini et al., 2008 **Country:** US **Participant source:** Database (Matria) **Intervention setting:** Home **Enrollment period:** 05/2004 to 05/2006 **Funding:** Industry (Matria) **Author Industry Relationship Disclosure:** 4 of 8 Matria Healthcare (4) **Design:** Retrospective case series	**Intervention:** 250 mg of IM 17OHP using Z-track method; home delivery in unit-dose, benzyl alcohol preservative-free vials **Groups:** **G1:** Lean (BMI < 20) **G2:** Normal (BMI 20 – 24.9) **G3:** Overweight (BMI 25 – 29.9) **G4:** Obese (BMI ≥ 30) **N at enrollment:** **G1**: 85 **G2**: 214 **G3:** 137 **G4:** 170 **N at birth:** **G1**: 85 **G2**: 214 **G3:** 137 **G4:** 170 **N at follow-up:** NR **Age, mean yrs ± SD:** **G1**: 28.3 ± 5.9 **G2**: 30.0 ± 5.6 **G3:** 29.8 ± 5.7 **G4:** 30.4 ± 5.2 **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR	**Inclusion criteria:** Current singleton pregnancy History of ≥1documented PPTD who initiated therapy between 16 and 20.9 wks GA **Exclusion criteria:** See Inclusion Criteria	**1 Previous PTD, n** **G1**: 51 **G2**: 151 **G3:** 94 **G4:** 113 **>1 Previous PTD, n, (%):** **G1**: 34 (40.0) **G2**: 63 (29.4) **G3:** 43 (31.4) **G4:** 57 (33.5) *P* = 0.354 **Multiple gestation:** **G1**: 0 (0) **G2**: 0 (0) **G3:** 0 (0) **G4:** 0 (0) **Fetal fibronectin, baseline:** NR **Cerclage:** NR **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR **GA at initiation, mean wks ± SD:** **G1**: 17.8 ± 1.4 **G2**: 17.8 ± 1.5 **G3:** 17.7 ± 1.4 **G4:** 17.8 ± 1.5 *P* = 0.879	**Total injections, mean n ± SD:** **G1**: 15.1 ± 5.0 **G2**: 16.3 ± 4.3 **G3:** 15.2 ± 5.4 **G4:** 15.7 ± 4.6 *P* = 0.182 **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**Complications during pregnancy** **Pregnancy loss < 24 wks,** n (%)**:** Overall **G1**: 2 (2.4) **G2**: 5 (2.3) **G3:** 3 (2.2) **G4:** 7 (4.1) **P=** 0.682 **1 previous PTD** **G1**: (2.0) **G2**: (2.0) **G3:** (2.1) **G4:** (4.4) *P* = 0.615 **>1 previous PTD** **G1**: (2.9) **G2**: (3.2) **G3:** (2.3) **G4:** (3.5) *P* = 0.989 **Prematurity** **PTL incidence, %:** **Overall** **G1**: (50.6) **G2**: (38.3) **G3:** (42.3) **G4:** (37.1) *P* = 0.169 **1 previous PTD** **G1**: (43.1) **G2**: (32.5) **G3:** (36.2) **G4:** (24.8) *P* = 0.099 **> 1 previous PTD** **G1**: (61.8) **G2**: (52.4) **G3:** (55.8) **G4:** (61.4) **P=**0.722

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Ventolini et al., 2008 (continued)	**Maternal BMI, n (BMI score):** **G1:** 85 (<20) **G2:** 214 (20 – 24.9) **G3:** 137 (25 – 29.9) **G4:** 170 (≥30) **Maternal smoking, (%):** **G1**: (10.6) **G2**: (6.5) **G3:** (5.8**)** **G4:** (4.7) **Medicaid:** NR **Private insurance:** NR				**GA at birth, mean wks ± SD:** Overall **G1**: 36.1 ± 3.8 **G2**: 36.6 ± 3.6 **G3:** 36.3 ± 3.9 **G4:** 36.3 ± 4.1 *P* = 0.386 **1 previous PTD** **G1**: 36.3 ± 3.9 **G2**: 37.1 ± 3.2 **G3:** 36.6 ± 3.6 **G4:** 36.7 ± 4.2 *P* = 0.562 **>1 previous PTD** **G1**: 35.7 ± 3.7 **G2**: 35.5 ± 4.3 **G3:** 35.4 ± 4.4 **G4:** 35.4 ± 3.9 *P* = 0.878 **GA at birth <35 wks, (%):** **Overall** **G1**: (20.0) **G2**: (15.4) **G3:** (20.4) **G4:** (18.8) *P* = 0.614 **1 previous PTD** **G1**: (15.7) **G2**: (11.3) **G3:** (16.0) **G4:** (15.0) *P* = 0.689 **>1 previous PTD** **G1**: (26.5) **G2**: (25.4) **G3:** (30.2) **G4:** (26.3) *P* = 0.955

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Ventolini et al., 2008 (continued)					**GA at birth < 32 wks, (%):** **Overall** **G1**: (8.2) **G2**: (6.1) **G3:** (9.5) **G4:** (8.8) **P=** 0.645 **1 previous PTD** **G1**: (9.8) **G2**: (3.3) **G3:** (8.5) **G4:** (7.1) *P*= 0.240 **> 1 previous PTD** **G1**: (5.9) **G2**: (12.7) **G3:** (11.6) **G4:** (12.3) *P* = 0.756 **Mode of birth and complications during birth** **Stillbirth, n (%):** **G1**: 0 (0) **G2**: 1 (0.5) **G3:** 1 (0.7) **G4:** 0 (0) *P* = 0.652 **Postpartum and neonatal complications** **Neonatal Death, n (%):** **G1**: 0 (0) **G2**: 2 (0.9) **G3:** 1 (0.7) **G4:** 4 (2.4) *P* = 0.329 **Longer term outcomes** NR

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Author: Yemini et al., 1985 **Country:** Israel **Participant source:** Academic single site **Intervention setting:** Clinic **Enrollment period:** NR **Funding:** NR **Author Industry Relationship Disclosure:** NR **Design:** RCT – patients were randomly divided into 2 groups according the last digit of the clinical registration number	**Intervention:** 250 mg of IM 17OHP weekly, until wk 37 **Groups:** **G1:** IM 17OHP **G2:** Placebo (oily solution) **N at enrollment:** **G1***: 40 **G2**: 40 **N at birth†:** **G1**: 31 **G2**: 37 **N at follow-up:** **G1**: 31 **G2**: 37 **Age, mean yrs ± SD:** **G1**: 27.8 ± 4.6 **G2**: 28.3 ± 5.2 **Race/ethnicity:** NR **Parous:** NR **Maternal education:** NR **Maternal smoking, n:** **G1**: 3 **G2**: 2 **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR	**Inclusion criteria:** Pregnant women in whom the current pregnancy had been immediately preceded by at least 2 preterm deliveries or 2 spontaneous miscarriages or a combination of both **Exclusion criteria:** Women w/ multiple pregnancies DM Chronic renal disease Chronic HTN	**Prior PTB, mean ± SD:** **G1**: 1.4 ± 0.5 **G2**: 1.3 ± 0.5 **Prior mature delivery, mean ± SD:** **G1**: 1.5 ± 0.7 **G2**: 1.7 ± 0.7 **Prior spontaneous miscarriages, mean ± SD:** **G1**: 2.5 ± 1.8 **G2**: 2.2 ± 1.1 **Prior induced abortion, mean ± SD:** **G1**: 1.8 ± 1.4 **G2**: 1.2 ± 0.4 *P* < 0.01 **Multiple gestation, n (%):** **G1**: 0 (0) **G2**: 0 (0) Fetal fibronectin, baseline: NR **Cerclage, n (%):** **G1**: 40 (100) **G2**: 40 (100) **Cervical length, baseline:** NR **GA of prior PTB:** NR **Prior PPROM:** NR	**GA at 17OHP initiation, mean wks ± SD:** **G1**: 12.2 ± 3.3 **G2**: 12.2 ± 3.9 **Provider knowledge and attitudes:** NR **Provider specialty:** NR **Cost of drug:** NR **Drug availability:** NR	**Complications during pregnancy** **PPROM (< 37wks), n (%):** **G1**: 2 (6.4) **G2**: 3 (8.1) **Miscarriages, n (%):** **G1***: 8 (20.4) **G2:** 3 (7.5) **Imminent PTL, n (%):** **G1**: 9 (29.0) **G2**: 22 (59.4) P < 0.025 **Prematurity** **Premature births ≤ 36 wks or ≤ 2,500 g, n (%):** **G1**: 5 (16.1) **G2**: 14 (37.8) *P* < 0.05 **Term births, n:** **G1**: 26 **G2**: 23 **Birth weight, mean g ± SD (range)**: Premature **G1**: 1,580 ± 518.4 (810-2,080) **G2**: 1,888.6 ± 591.6 (800-2,480) **Term** **G1**: 3,406 ± 617.5 (range 2,700-4,850) **G2**: 3,161.7 ± 484.3 (range 2,690-4,540) **All** **G1**: 3,111.9 ± 905.5 (range 810-4,850) **G2**: 2,680 ± 813.4 (range 800-4,540) *P* < 0.05

Evidence Table D-1. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Yemini et al., 1985 (continued)					**GA at birth, wks ± SD:** **Term** **G1**: 38 ± 3.2 **G2**: 37 ± 3.7 **Premature** **G1:** 32.4 ± 4.0 **G2:** 33.8 ± 2.6 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications‡** **Sepsis (infant), n:** **G1**: 1 **G2**: 2 **Respiratory distress syndrome (infant), n:** **G1**: 1 **G2**: 4 **Hyperbilirubinemia (infant), n:** **G1**: 4 **G2**: 11 **Apnea/bradycardia (infant), n:** **G1**: 0 **G2**: 2 **Patent ductus arteriosus (infant), n:** **G1**: 1 **G2**: 0 **Longer term outcomes** NR

*G1: 39 due to one dropped case for population and clinical factors information
†G1 lost 8 and G2 lost 3 due to miscarriage (expulsion from uterus, embryo < 20 wks GA, <500 g or <25 cm)
‡ Postpartum and neonatal complications information given for premature births only (G1out of 5, G2 out of14)

Appendix E. Applicability and Quality Tables

Table 1. Key Question 1: Maternal, Fetal, and Neonatal Health Outcomes --Applicability

Domain	**Description of applicability of evidence compared to question**
Population	The participants in these 36 studies have a range of indications for progestogen treatment including a history of preterm birth in eight studies, preterm labor in ten studies, multiple gestation in five studies, mixed risk factors in nine studies, and unique indications (for example, abdominal surgery unrelated to pregnancy) in four studies. Eligibility criteria were generally well defined, and populations could be duplicated in clinical care. The preterm birth rate among the control group in studies of women with a history of preterm birth was frequently higher than that seen in other large-scale studies of preterm birth recurrence. Trials in which the indication for progestogen was preterm labor had wide variability how the diagnosis of threatened or actual preterm labor was made.
Intervention	The intervention was heterogeneous across studies. Overall, the 36 studies included 23 unique combinations of progestogen formulations, routes, and doses.
Comparators	The most frequent comparators were placebo treatment or no treatment. Some of the placebo treatments could have had an effect on PTB rate. Studies that used no treatment as a comparator have a risk of bias.
Outcomes	Studies commonly report preterm birth outcomes by gestational age, which is a surrogate outcome. Studies are less consistent in reporting maternal, fetal, and neonatal outcomes. Most trials are not large enough to adequately assess some critical outcomes, such as neonatal conditions associated with prematurity. Longer-term outcomes are not reported.
Setting	Studies were conducted in the United States (13), Europe (15), Asia (three), the Middle East (three), South America (one), and multiple continents (one), primarily in academic medical centers with standards of care comparable to women receiving prenatal care in the United States.

Table 2. Key Question 2: Harms of Progestogen Treatments--Applicability

Domain	**Description of applicability of evidence compared to question**
Population	The participants in these 50 unique populations have a range of indications for progestogen treatment including a history of preterm birth in eight studies, preterm labor in ten studies, multiple gestation in five studies, mixed risk factors in nine studies, and unique indications (for example, abdominal surgery unrelated to pregnancy) in four studies. Eligibility criteria were generally well defined, and populations could be duplicated in clinical care.
Intervention	The intervention was heterogeneous across studies and included numerous progestogen formulations, routes, and doses.
Comparators	The most frequent comparators were placebo treatment or no treatment, which are appropriate for harms assessment.
Outcomes	Studies did not consistently report harms and those that did track them were primarily conducting safety monitoring and ultimately underpowered to determine if the treatment or placebo group experienced a meaningfully disproportionate burden of adverse events. Most harms that are common, such as site pain with injections or vaginal discharge with vaginal preparations, appear to be a side effect of route and are experienced in similar high proportions across treatment and placebo groups.
Setting	Studies were conducted in the United States (27), Europe (14), Asia (4), the Middle East (1), South America (1), and multiple continents (2), in a variety of clinical settings with standards of care comparable to women receiving prenatal care in the United States.

Table 3. Key Question 3: Maternal Risk Factors as Modifiers of Outcomes--Applicability

Domain	**Description of applicability of evidence compared to question**
Population	Few trials included risk factor subdivision by gestational age of prior PTB. Few trials included risk factor subdivision by socioeconomic level. Trials that had data about race were not sufficiently powered to demonstrate a difference in effect based upon race. Trials that assessed degree of cervical shortening did not use a standard measure for defining short, nor did they have subdivision of the population by cervix length. Trials of patients after an episode of threatened preterm labor had much variability in gestational age at initiation, definition of preterm labor, and other cofactors.
Intervention	Oral progestogens have not been used in the USA for prevention of preterm birth. The IM progestogen may be unavailable or difficult to acquire in many communities. The vaginal progestogen must be compounded and carefully stored. Adherence may be more problematic in the real world, than in studies. There were differences in dosages and frequency of administration across studies, which would require practitioners to choose, without a head-to-head comparison to guide the choice.
Comparators	Some of the placebo treatments could have had an effect on preterm birth rate. Studies that used no treatment as a comparator have a risk of bias.
Outcomes	The critical outcomes are perinatal mortality and significant neonatal morbidity. None of the trials had sufficient power to determine if progestogens reduced these events. Heterogeneity across studies precludes combining the data. Preterm birth (determined by gestational age) and birth weight are surrogate outcomes for the critical outcomes.
Setting	The composite studies of progestogen include a wide variety of settings. Some international studies have a population that is not representative of the USA.

Table 4. Key Question 4: Type of Progestogne as Modifier of Outcomes--Applicability

Domain	**Description of applicability of evidence compared to question**
Population	The 43 studies had a range of indications for progestogen treatment that include history of preterm birth, preterm labor, multiple gestations, abdominal surgeries, and other risk factors for preterm birth. The majority used indicated preterm labor or history of preterm birth as the primary indication for treatment. These women received progestogen treatment using a wide range of dosages and treatments that was not consistent across studies. These studies also had a wide range of variability for the gestational age for initiation and discontinuation of treatment that were not always clearly documented in the study design.
Intervention	The progestogen intervention varied across studies. These included injected 17OHP, vaginal gels/suppositories/capsules, and oral formulations. Injected 17OHP was the most studied intervention and had the most documented literature regarding adverse effects, adherence, and outcomes for mother and infant.
Comparators	The comparison groups consisted predominately of a placebo group and/or a no treatment group. Details regarding the comparison groups were inconsistently documented across studies and often no treatment groups still included individuals who were administered tocolytics and/or received some other co-interventions such as increased access to nurses. This may introduce a bias for comparisons to the intervention group. Also, it was unclear whether the placebo used (e.g. oil injections rather than 17OHP) could have an influence on treatment outcome.
Outcomes	The primary outcomes included: gestational age at delivery, preterm birth rate as assessed through gestational age, birth weight, neonatal death, neonatal sepsis, and NICU admission. These outcomes were inconsistently reported and none of the studies had sufficient power to assess how these outcomes may have differed by gestational age at initiation/discontinuation and by treatment frequency and dosage. Few studies directly compared interventions within a single study. Few studies examined how outcomes were influenced by gestational age at initiation/discontinuation of treatment and/or frequency/dosage of the intervention.
Setting	These include studies conducted in the United States (23), Europe (13), Asia (3), Middle East (1), South America (1), and studies conducted at multiple locations (2). The settings were not homogenous across studies and direct comparisons could not be made directly to assess how this may have influenced outcomes.

Table 5. Key Question 5: Cointerventions as Modifiers of Outcomes--Applicability

Domain	Description of applicability of evidence compared to question
Population	The 18 studies that were examined for co-interventions had a range indications for progestogen treatment that include preterm labor, history of preterm birth, multiple gestations, abdominal surgeries, and other risk factor for preterm labor risk. The majority used indicated preterm labor or history of preterm birth as the primary indication for treatment. The co-interventions used were clearly indicated in most studies; however, several studies used more than one co-intervention in a single study and did not provide an informative comparison group for those analyses.
Intervention	The progestogen intervention and co-interventions varied across studies with heterogeneity in both the timing of administering the co-intervention. Primary interventions included injected micronized 17OHP, vaginal gels/suppositories, and oral progestogens. Co-interventions included: tocolytics, tocolytics and one or more co-intervention, cervical cerclage, nursing surveillance, bed rest, and "other" co-interventions.
Comparators	The comparison groups consisted predominately of a placebo group and/or a no treatment group. Informative comparisons groups for examination of co-interventions were not always provided for studies. Co-interventions were also not directly tested for in statistical analyses. Including more than one co-intervention made it unclear which con-intervention was providing a benefit.
Outcomes	The primary outcomes included: gestational age at delivery, preterm birth rate as assessed through gestational age, birth weight, neonatal death, neonatal sepsis, and NICU admission. These outcomes were inconsistently reported and none of the studies had sufficient power to assess how the co-intervention may have influenced outcome.
Setting	These include studies conducted in the United States (9), Europe (5), Asia (1), Middle East (2), and South America (1). The settings were heterogenous across studies.

Table 6. Key Question 6: Effect of Health System and Provider Factors--Applicability

Domain	**Description of applicability of evidence compared to question**
Population	This question encompassed two distinct populations: 1) **care providers** and 2) **women at risk of preterm birth**. In the first group, five surveys assessed provider self-report. Three were conducted in the United States with populations not consistently representative of the general population of providers. One study included providers in a clinic that participated in a 17OHP trial resulting in high knowledge and familiarity with progestogens treatment and low barriers to provision, two surveys are repeated inquiries of maternal-fetal medicine specialists, and a third was directed to a volunteer registry of obstetrician-gynecologist survey participants. The other two surveys were of complete professional groups – all obstetric care providers in Canada and all members of the Royal College in Australia and New Zealand. While the participants are expected to be a more representative, their responses indicated practice patterns differ from the US making the results of interest less informative for applying to US providers. The populations of women in the observations studies include a very small (n = 38) analysis of a Medicaid population, two analyses of women included in the Matria database, and another of a single care system. Approximately half of births in the United States are covered by Medicaid so it is an important population, however in small studies or those that draw on specialized home health resources, the experience and barriers to use may not be broadly informative.
Intervention	These studies sought to describe intervention use rather than to provide and assess an intervention. The questions and analyses are applicable to describing use of interventions in the United States.
Comparators	Studies are small or based on databases. Few analyses include comparisons or analytic models to describe differences between those who received and did not receive progesterone making the information less applicable than ideal. Provider surveys did explore factors associated with prescribing. Data from the US surveys are applicable with the caveats above.
Outcomes	Outcomes were use of progestogens. Most publications assessed provider behaviors for multiple uses that reflect real world scenarios. The databases imply a level of access to treatment and may not fully represent care in the United States.
Setting	As outlined above provider type and country in which they practiced is confounded. More generalists contributed data to surveys from outside the United States, and they have difference use patterns. In general, provider and patient data over-represent tertiary care settings and those with access to home health.

Table 7. Quality Rating of Individual Treatment Studies

Citation	Overall Quality	Randomization	Methods & masking	Pt selection criteria	Clinical setting	Participant flow diagram	Loss to followup	Drop-out rates	Power calculation	ITT	Confounding factors	Internal validity	Baseline characteristics	Intervention description	Primary Outcome	GA at Birth	Birthweight	Length of FU	Measurement methods	Measurement reliability	External validity
Bacq et al., 1997[1]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	-	+	+	+	-	+	+	fair
Bailit et al., 2007[2]	poor	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	-	-	-	-	-	-	+	+	poor
Berghella et al., 2010[3]	fair	NA	NA	+	+	NA	++	++	+	+	NA	good	+	+	+	+	-	-	+	+	fair
Borna et al., 2008[4]	fair	-	-	+	+	+	++	++	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Breart et al., 1979[5]	poor	+	-	-	+	-	+	++	-	-	NA	poor	-	+	+	+	+	-	+	+	fair
Briery et al., 2009[6]	fair	+	+	+	+	-	++	++	+	+	NA	fair	-	+	+	+	+	+	+	+	good
Caritis et al., 2009[7]	good	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	+	+	+	+	good
Cetingoz et al., 2010[8]	fair	+	+	+	+	+	++	NR	+	+	NA	good	-	+	+	+	-	-	+	+	fair
Combs et al., 2010[9]	fair	+	+	+	+	+	++	+	+	+	NA	fair	-	+	+	+	+	+	+	+	fair
Corrado et al., 2002[10]	poor	-	-	+	+	-	++	++	-	-	NA	poor	-	+	+	+	-	-	+	+	fair
Cortes-Prieto et al., 1980[11]	fair	NA	NA	+	-	NA	NA	NA	-	NA	-	fair	-	+	+	-	+	-	+	+	fair
da Fonseca et al., 2003[12]	fair	+	+	+	+	-	+	NR	+	-	NA	fair	+	+	+	+	-	-	+	+	fair
Dudas et al., 2006[13]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	-	+	+	+	++	+	+	fair
Durnwald et al., 2009[14]	fair	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	+	-	+	+	-	+	+	+	fair
Erny et al., 1986[15]	poor	-	+	-	+	-	++	++	-	-	NA	poor	-	+	+	+	+	-	+	+	fair
Facchinetti et al., 2007[16]	fair	-	-	+	+	-	++	++	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Facchinetti et al., 2008[17]	poor	+	-	+	+	-	++	NR	-	+	NA	poor	-	+	-	-	-	-	+	+	poor
Fonseca et al., 2007[18]	good	+	+	+	+	+	++	+	+	+	NA	good	+	+	+	+	+	+	+	+	good
Fuchs & Stakemann, 1960[19]	poor	-	+	+	+	-	NR	NR	-	-	NA	poor	-	+	+	-	+	+	+	+	fair
Gonzalez-Quintero et al., 2007[20]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Gonzalez-Quintero et al., 2010[21]	fair	NA	NA	+	+	NA	NA	NA	+	NA	+	good	+	+	+	+	-	-	+	+	fair
Gyamfi et al., 2009[22]	fair	+	+	+	+	-	NA	NA	-	NA	NA	fair	+	+	+	-	-	-	+	+	fair
Harper et al., 2010[23]	fair	NA	NA	+	+	NA	++	++	-	NA	-	fair	+	+	+	+	+	+	+	+	good
Hartikainen-Sorri et al., 1980[24]	fair	NA	NA	+	+	NA	++	++	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Hauth et al., 1983[25]	poor	-	+	+	+	-	NR	NR	-	+	NA	poor	-	+	+	-	+	-	+	+	fair
Hill et al., 1975[26]	poor	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	-	-	-	+	+	poor
Hobel et al., 1994[27]	poor	-	-	-	+	-	-	NR	+	-	NA	poor	-	+	+	+	+	-	+	+	fair
How et al., 2007[28]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	+	+	-	-	+	+	fair

Citation	Overall Quality	Randomization	Methods & masking	Pt selection criteria	Clinical setting	Participant flow diagram	Loss to followup	Drop-out rates	Power calculation	ITT	Confounding factors	Internal validity	Baseline characteristics	Intervention description	Primary Outcome	GA at Birth	Birthweight	Length of FU	Measurement methods	Measurement reliability	External validity
Johnson et al., 1975[29]	poor	-	+	+	+	-	+	+	-	-	NA	poor	+	+	+	+	+	-	+	+	fair
Johnson et al., 1979[30]	poor	NA	NA	-	+	NA	-	-	-	NA	-	poor	-	+	+	+	+	-	+	+	fair
Kauppila et al., 1980[31]	fair	NA	NA	-	+	NA	++	++	-	NA	-	fair	-	+	+	+	+	-	+	+	fair
Keeler et al., 2009[32]	fair	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	-	-	+	+	fair
Kester et al., 1980[33]	poor	NA	NA	-	+	NA	NA	NA	NA	NA	-	fair	-	-	-	-	-	++	-	-	poor
Kester et al., 1984[34]	poor	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	-	+	-	-	++	+	+	poor
Mason et al., 2008[35]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Majhi et al., 2009[36]	fair	+	-	+	+	+	++	++	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Mason et al., 2005[37]	poor	NA	NA	-	+	NA	NA	NA	-	NA	-	poor	-	+	+	-	-	+	+	+	fair
Mason et al., 2009[38]	fair	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	-	+	+	+	+	+	+	+	fair
Meis et al., 2003[39-43]	fair	+	+	+	+	-	++	+	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Meyer-Bahlburg et al., 1977; [44-45]	poor	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	-	+	-	-	++	+	-	poor
Noblot et al., 1991[46]	fair	+	+	+	+	-	++	++	-	+	NA	fair	-	+	+	+	+	-	+	+	fair
Norman et. al, 2009[47]	fair	+	+	+	+	+	++	++	+	-	NA	fair	-	+	+	+	-	+	+	+	fair
O'Brien et al., 2007[48-50]	good	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	+	+	+	+	good
Øvlisen & Iversen, 1963[51]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	-	+	-	+	+	fair
Rai et al., 2009[52]	fair	+	+	+	+	+	++	++	+	-	NA	fair	-	+	+	+	+	-	+	+	fair
Rebarber et al., 2007[53]	fair	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	+	+	+	+	-	-	+	+	fair
Rebarber et al., 2007[54]	fair	NA	NA	-	+	NA	NA	NA	-	NA	+	fair	-	+	+	+	+	+	+	+	fair
Rebarber et al., 2008[55]	fair	NA	NA	-	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Reinisch & Karrow, 1977[56]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	-	-	++	+	+	fair
Resseguie et al., 1985[57]	poor	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	-	-	+	-	-	++	+	+	poor
Rittenberg et al., 2009[58]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	+	+	-	-	+	+	fair
Rittenberg et al., 2007[59]	poor	NA	NA	+	+	NA	NA	NA	-	NA	NA	fair	-	+	-	+	-	-	+	+	poor
Rittenberg et al., 2008[60]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	-	+	-	-	+	+	fair
Rouse et al., 2007[61]	good	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	+	+	+	+	good
Suvonnakote, 1986[62]	poor	NA	NA	-	+	-	++	++	-	NA	NA	poor	-	+	+	+	+	-	+	+	fair
Szekeres-Bartho et al., 1983[63]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	+	-	+	+	fair
Ventolini et al., 2008[64]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	+	+	-	-	+	+	fair
Yemini et al., 1985[65]	fair	-	-	+	+	-	+	++	-	+	NA	poor	+	+	+	+	+	+	+	+	good

Table 8. Quality Rating of Individual Studies of Surveys

Citation	Description of Sampling (+/-)	Number Sampled (+/-)	Number Eligible (+/-)	Number of respondents (+/-)	Response rate: ≥50 = ++ ≥33 = + <33 or NR= -	Description of Respondents (+/-)	Overall Quality
Ness et al., 2006[66]	1	1	1	1	1	-1	Fair
Dodd et al., 2007[67]	1	1	1	1	2	1	Good
Hui et al., 2007[68]	1	1	1	1	1	1	Fair
Ness et al., 2006[69]	1	1	1	1	1	1	Fair
Henderson et al., 2009[70]	1	1	1	1	2	1	Good

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