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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 in 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 http://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 that 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 e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

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Structured Abstract

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

Data Sources: We search MEDLINE® and EMBASE for articles published in English from January 1966 to March 2010.

Review Methods: We excluded publications that did not address a key question, were not research, or had fewer than 20 participants. We included 64 publications: 7 were good quality; 38, fair; and 19, poor. Twelve randomized controlled trials (RCTs) contributed data for meta-analysis of effects using the random effects model.

Results: Among women with prior preterm birth and a singleton pregnancy (four RCTs), progestogen treatment decreased risk of preterm birth (RR = 0.70, 95 percent CI: 0.50 to 0.98). Evidence of benefit for other maternal, fetal, or neonatal health outcomes is inconsistent or absent. Progestogen treatment does not prevent prematurity, enhance birthweight, or improve other outcomes in multiple gestations (RR preterm birth = 1.00, 95 percent CI: 0.81 to 1.24).

No maternal factors, like severity or number of prior preterm births, have been definitively shown to modify effects of progestogen treatment. Direct comparisons have not been made between routes of administration or doses in RCTs. Evidence is insufficient to determine if time of initiation and adherence to treatment influence outcomes. Predominantly observational studies provide limited data about the ability of common cointerventions to prolong pregnancy. Factors associated with adherence to treatment have not been systematically studied.

Potential harms were not consistently sought. Similar small proportions of study participants withdrew from treatment across treatment and placebo groups. Long-term maternal and infant effects have not been well studied. No data were available from the types of large registries often developed for surveillance of rare outcomes. Publications about provider- and system-level factors confirm wide variability in use of progestogens; use in populations that lack clear evidence of benefit; and interest in research that examines longer term benefits and risk of harms.

Conclusions: Progestogen treatment reduces risk of preterm birth in singleton pregnancies in women with prior preterm birth. The strength of evidence for this indication is low because estimates across studies were inconsistent and imprecise. Consistent 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.

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http://www.ahrq.gov/downloads/pub/evidence/pdf/XXX/XXX.pdf

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 in the proportion of births in the United States that are preterm since 1990.[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, accruing evidence from randomized clinical trials (RCTs) led professional organizations and an Institute of Medicine working group to endorse use of progestogens for women with prior spontaneous preterm birth. However, these groups also note interest in 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, 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?
    - Mode of birth and complications during birth?
    - Prematurity?
    - Postpartum and neonatal complications?
    - Longer term 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?
    - Mode of birth and complications during birth?
    - Postpartum and neonatal complications?
    - 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 (GA) 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 is the effect of health systems and provider factors on the use of progestogens for eligible at-risk women, including provider knowledge and attitudes, provider specialty, cost of drug, availability of drug in formularies, and Medicaid and private payer coverage?

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 are referred to in the clinical literature. We also employed indexing terms within each database to exclude undesired publication types and articles in languages other than English.

Article selection process. We examined abstracts of articles 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 process 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.

Quality assessment. We used a quality assessment to capture key elements of study design and conduct. Quality was assessed by two reviewers independently, who resolved differences through discussion, review of the publications, and consensus with the team.

Evidence synthesis. Text that summarizes the research evidence is organized by key question. Within each key question evidence is organized by aspects of the question, such as indication and formulation. In the full report, we produced evidence tables, summary tables of common outcomes, and provided extended analysis.

Results

Literature search yield. We identified 393 non-duplicate publications. Sixty-four articles met criteria and were included. Seven were good quality; 38, fair; and 19, poor. They reflect 57 distinct study populations. Six articles report secondary analyses or repeated surveys of the same provider group. Forty articles pertain to KQ1, 54 to KQ2, 21 to KQ3, 51 to KQ4, 19 to KQ5, and 11 to KQ6.

KQ1. Maternal, Fetal, and Neonatal Health Outcomes

Thirty-six 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 eight

investigations, preterm labor in the study pregnancy in ten, multiple gestation in five, populations with mixed risk factors in nine studies, and unique indications (for example, abdominal surgery unrelated to pregnancy) in four. Progestogen treatment included natural progesterone and synthetic progestins administered via injection, vaginally, or orally. The most common route and formulation was intramuscular17OHP.

Among women with a history of preterm birth, progestogen treatment decreases the risk of preterm birth at < 37 weeks by 30 percent (meta-estimate RR = 0.70; 95 percent CI: 0.50, 0.98). The largest RCT among women with prior preterm birth (n = 611) is included in the aggregate estimate and is a notable exception.[6] This study did not find reduced risk of preterm birth or other benefits. We note that the aggregate effect estimate is imprecise. Mean birth weight was not consistently reported and lacks proof of advantage. Infants of women treated with progestogens weighed an average of 239 gm more than those who received placebo with poor precision (95 percent CI: -44.5, 523.3 gm) and inconsistency across studies. Likewise, 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 latency from treatment to birth in two uncontrolled trials;[7-8] with two other trials, including a placebo-controlled double-blind study, reporting nonsignificant differences and conflicting findings.[9-10] Preterm birth findings were more consistent supported by three of three studies. The aggregate estimate suggests progesterone treatment decreases the risk of preterm birth at < 37 weeks by about half (meta-estimate RR = 0.44; 95 percent CI: 0.26, 0.76).

Moderate strength of evidence indicates lack of effectiveness for multiple gestations (preterm birth at < 35 weeks RR = 1.00; 95 percent CI: 0.81, 1.24). The heterogeneity of the studies that included women with varied indications for progestogen treatment, combined with the lack of reporting by strata of risk factors, makes it impossible to interpret their significance for specific indications. Among studies that examined unique indications for progestogen treatment, such as post-operative management or treatment of active-duty military personnel, none demonstrated compelling improvements in maternal, fetal, or neonatal outcomes. Evidence for all uses other than 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

Surveillance for adverse effects or harms of progestogen treatment has not been well documented. 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; 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. Long-term effects have not been well studied. No high-quality studies aimed at surveillance of large populations of exposed women and/or children were identified. No data were available from the types of large registries often

developed for surveillance of rare outcomes. Numbers of gestations followed for rare outcomes like 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

Data are limited and evidence is insufficient for understanding potential differences in effectiveness of progestogens for prevention of preterm birth, based upon maternal factors including gestational age of the prior spontaneous preterm birth, number of prior spontaneous preterm births, gestational age at initiation of the intervention, or measures that suggest a short cervix. No evidence informs whether there are differences in adverse effects or safety based on maternal factors. No data were found for patients at risk of preterm birth due to prior preterm premature rupture of membranes, detection of fetal fibronectin, among women with cerclage, for those with uterine malformations, nor for patients who conceived with assisted reproductive technologies.

KQ4. Modifiers of outcomes by type of progestogen

Twenty-six studies evaluated injected 17OHP; among these there were 23 distinct dose/interval combinations.[8, 10-34] The majority initiated treatment between 16 and 21 weeks. Two retrospective case series (n = 156)[28] and (n =208)[21] and one retrospective cohort (n = 906)[22] compared initiating 17OHP before versus after 21 weeks 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; they found more than five injections prolonged gestation, while fewer did not confer benefit. Evidence is insufficient to determine if 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.[6-7, 35-39] All five studies using suppositories observed a statistically significant prolongation of gestation (total n = 189). Two studies of gel (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[9, 40-43] evaluated oral micronized progesterone (OMP); one documented prolongation of pregnancy and increase in birthweight, this study administered 100 mg twice daily. Four studies reported adverse effects, none were linked to dose or frequency of treatment.

Five studies, all conducted before 1980, used other progestogens.[44-48] 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.

Direct comparisons of routes, doses, and timing of initiation have not been investigated in randomized clinical trials of progestogens that are currently available to prescribe. No studies directly assessed adherence to treatment or evaluated whether varying frequency or dose influenced prolongation of pregnancy. It is not known if 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 reported using tocolytic treatments as a cointervention to prevent spontaneous preterm birth[9, 13, 16, 18, 31, 36, 39, 41, 43, 49] either alone or in combination with another cointervention. Six studies used other forms of cointerventions for their intervention group including cortisol,[10] daily nursing surveillance (DNS),[50] nurses to administer drugs and availability to ask questions but not daily,[23] bed rest,[51] estrogen,[47] and diethylstilbestrol (DES).[44]None of these studies provide data that allows 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. Effects of provider and health systems factors

Eleven publications assessed care provider knowledge, attitudes, and prescribing.[23-24, 27, 49, 52-58] Five surveyed providers. Among maternal-fetal medicine specialists (MFMS) in the United States (surveyed twice) prescribing increased from 38 percent for preterm birth prevention in 2003, to 67 percent in 2005 ($p < 0.001$).[56] If use in singleton gestations for mothers who have had a prior spontaneous preterm birth is used as a rubric 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 respondents prescribe weekly injections, with vaginal next most common, and oral rare.

Barriers 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.[56, 58] Non-prescribers 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.[58]

Two studies outside the United States found little use of progestogens – two percent in Australia/New Zealand and seven 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 percent 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,[23-24, 27, 49, 52-53] 40 to 52 percent of women eligible for treatment with progestogens do not receive treatment. Fifty-six percent of prescribing (at an NICHD 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.[24] Categorization of indications in the largest database study found 79.5 percent had a prior PTB and 63.6 percent met eligibility

criteria. Multiple gestations were eight percent of "non-standard use", with current preterm labor (PTL) treatment comprising 44.8 percent, and cerclage contributing 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 in other countries. While the literature includes a high proportion of RCTs, 26 of 57 study populations (46%), 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 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.

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 exceeded that observed in population-level data about recurrent preterm birth in some studies.[59] 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 among those treated in practice may be attenuated.

Summary Strength of Evidence and Findings

Use of progestogens in singleton pregnancy with prior spontaneous preterm birth is informed by evidence of low strength, based on small numbers of trials, using different progestogen, with the largest trial finding no evidence of effectiveness. Moderate strength of evidence indicates lack of effectiveness for multiple gestations. Evidence is insufficient for all other uses and for understanding factors associated with patient preference and adherence to different routes of birth of progestogens. Across indications, data are sparse to evaluate influence on near term and long-term maternal and infant health outcomes. Overall evidence is insufficient for understanding whether intervention has the ultimately desired outcome of preventing morbidity and promoting normal childhood development.

Conclusions

Many scenarios faced daily by care providers and women at risk of preterm birth and considering progestogen treatment are uninformed 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 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 if long-term outcomes are improved, and to rule out longer term risks, will require large-scale comparative effectiveness and surveillance research.

Evidence Report

Chapter 1. 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 mixed risk factors.

Use of Progestogens

Within the last decade, accruing evidence from RCTs led professional organizations and an Institute of Medicine working group to endorse use of progestogens for women with prior spontaneous preterm births. 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 good candidates for progestogens. 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. 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 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.[60] 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.[60] 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.[61-62] 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.[56] We undertook this review to systematically update what is known about use of progestogens for prevention of preterm birth.

Treatment Options

Progestogen is an encompassing term for substances with biologic activity similar to the endogenous sex steroid progesterone.[63] Progestogens include natural progesterone, pharmacologic agents that are chemically identical to endogenous progesterone, and synthetic progestins that are similar but not identical in chemical structure.[64] 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 oral formulations, only medroxyprogesterone acetate is currently available in the United States. Five studies used other progestogens.[44-48] 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:

1. In pregnant women who are at risk for preterm birth (which is birth before 37 weeks gestational age), 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 intraventricular hemorrhage (IVH))?
   - 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 with differ based on the maternal risk factors for preterm birth (PTB) such as: severity of prior PTB, degree of cervical shortening, order of multiple gestations, fetal fibronectin status, preterm premature rupture of membranes (PPROM), threatened PTB, 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 (GA) at initiation or discontinuation of therapy with the progestogen?
5. How do the effectiveness, adverse effects and safety of progestogen treatment differ based on cointerventions used to prevent PTB and its consequences, including antibiotics, corticosteroids, tocolysis, and surgical interventions such as cervical cerclage?
6. 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?

Organization of this Evidence Report

Chapter 2 describes our methods including our search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and for extraction of data into

evidence tables, and compiling evidence. We also describe the approach to grading the quality of the literature and to describing the strength of the literature.

Chapter 3 presents the results of the literature search and the review of the evidence by key question, 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. Chapter 4 discusses the results and enlarges on the methodologic considerations relevant to each key question. 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 healthcare 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.

Chapter 2. Methods

In this chapter, 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 and analytic framework. We also discuss our strategy for identifying articles relevant to our six key questions, 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, epidemiology, pharmacology, primary care, and patient advocacy to provide assistance during the project. The TEP (see Appendix E) 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 e-mail to:

- Refine the analytic framework and key questions 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 PTB

The analytic framework in Figure 1 summarizes the conceptual model used to guide this systematic review by focusing the key questions on the critical healthcare related pathways and decision points. Our analytic framework emphasizes that care takes place at the interface of the healthcare system and the individual. The pathway through care is indicated in the boxes along the center line where the person and care meet. Each key question 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 surround and 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 may or may not be applicable. Overall, we sought to examine factors within the central care pathway as well as selected contextual domains like health system factors (KQ6), and influence of individual characteristic on outcomes as a step towards enhancing applicability of the results (KQ3). Portions of the framework that are unexplored in the scientific literature are highlighted in the considerations of future research needs.

Literature Review Methods

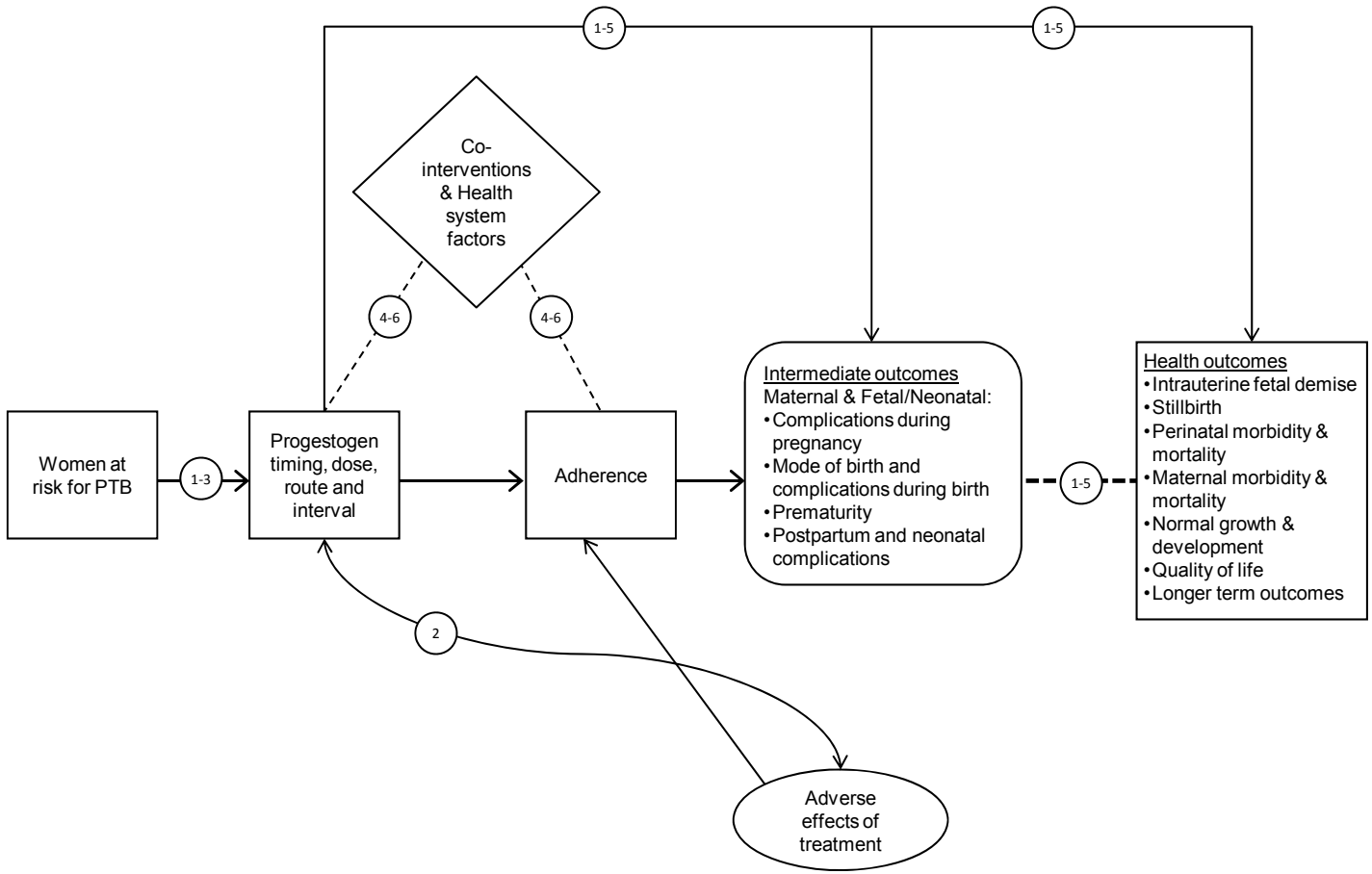
Literature Search and Retrieval Process

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, CME 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 March 2010, and were not limited by date.

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



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 key questions. Criteria are summarized below.

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 healthcare 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.[65]

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 B). 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 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 C. 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. A list of abbreviations and acronyms used in the tables appears at the beginning of that appendix.

Synthesis of the Evidence

Conduct of meta-analysis. Substantial variation in study populations, age, intervention and settings suggested that a random effects model would be most appropriate, and this was confirmed statistically using the I^2 and Cochran's Q-test.[66] We implemented the model using the DerSimonian and Laird method. Between-study variance was summarized using the Mantel-Haenszel fixed-effects summary estimate.[67] We produced risk ratios for group comparisons. MetaAnalyst (Beta 3.13; Tufts Medical Center) and R (Version 2.10.1; The R Foundation for Statistical Computing) meta-analysis packages were used to conduct statistical computations.[68] Binary data (i.e. gestational age and neonatal death) were summarized using the risk ratios to estimate intervention risks. Continuous data (i.e. mean birth weight) were summarized using mean difference as a measure of treatment effect.

Rating Quality of Individual Studies

Using a combination of quality metrics for randomized controlled trials and observational studies, two reviewers assessed presence or absence of key quality criteria.[69-74] Components of the quality score and the overall quality score for each individual study are presented in Appendix D.

Description of Research Methods

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.[69]

Rationale: "Pseudo-randomization" methods may be susceptible to bias, as demonstrated by evidence of unequal distribution of participant characteristics[70] and larger effect sizes compared with studies using more rigorous methods.[71] 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 care provider, assessor, or patient were not masked (-). Criterion was not applicable if treatment was not randomly allocated.

Adequate description of patients 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 patients 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., patients 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) patients 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.

Documentation of Study Population

Baseline characteristics. With input from the Technical Expert Panel (TEP), we selected candidate baseline characteristics that were essential for study quality and used 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 immediately preceding pregnancy.

Prior PTB.

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 Score

A composite quality score of good, fair, or poor was calculated for both the description of research methods and documentation of study population. The description of research methods 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 documentation of study population 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 description of research methods and documentation of study population were combined in order to determine overall quality. Studies with both a good description of research methods and documentation of the study population 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 description of research methods and documentation of study population were considered poor quality. The scoring algorithm for rating the quality of individual studies is included in Table 2.

Table 2. Scoring algorithm for quality rating

Definition and Scoring Algorithm	Rating
Algorithm for Quality of Description of Research Methods	
• No negative scores, lowest loss-to-followup score, and lowest dropout rate	Good methods
• One to three negative scores or intermediate loss-to-followup score or dropout rate	Fair methods
• High loss-to-followup score or high dropout rate ***OR*** • Four negative scores ***OR*** • Three negative scores and intermediate loss-to-followup score	Poor methods
Algorithm for Documentation of Study Population	
• No negative scores	Good documentation
• One to three negative scores	Fair documentation
• Four or more negative scores	Poor documentation
Score Algorithm for Overall Quality Rating	
• Good methods and good documentation	Good overall
• Fair methods and fair documentation ***OR*** • Good methods and fair documentation ***OR*** • Good methods and poor documentation ***OR*** • Fair methods and good documentation ***OR*** • Poor methods and good documentation	Fair overall
• Poor methods and poor documentation ***OR*** • Fair methods and poor documentation ***OR*** • Poor methods and fair documentation	Poor overall

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.[131] 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 key question was assessed for each of these four domains; the domains were combined qualitatively to develop the strength of evidence for each key question.

We graded the body of literature for each key question and present those ratings as part of the discussion in Chapter 4. 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

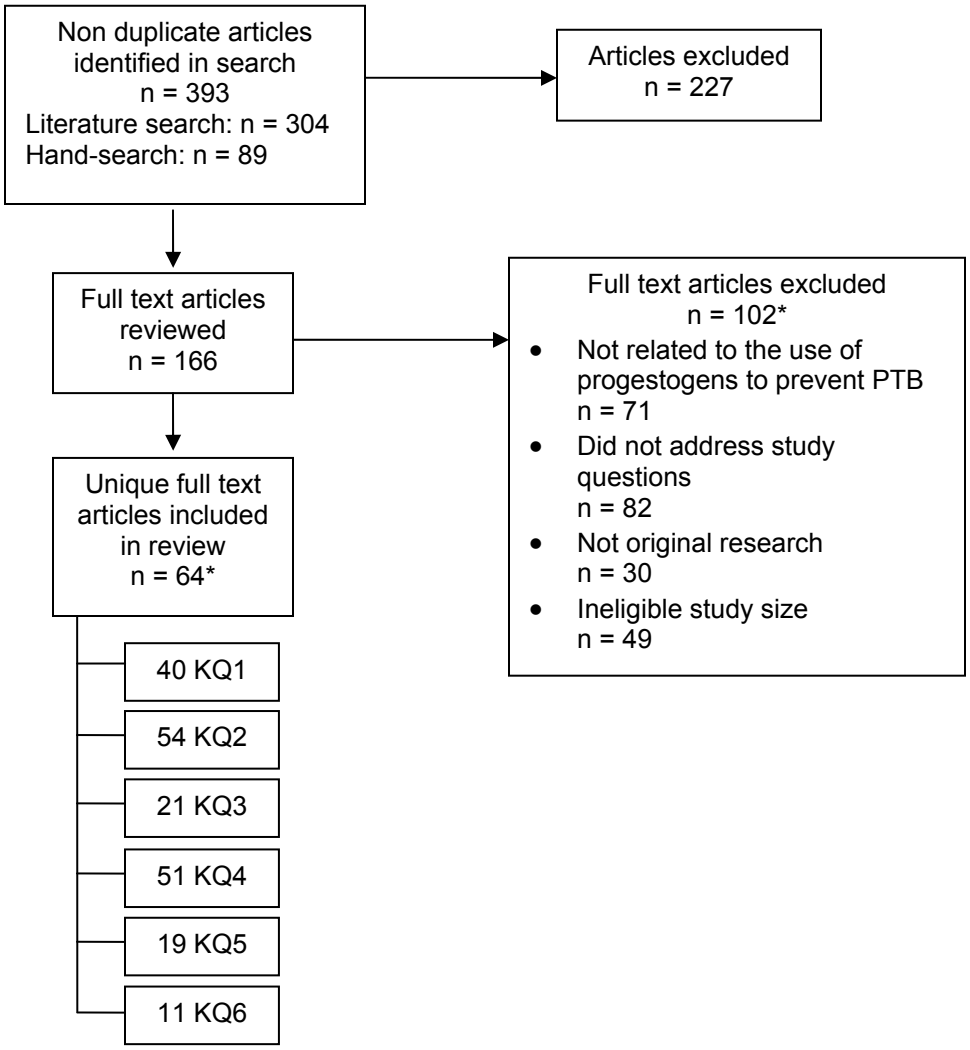
For decision makers to use this report to inform clinical care, it is important to consider the degree to which findings of the included research might be expected to apply in the types of populations and settings in which prenatal care is provided in the United States. Our assessment of applicability 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 key question (see Appendix D) and 2) eight questions on documentation of study population 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, repeatability?

Chapter 3. Results

We identified 393 non-duplicate publications through the search process, with 166 proceeding to full text review (Figure 2). Sixty-four articles were included in the review, representing 58 distinct study populations, with 40 articles pertaining to KQ1, 54 to KQ2, 21 to KQ3, 51 to KQ4, 19 to KQ5 , and 11 to KQ6.

Figure 2. Disposition of articles identified by the search strategy



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

Table 3 provides an overview of these 58 study populations. They were most frequently randomized controlled trials (n=26) conducted in the US (n=31) at a single academic site (n=22) using IM 17OHP (n=34). Table 3 provides a summary of the progestogen interventions represented in this review in reverse chronologic order. The progestogen interventions include 31 unique combinations of formulations, route, and dose.

Table 3. State of the literature related to progestogens for the prevention of preterm birth

Characteristic	Populations Studied				
	US (n=31)	**Asia** (n=4)	**Europe** (n=15)	**Other** (n=7)	**Total** (n=58)
Study Design					
RCT	10	3	8	5	26
Clinical trials	0	1	3	0	4
Cohort	11	0	0	0	11
Case-control	3	0	3	0	6
Case series	6	0	1	1	8
Cross-sectional	2	0	0	1	3
Intervention*					
IM 17OHP	25	1	7	1	34
IM natural progesterone	1	0	1	0	2
Vaginal progesterone	1	2	1	4	8
Oral progesterone	2	1	3	0	2
Other	3	0	4	1	8
NA	1	0	0	1	2
Participant Source					
Academic single site	6	4	8	4	22
Academic multi-site	6	0	3	2	11
Community	5	0	3	1	9
Database	13	0	1	0	14
Other	2	0	0	0	2
Funding*					
CDC/NIH	8	0	0	0	9
Foundation	2	0	0	2	4
Industry	6	0	2	1	9
Intramural	3	0	2	2	7
Not reported	13	4	10	2	29
None	0	0	1	0	1

*Total is greater than total number of studies as some had multiple interventions or funding sources.

In this chapter, each study is not presented individually. Instead, studies are discussed within the framework of the key questions. We have organized the presentation of results by three domains: 1) risk factor/indication for progestogen; 2) type of progestogen used; and 3) maternal preterm birth, and fetal and neonatal outcomes. Each study is included in all places where it contains applicable data.

Table 3. Summary of progestogen interventions

Study Country	Progestogen	Form	Dose & Interval	Target EGA, start; end (weeks)
Harper et al., 2010[75] US	17OHP	IM	250 mg q 7d	16-21.9; 36.9
Cetingoz et al., 2010[39] Turkey	Progesterone†	Vaginal Supp	100 mg qd	24; 34
Rittenberg et al., 2009[23] US	17OHP	IM	250 mg q 7-10d	< 21 (80.4%); 36
Rai et al., 2009[43] India	Progesterone†	Oral	100 mg b.i.d	18-24; 36
Norman et al., 2009[35] UK	Progesterone	Vaginal Gel	90 mg qd	24; 34
Majhi et al., 2009[38] India	Progesterone†	Vaginal Cap	100 mg qd	20-24; 36
Gyamfi et al., 2009[76] US	17OHP	IM	250 mg q 7d	16-20.9; 34-36
Durnwald et al., 2009[24] US	17OHP	IM	NR	15.0 ± 4.1; 36
Caritis et al., 2009[12] US	17OHP	IM	250 mg q 7d	16-21; 35
Briery et al., 2009[14] US	17OHP	IM	250 mg q 7d	20-30; NR
Ventolini et al., 2008[77] US	17OHP	IM	250 mg q 7d	16-20.9; NR
Rittenberg et al., 2008[50] US	17OHP	IM	250 mg q 7d	16-26; NR
Rebarber et al., 2008[26] US	17OHP	IM	250 mg q 7d	16-29; NR
Mason et al., 2008[21] US	17OHP	IM	250 mg q 7d	16-21 or > 21; NR
Facchinetti et al., 2008[17] Italy	17OHP	IM	341 mg q 4d	25-34; 36
Borna et al., 2008[7] Iran	Progesterone†	Vaginal Supp	400 mg qd	24-34; NR
Rouse et al., 2007[15] US	17OHP	IM	250 mg q 7d	16-20; 36
Rittenberg et al., 2007[52] US	17OHP	IM	250 mg q 7d	16-20.9 (56.5%); NR
Rebarber et al., 2007[49] US	17OHP	IM	250 mg q 7d	16-20.9; NR
Rebarber et al., 2007[78] US	17OHP	IM	250 mg q 7-10 d	16-20.9; 37
O'Brien et al., 2007[6] Multinational	Progesterone	Vaginal Gel	90 mg qd	16-23; 37
How et al., 2007[22] US	17OHP	IM	Unknown q 7d	16-20.9 (66%) NR
Gonzalez-Quintero et al., 2007[28] US	17OHP	IM	Unknown q 7d	16-20.9 (56.7%); NR
Fonseca et al., 2007[37] Multinational	Progesterone†	Vaginal Cap	200 mg qd	24; 34

Table 3. Summary of progestogen interventions (continued)

Study Country	Progestogen	Form	Dose & Interval	Target EGA, start; end (weeks)
Facchinetti et al., 2007[8] Italy	17OHP	IM	341 mg q 4d	25-34; 36
DeFranco et al., 2007[79] Multinational	Progesterone	Vaginal Gel	90 mg qd	16-23; 37
Bailit et al., 2007[53] US	Progesterone	IM, Vaginal	NR	NR
Dudas et al., 2006[34] Hungary	17OHP	IM	250 mg qd	NR
Mason et al., 2005[27] US	17OHP	IM	250 mg q 7d	16-21; 36
Meis et al., 2003[13] US	17OHP	IM	250 mg q 7d	16-21; 36
da Fonseca et al., 2003[36] Brazil	Progesterone	Vaginal Supp	100 mg qd	24; 34
Corrado et al., 2002[80] Italy	Progesterone	IM	200 mg qd for 3 d after amniocentesis	16.7 ± 0.8 at amniocentesis
	17OHP	IM	340 mg twice a week until 2nd week after amniocentesis	
Bacq et al., 1997[40] France	Progesterone† (68.0%)	Oral	200-1,000 mg qd	NR
Hobel et al., 1994[41] US	Provera	Oral	20 mg (NR)	> 20; NR
Noblot et al., 1991[9] France	Ritodrine	IV drip	0.2 mg/min for 1h	NR
	Progesterone†	Oral	4x 100 mg q6h for 24h; 4x 100 mg q8h for 24h; 3 100 mg q8h	
Suvonnakote, 1986[32] Thailand	17OHP	IM	250 mg q 7d	16-20; 38
Erny et al., 1986[42] France	Progesterone†	Oral	4, 100 mg capsules (NR)	30-36; NR
Yemini et al., 1985[16] Israel	17OHP	IM	250-12,500 mg over 36 wks (NR)	12.2 ± 3.3; 37
Resseguie et al., 1985[81] US	17OHP	NR	NR	8.6 (median); NR
	Progesterone	NR	NR	8.5 (median); NR
Kester et al., 1984[29] US	17OHP	IM	250 mg q 7d	4-24; NR
Szekeres-Bartho et al., 1983[33] Hungary	17OHP	IM	250 mg q 7d	27-30; 34
Hauth et al., 1983[19] US	17OHP	IM	1,000 mg q 7d	16-20; 36
Kauppila et al., 1980[10] Finland	17OHP	IM	250 mg day 1 and 3; 250 mg q 7d	27-36; 37
Hartikainen-Sorri et al., 1980[31] Finland	17OHP	IM	250 mg q 7d	28-33; 36
Cortes-Prieto et al., 1980[51] Spain	Allylestrenol	Oral	10-40 mg qd	NR; 1-2 before term

Table 3. Summary of progestogen interventions (continued)

Study Country	Progestogen	Form	Dose & Interval	Target EGA, start; end (weeks)
Kester et al.,[44] 1980 US	DES	NR	50-14,000 mg (NR)	6, 36
	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., 1979[30] US	17OHP	IM	250 mg q 7d	16; 36
Breart et al., 1979[18] France	17OHP	IM	500 mg 2x/wk	20-34; 37
	Chlormadinone acetate	Oral	25 mg qd	
Reinisch & Karrow, 1977[47] US	Unspecified progestin	NR	Total: 478-10,650 mg (NR)	4.0; 36.1
Meyer-Bahlburg et al., 1977;[46] US	Unspecified	NR	NR	NR
Johnson et al., 1975[11] US	17OHP	IM	250 mg q 7d	< 24; 37
Hill et al., 1975[25] US	17OHP	NR	250-7,500 mg (NR)	13.6; NR
	Progesterone	IM	100 mg (NR)	
Øvlisen & Iversen, 1963[48] Denmark	6α-methyl-17α-acetoxy-progesterone	NR	180 mg qd for 3 d, then 60 mg qd for 4 d	NR
Fuchs & Stakemann, 1960[45] Denmark	Progesterone	NR	200 mg qd for 3 d, then 150 mg for 2 d, & then 100 mg qd	NR

† Micronized progesterone; Supp = suppository, Cap = capsule

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.

With the assistance of the Technical Expert Panel for this review, we identified maternal, preterm birth, fetal, and neonatal outcomes that we believed were crucial for understanding the effects of intervention with progestogens. The frequency of "not reported" results in the tables demonstrates how inconsistently studies reported these important clinical outcomes. 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 publications address maternal, fetal, and neonatal health outcomes of progestogen treatment for prevention of preterm birth. They represent 36 unique study populations. These 36 studies include 23 RCTs[6-9, 11-19, 35-39, 41-43, 45, 80]; four clinical trials;[10, 31-33] and nine observational studies, including five retrospective cohort studies[23-27], two prospective cohort studies,[30, 51] one prospective case series;[48] and one case-control study.[34] Of the 36, 13 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 US centers.

The preterm birth risk factor prompting progestogen treatment varied. Eight studies focused on women with a history of preterm birth;[6, 13, 23-24, 26-27, 38, 43] ten on preterm labor;[7-10, 17-18, 33, 42, 45, 48] five on multiple gestations (four studies of twin pregnancies[14-15, 31, 35] and one with triplets);[12] nine studies enrolled populations with mixed risk factors;[11, 16, 30, 32, 34, 36, 39, 41, 51] one focused on asymptomatic women with a short cervix on midgestation ultrasound;[37] one on active-duty military personnel;[19] one on abdominal surgery during but unrelated to the pregnancy;[25] and one on midtrimester amniocentesis.[80] Studies of populations with mixed 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, and incompetent cervix.

The 36 studies include 23 unique combinations of progestogen formulation, route, and dose. The intramuscular route was most common with 20 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.

Of the 36 treatment studies we identified, six were randomized controlled trials with more than 200 participants. These are the studies most likely to be adequately powered for key outcomes and familiar to those who stay apprised of results of obstetric intervention trials. Two trials studied women with a history of preterm birth, two trials studied women with twin gestations, and two enrolled populations with mixed risk factors. The two that investigated progestogen treatment in women with a history of preterm birth had conflicting findings and different progestogen formulations under study.[6, 13] In the first,[13] which was of fair quality, 306 women in the treatment group received intramuscular 17OHP 250 mg injections weekly while 153 women received placebo (castor oil) injections. This National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) research network study was stopped prior to completion of enrollment of the initially projected number of participants because evidence of benefit was felt to be compelling. Important results favoring progestogen use included a reduction in preterm birth at less than 37 weeks (RR = 0.66; 95 percent CI: 0.54, 0.81), 35 weeks (RR = 0.67; 95 percent CI: 0.48, 0.93), and 32 weeks (RR = 0.58; 95 percent CI: 0.37, 0.91); fewer low-birth-weight infants < 2500 g (RR = 0.66; 95 percent CI: 0.51, 0.87); less frequent use of supplemental oxygen (RR = 0.62; 95 percent CI: 0.42, 0.92); and fewer intraventricular hemorrhages (RR = 0.25; 95 percent CI: 0.80, 0.82). In the second, a good quality, multinational RCT among women with prior preterm birth,[6] 309 women in the treatment group used 90mg of vaginal progesterone gel daily while 302 women used a placebo. There were no statistically significant improvements in maternal, preterm birth, fetal, or neonatal outcomes.

Of the two trials of women with twin gestations, the results found no benefit in preterm birth or neonatal outcomes.[15, 35] In the first, a fair quality study conducted in the United Kingdom, authors did note a lower rate of cesarean birth (OR 0.53, 95 percent CI 0.34-0.84) among 247 women who used 90mg of vaginal progesterone gel daily compared with 247 women who inserted a placebo. In the second,[15] a good quality study conducted by the NICHD MFMU research network, 325 women received intramuscular 17OHP 250 mg injections weekly while 330 women received placebo (castor oil) injections, comparable to the protocol of injected 17OHP for women with prior preterm birth.

Neither trial that enrolled populations with mixed risk factors documented improvement in maternal, preterm birth, fetal, or neonatal outcomes with progestogen treatment.[18, 41] Both were of poor quality. The first,[18] conducted in France with 211 participants, compared two progestogen formulations: 25 mg of chlormadinone acetate daily and two intramuscular injections of 17OHP 500 mg per week. In the second study,[41] which was a preterm birth prevention project in West Los Angeles, California with multiple intervention arms, 411 women received Provera 20 mg twice daily versus 422 who received placebo. This was in addition to more frequent prenatal visits and education.

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. Twenty-nine 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 5-8. 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 5-8, other reported maternal health outcomes include spontaneous abortion;[13, 16, 80] changes in cervical length;[8, 17, 24] cerclage placement;[11-12, 15] contraction frequency in women diagnosed with preterm labor;[9, 36, 42] details of tocolysis use, such as timing, quantity, and duration;[9, 18] use of antenatal steroids;[6, 12-15] hypertensive disorders;[12, 15, 19] premature rupture of membranes;[80] chorioamnionitis;[12-13, 15, 35] timing of birth in relation to treatment using categorical measures for time;[45, 48] duration of labor stages;[35] and postterm pregnancy.[19]

History of preterm birth. Among studies reporting maternal health outcomes, seven examined progestogen treatment in women with a history of preterm birth, including four RCTs[6, 13, 38, 43] and three observational studies.[23-24, 26] Six of these studies reported maternal outcomes presented in Table 5, and one reported maternal outcomes not presented in the table.[24] Of the six studies presented in Table 5, the intervention was intramuscular 17OHP in three,[13, 23, 26] a vaginal micronized progesterone capsule in one,[38] vaginal progesterone gel in one,[6] and oral micronized progesterone in one.[43] Three of the RCTs had a placebo arm,[6, 13, 43] and the fourth had a no-treatment arm.[38] In the two retrospective cohort studies,[23, 26] the women not receiving progesterone had daily nursing surveillance.

Table 5. 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.[13] 2003 RCT	IM (305)	16.0	NR	17.3	NR	25.2
	Placebo (153)	13.8	NR	15.9	NR	26.8
Rittenberg et al.[23] 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.[26] 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.[38] 2009 RCT	Vaginal (50)	2.0	NR	NR	NR	8.0
	None (50)	6.0	NR	NR	NR	14.0
O'Brien et al.[6] 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.[43] 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

Five studies reported antenatal hospitalizations. Three RCTs did not find a significant difference in antenatal hospitalizations with progestogen treatment compared with no treatment.[6, 13, 38] One of these trials[38] found the rate of antenatal hospitalizations was lower with vaginal progesterone compared with no treatment (2 percent versus 6 percent, $p = 0.30$). The other two trials found a higher rate of antenatal hospitalizations with progestogens, including one[13] with intramuscular 17OHP versus placebo (16.0 percent versus 13.8 percent; RR = 1.14; 95 percent CI: 0.72, 1.86) and another[6] with vaginal progesterone versus placebo (25.6 percent versus 24.8 percent; RR = 1.14; 95 percent CI: 0.38, 3.37). The two retrospective cohort studies[23, 26] 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[26] found a 45.7 percent hospitalization rate in the 17OHP group compared with 70.8 percent in the control group, and the other study[23] had a 12.6 percent hospitalization rate in the 17OHP group compared with 43.0 percent in the control group.

These two retrospective cohort studies[23, 26] 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[26] found a 45.7 percent rate of preterm labor in the 17OHP group compared with 70.8 percent in the control group, and the other study[23] had a 39.2 percent preterm labor rate in the 17OHP group compared with 60.8 percent in the control group. None of the other studies reported preterm labor rates.

Four studies reported the rates of tocolysis. Three RCTs did not report a significant difference in tocolysis when women received progestogens.[6, 13, 43] The rate of tocolysis was higher with progestogen treatment in a trial[13] comparing intramuscular 17OHP with placebo (17.3 percent versus 15.9 percent; RR = 1.09; 95 percent CI: 0.70, 1.69) and a trial[6] comparing vaginal progesterone with placebo (11.3 percent versus 10.3 percent; OR = 1.12; 95 percent CI: 0.67, 1.86). The third RCT with nonsignificant findings[43] found a lower rate of tocolysis with oral progesterone compared with placebo (20.3 percent versus 27. 0 percent, p = 0.686). One of the retrospective cohort studies[23] found a significantly lower rate of tocolysis in women treated with intramuscular 17OHP compared with those who received daily nursing surveillance (12.9 percent versus 49.7 percent, p < 0.001).

Three studies reported PPROM rates,[6, 23, 26] and did not find a significant difference. The PPROM rate was minimally higher in one study[26] comparing intramuscular 17OHP and placebo (8.6 percent versus 8.1 percent, p = 0.770). The other studies found a lower PPROM rate with progestogen treatment, including one study[6] with vaginal progesterone versus placebo (12.0 percent versus 12.6 percent; OR = 0.95; 95 percent CI: 0.58, 1.53) and another study[23] with intramuscular 17OHP versus outpatient nursing surveillance (7.3 percent versus 8.5 percent, p = 0.677).

Three studies reported cesarean rates[6, 13, 38] and did not find a significant difference. One study[6] found a higher cesarean rate with vaginal progesterone compared with placebo (29.0 percent versus 27.8 percent; OR = 1.06; 95 percent CI: 0.75, 1.51). The other studies found a lower rate of cesarean with progestogen treatment, including one study[38] with vaginal progesterone versus no treatment (8 percent versus 14 percent; p = 0.33) and another study[13] with intramuscular 17OHP versus placebo (25.2 percent versus 26.8 percent; RR = 0.94; 95 percent 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[7-9, 17-18, 42, 45] and two observational studies.[10, 48] Five of these studies reported maternal outcomes presented in Table 6, and four reported maternal outcomes not presented in the table.[17, 33, 42, 45, 48] Each the five trials in Table 6 used a different dose and route of progestogens. The second trial arm was placebo in one trial;[9] no treatment in two trials;[7-8] and a different intervention in two trials, including a different progestogen in one[18] and a tocolytic[10] in the other.

Table 6. 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.[8] 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.[18] 1979 RCT	IM (105)	NR	NR	37.0	NR	NR	NR
	Oral (106)	NR	NR	35.0	NR	NR	NR
Kauppila et al.[10] 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.[7] 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.[9] 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

One trial[9] 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 versus 17.8 days, $p < 0.05$). One trial[7] evaluated the recurrence rate of preterm labor and found it was lower with vaginal progesterone compared to no treatment (35.1 percent versus 57.6 percent), 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[9] or second arm.[10] The other trial[18] with tocolysis data analyzed rates in women receiving two progestogens (oral chlormadinone acetate versus intramuscular 17OHP) and found a nonsignificant difference between the two treatments (35 percent for oral versus 37 percent for intramuscular, p-value not reported). One trial[9] reported rates of PPROM and found a nonsignificant difference between groups treated with oral micronized progesterone and Ritodrine versus placebo and Ritodrine (4.5 percent versus 13.6 percent, 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[7] with vaginal progesterone versus no treatment (36.1 ± 17.9 days versus 24.5 ± 27.2 days, $p = 0.037$) and another[8] with intramuscular 17OHP versus no treatment (35.3 ± 19.1 days versus 25.5 ± 15.1 days, $p = 0.003$).[8] 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 versus 35.9 ± 5.7 days) in

one trial[10] and in the placebo group (6.0 weeks with progestogen versus 6.4 weeks with placebo) in the other trial.[9]

Multiple gestation. Multiple gestation was the indication for progestogen treatment in five studies, including four RCTs[12, 14-15, 35] and one clinical trial,[31] all of which reported maternal health outcomes presented in Table 7. Four trials included twin gestations,[14-15, 31, 35] and one trial included triplet gestations.[12] The intervention was intramuscular 17OHP 250 mg weekly in four trials[12, 14-15, 31] and vaginal progesterone gel 90 mg in one trial.[35] All of the trials included a placebo arm.

Table 7. Maternal outcomes for women with multiple gestation

Author Year Study Type	Intervention (N)	Antenatal admission (%)	Preterm labor (%)	Tocolysis (%)	PPROM (%)	Cesarean birth (%)
Briery et al.[14] 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.[12] 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.[15] 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.[31] 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

One trial of twin pregnancies[31] reported antenatal admission rates and duration of hospitalization. More women treated with intramuscular 17OHP (94.9 percent) than placebo (89.5 percent) 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). 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[14] reported rates of preterm labor and found a higher, but not statistically significant difference, in women treated with intramuscular 17OHP compared with placebo (45 percent versus 35 percent, $p = 0.98$). Three multiple gestation trials reported tocolysis rates.[12, 14-15] A RCT of triplet pregnancies[12] found a higher rate of tocolysis with intramuscular 17OHP compared with placebo (47 percent versus 44 percent; RR = 1.0; 95 percent CI: 0.7, 1.5) as did a RCT of twin pregnancies[14] comparing intramuscular 17OHP with placebo (45 percent versus 35 percent, $p = 0.98$). The third RCT reporting tocolysis rates[15] found

a lower rate of tocolysis with intramuscular 17OHP in twin pregnancies compared with placebo (21.9 percent versus 29.4 percent; RR = 0.7; 95 percent CI: 0.6, 1.0).

Two trials reported rates of PPROM[12, 14] and both found a slightly lower rate with progestogen treatment, including a RCT of triplet pregnancies[12] comparing intramuscular 17OHP with placebo (8 percent versus 11 percent; RR = 0.8; 95 percent CI: 0.3, 2.1) and a RCT of twin pregnancies[14] comparing intramuscular 17OHP with placebo (6 percent versus 7 percent, p = 0.525). Three trials reported cesarean birth rates.[12 #26, 35] One RCT[35] found significantly lower cesarean birth rates with treatment with vaginal progesterone gel versus placebo (59.2 percent versus 64.4 percent, p = 0.006). The other two trials that reported cesarean birth rates did not find a significant difference with progestogen treatment, including a RCT of triplet pregnancies[12] comparing intramuscular 17OHP with placebo (100 percent versus 98 percent; RR = 1.0; 95 percent CI: 1.0, 1.1) and a RCT of twin pregnancies[15] comparing intramuscular 17OHP with placebo (61.7 percent versus 62.2 percent; RR = 1.0; 95 percent CI: 0.9, 1.1).

Populations with mixed risk factors. Among studies reporting maternal outcomes other than preterm birth, four examined progestogen treatment in populations with mixed risk factors. Three were RCTs[16, 36, 39] that included outcomes presented in Table 8, and one was an observational study that reported maternal outcomes not presented in the table.[11] Of the trials presented in Table 8, two used a vaginal progesterone suppository,[36, 39] one used intramuscular 17OHP,[16] and all three had a placebo arm.

Table 8. Maternal outcomes for populations with mixed risk factors

Author Year Study Type	Intervention (N)	Antenatal admission (%)	Preterm labor (%)	Tocolysis (%)	PPROM (%)	Cesarean birth (%)
Yemini et al.[16] 1985 RCT	IM (39)	NR	29.0*	NR	6.4	NR
	Placebo (40)	NR	59.4	NR	8.1	NR
Cetingoz et al.[39] 2010 RCT	Vaginal (70)	25.0*	NR	NR	3.8	NR
	Placebo (80)	45.7	NR	NR	2.9	NR
da Fonseca et al.[36] 2003 RCT	Vaginal (72)	19.4	NR	NR	NR	NR
	Placebo (70)	31.4	NR	NR	NR	NR

*Findings are statistically significant

Two trials analyzed the rate of antenatal hospitalizations among women receiving vaginal progesterone suppositories. One trial[39] found they were significantly higher among women who received placebo than those who received progesterone (45.7 percent versus 25 percent; OR = 2.5; 95 percent CI: 1.27, 5.04), and the other trial[36] found no significant difference between women who received placebo and progesterone (31.4 percent versus 19.4 percent, p-value not reported). One trial[16] evaluated preterm labor rates and found they were significantly lower among women treated with intramuscular 17OHP compared with those who received placebo (29.0 percent versus 59.4 percent, p < 0.025). Two trials[16, 39] reported PPROM rates and did not find a significant difference between treatment and placebo arms. One trial[16] compared intramuscular 17OHP and placebo (6.4 percent versus 8.1 percent, p-value not reported), and the

other trial[39] compared vaginal progesterone suppositories and placebo (3.8 percent versus 2.9 percent, $p > 0.05$).

Active-duty military personnel. In the one study[19] 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 percent versus 5.7 percent, p-value not reported).

Abdominal surgery unrelated to pregnancy. In the one study[25] 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

Twenty-eight 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 versus < 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 9-12. 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, eight examined progestogen treatment in women with a history of preterm birth, including four RCTs[6, 13, 38, 43] and four retrospective cohort studies.[23-24, 26-27] Seven of these studies are presented in Table 9. The eighth[27] 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. Of the seven studies in Table 9, four used intramuscular 17OHP,[13, 23-24, 26] one used a vaginal progesterone capsule,[38] one used vaginal progesterone gel,[6] and one used oral micronized progesterone.[43] Three of the RCTs had a placebo arm,[6, 13, 43] and the fourth had a no-treatment arm.[38]

Table 9. 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.[13] 2003 RCT	IM (306)	NR	36.3*	20.6*	NR	11.4*	NR
	Placebo (153)	NR	54.9	30.7	NR	19.6	NR
Durnwald et al.[24] 2009 Retrospective cohort	IM (105)	NR	42.9	NR	NR	NR	NR
	None (95)	NR	35.8	NR	NR	NR	NR
Rittenberg et al.[23] 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.[26] 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.[38] 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.[6] 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.[43] 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

Four studies[6, 23, 26, 43] reported mean gestational age at birth. One RCT[6] found the mean gestational age to be virtually identical among women treated with vaginal progesterone compared with placebo (36.6 ± 3.8 weeks versus 36.6 ± 4.2, mean diff = 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[26] and 36.6 ± 3.0 weeks versus 36.7 ± 2.9 weeks ($p = 0.842$) in the other.[23] One RCT[43] found mean gestational age at birth was significantly higher in women who received oral progesterone versus placebo (36.1 ± 2.66 weeks versus 34.0 ± 3.25 weeks, $p < 0.001$).

All seven 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[38] comparing women using vaginal progesterone with no treatment (12 percent versus 38

percent; RR = 0.315; 95 percent CI: 0.137, 0.724; p = 0.0027), one[13] comparing intramuscular 17OHP with placebo (36.3 percent versus 54.9 percent; RR = 0.66; 95 percent CI: 0.54, 0.81; p = 0.001), and one[43] comparing oral progesterone with placebo (39.2 percent versus 59.5 percent, p = 0.002). One retrospective cohort study[26] also found a lower rate of preterm birth at less than 37 weeks with intramuscular 17OHP compared with daily nursing surveillance (40.5 percent versus 46.2 percent), but this difference was not significant (p = 0.121). 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[6] was a RCT comparing vaginal progesterone with placebo (41.7 percent versus 40.7 percent; OR = 1.08; 95 percent CI: 0.76, 1.52). The other two were retrospective cohort studies, including one[23] comparing intramuscular 17OHP and daily nursing surveillance (45.9 percent versus 42.7 percent, p = 0.436) and another[24] comparing women who did and did not receive intramuscular 17OHP (42.9 percent versus 35.8 percent, p = 0.31).

The meta-estimate of the four RCTs reporting the proportion of births at less than 37 weeks is a relative risk of 0.70 (95 percent CI: 0.50, 0.98). A second meta-estimate was calculated using those four RCTs plus two additional RCTs in which a history of preterm birth was one of multiple indications for progestogen treatment. In one of these trials.[36] the vast majority of participants had a history of preterm birth (97.2 percent in placebo group and 90.3 percent in progesterone group), and the rate of preterm birth was significantly lower with vaginal progesterone versus placebo (13.8 percent versus 28.5 percent, p = 0.03). In the other trial,[39] preterm birth findings were analyzed and reported for specific risk groups, one of which was women with a history of preterm birth. In those women, the preterm birth rate was significantly lower with vaginal progesterone versus placebo (24.3 percent versus 50 percent; OR = 3.11; 95 percent CI: 1.13, 8.53; p = 0.045).[39] Results from all participants in this study can be found in Table 12. The meta-estimate of the relative risk of preterm birth prior to 37 weeks is 0.49 (95 percent CI: 0.30, 0.78) for these two studies, and 0.64 (95 percent CI: 0.48, 0.87) when all six studies are included.

Four studies[6, 13, 23, 26] reported the rate of preterm birth at less than 35 weeks, and one RCT[13] found a significantly lower rate with intramuscular 17OHP compared with placebo (20.6 percent versus 30.7 percent; RR = 0.67; 95 percent CI: 0.48, 0.93; p = 0.02). Another RCT[6] also found a lower rate of preterm birth at less than 35 weeks in women who received vaginal progesterone compared with placebo (22.7 percent versus 26.5 percent), but this difference was not statistically significant (OR = 0.9; 95 percent CI: 0.61, 1.34). Two retrospective cohort studies found a higher, but not statistically significant, rate of preterm birth at less than 35 weeks with intramuscular 17OHP compared with daily nursing surveillance with rates of 25.9 percent versus 21.5 percent (p = 0.152) in one study[26] and 12.0 percent versus 10.8 percent (p = 0.712) in the other study.[23]

Two RCTs[38, 43] reported the rate of preterm birth at ≤ 34 weeks, and both found it was lower with progestogen treatment. One trial[38] compared vaginal progesterone with no treatment (4 percent versus 6 percent; RR = 0.666; 95 percent CI: 0.116, 3.82; p = 0.64), and the other trial[43] compared oral progesterone with placebo (29.7 percent versus 50 percent, no test of statistical significance reported).

Five studies[6, 13, 23, 26, 43] reported the rate of preterm birth at ≤ 32 weeks. One RCT[13] comparing intramuscular 17OHP with placebo found a significantly lower rate of preterm birth at ≤ 32 weeks with progestogen treatment (11.4 percent versus 19.6 percent; RR = 0.58; 95 percent CI: 0.37, 0.91; p = 0.02). Three 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[23] comparing intramuscular 17OHP and daily nursing surveillance (3.8 percent versus 5.0 percent, p = 0.584), a RCT[6] comparing vaginal progesterone with placebo (10.0 percent versus 11.3 percent; OR = 0.9; 95 percent CI: 0.52, 1.56), and a RCT[43] comparing oral progesterone with placebo (2.7 percent versus 20.3 percent, no test of statistical significance reported). One retrospective cohort study[26] found a significantly higher rate of preterm birth at less than 32 weeks among women treated with intramuscular 17OHP compared with those who did not receive 17OHP (13.4 percent versus 7.9 percent, 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[6] compared vaginal progesterone with placebo (3.2 percent versus 3.0 percent; OR 1.07; 95 percent CI: 0.38, 2.96), and the other[43] compared oral progesterone with placebo (0 versus 4 percent, p = 0.25).

Preterm labor. Preterm labor was the indication for progestogen treatment in seven studies reporting preterm birth outcomes, including five RCTs[7-9, 17-18] and two observational studies.[10, 33] Five of these studies are included in Table 10. Of these five studies, three used intramuscular 17OHP at varying doses and frequency.[8, 10, 17] The other two used a vaginal progesterone suppository[7] and oral progesterone.[9] Three of the RCTs had a no-treatment arm, and the fourth used placebo treatment.

Table 10. 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.[17] 2008 RCT	IM (23)	NR	22.0	NR	NR	NR	NR
	None (22)	NR	54.0*	NR	NR	NR	NR
Facchinetti et al.[8] 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.[10] 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.[7] 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.[9] 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

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[7] comparing a vaginal progesterone suppository with no treatment (36.7 ± 1.5 weeks

versus 34.5 ± 1.2 weeks, p = 0.041), and the other was a clinical trial[10] in which women received intramuscular 17OHP or Ritodrine (39.1 ± 0.3 weeks versus 37.7 ± 0.4 weeks, p < 0.01). Three RCTs reported the rate of preterm birth at less than 37 weeks.[8-9, 17] Two found a significantly lower rate of preterm birth at less than 37 weeks with intramuscular 17OHP compared with no treatment, with rates of 22 versus 54 percent (p = 0.049) in one trial,[17] and rates of 16 percent versus 57 percent (p = 0.004) in another trial.[8] The third trial[9] found no statistically significant difference between women treated with oral progesterone and placebo (27.3 percent versus 36.4 percent, p-value not reported). The meta-estimate combining these three trials is a relative risk of 0.44 (95 percent CI: 0.26, 0.76).[8-9, 17] One study[8] 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 percent versus 23.3 percent, p-value not reported).

Two additional studies that reported preterm birth outcomes are not shown in Table 10 because no definition of preterm birth was provided, thus the gestational age cut point could not be determined. One of these studies[18] compared oral chlormadinone acetate with intramuscular 17OHP and did not find a statistically significant difference in the rate of preterm birth between the two progestogens (4 percent versus 8 percent respectively, p-value not reported). The other study[33] found a significantly lower rate of preterm birth among women treated with beta-mimetic drugs plus intramuscular 17OHP compared with women treated only with beta-mimetic drugs (27.3 percent versus 69.2 percent, p < 0.05).

Multiple gestation. Multiple gestation was the indication for progestogen treatment in five studies, including four RCTs[12, 14-15, 35] and one clinical trial[31], all of which reported preterm birth outcomes presented in Table 11. Four trials included twin gestations,[14-15, 31, 35] and one trial included triplet gestations.[12] The intervention was intramuscular 17OHP 250 mg weekly in four trials[12, 14-15, 31] and vaginal progesterone gel 90 mg in one trial.[35] All of the trials included a placebo arm.

Table 11. 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 (%)
Briery et al.[14] 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.[12] 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.[15] 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

Table 11. Preterm birth outcomes for women with multiple gestation (continued)

Hartikainen-Sorri et al.[31] 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

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 versus 33.1 ± 2.9 weeks, p = 0.190) in one trial.[14] 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,[12] 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,[15] and 36.9 ± 2.6 weeks versus 37.3 ± 2.4 weeks (p-value not reported) in one trial.[31]

Two trials, one with adequate power, reported no difference in preterm births using a 37-week cutpoint.[15, 31] Three trials[12, 14-15] reported the preterm birth risk at less than 35 weeks. Two trials found the rate of preterm birth at less than 35 weeks was lower with progestogen treatment, including one trial of twin pregnancies[14] comparing intramuscular 17OHP with placebo (44 percent versus 79 percent, p = 0.117) and another trial of triplet pregnancies[12] also comparing intramuscular 17OHP with placebo (83.1 percent versus 84.1 percent; RR = 1.0; 95 percent CI: 0.9, 1.1). One trial[15] found the rate of preterm birth at less than 35 weeks was higher with intramuscular 17OHP compared with placebo (41.5 percent versus 37.3 percent; RR = 1.1; 95 percent CI: 0.9, 1.3). The meta-estimate combining the two twin trials is a relative risk of 0.84 (95 percent CI: 0.43, 1.64) for preterm birth prior to 35 weeks.[14-15] When the triplet trial is added to the analysis, the meta-estimate is 1.00 (95 percent CI: 0.81, 1.24).[12, 14-15]

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 percent versus 19.4 percent; OR = 1.36; 95 percent CI: 0.89, 2.09; p = 0.16). Two trials[12, 15] reported the preterm birth rate at ≤ 32 weeks, and both found it was higher with progestogen treatment. One trial[12] compared intramuscular 17OHP and placebo in triplet pregnancies (41 percent versus 30 percent; RR = 1.4; 95 percent CI: 0.8, 2.2), and the other trial[15] compared intramuscular 17OHP and placebo in twin pregnancies (16.9 percent versus 14.5 percent; RR = 1.2; 95 percent CI: 0.8, 1.7). Two trials[12, 15] reported the preterm birth rate at ≤ 28 weeks. A trial of triplet pregnancies[12] found the rate was lower with intramuscular 17OHP compared with placebo (10 percent versus 11 percent; RR = 0.9; 95 percent CI: 0.3, 2.4). A trial of twin pregnancies[15] found the rate was higher with intramuscular 17OHP compared with placebo (8.0 percent versus 6.1 percent; RR = 1.3; 95 percent CI: 0.8, 2.3).

Populations with mixed risk factors. Among studies reporting preterm birth outcomes, eight examined progestogen treatment in populations in mixed risk factors. Four RCTs,[11, 36, 39, 41] one clinical trial,[32] and one case-control study[34] included preterm birth outcomes presented in Table 12. Two additional studies[16, 30] are not included in the table but are discussed in the text at

the end of this section. Of the six studies included in Table 12, three used intramuscular 17OHP[11, 32, 34], two used a vaginal progesterone suppository,[36, 39] and one used an oral progestin.[41]

Three studies reported mean gestational age at birth.[11, 34, 39] Two RCTs found a significantly higher gestational age at birth among women treated with progestogens, including one trial[39] comparing vaginal progesterone with placebo (36w6d ± 2w3d versus 35w6d ± 3w2d, $p < 0.05$) and one trial[11] comparing intramuscular 17OHP with placebo (38.6 ± 1.4 weeks versus 35.2 ± 6.2 weeks, $p < 0.025$). A case-control study[34] found a lower gestational age among women who received intramuscular 17OHP compared with women who did not (38.8 ± 2.4 weeks versus 39.4 ± 2.0 weeks), and this result was significant in unadjusted and adjusted models ($p < 0.0001$ for both).

Four studies reported the rate of preterm birth at less than 37 weeks.[32, 36, 39, 41] The rate was significantly lower with progestogen treatment in two RCTs[39] comparing vaginal progesterone with placebo, with rates of 40 percent versus 57.2 percent (OR = 2; 95 percent CI: 1.04, 3.83; $p = 0.036$) in one study[39] and 13.8 percent versus 38.5 percent ($p = 0.03$) in the other.[36] The rate of preterm birth at less than 37 weeks was also significantly lower with progestogen treatment in a RCT[32] comparing intramuscular 17OHP with no treatment (85.71 percent versus 51.28 percent, $p = 0.0036$). The fourth study[41] found a nonsignificant but higher rate of preterm birth at less than 37 weeks among women who received an oral progestin (Provera) compared to placebo (11.2 percent versus 7.3 percent). 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 12. Preterm birth outcomes for populations with mixed 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 (%)
Johnson et al.[11] 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[32] 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.[34] 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.[39] 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
da Fonseca et al.[36] 2003 RCT	Vaginal (72)	NR	13.8*	NR	2.8*	NR	NR
	Placebo (70)	NR	28.5	NR	18.6	NR	NR

Table 12. Preterm birth outcomes for populations with mixed 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 (%)
Hoebel et al.[41] 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

Three studies reported the preterm birth rate at ≤ 34 weeks.[32, 36, 39] The rate was significantly lower with progestogen treatment in two RCTs[39] comparing vaginal progesterone with placebo, with rates of 8.8 percent versus 24.3 percent (OR = 3.35; 95 percent CI: 1.3, 8.63; p = 0.010) in one study[39] and 2.8 percent versus 18.6 percent (p = 0.002) in the other.[36] The rate was significantly lower in two RCTs[36, 39] in which women used a vaginal progesterone suppository (OR = 3.35; 95 percent CI: 1.3, 8.63; p = 0.010 and p = 0.002 respectively). The third study[32] reported a lower preterm birth rate at ≤ 34 weeks with intramuscular 17OHP compared to no treatment (11.43 percent versus 17.95 percent) but did not report a statistical test result for this finding. The one study[32] that reported the birth rate at ≤ 28 weeks found it was lower with intramuscular 17OHP compared to no treatment (0 versus 5.13 percent) but did not report a statistical test result for this finding.

One study[16] is not included in Table 12 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 with 37.8 percent who received placebo, which was statistically significant (p < 0.05). A second study[30] is a prospective cohort study that includes participants whose results are reported in a RCT[11] included in Table 12. 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.

Asymptomatic short cervix on midgestation ultrasound. In the one study[37] 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 percent CI: 0.38, 0.87; p = 0.008 and ARR = 0.60; 95 percent CI: 035, 0.94; p = 0.02).

Midtrimester amniocentesis. In the one study[80] 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 percent versus 7.3 percent, p-value not reported).

Fetal and Neonatal Health Outcomes

Twenty-eight 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 13-17. Outcomes for neonatal conditions associated with prematurity are presented in Table 14. Each of Tables 13-17 is for a specific indication, while Table 14 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 13-17, other reported neonatal characteristics include Apgar scores,[6, 9-10, 12, 14-15, 43, 80] cord pH,[38] placenta weights,[30] head circumference,[6] very low birth weight,[12-13, 15, 37] small for gestational age,[12] birth weight differences across groups,[30] and neonatal age at birth per Ballard score.[43] 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,[13] need for supplemental oxygen,[13] bronchopulmonary dysplasia,[12, 13, 15] pneumonia,[12, 15] pulmonary infection,[31] respiratory problems (nonspecific),[31] apnea/bradycardia,[16] patent ductus arteriosus,[12-16] periventricular leukomalacia,[12, 15] seizures,[12, 15] hyperbilirubinemia,[16, 31, 38] phototherapy,[37] blood transfusion,[37] omphalitis,[31] anemia,[16] and the financial impact of the number of days in the NICU.[27]

History of preterm birth. Among studies reporting fetal and neonatal outcomes, five examined progestogen treatment in women with a history of preterm birth, including four RCTs[6, 13, 38, 43] and one retrospective cohort study.[27] All five of these studies are presented in Table 13, and three are included in Table 14. Two of the studies used intramuscular 17OHP,[13, 27] one used a vaginal micronized progesterone capsule,[38] one used vaginal progesterone gel,[6] and one used oral micronized progesterone.[43] Three of the RCTs had a placebo arm,[6, 13, 43] and the fourth had a no-treatment arm.[38]

Table 13. 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.[13] 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] 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.[38] 2009 RCT	Vaginal (50)	NR	NR	2813.0 ± 501.0*	NR	0	NR
	None (50)	NR	NR	2599.0 ± 421.0	NR	8.0	NR
O'Brien et al.[6] 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.[43] 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

Table 14. Neonatal conditions associated with prematurity

Author Year Study Type Indication	Intervention (N)	RDS (%)	NEC (%)	IVH (%)	Sepsis (%)	Vent (%)	ROP (%)
Meis et al.[13] 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.[38] 2009 RCT History of PTB	Vaginal (50)	NR	0	NR	0	NR	NR
	None (50)	NR	2.0	NR	6.0	NR	NR
O'Brien et al.[6] 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.[7] 2008 RCT PTL	Vaginal (37)	36.4*	0	0	18.2	18.2	NR
	None (33)	10.8	0	0	5.4	5.4	NR
Briery et al.[14] 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.[12] 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.[15] 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.[16] 1985 RCT Mixed 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.[37] 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

Two RCTs[6, 13] reported intrauterine fetal death rates, and four RCTs[6, 13, 38, 43] reported neonatal fetal death rates. No significant differences were reported with progestogen treatment. The meta-estimate for neonatal death is a relative risk of 0.54 (95 percent CI: 0.29, 1.01).

Three RCTs reported mean birth weight. Two of these[38, 43] 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[6] 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 gm (95 percent CI: -44.5, 523.3).

One RCT[13] found a significantly lower rate of low birth weight (< 2500 gm) in infants whose mothers were treated with intramuscular 17OHP (RR = 0.66; 95 percent CI: 0.51, 0.87). Four studies[6, 27, 38, 43] reported NICU admission rates, and two[6, 27] 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]).[27] Three RCTs reported rates of neonatal conditions associated with prematurity, including respiratory distress syndrome,[6, 13] necrotizing enterocolitis,[6, 13, 38] intraventricular hemorrhage,[6, 13] sepsis,[13, 38] mechanical ventilation,[13] and retinopathy.[13] One trial[13] found significantly lower rates of necrotizing enterocolitis (p = 0.01) and intraventricular hemorrhage (RR = 0.25; 95 percent CI: 0.8, 0.82) in infants whose mothers received intramuscular17OHP. 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[7-9, 18, 45] and two observational studies.[10, 48] All seven of these studies are included in Table 15, and one is included in Table 14. Each of these seven studies used a different type, dose, and route of progestogens.

Table 15. 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.[8] 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.[18] 1979 RCT	IM (105)	NR	NR	2156.0	NR	NR	NR
	Oral (106)	NR	NR	3099.0	NR	NR	NR
Fuchs et al.[45] 1960 RCT	IM (63)	0	NR	NR	55.6	NR	NR
	Placebo (63)	3.2	NR	NR	55.6	NR	NR
Kauppila et al.[10] 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.[48] 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
Borna et al.[7] 2008 RCT	Vaginal (37)	NR	NR	2609.4 ± 662.9*	51.5*	39.4	3.8 ± 8.2
	None (33)	NR	NR	3101.5 ± 587.9	27.0	24.3	3.4 ± 7.6
Noblot et al.[9] 1991 RCT	Oral (22)	NR	NR	3077.0	NR	NR	NR
	Placebo (22)	NR	NR	2832.0	NR	NR	NR

*Findings are statistically significant

One RCT[45] reported the rate of intrauterine fetal death, and one clinical trial[10] 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[7] and < 0.05 with intramuscular 17OHP.[10] Two studies[9, 18] found no significant difference in birth weight with progestogen treatment, and one[8] did not report statistical findings for this outcome. Three studies analyzed the rate of low birth weight. One[7] found a significant difference between infants whose mothers did and did not receive vaginal progesterone suppositories (p = 0.040), one[10] found the difference was not significant with intramuscular 17OHP (p-value not reported), and one[45] did not report statistical findings for this outcome. One study[7] 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[7] 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 five studies, including four RCTs[12, 14-15, 35] and one clinical trial,[31] all of which reported fetal and neonatal health outcomes presented in Tables 14 and 16. Four trials included twin gestations,[14-15, 31, 35] and one trial included triplet gestations.[12] The intervention was intramuscular 17OHP 250 mg weekly in four trials[12, 14-15, 31] and vaginal progesterone gel 90 mg in one trial.[35] All of the trials included a placebo arm.

Table 16. 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
Briery et al.[14] 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.[12] 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
Rouse et al.[15] 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.[31] 1980 CT	IM (39/78)	1.3	3.8	NR	NR	NR	NR
	Placebo (38/76)	1.3	1.3	NR	NR	NR	NR

Table 16. 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
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

All of the trials reported intrauterine fetal deaths and neonatal deaths. The meta-estimate for neonatal death combining the three twin trials is a relative risk of 1.58 (95 percent CI: 0.86, 2.93) for preterm birth prior to 35 weeks. When the triplet trial is added to the analysis, the meta-estimate is 1.65 (95 percent CI: 0.93, 2.92).

Two trials[12, 14] reported mean birth weights, and two[12, 15] reported the rate of low birth weight. One trial[35] reported the rate of NICU admissions, and two[14, 35] reported the mean number of NICU days. Three trials[12, 14-15] reported rates of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage. Two trials[12, 15] reported rates of sepsis, mechanical ventilation, and retinopathy. None of the trials found any significant differences in fetal or neonatal outcomes with progestogen treatment.

Populations with mixed risk factors. Among studies reporting fetal and neonatal health outcomes, seven examined progestogen treatment in populations with mixed risk factors. Three RCTs[11, 16, 39] and three observational studies[32, 34, 51] included outcomes presented in Tables 14 and 17. One observational study reported other neonatal outcomes.[30] Of the studies in Tables 14 and 17, four used intramuscular 17OHP[11, 16, 32, 34], one used a vaginal progesterone suppository,[39] and one used oral allylestrenol.[51]

Table 17. Fetal and neonatal outcomes for populations with mixed 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.[16] 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.[11] 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[32] 1986 CT	IM (35)	NR	NR	NR	31.4	NR	NR
	None (39)	NR	NR	NR	48.7	NR	NR
Dudas et al.[34] 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

Table 17. Fetal and neonatal outcomes for populations with mixed risk factors (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
Cetingoz et al.[39] 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.[51] 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

One RCT[11] 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.[16] A third RCT[39] 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[11, 16] 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 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.[51] Two studies reported the rate of low birth weight infants. One case-control study[34] found a higher rate of low birth weight in infants whose mothers were treated with intramuscular 17OHP, which was significant when unadjusted (POR = 1.7; 95 percent CI: 1.2, 2.3) but lost significance when adjusted (POR = 1.4; 95 percent CI: 0.9, 2.0). The other study, which was a clinical trial,(#152} reported no significant findings with regard to with low birth weight. One RCT[39] 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 percent CI: 1.41, 6.54; $p = 0.004$). One RCT[16] reported rates of neonatal conditions associated with prematurity, including respiratory distress syndrome and sepsis, with no significant findings when mothers received intramuscular 17OHP.

Asymptomatic short cervix on midgestation ultrasound. In the one study[37] 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 percent versus 0.7 percent), neonatal death (1.5 percent versus 5.1 percent), low birth weight (41.2 percent versus 42.8 percent), respiratory distress syndrome (8.1 percent versus 13.8 percent), necrotizing enterocolitis (0 versus 0.7 percent), intraventricular hemorrhage (0.7 percent versus 1.4 percent), sepsis (2.2 percent versus 8.0 percent), mechanical ventilation (11.8 percent versus 18.1 percent), and retinopathy (1.5 percent versus 0).

Active-duty military personnel. In the one study[19] in which progesterone was given to active-duty military personnel, there was no significant difference in rates of intrauterine fetal death (1.3 percent versus 3.4 percent), neonatal death (2.5 percent versus 0), or low birth weight

(7.5 percent versus 9.0 percent) with intramuscular 17OHP compared with placebo (p-values not reported).

Abdominal surgery unrelated to pregnancy. In the one study[25] 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 and 2.9 percent versus 8.6 percent respectively. No test of statistical significance was reported.

Midtrimester amniocentesis. In the one study[80] in which intramuscular natural progesterone and 17OHP were given to women who had midtrimester amniocentesis, the intrauterine fetal death rate was lower (0.6 percent versus 1.1 percent) and the mean birth weight was higher (3138.9 ± 665.9 gm versus 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, which we term "harms", of progestogens use varied widely across studies with few explicitly describing a universal approach to inquiring about or establishing operational definitions of harms. Eleven treatment studies, five RCTs and six other study types, 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.[6-8, 11-16, 35, 37, 42-43, 76, 79-80] 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 to13 percent of those treated compared to zero to 7 percent in comparison groups. 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 patients in the treatment and comparison groups.

Table 18. Side effects and harms of progestogen treatment

	RCT Arms				Other studies by treatment			
Range (Number of studies reporting)	**Placebo (n=23)**	**Injection (n=13)**	**Vaginal (n= 7)**	**Oral (n=3)**	**Comparison group (n=12)**	**Injection (n=15)**	**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)					

Table 18. Side effects and harms of progestogen treatment (continued)

	RCT Arms				Other studies by treatment			
Range (Number of studies reporting)	**Placebo (n=23)**	**Injection (n=13)**	**Vaginal (n= 7)**	**Oral (n=3)**	**Comparison group (n=12)**	**Injection (n=15)**	**Vaginal (n=0)**	**Oral (n=2)**
Gestational diabetes	6.9% (1)	6.7% (1)			4.9% (1)	5.5-12.9% (2)		
Hypertension (PIH)	0-29% (4)	12.5-21% (3)		0 (1)		4.8% (1)		
Chorioamnionitis	0-3.3% (4)	1.4% (1)	0-3.6% (3)					
Cesarean birth	14-98%[a] (6)	100%[a] (1)	8-59.2%[a] (5)		4% (1)	12% (1)		
Bleeding disorders post-partum (maternal)	0-4% (3)	0 (1)	0.6 (1)	0 (1)		12.5% (1)		
Other complication in pregnancy (maternal)	0-21% (6)	7.5% (1)	0-17% (3)	0-6.8% (2)				0% (1)
Neonatal infection/sepsis	2.6-18.2% (7)	3.0-20% (4)	0-5.4% (3)		5.3% (1)	0.7-2.6% (2)		
Fetal/neonatal death[b]	0-27% (14)	0-6.3% (8)	0-3.8% (5)	4.1% (1)	0-25% (4)	1.5-5.2% (5)		3.8% (1)
Congenital anomalies	0-12% (8)	0.5-11% (5)	0-0.6% (3)		0-27.3% (6)	0-24.1% (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]
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	6	3	2	1	3	5		

[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

The most commonly reported progestogen-related harm in RCTs was injection site discomfort, in 17 to 62 percent of the treatment group and eight to 62 percent of the placebo group;[12-13, 15] one prospective study reported injection site reactions in eight percent of patients.[27] 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 patients receiving a vaginal placebo. Two other studies mentioned injection or vaginal site discomfort, but did not report a specific number or proportion of patients.[11, 32] Urticaria or pruritus, reported in two RCTs, were experienced by up to four percent of progestogen treated patients and two percent receiving placebo.[15, 35] Nausea was assessed in three RCTs. Nausea was reported by two percent of participants receiving 17OHP injections, five percent of patients receiving progesterone via vaginal suppository, and up to 12 percent of patients receiving placebos via vaginal or injected

route.[15, 35, 42] Neither of the trials using oral progesterone had any participants with nausea in the placebo or treatment arms.

Two 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.[76] A retrospective cohort found a statistically significant association between 17OHP injections and gestational diabetes with 13 percent of progesterone treated patients (n = 557) receiving the diagnosis compared to five percent of comparison patients (RR = 3.09; 95 percent CI: 2.2, 4.4).[49]

Four RCTs assessed occurrence of pregnancy-induced-hypertension (PIH) in their patients. In three trials 13 to 21 percent of patients receiving progesterone and up to 29 percent of patients receiving placebo met criteria. None of those receiving oral progesterone or placebo reported development of PIH.

Four studies reported incidence of chorioamnionitis, with ranges from 1.4 up to 3.6 percent among patients receiving injectable or vaginal progestogens, compared to zero to 3.3 percent of patients receiving the related placebos. Cesarean birth varied widely among five RCTs reporting this outcome. Proportions of women having a cesarean spanned eight to 100 percent in treatment groups and 14 to 98 percent of placebo groups. These numbers are skewed higher than one might expect because of trials that included multiple pregnancies. 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.

Six RCTs tracked other maternal harms in pregnancy. These included milder effects like headache, fatigue, and dizziness, as well as more severe effects such as cardiac rhythm abnormalities and jaundice. Events ranged in frequency from zero to 17 percent of patients in the progestogen arms to zero to 21 percent of patients receiving placebo. Postpartum bleeding disorders were reported in fewer than one percent of patients treated with vaginal progesterone and up to four percent of placebo group members. No bleeding problems 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 11 RCTs[6, 11-16, 19, 35, 37, 43] and three other studies[30, 51, 77] noted mortality in six 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 six RCTs with similar broad ranges of incidence between patients receiving 17OHP (3.0 to 20 percent), and placebo injections or suppositories (two to 18 percent). Congenital anomalies among neonates were reported by seven RCTs, one prospective cohort study, and one case-control study. 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.[6, 35, 38] Among patients receiving 17OHP or placebo, anomaly rates were zero to 11 percent in the treatment groups and zero to 12 percent in the placebo groups.[11, 13, 15-16, 19] The high percentage in this group is due to the inclusion of a study with only 43 patients and five affected by anomalies including accessory digits and functional cardiac murmurs.[11] Among the other study types, zero to three percent of fetuses or

neonates in the treatment group and fewer than one percent in the comparison groups were affected by an anomaly. One study not cited in the harms table demonstrated a higher incidence of hypospadias in patients 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.[82]

None of the studies collected information about macrosomia as an adverse outcome of progestogen therapy. A more recent study found that four 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.[75]

Long-term effects of progestogen therapy on infants 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 six and 35 weeks of gestation. These findings were not quantified and required 30 year recall to report on exposure.[44]

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 IM 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 preterm birth 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 I diabetes have higher risk of intrauterine fetal demise than women with Type II 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 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 to women with a less severe, later prior preterm birth. Two publications aimed to address this question.[38, 83]

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.[83] 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.[38] The sample size of the original study was adequate, but subdivision of the study population into three subgroups resulted in groups with n = 39, n = 27, and n = 9.

The body of evidence is poor for understanding if there is differential effectiveness of progestogens for prevention of preterm birth, based upon gestational age (GA) of the prior spontaneous preterm birth. No data evaluated other maternal, neonatal, or childhood outcomes. No evidence addresses potential for different adverse effects or safety, based on severity of prior 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.[38, 84] 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 (NICHD Maternal Fetal Medicine Units Trial)[84]
    - 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[38]
    - 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)[84]
    - 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[38]
    - 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 percent CI: -2.7 percent, 28.8 percent) and for those with more than one prior, absolute risk reduction was 22.7 percent (95 percent CI: 9.5 percent, 36.0 percent). 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 patients treated with 17OHP and those treated with placebo. The logistic regression analysis yielded an odds ratio of 3.38 (95 percent CI: 1.36, 8.40) when comparing patients with more than one prior spontaneous preterm to patients with 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 percent CI: 0.85, 2.79) when comparing patients with more than one prior spontaneous preterm birth to patients with one prior preterm birth, not a statistically significant difference.[84]

The post-hoc subgroup analysis of data from a non-blinded 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.[38]

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 PTB. These five women were an inadequate sample size for comparative analysis of effectiveness.[19] 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 PTB rate was higher in patients with a higher number of prior spontaneous preterm births; this risk factor has already been established.[22]

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

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 Key Question 1.) 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.[37] 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 patients 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 patients 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.[6}[79]

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 percent of the study population, and reported that a separate analysis of these patients would not be meaningful.[79] 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.[14-15, 35] 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.[39] 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.[12]

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 Key Question 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).[9] 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 PTB before 37 weeks in both subgroups assessed: black, non-Hispanic women and all other women. Relative risk and absolute risk reduction are very similar:[13, 84]

- Black, non-Hispanic: RR = 0.68 (95 percent CI: 0.51, 0.90); ARR = 9.8 percent (95 percent CI: 1.19 percent, 18.42 percent); NNT = 11 (95 percent CI: 5.4, 84)
- White, Hispanic, Asian, & Other: RR = 0.64 (95 percent CI: 0.47, 0.87); ARR = 8.8 percent (95 percent CI: 0.93 percent, 16.7 percent); NNT = 12 (95 percent 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 PTB of all types.[85] 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 percent CI: 0.80, 0.92) for PTB. The obese group (BMI = 30-34.9) had a reduced adjusted OR = 0.83 (95 percent CI: 0.75, 0.92) for PTB. The severely obese group (BMI = 35-39.9) had an increased adjusted OR = 1.33 (95 percent CI: 1.12, 1.57) for PTB. The morbidly obese group (BMI > 40) had an increased adjusted OR = 2.27 (95 percent CI: 1.76, 2.94) for PTB.[85] The entanglement of BMI with both risk of preterm birth and potentially with the biological activity or risk of treatment make if 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 PTB before 37 weeks in women with pre-pregnant BMI < 29, and no benefit for women with a pre-pregnant BMI >29.[84] 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 percent higher point estimate; 95

percent CI: 0.58, 2.88) or not, with three-fold higher odds in the placebo group compared to women of normal weight (95 percent CI: 0.78, 19.19); however the study was underpowered for this factor with especially sparse data for low BMI patients (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 patients with a high pregravid BMI or that higher pregravid is protective for reduction of future PTB after prior PTB, and that progestogen does not confer additional benefit for this subgroup of patients. Last, in keeping with the broader literature about the relationship between obesity and PTB, 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.[84]

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.

Other Candidate Modifiers

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

- Fetal fibronectin testing results
- Cerclage
- Prior preterm premature rupture of membranes
- Uterine malformation
- Conception using assisted reproductive technology (e.g., in vitro fertilization, intracytoplasmic sperm injection of eggs)

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.[18] 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 Key Question 1 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 26 studies that administered injected 17OHP for prevention of preterm birth, 11 were RCTs [8, 11-20]; three were clinical trials;[10, 32-33] two, prospective cohorts;[30-31] eight were retrospective cohorts;[22-29] one, a retrospective case series;[21] and one, a case-control study.[34] Four of these publications are ancillary publications from a single study population[13, 83-84, 86] and two share another population.[6, 79] We considered them as only two study populations. The majority of studies (18) were conducted in the United States,[11-15, 19-30, 78] seven in Europe,[8, 10, 17-18, 31, 33-34] and one in Asia.[32] Exact combinations of dose, interval, and target window is provided in Table 4. The majority of 17OHP studies initiated treatment between 16-21 weeks gestation with a range of 15-36 weeks (Table 4).

Table 19 summarizes the eight 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, mixed 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.

Table 19. 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., 2009[12]	250 mg q 7d	< 35		RR = 1.0 (0.9, 1.1)	
Briery et al., 2009[14]	250 mg q 7d	< 35		NR p = 0.117	
Facchinetti et al., 2008[17]	341 mg q 4d	< 37	NR p = 0.049		
Rouse et al., 2007[15]	250 mg q 7d	< 35		RR = 1.1 (0.09, 1.3)	
Facchinetti et al., 2007[8]	341 mg q 4d	< 37	NR p = 0.004		
Meis et al., 2003[13]	250 mg q 7d	< 37	RR = 0.66 (0.54, 0.81)		
Corrado et al., 2002[80]	340 mg twice a week until 2nd week after amniocentesis	< 37		NR p > 0.05	
Yemini et al., 1985[16]	250-12,500 mg over 36 wks (NR)	< 36	NR p < 0.05		

Vaginal Administration of Progestogens

We identified seven publications that report on either a vaginal gel, capsule, or suppository for administering progestogen treatment.[6-7, 35-39] Two studies[6, 79] are part of a single family of

studies and are considered a single study population in this report. All studies[6-7, 35-39] were RCTs with four conducted outside of the United States. These include the United Kingdom,[35] Brazil,[36] India,[38] and Iran.[7] The remaining studies were either in the United States[39] or conducted at multiple sites. These include one study that included United States, South Africa, India, Czech Republic, Chile, and El Salvador[6] and another study that included the United Kingdom, Chile, Brazil, and Greece.[37] Exact combinations of dose, interval, and target window are provided in Table 4.

In the six RCTs of vaginal administration, five different doses were used. The indication for treatment was history of preterm birth in two studies,[6, 38] multiple gestation in one, [35] mixed risk factors in tow, [36, 39], and shortened cervical length in one.[37] The gestational age at initiation of treatment was 24 weeks for three out of seven of these studies.[35-37] The remaining studies initiated treatment at 18-22+6 weeks,[6] 20-24 weeks,[38] 24-34,[39] and after tocolysis obtained.[7] Table 20 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 = 1109).[6, 35]

Table 20. Vaginal progestogens in RCTs reporting prematurity outcomes at < 35 or < 37 weeks*

Study Country	Form	Dose	Outcome	Favors 17OHP	NS	Favors Placebo
Cetingoz et al., 2010[39] Turkey	Vaginal Supp	100 mg qd	< 37	OR = 0.5 (0.26, 0.96)		
Norman et al., 2009[35] UK	Vaginal Gel	90 mg qd	< 34		OR = 0.74 (0.48, 1.12)	
Majhi et al., 2009[38] India	Vaginal Cap	100 mg qd	< 37	RR = 0.315 (0.137, 0.724)		
O'Brien et al., 2007[6] Multinational	Vaginal Gel	90 mg qd	< 37		OR = 0.93 (0.66, 1.32)	
Fonseca et al., 2007[37] Multinational	Vaginal Cap	200 mg qd	< 34	RR = 0.60 (0.35, 0.94)		
da Fonseca et al., 2003[36] Brazil	Vaginal Supp	100 mg qd	< 37	NR p =.03		

† Micronized progesterone; Supp = suppository, Cap = capsule; * Two studies were not included because they report at 34 weeks gestation

Oral Administration of Progestogens

Five studies[9, 40-43] used oral progestogens alone or in combination with Ritodrine in the treatment group. Three recruited patients in the Europe (France),[9, 40, 42] one in the United States,[41] and one in Asia (India).[43] Four were RCTs. [9, 41-43] One was a case-control study.[40]

Exact combinations of dose, interval, and target window are provided in Table 4. Two studies did not indicate gestational age at initiation[9, 40] and three reported ranges between 18-36 weeks.[35, 41-42] One study required a previous history of preterm birth.[43] None enrolled multiple gestations as an indication for progestogen treatment.

Three RCTs reported prematurity outcomes at < 37 weeks and are summarized in Table 21. Each of the three RCTs use different doses and had different indications for treatment, including history of preterm birth, preterm labor, and mixed risk factors. Two of three demonstrated effectiveness of oral progestogens, one had nonsignificant findings, and none found significant advantage for the placebo group.

Table 21. Oral progestogens in RCTs reporting prematurity outcomes at < 37 weeks

Study Country	Progestogen	Dose	Outcome	Favors Progestogen	NS	Favors Placebo
Rai et al., 2009[43] India	Progesterone†	100 mg b.i.d	< 37	NR p = 0.002		
Hobel et al., 1994[41] US	Provera	20 mg b.i.d	< 37	NR p = 0.98		
Noblot et al., 1991[9] 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

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).[22, 28] 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 percent CI: 0.54, 0.81) with 17OHP and n = 459[13]
- RR = 1.03 (95 percent CI: 0.85, 1.24) with progesterone vaginal gel and n = 611[6]

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

- RR = 0.49 (95 percent CI: 0.25, 0.96) with progesterone vaginal suppository and n = 142[36]

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.[8, 12-13, 20-21, 23-24, 27] Two RCTs directly compared adherence between intervention and placebo groups. An RCT from Italy (n = 38), reported 100 percent adherence in both the 17OHP intervention group and their control group,[8]and a large RCT in the United States (n = 459) reported 8.5% of the17OHP

intervention group was nonadherent, but not statistically different from the placebo group.[13] Another RCT in the United States (n = 278), noted that 91.4% 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% of the intervention group missed greater than two doses.[27] 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.[23] Only one study,[21] a retrospective case series (n = 208), directly assessed adherence in the context of frequency of injections; they observed that only 2.2% of participants missed a dose and they all received less than five injections.[13] 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.[6, 37] One study[6] directly tested for differences in adherence between their treatment and intervention group and observed no significant difference between the two groups (96.2 percent compliance in treatment group vs. 96.4 percent compliance in placebo group). The other[37] 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 what data are available. 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[9, 13, 16, 18, 31, 36, 39, 41, 43, 49] either alone or in combination with another cointervention. Six studies used other forms of cointerventions for their intervention group including cortisol,[10] daily nursing surveillance (DNS),[50] nurses to administer drugs and availability to ask questions but not daily,[23] bed rest,[51] estrogen,[47] and diethylstilbestrol (DES).[44]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 Systems 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.[23-24, 27, 49, 52-58] 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.[23, 49, 52] The other study populations were women enrolled in the high-risk clinic,[53] or a "prematurity prevention" clinic[24] of academic tertiary care centers, and an analysis of use within the Missouri Medicaid managed care component.[27]

Five studies directly surveyed providers about their practice patterns, knowledge, attitudes, and concerns. Three of these surveys were conducted in the United States,[56-58]with two directed to board-certified MFMS[56-57] and one directed to members of the American Congress of Obstetricians and Gynecologists (ACOG) Collaborative Ambulatory Research Network.[58] The remaining surveys were conducted in Canada (national registry of obstetricians)[55] and Australia and New Zealand (members of the Royal College).[54] 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.[13]

Among the six observational studies that provide data about use of progestogens in defined populations of patients, four publications had study objectives related to understanding prescribing practices or patterns of use;[23, 27, 52-53] and two provide data that are informative for this key question but were incidental to the aims of the publications.[24, 49] All reflect care for women in the United States from 1995 forward; the majority in 2003 and later.[27, 49, 52-53]

The provider survey studies reflect responses from 1,098 specialist (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[57] to 74 percent of ACOG network members by 2007.[58] 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, 67 percent prescribing ($p < 0.001$).[56] 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.[56, 58] 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.[58]

The survey of obstetricians participating in the ACOG research network was the only to ask about patient demand. Overall, 63 percent of respondents reported that patients "never request"; 35 percent, "infrequently request"; and 2 percent "frequently request".[58] 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 – two 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 percent and 65 percent 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. 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 patients, 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.[24]

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.[27]

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 percent of women enrolling before this time among those that did not receive 17OHP injections is not reported).[23] 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.[49] 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 ages of 16 and 20.9 weeks. Multiple gestations made up eight percent of non-standard 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 confirm, 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.

Chapter 4. Discussion

State of the Literature

We identified a total of 64 publications, representing 58 distinct study populations: seven 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 percent), and the balance are observational research, a number of which are analyses of administrative databases.

Table 3. State of the literature related to progestogens for the prevention of preterm birth

Characteristic	Populations Studied				
	US (n=31)	**Asia** (n=4)	**Europe** (n=15)	**Other** (n=7)	**Total** (n=58)
Study Design					
RCT	10	3	8	5	26
Clinical trials	0	1	3	0	4
Cohort	11	0	0	0	11
Case-control	3	0	3	0	6
Case series	6	0	1	1	8
Cross-sectional	2	0	0	1	3
Intervention*					
IM 17OHP	25	1	7	1	34
IM natural progesterone	1	0	1	0	2
Vaginal progesterone	1	2	1	4	8
Oral progesterone	2	1	3	0	2
Other	3	0	4	1	8
NA	1	0	0	1	2
Participant Source					
Academic single site	6	4	8	4	22
Academic multi-site	6	0	3	2	11
Community	5	0	3	1	9
Database	13	0	1	0	14
Other	2	0	0	0	2
Funding*					
CDC/NIH	8	0	0	0	9
Foundation	2	0	0	2	4
Industry	6	0	2	1	9
Intramural	3	0	2	2	7
Not reported	13	4	10	2	29
None	0	0	1	0	1

*Total is greater than total number of studies as some had multiple interventions or funding sources.

Strength of Evidence

Overall the strength of evidence to answer the key questions was insufficient or low, with a single exception in which evidence is moderate for lack of benefit. 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 key question.

Table 22. Strength of Evidence for progestogens for prevention of preterm birth

Outcomes	**Domains Pertaining to Strength of Evidence**				**Strength of Evidence**
(n total studies; n total participants)	Risk of Bias	Consistency	Directness	Precision	
Progestogens vs placebo or no treatment for women with prior preterm birth					
PTB prevention <37w (7; 4084)	Low	Inconsistent	Direct	Imprecise	Low; effect size in meta-analysis: 0.70; 95% CI: 0.50, to 0.98
Mean birth weight (3; 859)	Low	Consistent	Direct	Imprecise	Insufficient; meta-analysis mean difference = 239 gm; 95 % CI: -44.5, 523.3 gm
Fetal/neonatal death (4; 1318)	Mod	Inconsistent	Direct	Imprecise	Insufficient: lack of precision to estimate
Progestogen vs placebo or no treatment in patients with threatened preterm labor					
PTB prevention <37w (3; 149)	High*	Inconsistent	Direct	Imprecise	Insufficient RR = 0.44; 95% CI: 0.26, 0.76
Mean birth weight (5; 433)	High*	Inconsistent	Direct	Imprecise	Insufficient; only two small trials reported BW
Fetal/neonatal death (2; 126)	High*	Inconsistent	Direct	Imprecise	Insufficient: lack of precision to estimate
Progestogen vs placebo or no treatment in patients with multiple gestations					
PTB prevention <35w (3; 819)	Low	Consistent	Direct	Imprecise	Moderate; no effect in meta-analysis: RR = 1.00; 95% CI: 0.81, 1.24
Mean birth weight (2; 455)	Low	Consistent	Direct	Imprecise	Moderate; no effect
Fetal/neonatal death (5; 2877)	High	Consistent	Direct	Imprecise	Insufficient: lack of precision to estimate
Progestogen vs placebo or no treatment in study populations with mixed risk factors					
PTB prevention <37w (4; 1189)	Mod-High	Inconsistent	Direct	Imprecise	Low
Mean birth weight (3; 38,270)	Mod-High	Inconsistent	Direct	Imprecise	Insufficient
Fetal/neonatal death (3, 269)	High	Inconsistent	Direct	Imprecise	Insufficient: lack of precision to estimate

Table 22. Strength of Evidence for progestogens for prevention of preterm birth (continued)

Progestogen vs placebo or no treatment in studies with unique indications					
PTB prevention <37w (1; 584)	High	N/A	Direct	Imprecise	Insufficient; single study per unique indication
Mean birth weight (1; 584)	High	N/A	Direct	Imprecise	Insufficient; single study per unique indication
Fetal/neonatal death (4; 1072)	High	N/A	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

Principal Findings and Considerations

KQ1. Maternal, Fetal, and Neonatal Health Outcomes

Forty publications, five of good quality, 23 fair, and 12 poor, examined outcomes of progestogen treatment to prevent preterm birth. They include 23 RCTs, four trials, and nine 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).

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 cut-points 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 a 30 percent reduction in relative risk of preterm birth (RR = 0.70; 95 percent CI: 0.50, 0.98) among those receiving progestogens (Figure 3). While 37 weeks is likely not the most meaningful cut-point for prediction of critical health outcomes -- preventing morbidity and mortality and promoting normal childhood development -- it is the one most frequently reported in the literature. Therefore, this is the most feasible cut-point for aggregate estimates.

Differences in birth weight did not differ meaningfully across trial arms in the three studies that reported mean birth weight (239 gm; 95 percent CI: -44.5, 523.3). Risk of neonatal death is not reduced 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. 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

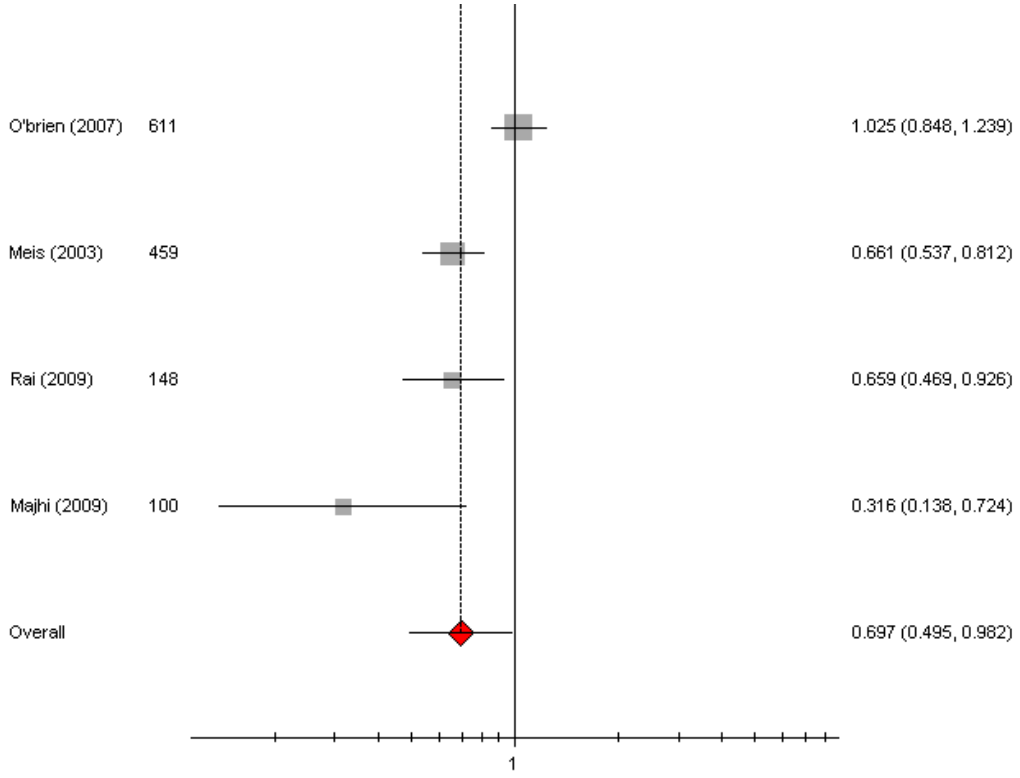
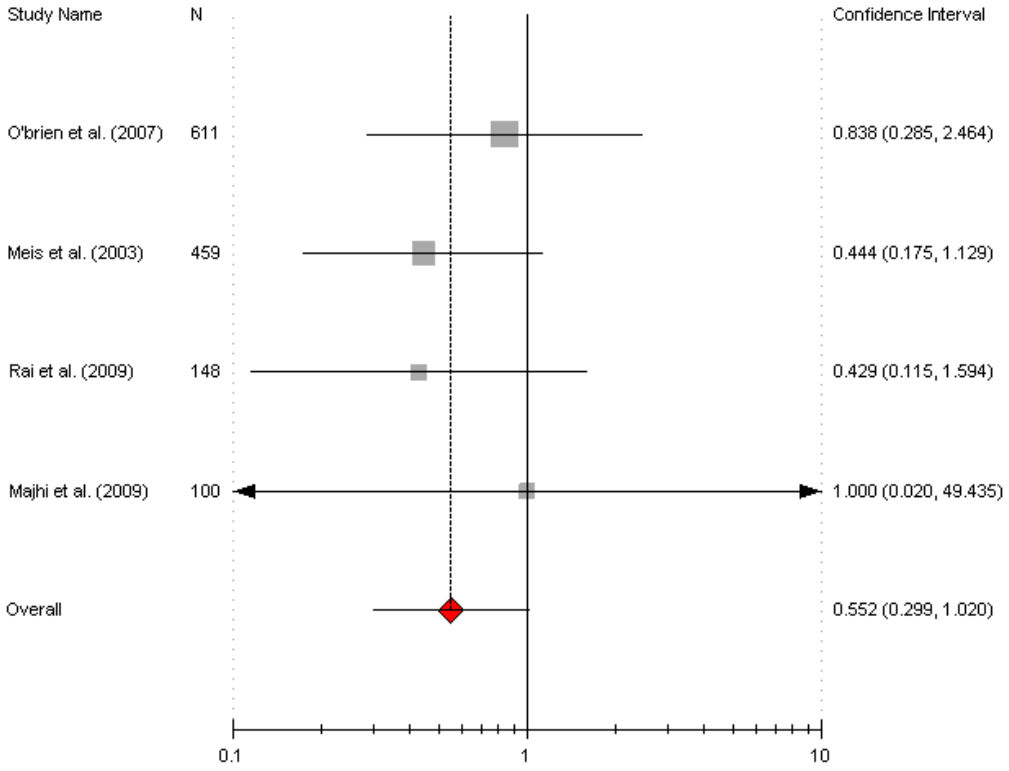


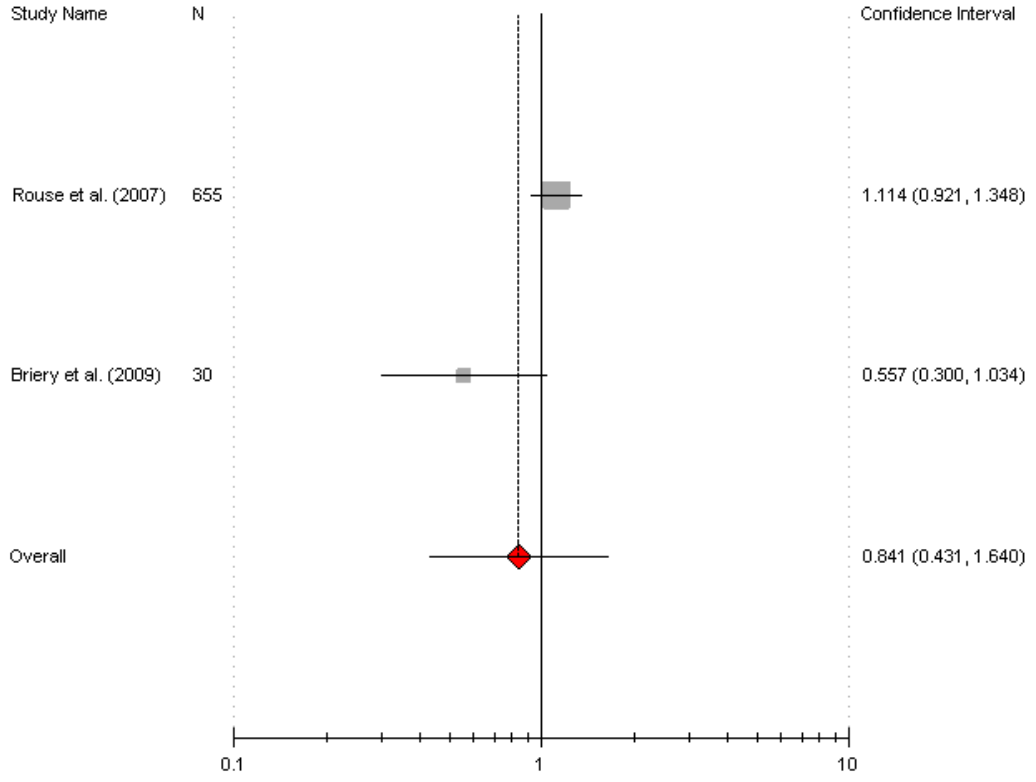
Figure 4. Meta-estimate of effectiveness for preventing neonatal death with maternal history of preterm birth



Seven RCTs used progestogens in populations of women who presented with symptoms of preterm labor (n = 613). 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 cut-point of 37 weeks. The meta-estimate for relative risk reduction was 56 percent (95 percent CI: 0.26, 0.76). These trials, and related non-randomized 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 (n = 1179), and one non-randomized trial focused on women with twins; and one RCT enrolled triplets (n = 134). The meta-estimate for relative risk reduction for preterm birth at less than 35 weeks for twins was 16 percent (95 percent CI: 0.43; 1.64; Figure 5). In aggregate neonatal deaths were not reduced by treatment with a meta-estimate of RR = 1.65 (95 percent CI: 0.93, 2.92). 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 twins



Among nine studies that included populations with mixed 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 for progestogen treatment demonstrated compelling findings; all provide insufficient evidence.

KQ2. Harms of Progestogen Treatments

Evidence about potential harms of progestogen treatment is insufficient. 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 not been reported. 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.

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 vs. 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, 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 patients 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. 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 key questions. 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 Systems 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 US 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 exceeds 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 attenuated. 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.

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.

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. Areas that would benefit from consideration include:

Methodologic Priorities

- Clear specifying of operational definitions for inclusion and exclusion criteria, for instance definition of preterm labor.
- 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 short cervix and 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 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 genetic pathways 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, 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).[5] 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 of 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 17 OHP 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

Many scenarios faced daily by care providers and women at risk of preterm birth and considering progestogen treatment are uninformed 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 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.

References and Included Studies

1. Behrman RE, Butler AS and Institute of Medicine (U.S.). Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth : causes, consequences, and prevention. Washington, D.C.: National Academies Press; 2007.
2. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2005. Natl Vital Stat Rep. 2007 Dec 5;56(6):1-103.
3. Hamilton BE, Martin JA and Ventura SJ. Births: Preliminary data for 2007. National vital statistics reports, Web release. Hyattsville, MD: National Center for Health Statistics; Released March 18, 2009.
4. Bailit JL and Votruba ME. Medical cost savings associated with 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2007 Mar;196(3):219 e1-7.
5. Simhan HN and Caritis SN. Prevention of preterm delivery. N Engl J Med. 2007 Aug 2;357(5):477-87.
6. O'Brien JM, Adair CD, Lewis DF, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007 Oct;30(5):687-96.
7. Borna S and Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labour: a randomised controlled trial. Aust N Z J Obstet Gynaecol. 2008 Feb;48(1):58-63.
8. Facchinetti F, Paganelli S, Comitini G, et al. Cervical length changes during preterm cervical ripening: effects of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2007 May;196(5):453 e1-4; discussion 421.
9. Noblot G, Audra P, Dargent D, et al. The use of micronized progesterone in the treatment of menace of preterm delivery. Eur J Obstet Gynecol Reprod Biol. 1991 Jul 25;40(3):203-9.
10. Kauppila A, Hartikainen-Sorri AL, Janne O, et al. Suppression of threatened premature labor by administration of cortisol and 17 alpha-hydroxyprogesterone caproate: a comparison with ritodrine. Am J Obstet Gynecol. 1980 Oct 15;138(4):404-8.
11. Johnson JW, Austin KL, Jones GS, et al. Efficacy of 17alpha-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975 Oct 2;293(14):675-80.
12. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Obstet Gynecol. 2009 Feb;113(2 Pt 1):285-92.
13. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Jun 12;348(24):2379-85.
14. Briery CM, Veillon EW, Klauser CK, et al. Progesterone does not prevent preterm births in women with twins. South Med J. 2009 Sep;102(9):900-4.
15. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med. 2007 Aug 2;357(5):454-61.
16. Yemini M, Borenstein R, Dreazen E, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985 Mar 1;151(5):574-7.
17. Facchinetti F, Dante G, Venturini P, et al. 17alpha-hydroxy-progesterone effects on cervical proinflammatory agents in women at risk for preterm delivery. Am J Perinatol. 2008 Sep;25(8):503-6.
18. Breart G, Lanfranchi M, Chavigny C, et al. A comparative study of the efficiency of hydroxyprogesterone caproate and of chlormadinone acetate in the prevention of premature labor. Int J Gynaecol Obstet. 1979 Mar-Apr;16(5):381-4.
19. Hauth JC, Gilstrap LC, 3rd, Brekken AL, et al. The effect of 17 alpha-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983 May 15;146(2):187-90.
20. Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. 2007 Oct;110(4):865-72.
21. Mason MV, House KM, Linehan J, et al. Optimizing the use of 17P in pregnant managed Medicaid members. Manag Care. 2008 Jan;17(1):47-52.
22. How HY, Barton JR, Istwan NB, et al. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? Am J Obstet Gynecol. 2007 Sep;197(3):260 e1-4.
23. Rittenberg C, Newman RB, Istwan NB, et al. Preterm birth prevention by 17 alpha-hydroxyprogesterone caproate vs. daily nursing surveillance. J Reprod Med. 2009 Feb;54(2):47-52.
24. Durnwald CP, Lynch CD, Walker H, et al. The effect of treatment with 17 alpha-hydroxyprogesterone caproate on changes in cervical length over time. Am J Obstet Gynecol. 2009 Oct;201(4):410 e1-5.
25. Hill LM, Johnson CE and Lee RA. Prophylactic use of hydroxyprogesterone caproate in abdominal surgery during pregnancy. A retrospective evaluation. Obstet Gynecol. 1975 Sep;46(3):287-90.
26. Rebarber A, Cleary-Goldman J, Istwan NB, et al. The use of 17 alpha-hydroxyprogesterone caproate

(17p) in women with cervical cerclage. Am J Perinatol. 2008 May;25(5):271-5.
27. Mason MV, House KM, Fuest CM, et al. 17 alpha-hydroxyprogesterone caproate (17P) usage in a Medicaid managed care plan and reduction in neonatal intensive care unit days. Manag Care. 2005 Oct;14(10):58-63.
28. Gonzalez-Quintero VH, Istwan NB, Rhea DJ, et al. Gestational age at initiation of 17-hydroxyprogesterone caproate (17P) and recurrent preterm delivery. J Matern Fetal Neonatal Med. 2007 Mar;20(3):249-52.
29. Kester PA. Effects of prenatally administered 17 alpha-hydroxyprogesterone caproate on adolescent males. Arch Sex Behav. 1984 Oct;13(5):441-55.
30. Johnson JW, Lee PA, Zachary AS, et al. High-risk prematurity--progestin treatment and steroid studies. Obstet Gynecol. 1979 Oct;54(4):412-8.
31. Hartikainen-Sorri AL, Kauppila A and Tuimala R. Inefficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy. Obstet Gynecol. 1980 Dec;56(6):692-5.
32. Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thai. 1986 Oct;69(10):538-42.
33. Szekeres-Bartho J, Csernus V, Hadnagy J, et al. Influence of treatment with prostaglandin synthesis inhibitor or progesterone on cytotoxic activity and progesterone binding capacity of lymphocytes during pregnancy. Prostaglandins. 1983 Aug;26(2):187-95.
34. Dudas I, Gidai J and Czeizel AE. Population-based case-control teratogenic study of hydroxyprogesterone treatment during pregnancy. Congenit Anom (Kyoto). 2006 Dec;46(4):194-8.
35. Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. Lancet. 2009 Jun 13;373(9680):2034-40.
36. da Fonseca EB, Bittar RE, Carvalho MH, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24.
37. Fonseca EB, Celik E, Parra M, et al. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007 Aug 2;357(5):462-9.
38. Majhi P, Bagga R, Kalra J, et al. Intravaginal use of natural micronised progesterone to prevent pre-term birth: a randomised trial in India. J Obstet Gynaecol. 2009 Aug;29(6):493-8.
39. Cetingoz E, Cam C, Sakalli M, et al. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. Arch Gynecol Obstet. 2010 Jan 22.
40. Bacq Y, Sapey T, Brechot MC, et al. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology. 1997 Aug;26(2):358-64.
41. Hobel CJ, Ross MG, Bemis RL, et al. The West Los Angeles Preterm Birth Prevention Project. I. Program impact on high-risk women. Am J Obstet Gynecol. 1994 Jan;170(1 Pt 1):54-62.
42. Erny R, Pigne A, Prouvost C, et al. The effects of oral administration of progesterone for premature labor. Am J Obstet Gynecol. 1986 Mar;154(3):525-9.
43. Rai P, Rajaram S, Goel N, et al. Oral micronized progesterone for prevention of preterm birth. Int J Gynaecol Obstet. 2009 Jan;104(1):40-3.
44. Kester P, Green R, Finch SJ, et al. Prenatal 'female hormone' administration and psychosexual development in human males. Psychoneuroendocrinology. 1980 Dec;5(4):269-85.
45. Fuchs F and Stakemann G. Treatment of threatened premature labor with large doses of progesterone. Am J Obstet Gynecol. 1960 Jan;79:172-6.
46. Meyer Bahlburg HF, Grisanti GC and Ehrhardt AA. Prenatal effects of sex hormones on human male behavior: medroxyprogesterone acetate (MPA). Psychoneuroendocrinology. 1977 Oct;2(4):383-90.
47. Reinisch JM and Karow WG. Prenatal exposure to synthetic progestins and estrogens: effects on human development. Arch Sex Behav. 1977 Jul;6(4):257-88.
48. Ovlisen B and Iversen J. Treatment of threatened premature labor with 6alpha-methyl-17alpha-acetoxyprogesterone. Am J Obstet Gynecol. 1963 Jun 1;86:291-5.
49. Rebarber A, Istwan NB, Russo-Stieglitz K, et al. Increased incidence of gestational diabetes in women receiving prophylactic 17alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery. Diabetes Care. 2007 Sep;30(9):2277-80.
50. Rittenberg C, Sullivan S, Istwan N, et al. Women receiving 17-alpha-hydroxyprogesterone caproate hospitalized for preterm labor at less than 34 weeks benefit from daily perinatal nursing surveillance. Am J Obstet Gynecol. 2008 Oct;199(4):389 e1-4.
51. Cortes-Prieto J, Bosch AO and Rocha JA. Allylestrenol: three years of experience with Gestanon in threatened abortion and premature labor. Clin Ther. 1980;3(3):200-8.
52. Rittenberg C, Sullivan S, Istwan N, et al. Clinical characteristics of women prescribed 17 alpha-hydroxyprogesterone caproate in the community setting. Am J Obstet Gynecol. 2007 Sep;197(3):262 e1-4.

53. Bailit JL, Berkowitz R, Thorp JM, et al. Use of progesterone to prevent preterm birth at a tertiary care center. J Reprod Med. 2007 Apr;52(4):280-4.
54. Dodd JM, Ashwood P, Flenady V, et al. A survey of clinician and patient attitudes towards the use of progesterone for women at risk of preterm birth. Aust N Z J Obstet Gynaecol. 2007 Apr;47(2):106-9.
55. Hui D, Liu G, Kavuma E, et al. Preterm labour and birth: a survey of clinical practice regarding use of tocolytics, antenatal corticosteroids, and progesterone. J Obstet Gynaecol Can. 2007 Feb;29(2):117-30.
56. Ness A, Dias T, Damus K, et al. Impact of the recent randomized trials on the use of progesterone to prevent preterm birth: a 2005 follow-up survey. Am J Obstet Gynecol. 2006 Oct;195(4):1174-9.
57. Ness A, Baxter J, Hyslop T, et al. Progesterone for preventing premature birth: practice patterns of board-certified maternal-fetal medicine specialists in the United States. J Reprod Med. 2006 May;51(5):411-5.
58. Henderson ZT, Power ML, Berghella V, et al. Attitudes and practices regarding use of progesterone to prevent preterm births. Am J Perinatol. 2009 Aug;26(7):529-36.
59. Iams JD. Was the preterm birth rate in the placebo group too high in the Meis MFMU Network trial of 17-OHPC? Am J Obstet Gynecol. 2010 May;202(5):409-10.
60. Meis PJ and Aleman A. Progesterone treatment to prevent preterm birth. Drugs. 2004;64(21):2463-74.
61. ACOG Committee Opinion number 419 October 2008 (replaces no. 291, November 2003). Use of progesterone to reduce preterm birth. Obstet Gynecol. 2008 Oct;112(4):963-5.
62. ACOG Committee Opinion. Use of progesterone to reduce preterm birth. Obstet Gynecol. 2003 Nov;102(5 Pt 1):1115-6.
63. Loose DS and Stancel GM. Estrogens and progestins. In: Brunton LL, Parker KL, Murri N, et al., editors. Goodman & Gilman's the pharmacological basis of therapeutics, 11th edition. New York: McGraw-Hill; 2006.
64. Brucker MC and Likis FE. Steroid hormones. In: King TL and Brucker MC, editors. Pharmacology for Women's Health. Sudbury, MA: Jones & Bartlett; 2011.
65. Juni P, Holenstein F, Sterne J, et al. Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol. 2002 Feb;31(1):115-23.
66. Higgins JP and Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. The Cochrane Collaboration; 2009.
67. Wallace BC, Schmid CH, Lau J, et al. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol. 2009;9:80.
68. Tufts Medical Center. MetaAnalyst: Powerful meta-analysis software.http://tuftscaes.org/meta_analyst.
69. Matchar DB, Myers ER, Barber MW, et al. Management of uterine fibroids. Evid Rep Technol Assess (Summ). 2001 Jan(34):1-6.
70. Schulz KF, Chalmers I, Grimes DA, et al. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. JAMA. 1994 Jul 13;272(2):125-8.
71. Schulz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995 Feb 1;273(5):408-12.
72. West S, King V, Carey TS, et al. Systems to rate the strength of scientific evidence. Evid Rep Technol Assess (Summ). 2002 Mar(47):1-11.
73. Moher D, Jadad AR and Tugwell P. Assessing the quality of randomized controlled trials. Current issues and future directions. Int J Technol Assess Health Care. 1996 Spring;12(2):195-208.
74. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996 Feb;17(1):1-12.
75. Harper M, Thom E, Klebanoff MA, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol. 2010 Feb;115(2 Pt 1):234-42.
76. Gyamfi C, Horton AL, Momirova V, et al. The effect of 17-alpha hydroxyprogesterone caproate on the risk of gestational diabetes in singleton or twin pregnancies. Am J Obstet Gynecol. 2009 Oct;201(4):392 e1-5.
77. Ventolini G, Duke J, Po W, et al. The impact of maternal body mass on the effectiveness of 17 alpha-hydroxyprogesterone caproate. J Reprod Med. 2008 Sep;53(9):667-71.
78. Rebarber A, Ferrara LA, Hanley ML, et al. Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2007 Mar;196(3):224 e1-4.
79. DeFranco EA, O'Brien JM, Adair CD, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007 Oct;30(5):697-705.
80. Corrado F, Dugo C, Cannata ML, et al. A randomised trial of progesterone prophylaxis after midtrimester amniocentesis. Eur J Obstet Gynecol Reprod Biol. 2002 Jan 10;100(2):196-8.
81. Resseguie LJ, Hick JF, Bruen JA, et al. Congenital malformations among offspring exposed

in utero to progestins, Olmsted County, Minnesota, 1936-1974. Fertil Steril. 1985 Apr;43(4):514-9.
82. Czeizel A and Huiskes N. A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. Clin Ther. 1988;10(6):725-39.
83. Spong CY, Meis PJ, Thom EA, et al. Progesterone for prevention of recurrent preterm birth: impact of gestational age at previous delivery. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 2):1127-31.
84. Meis PJ, Klebanoff M, Dombrowski MP, et al. Does progesterone treatment influence risk factors for recurrent preterm delivery? Obstet Gynecol. 2005 Sep;106(3):557-61.
85. Torloni MR, Betran AP, Daher S, et al. Maternal BMI and preterm birth: a systematic review of the literature with meta-analysis. J Matern Fetal Neonatal Med. 2009 Nov;22(11):957-70.
86. Klebanoff MA, Meis PJ, Dombrowski MP, et al. Salivary progesterone and estriol among pregnant women treated with 17-alpha-hydroxyprogesterone caproate or placebo. Am J Obstet Gynecol. 2008 Nov;199(5):506 e1-7.

List of Acronyms/Abbreviations

17P, 17OHP	17 alpha-hydroxyprogesterone caproate
AF	amniotic fluid
ALT	alanine aminotransferase
ARR	adjusted relative risk
ART	assisted reproductive techniques
BMI	body mass index <kg/m2>
CA(s)	congenital abnormality(ies)
CD4	cluster of differentiation 4
CHF	congestive heart failure
CI	confidence interval
CT	clinical trial
Dept	department
DES	diethylstilbestrol
DM	Diabetes Mellitus
dPNS	daily perinatal nursing surveillance
EBV	Epstein-Barr Virus
g/gm(s)	grams
GA	gestational age <weeks>
GU	genito-urinary
HIV	Human Immunodeficiency Virus
hr(s)	hour(s)
HTN	hypertension
HUAM	home uterine activity monitoring
Hx	history
ICP	intrahepatic cholestasis of pregnancy
IL	interleukin
IM	intramuscular (injection)
IQR	interquartile range
IUFD	intrauterine fetal death
IV	intravenous (injection)
IVH	intraventricular hemorrage
kg(s)	kilogram(s)
LBW	low birth weight
LFT	liver function test
LOS	Length of stay
mg(s)	milligram(s)
[mh]	Medical Subject Heading
NA	not applicable
NEC	necrotizing enterocolitis
NICU	neonatal intensive care until
[nm]	substance name
NR	not reported

NS	not significant
Ob/gyn	obstetrician/gynecologist
OMP	oral micronized natural progesterone
ONS	outpatient nursing surveillance
ONS	outpatient nursing surveillance
OR	odds ratio
P	progesterone
[pa]	pharmacological action
POR	prevalence odds ratio
PPROM	preterm premature rupture of membranes
PPTB	prior preterm birth
PPTD	prior preterm delivery
PTB	preterm birth
PTD	preterm delivery
PTL	preterm labor
RCT	randomized control trial
RDS	respiratory distress syndrome
ROP	retinopathy
RR	relative risk
SA	spontaneous abortion
SCN	special care nursery
SD	standard deviation
SPTB	spontaneous preterm birth
SPTD	spontaneous preterm delivery
TBA	total bile acid
[tx]	textword
Tx	treatment
US	United States of America
Vent	mechanical ventilator
wk(s)	week(s)
yr(s)	year(s)
μM/mL	micromoles per milliliter

APPENDIX A. Exact Search Strings and Results

Table 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]))	46,479
#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]	69,411
#3	#1 AND #2 AND eng[la] AND humans[mh]	404
#4	#3 AND editorial[pt]	9
#5	#3 AND letter[pt]	12
#6	#3 AND comment[pt]	18
#7	#3 AND case reports[pt]	17
#8	#3 AND review[pt]	95
#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)	298

Table 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.	25,419
#2	exp gestagen/ or (progesterone or hydroxyprogesterone or hydroxy-progesterone or progestogen or progestogens or progestins or progestin).af.	91,915
#3	#1 and #2, limited to human and English language	738
#4	#3 and review.pt	256
#5	#3 and conference paper.pt	46
#6	#3 and editorial.pt	26
#6	#3 and letter.pt	23
#7	#3 and note.pt	15
#8	#3 and short survey.pt	11
#9	#3 and case report/	41
#10	#3 and practice guideline/	14
#11	#3 and “systematic review”/	40
#12	#3 and meta analysis/	43
#13	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	422
#14	#3 not #13	28*

***References included that do not overlap with PubMed search results**

APPENDIX B. Sample Data Abstraction 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 C. Evidence Tables

Tables are sorted by last name of first author.

Evidence Table. 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 **G1b:** 18 **G2:** 48 **G2a:** 16 **G2b:** 32 **Age, mean yrs (range):** **G1**a+**G2**a: 29 (18-39) **G1**b+**G2**b: NR **Race/ethnicity:** NR **Parous, n:** **G1**a+**G2**a: 25 **G1**b+**G2**b*: NR	**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 **G1b+G2b** • Pruritus or jaundice • Dermatological disease • Signs of pre-eclampsia or 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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Bacq et al., 1997 (continued)	**Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance coverage:** NR				

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

Evidence Table. 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. 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)	**<u>Complications during pregnancy</u>** **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 **<u>Prematurity</u>** **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 **<u>Mode of birth and complications during birth</u>** NR **<u>Postpartum and neonatal complications</u>** **Need for mechanical ventilator, n (%):** **G1**: 2 (5.4) **G2**: 6 (18.2) *P* = 0.136 NICU admission, n (%): **G1**: 9 (24.3) **G2**: 13 (39.4) *P* = 0.205

Evidence Table. 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 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. 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	**Complications during pregnancy** **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 **32-33 wks** 18 **≥34wks** 14 **All** 32 *P* < 0.005

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Breart et al., 1979 (continued)					**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. 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	**<u>Complications during pregnancy</u>** **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 **<u>Prematurity</u>** **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. 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. 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 **<u>Longer term outcomes</u>** NR

Evidence Table. 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 **Nulliparous, n (%):** **G1**: 45 (63) **G2**: 33 (52)	**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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)	**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 **Delivery or fetal loss < 35 wks, n/N:** **Spontaneously conceived** **G1:** 18/21 **G2:** 16/18 **ART conceived** **G1:** 41/50 **G2:** 37/45

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)					**Mode of birth and complications during birth** **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) **Postpartum and neonatal complications** Composite adverse outcome, n (%)*: **G1**a: 78 (37) **G2**a: 65 (34) RR: 1.1 (95% CI: 0.7 to 1.7) 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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)					**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) 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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Caritis et al., 2009 (continued)					**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. 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. **Groups:** **G1:** women given progesterone suppositories **G1a:** women given progesterone suppositories with a history of PTB	**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) **Positive cervicovaginal culture for bacterial vaginosis, n (%):** **G1**: 6 (7.5) **G2**: 6 (8.6)	**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 (%):** 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 **G1**a vs **G2**a: OR (95% CI) = 6.3 (1.25-31.7); P=0.033 **G1**b vs **G2**b: 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) **<u>Prematurity</u>** **Birth weight**: NR

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Cetingoz et al., 2010 (continued)	**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 **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				**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 **G1**a vs **G2**a: OR (95% CI) = 6.3 (1.25-31.7); P=0.033 **G1**b vs **G2**b: 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 **G1**a vs **G2**a: OR (95% CI) = 3.11 (1.13-8.53); p=0.045 **G1**b vs **G2**b: OR (95% CI) = 3.48 (1.16-10.46); P=0.043

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Cetingoz et al., 2010 (continued)	**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				**<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. 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. 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. 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 **Race/ethnicity:** NR **Parous:** 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	**Complications during pregnancy** **PROM:** **G1b:** 37 **G1c:** 0 **Spontaneous abortions, n:** **G1**: 93 **G1a:** 90 **G1b:** 1 ***G1c:** 2 **G2**: 0 **Prematurity** **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 **Mode of birth and complications during birth** **Cesarean birth, n (%):** **G1**: 1 **G1a:** 0 **G1b:** 0 **G1c:** 1 **G2**: NR **Postpartum and neonatal complications** **Tetralogy of fallot, n:** **G1:** 1 **G2:** NR **Evidence of masculinization, n:** **G1:** 0

Evidence Table. 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)	**Maternal education:** NR **Maternal smoking:** NR **Maternal BMI:** NR **Medicaid:** NR **Private insurance:** NR				**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. 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 **Private insurance coverage:** 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	**<u>Complications during pregnancy</u>** **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. 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)					**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. 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. 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) Patients not planning to become pregnant again: **G1b:** 9 (8)

Evidence Table. 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 **Race/ethnicity:** NR	**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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Dudas et al., 2006 (continued)	**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: 2nd/3rd 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) **Rectal/anal atresia/stenosis** **G1**a+b: 2nd/3rd months: 2 (0.9) Entire pregnancy: 5 (2.3)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Dudas et al., 2006 (continued)					**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) **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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Dudas et al., 2006 (continued)					**Limbdeficiencies** **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) **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. 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. 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. 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. **Groups:** **G1:** OMP **G1a:** Paris OMP **G1b:** Marseilles OMP **G2:** Placebo **G2a:** Paris placebo **G2b:** Marseilles placebo	**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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Erny et al., 1986 (continued)	**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: $P > 0.05$. **<u>Prematurity</u>** **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 **<u>Mode of birth and complications during birth</u>** NR **<u>Postpartum and neonatal complications</u>** NR **<u>Longer term outcomes</u>** NR

Evidence Table. 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 **Private insurance coverage:** 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 **Cervical lengthening > 2mm, n:** **G1**: 3 **G2**: 1

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Facchinetti et al., 2007 (continued)					**Prematurity** **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 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

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

Evidence Table. 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 **Private insurance:** 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) **Cervical IL-8, baseline, median µM/mL (IQR):** **G1**: 22.3 (12.7, 38.1) **G2**: 28.9 (15.2, 42)	**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) **Cervical nitrites/nitrates, 21 ds, mean µM/mL ±SD:** **G1**: 0.40 ± 0.28 **G2**: 0.38 ± 0.32

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Facchinetti et al., 2008 (continued)			**Cervical TNF-α, baseline, median μM/mL (IQR):** **G1**: 15.66 (8.8, 21.7) **G2**: 12.4 (0.6, 18.4)		**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 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table. 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) **Nulliparous, n (%):** **G1**: 71 (56.8) **G2**: 69 (55.2**)**	**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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fonseca et al., 2007 (continued)	**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. 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. 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 **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**

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

Evidence Table. 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 **G2a:** G2 participants with vaginal hemorrhage as cause of admission	**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 **Uterine contractions:** **G1:** 24 **G2:** 27 **No objective symptoms:** **G1:** 11 **G2:** 4	**<u>Complications during pregnancy</u>** **Chorioamnionitis, n (%):** NR Antenatal hospitalizations, n (%): NR **IUGR, n (%):** NR **Allergic reactions, n (%):** 0 **GDM, n (%):** NR **<u>Prematurity</u>** **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 **After 28th day** **G1a:** 1 **G1b:** 1 **G1c:** 0 **G2a:** 1 **G2b:** 0 **G2c:** 0

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fuchs and Stakemann,1960 (continued)	**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 **>40** **G1:** 1 **G2:** 1 **Race/ethnicity, n (%):** NR **Parous, n (%):** **G1**: 44 (70) **G2**: 34 (54) **Maternal education, n (%):** NR			**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 **>4 weeks** **G1:** 1 **G2:** 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 **2000-2450g** **G1:** 15 **G2:** 13 **2500-2950g** **G1:** 9 **G2:** 15 **>3000g** **G1:** 19 **G2:** 13 **GA at birth:** NR

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Fuchs and Stakemann,1960 (continued)	Maternal BMI, n (%): NR **Maternal smoking, n (%):** NR **Medicaid:** NA **Private insurance coverage:** NR				**Mode of birth and complications during birth** **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 **Postpartum and neonatal complications** **Postpartum hemorrhage,** n (%): NR IVH, **n (%):** NR **Infections, n (%):** NR **Sepsis, n (%):** NR **Longer term outcomes** NR

Evidence Table. 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 **Maternal education:** NR **Maternal BMI:** 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 **G1**b/**G1**d: *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 **G1**b/**G1**d: *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 **G1**b/**G1**d: *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 **G1**b/**G1**d: *P* = 0.730

Evidence Table. 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 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 **G1**b/**G1**d: *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 **G1**b/**G1**d: *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 **G1**b/**G1**d: *P* = 0.298 **Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table. 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) **Parous, n (%):** **G1:** 293 (100) **G2:** 148 (100) **G3:** 176 (53.8) **G4:** 189 (56.6)	**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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Gyamfi et al., 2009 (continued)	**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. 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:** Intervention setting **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 • Clotting disorder • Current or planned cerclage • A plan to deliver either elsewhere or < 37 wks of gestation	**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)	**<u>Complications during pregnancy</u>** **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 **<u>Prematurity</u>** **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. 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				**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. 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) *Retinopathy of prematurity, n **(%); RR (95%CI):** **G1**: 5 (1.2) **G2**: 4 (1.0) 1.18 (0.32-4.37)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Harper et al., 2010 (continued)					*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) †**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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Harper et al., 2010 (continued)					†**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 **<u>Longer term outcomes</u>** 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. 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 **Perinatal mortality, n of fetuses/ neonates:** **G1:** 4 (5.2) **G2:** 2 (2.6) P=NS

Evidence Table. 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)					**<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 **Phototherapy for hyperbilirubinemia, n among surviving neonates::** **G1:** 8 **G2:** 8 **Omphalitis, n among surviving neonates:** **G1:** 1 **G2:** 2

Evidence Table. 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)					**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 **Sepsis, n (%):** NR **<u>Longer term outcomes</u>** NR

Evidence Table. 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:** 07/1977 to 03/1981 **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 **Maternal smoking, (%):** **G1**: (28) **G2**: (25) **G3:** NR **Maternal BMI:** 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	**<u>Complications during pregnancy</u>** **Pregnancy-induced HTN, (%):** **G1:** (12.5) **G2:** (13.6) **G3:** (3.0) *P* = 0.01 **<u>Prematurity</u>** **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 **<u>Mode of birth and complications during birth</u>** **Stillbirth, n:** **G1:** 1 **G2:** 3 **G3:** 0

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hauth et al., 1983 (continued)	**Medicaid:** NR **Private insurance:** NR				**<u>Postpartum and neonatal complications</u>** **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 **<u>Longer term outcomes</u>** 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. 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 **Physician's preferred route for administration of progesterone, %:** Intramuscular **G1a**: 83 Vaginal **G1a**: 9

Evidence Table. 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	**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 **Most frequent indication = prior spontaneous PTB<37 wks, n (%):** **G1:** 137 (42)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Henderson et al., 2009 (continued)					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 No prior PTB, uterine anomalies **G1a:**18.5

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Henderson et al., 2009 (continued)					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** Concerns of non-users (n=91), %: Need for more data: 87 Efficacy: 82 Long-term effects: 72 **Safety:** 53

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Assessment & Population	Inclusion & Exclusion Criteria	Indications	Provider Characteristics	Findings
Henderson et al., 2009 (continued)					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. 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 **Maternal education:** NR **Maternal smoking:** NR	**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 **Provider knowledge and attitudes:** NR **Provider specialty:** NR	**<u>Complications during pregnancy</u>** **Stillbirth, n:** **G1**: 1 **G2**: 0 **Abortion, n:** **G1**: 3 **G2:** 3 **<u>Prematurity</u>** **Premature labor w/ fetal death, n:** **G1**: 1 **G2**: 3 **Birth weight**: NR **GA at birth:** NR **<u>Mode of birth and complications during birth</u>** **Normal delivery, n:** **G1**: 30 **G2:** 29 **Total fetal loss, n:** **G1**: 5 **G2:** 6 **Fetal mortality, (%):** **G1**: (14.3) **G2:** (17.1) **<u>Postpartum and neonatal complications</u>** NR **<u>Longer term outcomes</u>** NR

Evidence Table. 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 BMI:** NR **Medicaid:** NR **Private insurance:** NR			**Cost of drug:** NR **Drug availability:** NR	

Evidence Table. 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 **Black** **G1:** 8.1 **G2:** 8.5 **Asian** **G1:** 4.8 **G2:** 1.4	**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 • English or Spanish speaking	**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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Hobel et al., 1994 (continued)	**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%*	**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. 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 **<u>Mode of birth and Complications during birth</u>** NR

Evidence Table. 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. 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)* **Postpartum and neonatal complications** **Neonatal deaths, n:** **G1:** 3 (0.5)* **G2:** 1 (0.33)*

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
How et al., 2007 (continued)					**Longer term outcomes** NR

*Calculated by the reviewer

Evidence Table. 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) **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)	**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. 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 **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	**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)	**<u>Complications during pregnancy</u>** **Tocolytic (Isoxsuprine) administration, n (%):** **G1:** 2 (11) **G2:** 2 (8) **IUFD, n (%):** **G1:** 0 (0) **G2**[‡]**:** 5 (19.2) *P* < 0.05 **<u>Prematurity</u>** **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 **<u>Mode of birth and complications during birth</u>** NR

Evidence Table. 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 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. 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 **Medicaid:** NR **Private insurance:** 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

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

Evidence Table. 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 **Race/ethnicity:** NR **Parity, mean ± SEM:** **G1**: 1.8 ± 0.2 **G2**: 1.8 ± 0.2	**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 ∆ = 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	**<u>Complications during pregnancy</u>** **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 **<u>Prematurity</u>** ***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 ***GA at birth, mean wks ± SEM:** **G1**: 39.1 ± 0.3 **G2**: 37.7 ± 0.4 *P* < 0.01

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kauppila et al., 1980 (continued)	**Maternal education:** NR **Maternal BMI:** NR **Maternal smoking:** NR **Medicaid:** NR **Private insurance:** NR				**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 **<u>Mode of birth and complications during birth</u>** **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 **<u>Postpartum and neonatal complications</u>** **Transient postpartum asphyxia, n:** **G1**: 0 **G2**: 2 Aspiration syndrome, **n:** **G1**: 0 **G2**: 1 Mild cerebral lesions, **n:** **G1**: 0 **G2**: 1

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kauppila et al., 1980 (continued)					**Death due to RDS, n:** **G1**: 1 **G2**: 0 **Neonatal neurological disorder, n:** **G1**: 1 **G2**: 0 **<u>Longer term outcomes</u>** NR

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

Evidence Table. 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 **Maternal education:** 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 **Provider specialty:** NR **Cost of drug:** 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 **G3:** 0 **G5:** 10 **G4:** 23 **G5:** 23

Evidence Table. 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 smoking:** NR Maternal BMI: NR **Medicaid:** NR **Private insurance:** NR			**Drug availability:** NR	**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) **G2:** (61) **G5:** (39) **G3:** (10) **G5:** (10) **G4:** (0) **G5:** (25)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**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) **G2:** (5) **G5:** (17) **G3:** (70) **G5:** (70) **G4:** (33) **G5:** (17)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**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 Subjects exposed in first trimester having higher scores on academic achievement: p <0.05 Subjects exposed to drug being more extroverted: p <0.05

Evidence Table. 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 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 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

Evidence Table. 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 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: $p < 0.1$ **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: $p < 0.1$

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**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: $p < 0.05$ **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: $p < 0.01$

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**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: $p < 0.05$ 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: $p < 0.05$

Evidence Table. 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:** 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 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

Evidence Table. 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 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: $p < 0.1$ 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: $p <0.01$

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**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: $p < 0.05$ 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: $p < 0.1$

Evidence Table. 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 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: $p < 0.05$ **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: $p < 0.01$

Evidence Table. 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 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: $p < 0.1$ 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: $p < 0.1$

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1980 (continued)					**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: $p < 0.05$ **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: $p < 0.05$

Evidence Table. 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 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 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

Evidence Table. 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 tended to masturbate less often: p <0.1 Drug-exposed after first trimester subjects tended to masturbate less often: p <0.05 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. 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. 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 **Exclusively heterosexual** **G1:** NR **G5:** NR **G2:** 1 **G5:** NR **G3:** NR **G5:** NR **G4:** 1 **G5:** 1

Evidence Table. 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) **Race/ethnicity, n (%):** Caucasion: 50 (100) **Parous, n (%):** NR	**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 **Surgical complications, n (%):** NR

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Kester et al., 1984 (continued)	**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				Maternal harms, **n (%):** NR **<u>Postpartum and neonatal complications</u>** **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 **<u>Longer term outcomes</u>** NR

Evidence Table. 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 PTB at ≤34 weeks, n (%): **G1**: 2 (4) **G2**: 3 (6) P=.64

Evidence Table. 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 **Parity, mean±SD:** **G1**: 2.2±1.2 **G2**: 2.3±1.2 **Maternal education, n (%):** NR				**<u>Mode of birth and complications during birth</u>** **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 **<u>Postpartum and neonatal complications</u>** **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 **Hyperbilirubinemia, n (%):** **G1**: 1 (2) **G2**: 3 (6) P=.30

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Majhi et al., 2009 (continued)	**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				**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 **<u>Longer term outcomes</u>** NR

Evidence Table. 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) **Private insurance coverage, (%):** **G1**: 0 (0) **G2**: 0 (0)	**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) ***Well delivery adherence, n (%):** **90% adherence** **G1:** 13 (72.2) **<90% adherence** **G1:** 5 (27.7)	**<u>Complications during pregnancy</u>** **Allergic reaction at injection site, n (%):** **G1**: 2 **<u>Prematurity</u>** **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 **<u>Mode of birth and complications during birth</u>** **Well delivery at full term, n (%):** **G1**: 19 (79.1) **G2:** 11 (78.6) ∆ = NS **NICU/SCN delivery, n:** **G1:** 5 (27.7) **G2:** 3 (21.4) **<u>Postpartum and neonatal complications</u>** **NICU admissions, n (%):** **G1**: 2 (8.33) **G2**: 2 (14.3) ∆ **=** NS **NICU LOS, ds :** **G1**: 149 **G2**: 231 *P* < 0.000

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Mason et al., 2005 (continued)				***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)	**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. 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) **Private insurance:** NA	**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 **Fetal demise, n:** 1 in each category (<32, <37 wks), not reported by group **Longer term outcomes** NR

Evidence Table. 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 **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	**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. 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, mean ± SD:** **G1**: 26.9 ± 7.9 **G2**: 26.0 ± 7.0			**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 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.	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. 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)	**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				**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. 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. **<u>Mode of birth and complications during birth</u>** **Cesarean birth, n (%):** **G1**: 77 (25.2) **G2**: 41 (26.8) RR: 0.94 (95% CI: 0.68 to 1.30)

Evidence Table. 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)					**Postpartum and neonatal complications** 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) **Bronchopulmonary dysplasia, n/N (%):** **G1**: 4/305 (1.3) **G2**: 5/152 (3.3) RR: 0.40 (95%CI: 0.11 to 1.46)

Evidence Table. 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)					**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) **<u>Longer term outcomes</u>** NR

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

Evidence Table. 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 **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	**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 **Future fertility, n (%):** NR

Evidence Table. 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 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 **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NR **Private insurance coverage:** NR				**Full IQ (WISC-R), mean (range):** **G1**a: 108.2 (74-133) **G1**a: 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.

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

Evidence Table. 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 **Premature dilatation or effacement of the cervix** **G1b**: 85/148 (57)	**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) **Administration preference, n (%):** **Weekly IM** **G1a**: 147 (74) **G1b**: (87) *P* = 0.023 **Vaginal** **G1a**: 51 (26) **G1b**: (13)	**<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. 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)	**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) **Type of medicine, (%):** **Academic** **Gb:** (54) **Clinical practice** **Gb:** (99)			**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) **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)	

Evidence Table. 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)				**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) **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)	

Evidence Table. 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)				**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 **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. 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 **Maternal weight, mean kg*:** **G1:** 61.5 **G2:** 58.9	**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	**<u>Complications during pregnancy</u>** †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 **<u>Prematurity</u>** **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

Evidence Table. 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 height, mean cm*:** **G1:** 162 **G2:** 161 **Medicaid:** NR **Private insurance coverage:** NR				**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 ‡**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. 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. 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 **Itching, n (%):** **G1**: 19 (10) **G2**: 21 (11) OR: 0.92 (95% CI: 0.48 to 1.77) *P* = 0.79

Evidence Table. 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	**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 **Jaundice, n (%):** **G1**: 0 (0) **G2**: 0 (0) **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 **Vaginal itching, n (%):** **G1**: 19 (10) **G2**: 18 (9) OR: 1.09 (95% CI: 0.55 to 2.14) *P* = 0.81

Evidence Table. 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 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 **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 **<u>Prematurity</u>** **GA at birth mean wks ± SD:** **G1**: 35.4 ± 3.5 **G2**: 35.7 ± 3 ∆: -0.3(95% CI: -0.9 to 0.3) *P* = 0.31 **<u>Longer term outcomes</u>** NR

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)					**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 **Spontaneous vertex delivery or vaginal breech, n (%)†:** **G1**: 66 (26.4) **G2**: 38 (15.2) *P* = 1.00

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Norman et. al, 2009 (continued)					**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 Δ: 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 Δ: 3.3 (95% CI: -5.3 to 11.9) *P* = 0.45 **Neonatal death, n:** **G1:** 8 **G2:** 6 *P* = 0.59 **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. 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) **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)	**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 **Infections, n (%):** NR

Evidence Table. 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				**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) **<u>Longer term outcomes</u>** **Neurodevelopmental delay, n (%):** NR

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**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 **<u>Medical diagnoses*:</u>** **Anemia, n (%):** **G1**: 5 (2.6) **G2**: 4 (4.9) **Arthritis, n (%):** **G1**: 1 (0.5) **G2**: 0 **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

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**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) **Hay fever, n (%):** **G1**: 19 (9.9) **G2**: 5 (6.1) **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) **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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**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) 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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**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) 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

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Northen et al., 2007 (continued)					**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) **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. 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 **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 **N at birth:** **G1**: 309 **G1a:** 19 **G1b:** 83 **G2**: 302 **G2a:** 27 **G2b:** 89	**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 • Hx of acute or chronic CHF, renal failure, uncontrolled DM, active liver disorder	**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) **PPROM, n (%):** **G1**: 37 (12.0) **G2**: 38 (12.6) OR: 0.95 (95% CI: 0.58 to 1.53)

Evidence Table. 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 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 **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	• 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			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 **Change in cervical length, mean mm ± SD:** **G1a:** 2 ± 0.9 **G2a:** 0 ± 0.9 *P* = 0.70

Evidence Table. 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)	**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				**<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:** ∆: 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:** ∆: 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. 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) **Postpartum and neonatal complications**

Evidence Table. 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)					**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. 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. 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. 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 **Race/ethnicity, n (%):** NR **Parous:** NR	**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	**<u>Complications during pregnancy</u>** **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 **<u>Prematurity</u>** Delivery during treatment, n: 1st day: **G1a**: 3 **G1b**: 1 **G1c**: 12nd day: **G1a**: 2 **G1b**: 2 **G1c**: 0 3rd day: **G1a**: 2 **G1b**: 1 **G1c**: 0 4th day: **G1a**: 0 **G1b**: 2 **G1c**: 0

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Ovlisen and Iversen, 1963 (continued)	**Maternal education, n (%):** NR **Maternal BMI, n (%):** NR **Maternal smoking, n (%):** NR **Medicaid:** NA **Private insurance coverage:** NR				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. 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. 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 ± 7.38 **G2**: 11.10 ± 7.01 *P* < 0.001 **Duration index pregnancy prolonged compared w/ previous births, mean wks ± SD:** **G1**: 14.68 ± 3.53 **G2**: 12.23 ± 3.17 P<0.001 Neonatal age at birth, mean wks ± SD (Ballard Score)**:** **G1**: 34.26 ± 2.88 **G2**: 32.95 ± 3.20 *P* < 0.001

Evidence Table. 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 **Apgar score at 1 min:** **<6** **G1**: 10 **G2**: 42 **>6** **G1**: 64 **G2**: 32 *P* < 0.001

Evidence Table. 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 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. 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) **Race/ethnicity:** NR	**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 **Association of maternal age < 20 yrs w/ SPTB outcome at 37 wks, mean (min, max):** 0.24 (0.05, 1.18) *P* = 0.079

Evidence Table. 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)	**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 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 **<u>Mode of birth and complications during birth</u>** ***Infant loss (stillbirths, miscarriages and PTB at 21 wks GA), n:** **G1a**: 1 **G1b**: 13

Evidence Table. 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)					**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. 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) **Maternal tobacco use, n (%):** **G1**: 54 (9.7) **G2**: 87 (5.7) **Medicaid:** NR	**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) **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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rebarber et al., 2007 (continued)	**Private insurance coverage:** NR				**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. 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 **Parous, n (%):** **G1**: 232 (100) **G2**: 1650 (100) **Maternal education:** 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	**<u>Complications during pregnancy</u>** *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 **<u>Prematurity</u>** **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. Progestogens for Prevention of PTB (continued)

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

*AP hospitalizations defined the same as PTL diagnosis and are combined here

Evidence Table. 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 **G1b:** unexposed children matched to those exposed to intermediate dosages of progestin and the lowest amounts of estrogen	**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	**Complications during pregnancy** **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. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)	**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) **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				**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) **Premature birth, n:** **G1**: 6 **G2**: 1

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)	**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				**<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 **Prolonged labor, n:** **G1**: 2 **G2**: 1

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Reinisch and Karrow, 1977 (continued)					**Placenta issues, n:** **G1**: 2 (1 abruptio/ablatio, 1 adherent) **G2**: 4 (2 adherent, 2 retained) **<u>Postpartum and neonatal complications</u>** NR **<u>Longer term outcomes</u>** **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. 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. 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. 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 **N at follow-up:** **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) **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>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 **<u>Postpartum and neonatal complications</u>** **Postpartum hemorrhage, n (%):** NR **IVH,** n (%): NR **Infections, n (%):** NR

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Resseguie et al., 1985 (continued)	**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				**Sepsis, n (%):** NR **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) **Genitourinary anomaly, excluding hydrocele, n (%):** **G1**: 36 (3.6) **G1**a: 22 (3.6) **G2**: 53 (2.7) **G2**a: 28 (2.3)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Resseguie et al., 1985 (continued)					**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) **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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Resseguie et al., 1985 (continued)					**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. 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 **Maternal education, n (%):** 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) 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)

Evidence Table. 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 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)				**Mode of birth and complications during birth** NR **Postpartum and neonatal complications** NR **Longer term outcomes** NR

Evidence Table. 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 **Medicaid, (%):** **G1**: (15.7) **G2**: (15.7) **Private insurance coverage:** 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. 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	**<u>Complications during pregnancy</u>** **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 **<u>Prematurity</u>** **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. 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. 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) **Other:** **G1**: 26 (8.0) **G2**: 31 (9.3) **Nulliparous, n (%):** **G1**: 151 (46.2) **G2**: 145 (43.4)	**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) **Side effect leading to discontinuation , n (%)†:** **G1**: 2 (0.6) **G2**: 1 (0.3)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)	**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				**<u>Prematurity</u>** **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) **<u>Mode of birth and complications during birth</u>** **Cesarean birth, n/N (%):** **G1**: 200 (61.7)* **G2:** 204 (62.2)‡ RR: 1.0 (95% CI: 0.9 to1.1)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)					**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) **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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)					**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) **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)

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Rouse et al., 2007 (continued)					**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. 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 **GA of prior PTB:** NR **Prior PPROM:** 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 **Mode of birth and complications during birth** NR

Evidence Table. Progestogens for Prevention of PTB (continued)

Study Description	Intervention & Population	Inclusion & Exclusion Criteria	Clinical Factors	Aspects of Care	Outcomes
Suvonnakote, 1986 (continued)					**Postpartum and neonatal complications** NR **Longer term outcomes** NR

*1 patient had anencephalic fetus and was excluded from the analysis

Evidence Table. 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 **Medicaid:** NR **Private insurance:** 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 **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. 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 **Maternal BMI, n (BMI score):** **G1:** 85 (<20) **G2:** 214 (20 – 24.9) **G3:** 137 (25 – 29.9) **G4:** 170 (≥30)	**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	**<u>Complications during pregnancy</u>** **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 **<u>Prematurity</u>** **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. 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 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. 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. 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. 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 D: Applicability and Quality Tables

Table 1. Key Question 1--Applicability
Table 2. Key Question 2--Applicability
Table 3. Key Question 3--Applicability
Table 4. Key Question 4--Applicability
Table 5. Key Question 5--Applicability
Table 6. Key Question 6--Applicability
Table 7. Quality Rating of Individual Treatment Studies
Table 8. Quality Rating of Individual Studies of Surveys

Table 1. Key Question 1--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--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--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--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--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--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
Borna et al., 2008[3]	fair	-	-	+	+	+	++	++	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Breart et al., 1979[4]	poor	+	-	-	+	-	+	++	-	-	NA	poor	-	+	+	+	+	-	+	+	fair
Briery et al., 2009[5]	fair	+	+	+	+	-	++	++	+	+	NA	fair	-	+	+	+	+	+	+	+	good
Caritis et al., 2009[6]	good	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	+	+	+	+	good
Cetingoz et al., 2010[7]	fair	+	+	+	+	+	++	NR	+	+	NA	good	-	+	+	+	-	-	+	+	fair
Corrado et al., 2002[8]	poor	-	-	+	+	-	++	++	-	-	NA	poor	-	+	+	+	-	-	+	+	fair
Cortes-Prieto et al., 1980[9]	fair	NA	NA	+	-	NA	NA	NA	-	NA	-	fair	-	+	+	-	+	-	+	+	fair
da Fonseca et al., 2003[10]	fair	+	+	+	+	-	+	NR	+	-	NA	fair	+	+	+	+	-	-	+	+	fair
DeFranco et al., 2007[11]	good	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	+	+	+	+	good
Dudas et al., 2006[12]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	-	+	+	+	++	+	+	fair
Durnwald et al., 2009[13]	fair	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	+	-	+	+	-	+	+	+	fair
Erny et al., 1986[14]	poor	-	+	-	+	-	++	++	-	-	NA	poor	-	+	+	+	+	-	+	+	fair
Facchinetti et al., 2007[15]	fair	-	-	+	+	-	++	++	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Facchinetti et al., 2008[16]	poor	+	-	+	+	-	++	NR	-	+	NA	poor	-	+	-	-	-	-	+	+	poor
Fonseca et al., 2007[17]	good	+	+	+	+	+	++	+	+	+	NA	good	+	+	+	+	+	+	+	+	good
Fuchs & Stakemann, 1960[18]	poor	-	+	+	+	-	NR	NR	-	-	NA	poor	-	+	+	-	+	+	+	+	fair
Gonzalez-Quintero et al., 2007[19]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Gyamfi et al., 2009[20]	fair	+	+	+	+	-	NA	NA	-	NA	NA	fair	+	+	+	-	-	-	+	+	fair
Harper et al., 2010[21]	fair	NA	NA	+	+	NA	++	++	-	NA	-	fair	+	+	+	+	+	+	+	+	good
Hartikainen-Sorri et al., 1980[22]	fair	NA	NA	+	+	NA	++	++	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Hauth et al., 1983[23]	poor	-	+	+	+	-	NR	NR	-	+	NA	poor	-	+	+	-	+	-	+	+	fair
Hill et al., 1975[24]	poor	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	-	-	-	+	+	poor
Hobel et al., 1994[25]	poor	-	-	-	+	-	-	NR	+	-	NA	poor	-	+	+	+	+	-	+	+	fair
How et al., 2007[26]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	+	+	-	-	+	+	fair
Johnson et al., 1975[27]	poor	-	+	+	+	-	+	+	-	-	NA	poor	+	+	+	+	+	-	+	+	fair
Johnson et al., 1979[28]	poor	NA	NA	-	+	NA	-	-	-	NA	-	poor	-	+	+	+	+	-	+	+	fair
Kauppila et al., 1980[29]	fair	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
Kester et al., 1980[30]	Poor	NA	NA	-	+	NA	NA	NA	NA	NA	-	Fair	-	-	-	-	-	++	-	-	
Kester et al., 1984[31]	poor	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	-	+	-	-	++	+	+	poor
Mason et al., 2008[32]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Majhi et al., 2009[33]	fair	+	-	+	+	+	++	++	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Mason et al., 2005[34]	poor	NA	NA	-	+	NA	NA	NA	-	NA	-	poor	-	+	+	-	-	+	+	+	fair
Meis et al., 2003[35-39]	fair	+	+	+	+	-	++	+	+	+	NA	fair	+	+	+	+	+	+	+	+	good
Meyer-Bahlburg et al., 1977; [40-41]	poor	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	-	+	-	-	++	+	-	poor
Noblot et al., 1991[42]	fair	+	+	+	+	-	++	++	-	+	NA	fair	-	+	+	+	+	-	+	+	fair
Norman et. al, 2009[43]	fair	+	+	+	+	+	++	++	+	-	NA	fair	-	+	+	+	-	+	+	+	fair
O'Brien et al., 2007[44]	good	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	+	+	+	+	good
Øvlisen & Iversen, 1963[45]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	-	+	-	+	+	fair
Rai et al., 2009[46]	fair	+	+	+	+	+	++	++	+	-	NA	fair	-	+	+	+	+	-	+	+	fair
Rebarber et al., 2007[47]	fair	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	+	+	+	+	-	-	+	+	fair
Rebarber et al., 2007[48]	fair	NA	NA	-	+	NA	NA	NA	-	NA	+	fair	-	+	+	+	+	+	+	+	fair
Rebarber et al., 2008[49]	fair	NA	NA	-	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	-	-	+	+	fair
Reinisch & Karrow, 1977[50]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	-	-	++	+	+	fair
Resseguie et al., 1985[51]	poor	NA	NA	+	+	NA	NA	NA	-	NA	+	fair	-	-	+	-	-	++	+	+	poor
Rittenberg et al., 2009[52]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	+	+	-	-	+	+	fair
Rittenberg et al., 2007[53]	poor	NA	NA	+	+	NA	NA	NA	-	NA	NA	fair	-	+	-	+	-	-	+	+	poor
Rittenberg et al., 2008[54]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	-	+	-	-	+	+	fair
Rouse et al., 2007[55]	good	+	+	+	+	+	++	++	+	+	NA	good	+	+	+	+	+	+	+	+	good
Suvonnakote, 1986[56]	poor	NA	NA	-	+	-	++	++	-	NA	NA	poor	-	+	+	+	+	-	+	+	fair
Szekeres-Bartho et al., 1983[57]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	-	+	+	+	+	-	+	+	fair
Ventolini et al., 2008[58]	fair	NA	NA	+	+	NA	NA	NA	-	NA	-	fair	+	+	+	+	-	-	+	+	fair
Yemini et al., 1985[59]	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[60]	1	1	1	1	1	-1	Fair
Dodd et al., 2007[61]	1	1	1	1	2	1	Good
Hui et al., 2007[62]	1	1	1	1	1	1	Fair
Ness et al., 2006[63]	1	1	1	1	1	1	Fair
Henderson et al., 2009[64]	1	1	1	1	2	1	Good

References

1. Bacq Y, Sapey T, Brechot MC, et al. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology. 1997 Aug;26(2):358-64.
2. Bailit JL, Berkowitz R, Thorp JM, et al. Use of progesterone to prevent preterm birth at a tertiary care center. J Reprod Med. 2007 Apr;52(4):280-4.
3. Borna S and Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labour: a randomised controlled trial. Aust N Z J Obstet Gynaecol. 2008 Feb;48(1):58-63.
4. Breart G, Lanfranchi M, Chavigny C, et al. A comparative study of the efficiency of hydroxyprogesterone caproate and of chlormadinone acetate in the prevention of premature labor. Int J Gynaecol Obstet. 1979 Mar-Apr;16(5):381-4.
5. Briery CM, Veillon EW, Klauser CK, et al. Progesterone does not prevent preterm births in women with twins. South Med J. 2009 Sep;102(9):900-4.
6. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Obstet Gynecol. 2009 Feb;113(2 Pt 1):285-92.
7. Cetingoz E, Cam C, Sakalli M, et al. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. Arch Gynecol Obstet. 2010 Jan 22.
8. Corrado F, Dugo C, Cannata ML, et al. A randomised trial of progesterone prophylaxis after midtrimester amniocentesis. Eur J Obstet Gynecol Reprod Biol. 2002 Jan 10;100(2):196-8.
9. Cortes-Prieto J, Bosch AO and Rocha JA. Allylestrenol: three years of experience with Gestanon in threatened abortion and premature labor. Clin Ther. 1980;3(3):200-8.
10. da Fonseca EB, Bittar RE, Carvalho MH, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. 2003 Feb;188(2):419-24.
11. DeFranco EA, O'Brien JM, Adair CD, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007 Oct;30(5):697-705.
12. Dudas I, Gidai J and Czeizel AE. Population-based case-control teratogenic study of hydroxyprogesterone treatment during pregnancy. Congenit Anom (Kyoto). 2006 Dec;46(4):194-8.
13. Durnwald CP, Lynch CD, Walker H, et al. The effect of treatment with 17 alpha-hydroxyprogesterone caproate on changes in cervical length over time. Am J Obstet Gynecol. 2009 Oct;201(4):410 e1-5.
14. Erny R, Pigne A, Prouvost C, et al. The effects of oral administration of progesterone for premature labor. Am J Obstet Gynecol. 1986 Mar;154(3):525-9.
15. Facchinetti F, Paganelli S, Comitini G, et al. Cervical length changes during preterm cervical ripening: effects of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2007 May;196(5):453 e1-4; discussion 421.
16. Facchinetti F, Dante G, Venturini P, et al. 17alpha-hydroxy-progesterone effects on cervical proinflammatory agents in women at risk for preterm delivery. Am J Perinatol. 2008 Sep;25(8):503-6.
17. Fonseca EB, Celik E, Parra M, et al. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. 2007 Aug 2;357(5):462-9.
18. Fuchs F and Stakemann G. Treatment of threatened premature labor with large doses of progesterone. Am J Obstet Gynecol. 1960 Jan;79:172-6.
19. Gonzalez-Quintero VH, Istwan NB, Rhea DJ, et al. Gestational age at initiation of 17-hydroxyprogesterone caproate (17P) and recurrent preterm delivery. J Matern Fetal Neonatal Med. 2007 Mar;20(3):249-52.
20. Gyamfi C, Horton AL, Momirova V, et al. The effect of 17-alpha hydroxyprogesterone caproate on the risk of gestational diabetes in singleton or twin pregnancies. Am J Obstet Gynecol. 2009 Oct;201(4):392 e1-5.
21. Harper M, Thom E, Klebanoff MA, et al. Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial. Obstet Gynecol. 2010 Feb;115(2 Pt 1):234-42.
22. Hartikainen-Sorri AL, Kauppila A and Tuimala R. Inefficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy. Obstet Gynecol. 1980 Dec;56(6):692-5.
23. Hauth JC, Gilstrap LC, 3rd, Brekken AL, et al. The effect of 17 alpha-hydroxyprogesterone caproate on pregnancy outcome in an active-duty military population. Am J Obstet Gynecol. 1983 May 15;146(2):187-90.
24. Hill LM, Johnson CE and Lee RA. Prophylactic use of hydroxyprogesterone caproate in abdominal surgery during pregnancy. A retrospective evaluation. Obstet Gynecol. 1975 Sep;46(3):287-90.
25. Hobel CJ, Ross MG, Bemis RL, et al. The West Los Angeles Preterm Birth Prevention Project. I. Program impact on high-risk women. Am J Obstet Gynecol. 1994 Jan;170(1 Pt 1):54-62.

26. How HY, Barton JR, Istwan NB, et al. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? Am J Obstet Gynecol. 2007 Sep;197(3):260 e1-4.
27. Johnson JW, Austin KL, Jones GS, et al. Efficacy of 17alpha-hydroxyprogesterone caproate in the prevention of premature labor. N Engl J Med. 1975 Oct 2;293(14):675-80.
28. Johnson JW, Lee PA, Zachary AS, et al. High-risk prematurity--progestin treatment and steroid studies. Obstet Gynecol. 1979 Oct;54(4):412-8.
29. Kauppila A, Hartikainen-Sorri AL, Janne O, et al. Suppression of threatened premature labor by administration of cortisol and 17 alpha-hydroxyprogesterone caproate: a comparison with ritodrine. Am J Obstet Gynecol. 1980 Oct 15;138(4):404-8.
30. Kester P, Green R, Finch SJ, et al. Prenatal 'female hormone' administration and psychosexual development in human males. Psychoneuroendocrinology. 1980 Dec;5(4):269-85.
31. Kester PA. Effects of prenatally administered 17 alpha-hydroxyprogesterone caproate on adolescent males. Arch Sex Behav. 1984 Oct;13(5):441-55.
32. Mason MV, House KM, Linehan J, et al. Optimizing the use of 17P in pregnant managed Medicaid members. Manag Care. 2008 Jan;17(1):47-52.
33. Majhi P, Bagga R, Kalra J, et al. Intravaginal use of natural micronised progesterone to prevent pre-term birth: a randomised trial in India. J Obstet Gynaecol. 2009 Aug;29(6):493-8.
34. Mason MV, House KM, Fuest CM, et al. 17 alpha-hydroxyprogesterone caproate (17P) usage in a Medicaid managed care plan and reduction in neonatal intensive care unit days. Manag Care. 2005 Oct;14(10):58-63.
35. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. 2003 Jun 12;348(24):2379-85.
36. Klebanoff MA, Meis PJ, Dombrowski MP, et al. Salivary progesterone and estriol among pregnant women treated with 17-alpha-hydroxyprogesterone caproate or placebo. Am J Obstet Gynecol. 2008 Nov;199(5):506 e1-7.
37. Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. 2007 Oct;110(4):865-72.
38. Meis PJ, Klebanoff M, Dombrowski MP, et al. Does progesterone treatment influence risk factors for recurrent preterm delivery? Obstet Gynecol. 2005 Sep;106(3):557-61.
39. Spong CY, Meis PJ, Thom EA, et al. Progesterone for prevention of recurrent preterm birth: impact of gestational age at previous delivery. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 2):1127-31.
40. Meyer Bahlburg HF, Grisanti GC and Ehrhardt AA. Prenatal effects of sex hormones on human male behavior: medroxyprogesterone acetate (MPA). Psychoneuroendocrinology. 1977 Oct;2(4):383-90.
41. Ehrhardt AA, Grisanti GC and Meyer-Bahlburg HF. Prenatal exposure to medroxyprogesterone acetate (MPA) in girls. Psychoneuroendocrinology. 1977 Oct;2(4):391-8.
42. Noblot G, Audra P, Dargent D, et al. The use of micronized progesterone in the treatment of menace of preterm delivery. Eur J Obstet Gynecol Reprod Biol. 1991 Jul 25;40(3):203-9.
43. Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. Lancet. 2009 Jun 13;373(9680):2034-40.
44. O'Brien JM, Adair CD, Lewis DF, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007 Oct;30(5):687-96.
45. Ovlisen B and Iversen J. Treatment of threatened premature labor with 6alpha-methyl-17alpha-acetoxyprogesterone. Am J Obstet Gynecol. 1963 Jun 1;86:291-5.
46. Rai P, Rajaram S, Goel N, et al. Oral micronized progesterone for prevention of preterm birth. Int J Gynaecol Obstet. 2009 Jan;104(1):40-3.
47. Rebarber A, Istwan NB, Russo-Stieglitz K, et al. Increased incidence of gestational diabetes in women receiving prophylactic 17alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery. Diabetes Care. 2007 Sep;30(9):2277-80.
48. Rebarber A, Ferrara LA, Hanley ML, et al. Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2007 Mar;196(3):224 e1-4.
49. Rebarber A, Cleary-Goldman J, Istwan NB, et al. The use of 17 alpha-hydroxyprogesterone caproate (17p) in women with cervical cerclage. Am J Perinatol. 2008 May;25(5):271-5.
50. Reinisch JM and Karow WG. Prenatal exposure to synthetic progestins and estrogens: effects on human development. Arch Sex Behav. 1977 Jul;6(4):257-88.
51. Resseguie LJ, Hick JF, Bruen JA, et al. Congenital malformations among offspring exposed in utero to progestins, Olmsted County, Minnesota, 1936-1974. Fertil Steril. 1985 Apr;43(4):514-9.
52. Rittenberg C, Newman RB, Istwan NB, et al. Preterm birth prevention by 17 alpha-hydroxyprogesterone caproate vs. daily nursing surveillance. J Reprod Med. 2009 Feb;54(2):47-52.
53. Rittenberg C, Sullivan S, Istwan N, et al. Clinical characteristics of women prescribed 17 alpha-hydroxyprogesterone caproate in the community setting. Am J Obstet Gynecol. 2007 Sep;197(3):262 e1-4.
54. Rittenberg C, Sullivan S, Istwan N, et al. Women receiving 17-alpha-hydroxyprogesterone caproate hospitalized for preterm labor at less than 34 weeks benefit from daily perinatal nursing surveillance. Am J Obstet Gynecol. 2008 Oct;199(4):389 e1-4.
55. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med. 2007 Aug 2;357(5):454-61.
56. Suvonnakote T. Prevention of pre-term labour with progesterone. J Med Assoc Thai. 1986 Oct;69(10):538-42.
57. Szekeres-Bartho J, Csernus V, Hadnagy J, et al. Influence of treatment with prostaglandin synthesis inhibitor or progesterone on cytotoxic activity and progesterone binding capacity of lymphocytes during pregnancy. Prostaglandins. 1983 Aug;26(2):187-95.
58. Ventolini G, Duke J, Po W, et al. The impact of maternal body mass on the effectiveness of 17 alpha-hydroxyprogesterone caproate. J Reprod Med. 2008 Sep;53(9):667-71.
59. Yemini M, Borenstein R, Dreazen E, et al. Prevention of premature labor by 17 alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 1985 Mar 1;151(5):574-7.
60. Ness A, Baxter J, Hyslop T, et al. Progesterone for preventing premature birth: practice patterns of board-certified maternal-fetal medicine specialists in the United States. J Reprod Med. 2006 May;51(5):411-5.

61. Dodd JM, Ashwood P, Flenady V, et al. A survey of clinician and patient attitudes towards the use of progesterone for women at risk of preterm birth. Aust N Z J Obstet Gynaecol. 2007 Apr;47(2):106-9.
62. Hui D, Liu G, Kavuma E, et al. Preterm labour and birth: a survey of clinical practice regarding use of tocolytics, antenatal corticosteroids, and progesterone. J Obstet Gynaecol Can. 2007 Feb;29(2):117-30.
63. Ness A, Dias T, Damus K, et al. Impact of the recent randomized trials on the use of progesterone to prevent preterm birth: a 2005 follow-up survey. Am J Obstet Gynecol. 2006 Oct;195(4):1174-9.
64. Henderson ZT, Power ML, Berghella V, et al. Attitudes and practices regarding use of progesterone to prevent preterm births. Am J Perinatol. 2009 Aug;26(7):529-36.

Appendix E: 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

Appendix E. List of Excluded Studies

1. Arresting premature labour: orciprenaline and other drugs. Drug Ther Bull. 1973 Mar 30;11(7):25-7. X-1, X-2, X-4
2. Editorial: The initiation of labour. Lancet. 1974 Jan 26;1(7848):124-5. X-1
3. ACOG Committee Opinion. Use of progesterone to reduce preterm birth. Obstet Gynecol. 2003 Nov;102(5 Pt 1):1115-6. X-1
4. Use of progesterone to reduce preterm birth. Int J Gynaecol Obstet. 2004 Jan;84(1):93-4. X-1, X-2, X-4
5. ACOG Committee Opinion number 419 October 2008 (replaces no. 291, November 2003). Use of progesterone to reduce preterm birth. Obstet Gynecol. 2008 Oct;112(4):963-5. X-1
6. 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
7. 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
8. 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
9. Anderson BL, Nau GJ and Simhan HN. Idiopathic vertebral abscess in pregnancy: case report and literature review. Am J Perinatol. 2007 Jun;24(6):377-9. X-2
10. 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
11. 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
12. 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
13. Attardi BJ, Zeleznik A, Simhan H, et al. Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alpha hydroxyprogesterone caproate, and related progestins. Am J Obstet Gynecol. 2007 Dec;197(6):599 e1-7. X-3
14. Aubry RH and Nesbitt RE, Jr. High-risk obstetrics. 3. Cytohormonal evaluations and their practical utility in managing high-risk patients. Am J Obstet Gynecol. 1970 May 1;107(1):48-64. X-3, X-4
15. Aubry RH and Nesbitt RE, Jr. High-risk obstetrics. V. Cytohormonal and interhormonal relationships in normal and abnormal pregnancy. Am J Obstet Gynecol. 1970 Aug 1;107(7):990-1001. X-3, X-4
16. 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
17. 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
18. 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
19. Beard CM, Melton LJ, 3rd, O'Fallon WM, et al. Cryptorchism and maternal estrogen exposure. Am J Epidemiol. 1984 Nov;120(5):707-16. X-3,
20. Behrman SJ. On reducing prematurity: the hospital's role. Hosp Pract (Hosp Ed). 1982 Jun;17(6):15-6. X-1
21. Bell R. Antenatal oestradiol and progesterone concentrations in patients subsequently having preterm labour. Br J Obstet Gynaecol. 1983 Oct;90(10):888-91. X-3
22. Bengtsson LP and Siener H. Experiments on the inhibition of uterine motility in premature labour. Bibl Gynaecol. 1966;42:79-92. X-2
23. Bibby JG, Higgs SA, Kent AP, et al. Plasma steroid changes in pre-term labour in association with salbutamol infusion. Br J Obstet Gynaecol. 1978 Jun;85(6):425-30. X-3
24. Block BS, Liggins GC and Creasy RK. Preterm delivery is not predicted by serial plasma estradiol or progesterone concentration measurements. Am J Obstet Gynecol. 1984 Nov 15;150(6):716-22. X-3
25. Bolt RJ, van Weissenbruch MM, Popp-Snijders C, et al. Fetal growth and the function of the adrenal cortex in preterm infants. J Clin Endocrinol Metab. 2002 Mar;87(3):1194-9. X-2, X-3
26. 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
27. 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
28. 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
29. 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
30. Branisteanu DD and Mathieu C. Progesterone in gestational diabetes mellitus: guilty or not guilty?

Trends Endocrinol Metab. 2003 Mar;14(2):54-6. X-1, X-2
31. Brenner WE and Hendricks CH. Effect of medroxyprogesterone acetate upon the duration and characteristics of human gestation and labor. Am J Obstet Gynecol. 1962 Apr 15;83:1094-8. X-3, X-4
32. Brent RL. Nongenital malformations following exposure to progestational drugs: the last chapter of an erroneous allegation. Birth Defects Res A Clin Mol Teratol. 2005 Nov;73(11):906-18. X-1, X-3
33. Brost BC, Newman RB, Hendricks SK, et al. Effect of hemodialysis on serum progesterone level in pregnant women. Am J Kidney Dis. 1999 May;33(5):917-9. X-2, X-3
34. 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
35. Calda P. Safety signals of 17-OHP-C use in pregnancy and efficacy in the prevention of preterm birth. J Matern Fetal Neonatal Med. 2009 Jun;22(6):540-2. X-1, X-2, X-4
36. Callejo J, Salvador C, Eduardo Gonzalez B, et al. Treatment of early menopause in women who whish to become pregnant. Revista de Iberoamericana de Revisiones en Menopausia. 2001;3(2):19-21. X-1, X-2, X-3
37. Caritis SN, Hirsch RP and Zeleznik AJ. Adrenergic stimulation of placental progesterone production. J Clin Endocrinol Metab. 1983 May;56(5):969-72. X-2, X-3
38. Carmichael SL and Abrams B. A critical review of the relationship between gestational weight gain and preterm delivery. Obstet Gynecol. 1997 May;89(5 Pt 2):865-73. X-1, X-3
39. Carmichael SL, Shaw GM, Laurent C, et al. Maternal progestin intake and risk of hypospadias. Arch Pediatr Adolesc Med. 2005 Oct;159(10):957-62. X-3
40. Casey ML and MacDonald PC. Endocrinology of preterm birth. Clin Obstet Gynecol. 1984 Sep;27(3):562-71. X-1, X-2, X-3, X-4
41. Cavarzere P, Camilot M, Teofoli F, et al. Neonatal screening for congenital adrenal hyperplasia in North-Eastern Italy: a report three years into the program. Horm Res. 2005;63(4):180-6. X-2, X-3
42. Cavarzere P, Samara-Boustani D, Flechtner I, et al. Transient hyper-17-hydroxyprogesteronemia: a clinical subgroup of patients diagnosed at neonatal screening for congenital adrenal hyperplasia. Eur J Endocrinol. 2009 Aug;161(2):285-92. X-2, X-3
43. Challis JRG, Matthews SG, Gibb W, et al. Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev. 2000 Oct;21(5):514-50. X-2, X-3
44. Chandiramani M, Tribe RM and Shennan AH. Preterm labour and prematurity. Obstetrics, Gynaecology and Reproductive Medicine. 2007;17(8):232-237. X-1, X-2
45. Chanrachakul B, Pipkin FB, Warren AY, et al. Progesterone enhances the tocolytic effect of ritodrine in isolated pregnant human myometrium. Am J Obstet Gynecol. 2005 Feb;192(2):458-63. X-2, X-3, X-4
46. Check JH, Lee G, Epstein R, et al. Increased rate of preterm deliveries in untreated women with luteal phase deficiencies. Preliminary report. Gynecol Obstet Invest. 1992;33(3):183-4. X-3, X-4
47. Check JH, Rankin A and Teichman M. The risk of fetal anomalies as a result of progesterone therapy during pregnancy. Fertil Steril. 1986 Apr;45(4):575-7. X-3
48. Chetkowski RJ, Kiltz RJ and Salyer WR. In premature luteinization, progesterone induces secretory transformation of the endometrium without impairment of embryo viability. Fertil Steril. 1997 Aug;68(2):292-7. X-2, X-3
49. Christian MS, Brent RL and Calda P. Embryo-fetal toxicity signals for 17 alpha-hydroxyprogesterone caproate in high-risk pregnancies: A review of the non-clinical literature for embryo-fetal toxicity with progestins. Journal of Maternal-Fetal & Neonatal Medicine. 2007 Feb;20(2):89-112. X-1, X-2
50. Cibils LA and Zuspan FP. Pharmacologic control of premature labor. Clin Obstet Gynecol. 1973 Dec;16(4):199-212. X-1, X-2, X-4
51. Cicinelli E, de Ziegler D, Bulletti C, et al. Direct transport of progesterone from vagina to uterus. Obstet Gynecol. 2000 Mar;95(3):403-6. X-3
52. Coleman VH, Power ML, Zinberg S, et al. Contemporary clinical issues in outpatient obstetrics and gynecology: findings of the Collaborative Ambulatory Research Network, 2001-2004: part I. Obstet Gynecol Surv. 2004 Nov;59(11):780-6. X-1, X-3
53. Coleman VH, Power ML, Zinberg S, et al. Contemporary clinical issues in outpatient obstetrics and gynecology: findings of the Collaborative Ambulatory Research Network, 2001-2004: part II. Obstet Gynecol Surv. 2004 Nov;59(11):787-94. X-1, X-3
54. Conly PW, Morrison T, Sandberg DH, et al. Concentrations of progesterone in the plasma of mothers and infants at time of birth. Pediatr Res. 1970 Jan;4(1):76-81. X-3, X-4, X-5
55. Cooper ES, Brooks AN, Miller MR, et al. Corticotrophin-releasing factor immunostaining is present in placenta and fetal membranes from the first trimester onwards and is not affected by labour or administration of mifepristone. Clin Endocrinol (Oxf). 1994 Nov;41(5):677-83. X-3
56. Cope E. Habitual Abortion Treated with 17 α-hydroxyprogesterone capronate. Journal of Obstetrics and Gynaecology. 1965;72(6):1035-1037. X-3
57. Copper RL, Goldenberg RL, Das A, et al. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1996 Nov;175(5):1286-92. X-3
58. Cousins LM, Hobel CJ, Chang RJ, et al. Serum progesterone and estradiol-17beta levels in premature

and term labor. Am J Obstet Gynecol. 1977 Mar 15;127(6):612-5. X-3
59. Csapo A, Pohanka O and Kaihola HL. Letter: Steroid profile of threatened premature labour. Lancet. 1973 Nov 10;2(7837):1097-8. X-1
60. Csapo AI. Model experiments and clinical trials in the control of pregnancy and parturition. Am J Obstet Gynecol. 1963 Feb 1;85:359-79. X-1, X-2, X-3, X-4
61. Csapo AI. Effects of progesterone, prostaglandin F2alpha and its analogue ICI 81008 on the excitability and threshold of the uterus. Am J Obstet Gynecol. 1976 Feb 15;124(4):367-78. X-2, X-3
62. Csapo AI. The 'see-saw' theory of parturition. Ciba Found Symp. 1977(47):159-210. X-1, X-2, X-3, X-4
63. Csapo AI and Herczeg J. Arrest of premature labor by isoxsuprine. Am J Obstet Gynecol. 1977 Nov 1;129(5):482-91. X-3, X-4
64. Csapo AI, Knobil E, van der Molen HJ, et al. Peripheral plasma progesterone levels during human pregnancy and labor. Am J Obstet Gynecol. 1971 Jul 1;110(5):630-2. X-3, X-4
65. Csapo AI, Pohanka O and Kaihola HL. Progesterone deficiency and premature labour. Br Med J. 1974 Jan 26;1(5899):137-40. X-3, X-4
66. Cypher R. Gestiva for preventing prematurity: a new view of an old therapy. Nurs Womens Health. 2007 Jun;11(3):322-5. X-1, X-2, X-4
67. Czeizel A and Huiskes N. A case-control study to evaluate the risk of congenital anomalies as a result of allylestrenol therapy during pregnancy. Clin Ther. 1988;10(6):725-39. X-3
68. Czeizel AE, Dudas I, Gidai J, et al. No effect of human chorionic gonadotropin treatment due to threatened abortion in early pregnancy for birth outcomes. Central European Journal of Medicine. 2008;3(1):71-76. X-3, X-4
69. Dalton K. Prenatal progesterone and educational attainments. Br J Psychiatry. 1976 Nov;129:438-42. X-3
70. Darling MR and Hawkins DF. Sex hormones in pregnancy. Clin Obstet Gynaecol. 1981 Aug;8(2):405-19. X-1, X-2, X-3, X-4
71. Darne J, McGarrigle HH and Lachelin GC. Increased saliva oestriol to progesterone ratio before preterm delivery: a possible predictor for preterm labor? Br Med J (Clin Res Ed). 1987 Jan 31;294(6567):270-2. X-3
72. Davis ME and Wied GL. 17-Alpha-hydroxyprogesterone-caproate: a new substance with prolonged progestational activity; a comparison with chemically pure progesterone. J Clin Endocrinol Metab. 1955 Aug;15(8):923-30. X-2, X-3, X-4
73. De Meeus JB, Pourrat O, Gombert J, et al. C-reactive protein levels at the onset of labour and at day 3 post-partum in normal pregnancy. Clin Exp Obstet Gynecol. 1998;25(1-2):9-11. X-3
74. Di Renzo GC, Rosati A, Mattei A, et al. The changing role of progesterone in preterm labour. BJOG. 2005 Mar;112 Suppl 1:57-60. X-1
75. Diaz-Zagoya JC and Arias F. Synthesis and catabolism of progesterone in placentas from normotensive and severely hypertensive patients before and after parturition. Am J Obstet Gynecol. 1981 Nov 15;141(6):637-40. X-3
76. Dickey RP and Thompson JP. Effect of ACTH and metyrapone on estriol, 17-hydroxycorticosteroid, 17-ketosteroid, pregnanediol and pregnanetriol excretion late in pregnancy. J Clin Endocrinol Metab. 1969 May;29(5):701-6. X-2, X-3, X-4
77. Dodd JM, Crowther CA, Cincotta R, et al. Progesterone supplementation for preventing preterm birth: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2005 Jun;84(6):526-33. X-1
78. Dodd JM, Crowther CA, McPhee AJ, et al. Progesterone after previous preterm birth for prevention of neonatal respiratory distress syndrome (PROGRESS): a randomised controlled trial. BMC Pregnancy Childbirth. 2009;9:6. X-4
79. Dodd JM, Flenady V, Cincotta R, et al. Prenatal administration of progesterone for preventing preterm birth. Cochrane Database Syst Rev. 2006(1):CD004947. X-1
80. Doerr HG, Sippell WG, Versmold HT, et al. Plasma mineralocorticoids, glucocorticoids, and progestins in premature infants: longitudinal study during the first week of life. Pediatr Res. 1988 May;23(5):525-9. X-2, X-3
81. Dorfman SG, Dillaplain RP and Gambrell RD, Jr. Antepartum pituitary infarction. Obstet Gynecol. 1979 Mar;53(3 Suppl):21S-24S. X-2, X-3
82. Edelstam G, Karlsson C, Westgren M, et al. Human chorionic gonadatropin (hCG) during third trimester pregnancy. Scand J Clin Lab Invest. 2007;67(5):519-25. X-3
83. Elovitz MA and Mrinalini C. The use of progestational agents for preterm birth: lessons from a mouse model. Am J Obstet Gynecol. 2006 Oct;195(4):1004-10. X-2
84. Ersch J, Beinder E, Stallmach T, et al. 17-Hydroxyprogesterone in premature infants as a marker of intrauterine stress. J Perinat Med. 2008;36(2):157-60. X-2, X-3
85. Facchinetti F, Fazzio M and Venturini P. Polyunsaturated fatty acids and risk of preterm delivery. Eur Rev Med Pharmacol Sci. 2005 Jan-Feb;9(1):41-8. X-1, X-2, X-3, X-4
86. Feldberg D, Goldman GA, Ashkenazi J, et al. The impact of high progesterone levels in the follicular phase of in vitro fertilization (IVF) cycles: A comparative study. Journal of In Vitro Fertilization and Embryo Transfer. 1989;6(1):11-14. X-3
87. Ferencz C, Matanoski GM, Wilson PD, et al. Maternal hormone therapy and congenital heart disease. Teratology. 1980 Apr;21(2):225-39. X-3
88. Ferre F, Uzan M, Janssens Y, et al. Oral administration of micronized natural progesterone in late human pregnancy. Effects on progesterone and estrogen concentrations in the plasma, placenta, and myometrium. Am J Obstet Gynecol. 1984 Jan 1;148(1):26-34. X-3, X-4
89. Ferre F, Uzan M, Jolivet A, et al. Influence of the oral administration of micronized progesterone on plasma

and tissue levels of steroids in human pregnancy. Acta Physiol Hung. 1985;65(4):443-51. X-3, X-4
90. Fogel M, Rubin BL and Ossowski R. Serum follicle-stimulating and luteinizing hormone and progesterone in single and multiple gestations following induction of ovulation. Am J Obstet Gynecol. 1972 Mar;112(5):629-39. X-2, X-3, X-4
91. Fox ME, Harris RE and Brekken AL. The active-duty military pregnancy: a new high-risk category. Am J Obstet Gynecol. 1977 Nov 15;129(6):705-7. X-3, X-4
92. Franczak J, Jagiello-Wojtowicz E and Kaminska H. The estimation of progesterone (P) in preterm delivery. Ann Univ Mariae Curie Sklodowska [Med]. 1995;50:157-60. X-3, X-4
93. Fuchs AR and Fuchs F. Mechanism and prevention of preterm birth. Prog Clin Biol Res. 1985;163B:223-30. X-1, X-2, X-3, X-4
94. Fuchs F. Prevention of prematurity. Am J Obstet Gynecol. 1976 Dec 1;126(7):809-20. X-1, X-2, X-3, X-4
95. Fuller WE. Management of premature labor. Clin Obstet Gynecol. 1978 Jun;21(2):533-45. X-1, X-2
96. Gal I. Risks and benefits of the use of hormonal pregnancy test tablets. Nature. 1972 Nov 24;240(5378):241-2. X-3, X-4
97. Garfield RE. Control of myometrial function in preterm versus term labor. Clin Obstet Gynecol. 1984 Sep;27(3):572-91. X-1
98. Garfield RE, Kannan MS and Daniel EE. Gap junction formation in myometrium: control by estrogens, progesterone, and prostaglandins. Am J Physiol. 1980 Mar;238(3):C81-9. X-2, X-3, X-4
99. Garfield RE, Puri CP and Csapo AI. Endocrine, structural, and functional changes in the uterus during premature labor. Am J Obstet Gynecol. 1982 Jan 1;142(1):21-7. X-2, X-3
100. Gatelais F, Berthelot J, Beringue F, et al. Effect of single and multiple courses of prenatal corticosteroids on 17-hydroxyprogesterone levels: implication for neonatal screening of congenital adrenal hyperplasia. Pediatr Res. 2004 Nov;56(5):701-5. X-3
101. Gay J. Theories regarding endocrine contributions to the onset of labor. JOGN Nurs. 1978 Sep-Oct;7(5):42-7. X-1, X-2
102. Genuis SJ. Fielding a current idea: exploring the public health impact of electromagnetic radiation. Public Health. 2008 Feb;122(2):113-124. X-1, X-3
103. Gibbs CE. Diagnosis and treatment of uterine conditions that may cause permaturity. Clin Obstet Gynecol. 1973 Dec;16(4):159-70. X-1, X-2
104. Gleicher N. Graft-versus-host disease and immunologic rejection: Implications for diagnosis and treatments of pregnancy complications. Expert Review of Obstetrics and Gynecology. 2008 Jan;3(1):37-49. X-1, X-3
105. Godo B, Visser HK and Degenhart HJ. Plasma 17-OH-progesterone in fullterm and preterm infants at birth and during the early neonatal period. Horm Res. 1981;15(2):65-71. X-3, X-4
106. Goldenberg RL. The management of preterm labor. Obstet Gynecol. 2002 Nov;100(5 Pt 1):1020-37. X-1
107. Goldstein P, Berrier J, Rosen S, et al. A meta-analysis of randomized control trials of progestational agents in pregnancy. Br J Obstet Gynaecol. 1989 Mar;96(3):265-74. X-1
108. Goldzieher JW. Double-Blind Trial of a Progestin in Habitual Abortion. JAMA. 1964 May 18;188:651-4. X-3, X-4
109. Gotkin JL, Celver J, McNutt P, et al. Progesterone reduces lipopolysaccharide induced interleukin-6 secretion in fetoplacental chorionic arteries, fractionated cord blood, and maternal mononuclear cells. Am J Obstet Gynecol. 2006 Oct;195(4):1015-9. X-2, X-3
110. Gruneiro-Papendieck L, Prieto L, Chiesa A, et al. Neonatal screening program for congenital adrenal hyperplasia: adjustments to the recall protocol. Horm Res. 2001;55(6):271-7. X-2, X-3
111. Grunieiro-Papendieck L, Chiesa A, Mendez V, et al. Neonatal screening for congenital adrenal hyperplasia: experience and results in Argentina. J Pediatr Endocrinol Metab. 2008 Jan;21(1):73-8. X-2
112. X-3
113. Hadjigeorgiou E, Malamitsi-Puchner A, Lolis D, et al. Cardiovascular birth defects and antenatal exposure to female sex hormones. Dev Pharmacol Ther. 1982;5(1-2):61-7. X-3
114. Hagler S, Schultz A, Hankin H, et al. Fetal Effects of Steroid Therapy During Pregnancy. Am J Dis Child. 1963 Dec;106:586-90. X-2
115. Haning Jr RV, Kiggens AJ and Leiheit TL. Maternal serum progesterone, 17beta-estradiol and estriol are increased in pregnancies which follow treatment with human menopausal gonadotropins: Effects of multiple gestation and maternal endocrine status. Journal of Steroid Biochemistry. 1985;22(6):823-829. X-3
116. Haning RV, Jr., Curet LB, Poole WK, et al. Effects of fetal sex and dexamethasone on preterm maternal serum concentrations of human chorionic gonadotropin, progesterone, estrone, estradiol, and estriol. Am J Obstet Gynecol. 1989 Dec;161(6 Pt 1):1549-53. X-3
117. Haning RV, Jr., Goldsmith LT, Seifer DB, et al. Relaxin secretion in in vitro fertilization pregnancies. Am J Obstet Gynecol. 1996 Jan;174(1 Pt 1):233-40. X-3
118. Haning RV, Jr., Kiggens AJ and Leiheit TL. Maternal serum progesterone, 17 beta-estradiol and estriol are increased in pregnancies which follow treatment with human menopausal gonadotropins: effects of multiple gestation and maternal endocrine status. J Steroid Biochem. 1985 Jun;22(6):823-9. X-3
119. Hanssens MC, Selby C, Filshie GM, et al. Changes in plasma steroid hormones during treatment of preterm labour with ritodrine-HCl. Br J Obstet Gynaecol. 1983 Sep;90(9):847-53. X-3
120. Hanssens MC, Selby C and Symonds EM. Sex steroid hormone concentrations in preterm labour and the outcome of treatment with ritodrine. Br J Obstet Gynaecol. 1985 Jul;92(7):698-702. X-3

121. Harger JH. Comparison of success and morbidity in cervical cerclage procedures. Obstet Gynecol. 1980 Nov;56(5):543-8. X-3
122. Harlap S, Prywes R and Davies AM. Letter: Birth defects and oestrogens and progesterones in pregnancy. Lancet. 1975 Mar 22;1(7908):682-3. X-1
123. Hawkins DF. Management of premature labour. Journal of Obstetrics and Gynaecology. 1989;10(SUPPL. 1):S10-S12. X-1, X-2
124. Hedegaard M, Henriksen TB, Sabroe S, et al. The relationship between psychological distress during pregnancy and birth weight for gestational age. Acta Obstet Gynecol Scand. 1996 Jan;75(1):32-9. X-3
125. Heinonen OP, Slone D, Monson RR, et al. Cardiovascular birth defects and antenatal exposure to female sex hormones. N Engl J Med. 1977 Jan 13;296(2):67-70. X-3
126. Henderson D and Wilson T. Reduced binding of progesterone receptor to its nuclear response element after human labor onset. Am J Obstet Gynecol. 2001 Sep;185(3):579-85. X-3
127. Henderson JJ, Newnham JP, Simmer K, et al. Effects of antenatal corticosteroids on urinary markers of the initiation of lactation in pregnant women. Breastfeed Med. 2009 Dec;4(4):201-6. X-3
128. Hendrickx AG, Korte R, Leuschner F, et al. Embryotoxicity of sex steroidal hormones in nonhuman primates: II. Hydroxyprogesterone caproate, estradiol valerate. Teratology. 1987 Feb;35(1):129-36. X-2, X-3
129. Hercz P. Quantitative changes in steroid and peptide hormones in the maternal-fetoplacental system between the 28th-40th weeks of pregnancy. Acta Med Hung. 1985;42(1-2):29-39. X-3
130. Hercz P, Ungar L and Siklos P. Perinatal progesterone in maternal-fetoplacental system during mature and premature deliveries. Acta Obstet Gynecol Scand. 1988;67(3):233-5. X-3
131. Herman A, Ron-El R, Golan A, et al. Impaired corpus luteum function and other undesired results of pregnancies associated with inadvertent administration of a long-acting agonist of gonadotrophin-releasing hormone. Hum Reprod. 1992 Apr;7(4):465-8. X-2, X-3
132. Hingre RV, Gross SJ, Hingre KS, et al. Adrenal steroidogenesis in very low birth weight preterm infants. J Clin Endocrinol Metab. 1994 Feb;78(2):266-70. X-2, X-3
133. Hiort O, Holterhus PM, Werner R, et al. Homozygous disruption of P450 side-chain cleavage (CYP11A1) is associated with prematurity, complete 46,XY sex reversal, and severe adrenal failure. J Clin Endocrinol Metab. 2005 Jan;90(1):538-41. X-1, X-2, X-3
134. Hobel CJ. Stress and preterm birth. Clin Obstet Gynecol. 2004 Dec;47(4):856-80; discussion 881-2. X-1, X-2, X-4
135. Hobel CJ, Dunkel-Schetter C, Roesch SC, et al. Maternal plasma corticotropin-releasing hormone associated with stress at 20 weeks' gestation in pregnancies ending in preterm delivery. Am J Obstet Gynecol. 1999 Jan;180(1 Pt 3):S257-63. X-3
136. Hofmann GE, Bentzien F, Bergh PA, et al. Premature luteinization in controlled ovarian hyperstimulation has no adverse effect on oocyte and embryo quality. Fertil Steril. 1993 Oct;60(4):675-9. X-3
137. Honour J. Biochemical aspects of congenital adrenal hyperplasia. J Inherit Metab Dis. 1986;9 Suppl 1:124-34. X-3
138. Huey QB and Rajadurai VS. Strategies for preventing chronic lung disease in premature babies. Perinatology. 2007 Mar;9(2):51-65. X-3
139. Huysman MW, Hokken-Koelega AC, De Ridder MA, et al. Adrenal function in sick very preterm infants. Pediatr Res. 2000 Nov;48(5):629-33. X-3
140. Iams JD. Supplemental progesterone to prevent preterm birth. Am J Obstet Gynecol. 2003 Feb;188(2):303. X-1, X-2, X-4
141. Iams JD, Goldenberg RL, Mercer BM, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1998 May;178(5):1035-40. X-3
142. Ibanez L, Potau N and De Zegher F. Endocrinology and metabolism after premature pubarche in girls. Acta Paediatr Suppl. 1999 Dec;88(433):73-7. X-3
143. Imai A, Khan AA and Tamaya T. Sex steroids enhance endotoxin-stimulated phospholipase A2 activity in hum endometrial cells. Arch Gynecol Obstet. 1991;249(3):129-34. X-3
144. Ingemarsson I. Pharmacology of tocolytic agents. Clin Obstet Gynaecol. 1984 Aug;11(2):337-51. X-3
145. Itskovitz-Eldor J, Kol S and Mannaerts B. Use of a single bolus of GnRH agonist triptorelin to trigger ovulation after GnRH antagonist ganirelix treatment in women undergoing ovarian stimulation for assisted reproduction, with special reference to the prevention of ovarian hyperstimulation syndrome: preliminary report: short communication. Hum Reprod. 2000 Sep;15(9):1965-8. X-2, X-3
146. Janne O, Perheentupa J, Viinikka L, et al. Plasma pregnenolone, progesterone, 17-hydroxyprogesterone, testosterone and 5alpha-dihydrotestosterone in different types of congenital adrenal hyperplasia. Clin Endocrinol (Oxf). 1975 Jan;4(1):39-48. X-2, X-3, X-4
147. Jarczok T, Zwirner M and Schindler AE. Progesterone and 5 alpha-pregnane-3,20-dione in human amniotic fluid. Exp Clin Endocrinol. 1987 Mar;89(1):39-47. X-3
148. Jewelewicz R, James SL, Finster M, et al. Quintuplet gestation after ovulation induction with menopausal gonadotropins and pituitary luteinizing hormone. Obstet Gynecol. 1972 Jul;40(1):1-5. X-2, X-3, X-4
149. Jeyasuria P, Wetzel J, Bradley M, et al. Progesterone-regulated caspase 3 action in the mouse may play a role in uterine quiescence during pregnancy through fragmentation of uterine myocyte contractile proteins. Biol Reprod. 2009 May;80(5):928-34. X-2, X-3
150. Johnson JW and Dubin NH. Prevention of preterm labor. Clin Obstet Gynecol. 1980 Mar;23(1):51-73. X-1, X-2

151. Jouppila P. Prognosis of threatened early pregnancy. J Perinat Med. 1981;9 Suppl 1:72-4. X-3, X-4
152. Jung H. The role of progesterone and gestagens in the protective mechanism of pregnancy and in therapy. Bibl Gynaecol. 1966;42:69-78. X-1, X-2, X-4
153. Kalantaridou SN, Calis KA, Mazer NA, et al. A pilot study of an investigational testosterone transdermal patch system in young women with spontaneous premature ovarian failure. J Clin Endocrinol Metab. 2005 Dec;90(12):6549-52. X-3, X-4
154. Katz Z, Lancet M, Skornik J, et al. Teratogenicity of progestogens given during the first trimester of pregnancy. Obstet Gynecol. 1985 Jun;65(6):775-80. X-3
155. Keirse MJ. Progestogen administration in pregnancy may prevent preterm delivery. Br J Obstet Gynaecol. 1990 Feb;97(2):149-54. X-1
156. Khan AA, Imai A and Tamaya T. Possible mechanism for preterm labor associated with bacterial infection. II: Enhancement of endotoxin-stimulated phosphoinositide metabolism by sex steroids in human endometrial fibroblasts. Res Commun Chem Pathol Pharmacol. 1990 Jul;69(1):123-6. X-2, X-3
157. King JL, Naber JM, Hopkin RJ, et al. Antenatal corticosteroids and newborn screening for congenital adrenal hyperplasia. Arch Pediatr Adolesc Med. 2001 Sep;155(9):1038-42. X-3
158. Klaus MH, Trause MA and Kennell JH. Does human maternal behaviour after delivery show a characteristic pattern? Ciba Found Symp. 1975(33):69-85. X-3
159. Kleinstein J. Efficacy and tolerability of vaginal progesterone capsules (Utrogest 200) compared with progesterone gel (Crinone 8%) for luteal phase support during assisted reproduction. Fertil Steril. 2005 Jun;83(6):1641-9. X-3
160. Knudsen UB. Cervical ripening. A rat model for investigation of contractile and passive biomechanical properties, with focus on antigestagens, eosinophil granulocytes and mast cells. Acta Obstet Gynecol Scand. 1996 Jan;75(1):88-9. X-2, X-3, X-4
161. Knudtzon J, Markestad T, Aakvaag A, et al. Elevated 17-hydroxyprogesterone levels in premature infants. Acta Paediatrica Scandinavica. 1991;80(1):96-97. X-3, X-4
162. Kohrman AF, Jones LA and Bern HA. Letter: Risks and benefits of hormonal agents in pregnancy. N Engl J Med. 1976 Mar 11;294(11):614-5. X-1
163. Kramer MS, Demissie K, Yang H, et al. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA. 2000 Aug 16;284(7):843-9. X-3
164. Kumar D, Goodno JA and Barnes AC. In Vivo Effects of Intravenous Progesterone Infusion on Human Gravid Uterine Contractility. Bull Johns Hopkins Hosp. 1963 Aug;113:53-6. X-2, X-3, X-4
165. Lachelin GC, Brant HA, Swyer GI, et al. Sextuplet pregnancy. Br Med J. 1972 Mar 25;1(5803):787-90. X-2, X-3, X-4
166. Lanier AP, Noller KL, Decker DG, et al. Cancer and stilbestrol. A follow-up of 1,719 persons exposed to estrogens in utero and born 1943-1959. Mayo Clin Proc. 1973 Nov;48(11):793-9. X-3, X-4
167. Lee JE, Moon Y, Lee MH, et al. Corrected 17-alpha-hydroxyprogesterone values adjusted by a scoring system for screening congenital adrenal hyperplasia in premature infants. Ann Clin Lab Sci. 2008 Summer;38(3):235-40. X-3
168. Lee MM, Rajagopalan L, Berg GJ, et al. Serum adrenal steroid concentrations in premature infants. J Clin Endocrinol Metab. 1989 Dec;69(6):1133-6. X-3
169. Leroy MJ and Ferre F. The cyclic AMP messenger system in the human pregnant myometrium: New perspectives for the treatment of preterm labor. IRCS Medical Science. 1986;14(10):969-972. X-1, X-2, X-3, X-4
170. Leslie KK, Zuckerman DJ, Schruefer J, et al. Oestrogen modulation with parturition in the human placenta. Placenta. 1994 Jan;15(1):79-88. X-3
171. Levine L. Habitual Abortion. A Controlled Study of Progestational Therapy. West J Surg Obstet Gynecol. 1964 Jan-Feb;72:30-6. X-3, X-4
172. Levy EP, Cohen A and Fraser FC. Hormone treatment during pregnancy and congenital heart defects. Lancet. 1973 Mar 17;1(7803):611. X-3, X-4
173. Lim AC, Bloemenkamp KW, Boer K, et al. Progesterone for the prevention of preterm birth in women with multiple pregnancies: the AMPHIA trial. BMC Pregnancy Childbirth. 2007;7:7. X-1
174. Linder N, Davidovitch N, Kogan A, et al. Longitudinal measurements of 17alpha-hydroxyprogesterone in premature infants during the first three months of life. Arch Dis Child Fetal Neonatal Ed. 1999 Nov;81(3):F175-8. X-3
175. Liu J, Matsuo H, Laoag-Fernandez JB, et al. The effects of progesterone on apoptosis in the human trophoblast-derived HTR-8/SV neo cells. Mol Hum Reprod. 2007 Dec;13(12):869-74. X-3
176. Lockwood CJ. Testing for risk of preterm delivery. Clin Lab Med. 2003 Jun;23(2):345-60. X1, X-3
177. Lockwood CJ, Murk W, Kayisli UA, et al. Progestin and thrombin regulate tissue factor expression in human term decidual cells. J Clin Endocrinol Metab. 2009 Jun;94(6):2164-70. X-2, X-3
178. Lopez Bernal A, Hansell DJ, Alexander S, et al. Steroid conversion and prostaglandin production by chorionic and decidual cells in relation to term and preterm labour. Br J Obstet Gynaecol. 1987 Nov;94(11):1052-8. X-3
179. Lyall F, Lye S, Teoh T, et al. Expression of Gsalpha, connexin-43, connexin-26, and EP1, 3, and 4 receptors in myometrium of prelabor singleton versus multiple gestations and the effects of mechanical stretch and steroids on Gsalpha. J Soc Gynecol Investig. 2002 Sep-Oct;9(5):299-307. X-3
180. Mackenzie AP, Schatz F, Krikun G, et al. Mechanisms of abruption-induced premature rupture of the fetal membranes: Thrombin enhanced decidual matrix metalloproteinase-3 (stromelysin-1) expression. Am J Obstet Gynecol. 2004 Dec;191(6):1996-2001. X-3

181. MacKenzie LW and Garfield RE. Hormonal control of gap junctions in the myometrium. Am J Physiol. 1985 Mar;248(3 Pt 1):C296-308. X-2, X-3
182. Mackenzie R, Walker M, Armson A, et al. Progesterone for the prevention of preterm birth among women at increased risk: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol. 2006 May;194(5):1234-42. X-1
183. MacRae DJ, Mohamedally SM and Willmot MP. Clinical and endocrinological aspects of dysmaturity and the use of intermittent abdominal decompression in pregnancy. J Obstet Gynaecol Br Commonw. 1971 Jul;78(7):636-41. X-3, X-4
184. Mahajan DK, Anderson G, Poole WK, et al. Changes in the concentration of 17 alpha,20 alpha-dihydroxypregn-4-en-3-one during pregnancy, labor, and delivery and the effect of dexamethasone treatment during the third trimester of pregnancy. J Clin Endocrinol Metab. 1983 Sep;57(3):585-91. X-3
185. Margolis KL, Bonds DE, Rodabough RJ, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia. 2004 Jul;47(7):1175-87. X-2, X-3
186. Martins PG and Procianoy RS. Cortisol and 17-alpha-hydroxy-progesterone levels in infants with refractory hypotension born at 30 weeks of gestation or less. Braz J Med Biol Res. 2007 Apr;40(4):577-82. X-2, X-3
187. Mathur RS, Landgrebe S and Williamson HO. Progesterone, 17-hydroxyprogesterone, estradiol, and estriol in late pregnancy and labor. Am J Obstet Gynecol. 1980 Jan 1;136(1):25-7. X-3
188. Mau G. Progestins during pregnancy and hypospadias. Teratology. 1981 Dec;24(3):285-7. X-3
189. Mavroudis K, Petsos P, Zulkifli Z, et al. Trial of 17-hydroxyprogesterone caproate (Proluton Depot) in women with long-standing infertility; failure of estrogen positive feedback the following cycle. Gynecol Endocrinol. 1987 Jun;1(2):177-93. X-3
190. Mazor M, Hershkovitz R, Chaim W, et al. Human preterm birth is associated with systemic and local changes in progesterone/17 beta-estradiol ratios. Am J Obstet Gynecol. 1994 Jul;171(1):231-6. X-3
191. Mazor M, Hershkowitz R, Ghezzi F, et al. Maternal plasma and amniotic fluid 17 beta-estradiol, progesterone and cortisol concentrations in women with successfully and unsuccessfully treated preterm labor. Arch Gynecol Obstet. 1996;258(2):89-96. X-3
192. McFaul PB, Traub AI and Thompson W. Premature luteinization and ovulation induction using human menopausal gonadotrophin or pure follicle stimulating hormone in patients with polycystic ovary syndrome. Acta Europaea Fertilitatis. 1989;20(3):157-161. X-3
193. Mercer BM, Goldenberg RL, Moawad AH, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol. 1999 Nov;181(5 Pt 1):1216-21. X-3
194. Meridis E and Lavery S. Drugs in reproductive medicine. Current Obstetrics and Gynaecology. 2006 Oct;16(5):281-288. X-3
195. Merlino AA, Welsh TN, Tan H, et al. Nuclear progesterone receptors in the human pregnancy myometrium: evidence that parturition involves functional progesterone withdrawal mediated by increased expression of progesterone receptor-A. J Clin Endocrinol Metab. 2007 May;92(5):1927-33. X-2, X-3
196. Mesiano S. Myometrial progesterone responsiveness and the control of human parturition. Journal of the Society for Gynecologic Investigation. 2004 May;11(4):193-202. X-1, X-3
197. Messinis IE, Loutradis D, Domali E, et al. Alternate day and daily administration of GnRH antagonist may prevent premature luteinization to a similar extent during FSH treatment. Hum Reprod. 2005 Nov;20(11):3192-7. X-2, X-3
198. Michaelis J, Michaelis H, Gluck E, et al. Prospective study of suspected associations between certain drugs administered during early pregnancy and congenital malformations. Teratology. 1983 Feb;27(1):57-64. X-3, X-4
199. Miles RA, Paulson RJ, Lobo RA, et al. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. Fertil Steril. 1994 Sep;62(3):485-90. X-3
200. Mitchell B, Cruickshank B, McLean D, et al. Local modulation of progesterone production in human fetal membranes. J Clin Endocrinol Metab. 1982 Dec;55(6):1237-9. X-3
201. Mitchell BF, Fang X and Wong S. Oxytocin: A paracrine hormone in the regulation of parturition? Reviews of Reproduction. 1998;3(2):113-122. X-1, X-3
202. Mitchell ML and Hermos RJ. Cortisol in dried blood screening specimens from newborns with raised 17-hydroxyprogesterone and congenital adrenal hyperplasia. Clin Endocrinol (Oxf). 1998 Jun;48(6):757-60. X-2, X-3
203. Mitreski A and Radeka G. Prostacyclin and hormone levels in patients with symptoms of miscarriage and infection. Med Pregl. 2002 Sep-Oct;55(9-10):371-9. X-3
204. Mohan AR and Bennett PR. Drugs acting on the pregnant uterus. Current Obstetrics and Gynaecology. 2006 Jun;16(3):174-180. X-1
205. Moran C, Romero MDLL, Hernandez T, et al. Ovulation induction with FSH in polycystic ovarian syndrome without clomiphene citrate response. Assisted Reproductive Technology/Andrology. 1997;9(1-2):59-63. X-3
206. Mosler KH. The dynamics of uterine muscle. Bibl Gynaecol. 1968;48:1-82. X-1, X-2
207. Murphy JF, Joyce BG, Dyas J, et al. Plasma 17-hydroxyprogesterone concentrations in ill newborn infants. Arch Dis Child. 1983 Jul;58(7):532-4. X-2, X-3

208. Naruki M, Mizutani S, Yamada R, et al. Changes in maternal serum oxytocinase activities in preterm labour. Medical Science Research. 1995;23(12):797-802. X-2, X-4
209. Nathanielsz PW, Jenkins SL, Tame JD, et al. Local paracrine effects of estradiol are central to parturition in the rhesus monkey. Nat Med. 1998 Apr;4(4):456-9. X-2, X-3
210. Niebyl JR, Blake DA, Johnson JW, et al. The pharmacologic inhibition of premature labor. Obstet Gynecol Surv. 1978 Aug;33(8):507-15. X-1 X-2 X-3
211. Niebyl JR, Blake DA, White RD, et al. The inhibition of premature labor with indomethacin. Am J Obstet Gynecol. 1980 Apr 15;136(8):1014-9. X-3
212. Nomura S. Immature adrenal steroidogenesis in preterm infants. Early Hum Dev. 1997 Oct 10;49(3):225-33. X-2, X-3
213. Norwitz ER, Snegovskikh V, Schatz F, et al. Progestin inhibits and thrombin stimulates the plasminogen activator/inhibitor system in term decidual stromal cells: implications for parturition. Am J Obstet Gynecol. 2007 Apr;196(4):382 e1-8. X-2, X-4
214. Novy MJ. Endocrine and pharmacological factors which influence the onset of labour in rhesus monkeys. Ciba Found Symp. 1977(47):259-95. X-2, X-3
215. Odeh M, Kaiis M, Markowitz J, et al. Progesterone levels in preterm labor are not affected by ritodrin treatment. Gynecol Obstet Invest. 1997;43(1):34-6. X-3
216. Odibo AO, Stamilio DM, Macones GA, et al. 17alpha-hydroxyprogesterone caproate for the prevention of preterm delivery: A cost-effectiveness analysis. Obstet Gynecol. 2006 Sep;108(3 Pt 1):492-9. X-2
217. Ogueh O, Jones J, Mitchell H, et al. Effect of antenatal dexamethasone therapy on maternal plasma human chorionic gonadotrophin, oestradiol and progesterone. Hum Reprod. 1999 Feb;14(2):303-6. X-2, X-3
218. Ohkubo S, Shimozawa K, Matsumoto M, et al. Analysis of blood spot 17 alpha-hydroxyprogesterone concentration in premature infants--proposal for cut-off limits in screening for congenital adrenal hyperplasia. Acta Paediatr Jpn. 1992 Apr;34(2):126-33. X-2, X-3
219. Ohno Y, Kasugai M, Kurauchi O, et al. Effect of interleukin 2 on the production of progesterone and prostaglandin E2 in human fetal membranes and its consequences for preterm uterine contractions. Eur J Endocrinol. 1994 May;130(5):478-84. X-3
220. Okada T, Matsuzaki N, Sawai K, et al. Chorioamnionitis reduces placental endocrine functions: the role of bacterial lipopolysaccharide and superoxide anion. J Endocrinol. 1997 Dec;155(3):401-10. X-3
221. Olgemoller B, Roscher AA, Liebl B, et al. Screening for congenital adrenal hyperplasia: adjustment of 17-hydroxyprogesterone cut-off values to both age and birth weight markedly improves the predictive value. J Clin Endocrinol Metab. 2003 Dec;88(12):5790-4. X-2, X-3
222. Omer H and Everly GS, Jr. Psychological factors in preterm labor: critical review and theoretical synthesis. Am J Psychiatry. 1988 Dec;145(12):1507-13. X-1, X-2, X-3
223. Oner C, Schatz F, Kizilay G, et al. Progestin-inflammatory cytokine interactions affect matrix metalloproteinase-1 and -3 expression in term decidual cells: implications for treatment of chorioamnionitis-induced preterm delivery. J Clin Endocrinol Metab. 2008 Jan;93(1):252-9. X-2, X-3, X-4
224. Palejwala S, Stein DE, Weiss G, et al. Relaxin positively regulates matrix metalloproteinase expression in human lower uterine segment fibroblasts using a tyrosine kinase signaling pathway. Endocrinology. 2001 Aug;142(8):3405-13. X-3
225. Paternoster DM, De Paoli M, Plebani M, et al. Risk factors and predictors of preterm delivery. Prenatal and Neonatal Medicine. 1999;4(4):308-311. X-3
226. Pau DA, Mackley A and Bartoshesky L. Newborn screening levels of 17-hydroxyprogesterone in very low birth weight infants and the relationship to chronic lung disease. J Pediatr Endocrinol Metab. 2006 Sep;19(9):1119-24. X-2, X-3
227. Paul DA, Leef KH, Stefano JL, et al. Factors influencing levels of 17-hydroxyprogesterone in very low birth weight infants and the relationship to death and IVH. J Perinatol. 2004 Apr;24(4):252-6. X-3
228. Pedersen AM, Fulton SK, Porter L, et al. Tumor necrosis factor-alpha affects in vitro hormone production by JEG-3 choriocarcinoma cell cultures. J Reprod Immunol. 1995 May;29(1):69-80. X-3
229. Peltier MR, Berlin Y, Tee SC, et al. Does progesterone inhibit bacteria-stimulated interleukin-8 production by lower genital tract epithelial cells? J Perinat Med. 2009;37(4):328-33. X-2, X-3
230. Peltier MR, Tee SC and Smulian JC. Effect of progesterone on proinflammatory cytokine production by monocytes stimulated with pathogens associated with preterm birth. Am J Reprod Immunol. 2008 Oct;60(4):346-53. X-2, X-4
231. Petrini JR, Callaghan WM, Klebanoff M, et al. Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. Obstet Gynecol. 2005 Feb;105(2):267-72. X-2
232. Raghupathy R, Al Mutawa E, Makhseed M, et al. Redirection of cytokine production by lymphocytes from women with pre-term delivery by dydrogesterone. Am J Reprod Immunol. 2007 Jul;58(1):31-8. X-2, X-3
233. Raman-Wilms L, Tseng AL, Wighardt S, et al. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. Obstet Gynecol. 1995 Jan;85(1):141-9. X-1, X-3
234. Rasmussen KM and Kjolhede CL. Prepregnant overweight and obesity diminish the prolactin response to suckling in the first week postpartum. Pediatrics. 2004 May;113(5):e465-71. X-3
235. Reifenstein EC, Jr. Introduction of marked as well as prolonged biologic activity by esterification; 17-alpha-hydroxyprogesterone caproate, a unique progestational

compound. Fertil Steril. 1957 Jan-Feb;8(1):50-79. X-1, X-2, X-3, X-4
236. Reijnders FJ, Thomas CM, Doesburg WH, et al. Endocrine effects of 17 alpha-hydroxyprogesterone caproate during early pregnancy: a double-blind clinical trial. Br J Obstet Gynaecol. 1988 May;95(5):462-8. X-3
237. Riley SC, Bassett NS, Berdusco ET, et al. Changes in the abundance of mRNA for type-I 3 beta-hydroxysteroid dehydrogenase/delta 5-->delta 4 isomerase in the human placenta and fetal membranes during pregnancy and labor. Gynecol Obstet Invest. 1993;35(4):199-203. X-3
238. Rock JA, Wentz AC, Cole KA, et al. Fetal malformations following progesterone therapy during pregnancy: a preliminary report. Fertil Steril. 1985 Jul;44(1):17-9. X-3
239. Rode L, Langhoff-Roos J, Andersson C, et al. Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies. Acta Obstet Gynecol Scand. 2009;88(11):1180-9. X-1
240. Romero R. Prevention of spontaneous preterm birth: the role of sonographic cervical length in identifying patients who may benefit from progesterone treatment. Ultrasound Obstet Gynecol. 2007 Oct;30(5):675-86. X-1, X-2
241. Rouse DJ. The Factor V Leiden mutation does not increase the risk of pregnancy-related venous thromboembolism. Evidence-based Obstetrics and Gynecology. 2003 Mar;5(1):56. X-3
242. Ruddock NK, Shi SQ, Jain S, et al. Progesterone, but not 17-alpha-hydroxyprogesterone caproate, inhibits human myometrial contractions. Am J Obstet Gynecol. 2008 Oct;199(4):391 e1-7. X-2, X-3
243. Ruiz RJ, Saade GR, Brown CE, et al. The effect of acculturation on progesterone/estriol ratios and preterm birth in Hispanics. Obstet Gynecol. 2008 Feb;111(2 Pt 1):309-16. X-3
244. Sallam HN, Sallam AN, Ezzeldin FE, et al. Minimal requirements for a successful outcome in anovulatory patients treated with human menopausal gonadotropins. Int J Fertil Womens Med. 2000 Jul-Aug;45(4):285-91. X-3
245. San Roman GA, Surrey ES, Judd HL, et al. A prospective randomized comparison of luteal phase versus concurrent follicular phase initiation of gonadotropin-releasing hormone agonist for in vitro fertilization. Fertil Steril. 1992 Oct;58(4):744-9. X-3
246. Sanchez-Ramos L, Kaunitz AM and Delke I. Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. Obstet Gynecol. 2005 Feb;105(2):273-9. X-1
247. Sarno JL, Schatz F, Lockwood CJ, et al. Thrombin and interleukin-1beta regulate HOXA10 expression in human term decidual cells: implications for preterm labor. J Clin Endocrinol Metab. 2006 Jun;91(6):2366-72. X-3
248. Sato K, Chisaka H, Okamura K, et al. Effect of the interaction between lipoxygenase pathway and progesterone on the regulation of hydroxysteroid 11-Beta dehydrogenase 2 in cultured human term placental trophoblasts. Biol Reprod. 2008 Mar;78(3):514-20. X-3
249. Schardein JL. Congenital abnormalities and hormones during pregnancy: a clinical review. Teratology. 1980 Dec;22(3):251-70. X-1
250. Schreyer P, Zer Y, Ariely S, et al. Plasma steroids and human placental lactogen level changes in late pregnancy in association with intravenous ritodrine administration. Gynecol Obstet Invest. 1981;12(2):99-106. X-2, X-3, X-4
251. Schwartz N, Xue X, Elovitz MA, et al. Progesterone suppresses the fetal inflammatory response ex vivo. Am J Obstet Gynecol. 2009 Aug;201(2):211 e1-9. X-2, X-3
252. Schwarz BE. Premature labor. Birth Defects Orig Artic Ser. 1981;17(1):85-94. X-1, X-2, X-3
253. Scialli AR. Developmental effects of progesterone and its derivatives. Reprod Toxicol. 1988;2(1):3-11. X-1, X-2, X-4
254. Scott EM, Thomas A, McGarrigle HHG, et al. A comparison of serial ultrasound measurements of fetal adrenal glands with maternal plasma and saliva oestriol and progesterone levels in normal pregnancy. Journal of Obstetrics and Gynaecology. 1991;11(6):381-385. X-3
255. Seegmiller RE, Nelson GW and Johnson CK. Evaluation of the teratogenic potential of delalutin (17 alpha-hydroxyprogesterone caproate) in mice. Teratology. 1983 Oct;28(2):201-8. X-2, X-3
256. Sexton DJ, O'Reilly MW, Friel AM, et al. Functional effects of 17alpha-hydroxyprogesterone caproate (17P) on human myometrial contractility in vitro. Reprod Biol Endocrinol. 2004 Dec 7;2:80. X-3
257. Sfakianaki AK and Norwitz ER. Mechanisms of progesterone action in inhibiting prematurity. J Matern Fetal Neonatal Med. 2006 Dec;19(12):763-72. X-1, X-3
258. Shahin AY, Hassanin IM, Ismail AM, et al. Effect of oral N-acetyl cysteine on recurrent preterm labor following treatment for bacterial vaginosis. Int J Gynaecol Obstet. 2009 Jan;104(1):44-8. X-4
259. Shalev J, Frankel Y, Eshkol A, et al. Breast engorgement and galactorrhea after preventing premature contractions with ritodrine. Gynecol Obstet Invest. 1984;17(4):190-3. X-2, X-3
260. Sharma S, Ou J, Strom S, et al. Identification of enzymes involved in the metabolism of 17alpha-hydroxyprogesterone caproate: an effective agent for prevention of preterm birth. Drug Metab Dispos. 2008 Sep;36(9):1896-902. X-3
261. Shearman RP and Garrett WJ. Double-blind study of effect of 17-hydroxyprogesterone caproate on abortion rate. Br Med J. 1963 Feb 2;1(5326):292-5. X-3, X-4
262. Sherman AI. Hormonal therapy for control of the incompetent os of pregnancy. Obstet Gynecol. 1966 Aug;28(2):198-205. X-4
263. Shields AD, Wright J, Paonessa DJ, et al. Progesterone modulation of inflammatory cytokine production in a fetoplacental artery explant model. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 2):1144-8. X-2, X-3

264. Shimozawa K, Matsumoto M, Okada K, et al. Analysis of blood spot 17 alpha-hydroxyprogesterone concentration in neonates. Horm Res. 1988;30(6):246-51. X-3
265. Shumin X, Johannisson E, Landgren BM, et al. Pituitary, ovarian and endometrial effects of progesterone released prematurely during the proliferative phase. Contraception. 1983 Feb;27(2):177-93. X-2, X-3
266. Sibai B, Meis PJ, Klebanoff M, et al. Plasma CRH measurement at 16 to 20 weeks' gestation does not predict preterm delivery in women at high-risk for preterm delivery. Am J Obstet Gynecol. 2005 Sep;193(3 Pt 2):1181-6. X-3, X-4
267. Siklosi G. Luteal insufficiency as the primary cause of habitual abortion--its successful treatment. Acta Biomed Ateneo Parmense. 1992;63(1-2):101-11. X-3
268. Siklosi G, Acs N, Demendi C, et al. Luteal function as the main determinant of pregnancy outcome: successful prevention of spontaneous abortion, prematurity and IUGR. Early Pregnancy. 2001 Jan;5(1):22-3. X-3, X-4
269. Smit DA, Essed GG and de Haan J. Predictive value of uterine contractility and the serum levels of progesterone and oestrogens with regard to preterm labour. Gynecol Obstet Invest. 1984;18(5):252-63. X-3
270. Smith R, Smith JI, Shen X, et al. Patterns of plasma corticotropin-releasing hormone, progesterone, estradiol, and estriol change and the onset of human labor. J Clin Endocrinol Metab. 2009 Jun;94(6):2066-74. X-3
271. Snegovskikh VV, Schatz F, Arcuri F, et al. Intra-amniotic infection upregulates decidual cell vascular endothelial growth factor (VEGF) and neuropilin-1 and -2 expression: implications for infection-related preterm birth. Reprod Sci. 2009 Aug;16(8):767-80. X-2, X-3
272. So KW and Ng PC. Treatment and prevention of neonatal osteopenia. Current Paediatrics. 2005 Apr;15(2):106-113. X-3
273. Soiva K and Castren O. Conservative treatment of threatened premature labour. Acta Obstet Gynecol Scand. 1965;44(2):281-8. X-3, X-4
274. Strauss A, Brakin M, Norris K, et al. Adrenal responsiveness in very-low-birth-weight infants treated with dexamethasone. Dev Pharmacol Ther. 1992;19(2-3):147-54. X-2, X-3
275. Sureau C and Breart G. The prevention of premature birth. Annales Nestle. 1989;47(2):89-96. X-1, X-2, X-4
276. Sweet RA, Schrott HG, Kurland R, et al. Study of the incidence of hypospadias in Rochester, Minnesota, 1940-1970, and a case-control comparison of possible etiologic factors. Mayo Clin Proc. 1974 Jan;49(1):52-8. X-3, X-4
277. Swyer GI and Daley D. Progesterone implantation in habitual abortion. Br Med J. 1953 May 16;1(4819):1073-7. X-3, X-4
278. Szekeres J, Csernus V, Hadnagy J, et al. Cytotoxic activity and progesterone binding capacity of maternal lymphocytes are not influenced by gestational age and by the number of previous pregnancies. Acta Med Acad Sci Hung. 1982;39(3-4):137-43. X-3
279. Szekeres-Bartho J, Csernus V, Hadnagy J, et al. Immunosuppressive effect of serum progesterone during pregnancy depends on the progesterone binding capacity of the lymphocytes. J Reprod Immunol. 1983 Mar;5(2):81-8. X-3
280. Szekeres-Bartho J, Csernus V, Hadnagy J, et al. Progesterone-prostaglandin balance influences lymphocyte function in relation to pregnancy. Am J Reprod Immunol. 1983 Oct-Nov;4(3):139-41. X-3
281. Szekeres-Bartho J, Faust Z and Varga P. The expression of a progesterone-induced immunomodulatory protein in pregnancy lymphocytes. Am J Reprod Immunol. 1995 Dec;34(6):342-8. X-3
282. Szekeres-Bartho J, Hadnagy J and Pacsa AS. The suppressive effect of progesterone on lymphocyte cytotoxicity: unique progesterone sensitivity of pregnancy lymphocytes. J Reprod Immunol. 1985 Feb;7(2):121-8. X-4
283. Szekeres-Bartho J, Kilar F, Falkay G, et al. The mechanism of the inhibitory effect of progesterone on lymphocyte cytotoxicity: I. Progesterone-treated lymphocytes release a substance inhibiting cytotoxicity and prostaglandin synthesis. Am J Reprod Immunol Microbiol. 1985 Sep;9(1):15-8. X-3
284. Szekeres-Bartho J, Varga P and Pacsa AS. Immunologic factors contributing to the initiation of labor--lymphocyte reactivity in term labor and threatened preterm delivery. Am J Obstet Gynecol. 1986 Jul;155(1):108-12. X-3
285. Szekeres-Bartho J, Varga P and Pejtsik B. ELISA test for the detection of an immunological blocking factor in human pregnancy serum. J Reprod Immunol. 1989 Sep;16(1):19-29. X-3
286. Tamby Raja RL, Anderson AB and Turnbull AC. Endocrine changes in premature labour. Br Med J. 1974 Oct 12;4(5936):67-71. X-3, X-4
287. TambyRaja RL and Salmon JA. Endocrinology of normal pregnancy and premature labour. N Z Med J. 1977 Jul 27;86(592):89-92. X-3
288. Tapanainen J, Huhtaniemi I, Koivisto M, et al. Hormonal changes during the perinatal period: FSH, prolactin and some steroid hormones in the cord blood and peripheral serum of preterm and fullterm female infants. J Steroid Biochem. 1984 May;20(5):1153-6. X-3
289. Tempfer CB, Kurz C, Bentz EK, et al. A combination treatment of prednisone, aspirin, folate, and progesterone in women with idiopathic recurrent miscarriage: a matched-pair study. Fertil Steril. 2006 Jul;86(1):145-8. X-3
290. Thomas S, Murphy JF, Dyas J, et al. Response to ACTH in the newborn. Arch Dis Child. 1986 Jan;61(1):57-60. X-3, X-4
291. Thome UH, Bischoff A, Maier L, et al. Amiloride-sensitive nasal potential difference is not changed by estradiol and progesterone replacement but relates to

BPD or death in a randomized trial on preterm infants. Pediatr Res. 2006 Nov;60(5):619-23. X-3
292. Thornton JG. Progesterone and preterm labor--still no definite answers. N Engl J Med. 2007 Aug 2;357(5):499-501. X-1, X-2, X-4
293. Torok I, Pohanka O, Dvoracsek E, et al. Beta-adrenergic sensitivity--imminent premature delivery. Acta Physiol Hung. 1985;65(3):347-54. X-3
294. Torresani T, Gruters A, Scherz R, et al. Improving the efficacy of newborn screening for congenital adrenal hyperplasia by adjusting the cut-off level of 17alpha-hydroxyprogesterone to gestational age. Screening. 1994;3(2):77-84. X-3
295. Toth B, Avar Z and Balint T. The effectivity of Bricanyl (terbutaline) treatment in the prevention and management of threatening abortion and premature delivery, respectively, within the frames of outpatients' services. Therapia Hungarica. 1982;30(2):88-92. X-4
296. Toth P. Clinical data supporting the importance of vascular LH/hCG receptors of uterine blood vessels. Semin Reprod Med. 2001;19(1):55-61. X-3, X-4
297. Trotter A, Maier L, Grill HJ, et al. Effects of postnatal estradiol and progesterone replacement in extremely preterm infants. J Clin Endocrinol Metab. 1999 Dec;84(12):4531-5. X-3
298. Trotter A, Maier L, Grill HJ, et al. 17Beta-estradiol and progesterone supplementation in extremely low-birth-weight infants. Pediatr Res. 1999 Apr;45(4 Pt 1):489-93. X-3
299. Trotter A, Maier L, Kohn T, et al. Growth of the uterus and mammary glands and vaginal cytologic features in extremely premature infants with postnatal replacement of estradiol and progesterone. Am J Obstet Gynecol. 2002 Feb;186(2):184-8. X-3
300. Trotter A, Maier L, Kron M, et al. Effect of oestradiol and progesterone replacement on bronchopulmonary dysplasia in extremely preterm infants. Arch Dis Child Fetal Neonatal Ed. 2007 Mar;92(2):F94-8. X-3
301. Trotter A, Maier L and Pohlandt F. Calcium and phosphorus balance of extremely preterm infants with estradiol and progesterone replacement. Am J Perinatol. 2002 Jan;19(1):23-9. X-3
302. Tsapoulis AD, Zourlas PA and Comninos AC. Observations on 320 infertile patients treated with human gonadotropins (human menopausal gonadotropin/human chorionic gonadotropin). Fertil Steril. 1978 May;29(5):492-5. X-3
303. Turnbull AC, Patten PT, Flint AP, et al. Significant fall in progesterone and rise in oestradiol levels in human peripheral plasma before onset of labour. Lancet. 1974 Jan 26;1(7848):101-3. X-3, X-4
304. Tyson EK, Smith R and Read M. Evidence that corticotropin-releasing hormone modulates myometrial contractility during human pregnancy. Endocrinology. 2009 Dec;150(12):5617-25. X-3
305. Unanue N, Bazaes R, Iniguez G, et al. Adrenarche in Prader-Willi syndrome appears not related to insulin sensitivity and serum adiponectin. Horm Res. 2007;67(3):152-8. X-3
306. van der Ploeg KR, Wolthers BG, Nagel GT, et al. The diagnosis of 21-hydroxylase deficiency in a prematurely born infant on the basis of the urinary steroid excretion pattern. Clin Chim Acta. 1982 Apr 23;120(3):341-53. X-2, X-3
307. Varma TR and Morsman J. Evaluation of the use of Proluton-Depot (hydroxyprogesterone hexanoate) in early pregnancy. Int J Gynaecol Obstet. 1982 Feb;20(1):13-7. X-3, X-4
308. Vassilakos P, Wyss R and Stastny J. Decidual changes during hypertonic saline-induced abortion. Am J Obstet Gynecol. 1974 Aug 1;119(7):889-94. X-2, X-3, X-4
309. Vidaeff AC, Ramin SM, Gilstrap LC, 3rd, et al. Impact of progesterone on cytokine-stimulated nuclear factor-kappaB signaling in HeLa cells. J Matern Fetal Neonatal Med. 2007 Jan;20(1):23-8. X-3
310. Walker J. Prognostic value of antenatal screening. Am J Obstet Gynecol. 1976 Jan 1;124(1):30-8. X-3, X-4
311. Walker J, Hughes IA and Wood PJ. Bloodspot testosterone assay suitable for study of neonates and monitoring of children with congenital adrenal hyperplasia. Ann Clin Biochem. 1999 Jul;36 (Pt 4):477-82. X-3
312. Wallace AM, Beesley J, Thomson M, et al. Adrenal status during the first month of life in mature and premature human infants. J Endocrinol. 1987 Mar;112(3):473-80. X-3
313. Wallace WH, Shalet SM, Tetlow LJ, et al. Ovarian function following the treatment of childhood acute lymphoblastic leukaemia. Med Pediatr Oncol. 1993;21(5):333-9. X-2
314. Watterberg KL, Gerdes JS and Cook KL. Impaired glucocorticoid synthesis in premature infants developing chronic lung disease. Pediatr Res. 2001 Aug;50(2):190-5. X-3
315. Weinberg MA and Maloney WJ. Periodontal changes in females. U.S. 2007 19;Pharmacist. 32(9):54-56. X-3
316. Weller A, Rozin A, Goldstein A, et al. Longitudinal assessment of pituitary-thyroid axis and adrenal function in preterm infants raised by 'kangaroo mother care'. Horm Res. 2002;57(1-2):22-6. X-3
317. Wilkins L. Masculinization of female fetus due to use of orally given progestins. J Am Med Assoc. 1960 Mar 5;172:1028-32. X-2, X-3
318. Wilkins L, Jones HW, Jr., Holman GH, et al. Masculinization of the female fetus associated with administration of oral and intramuscular progestins during gestation: non-adrenal female pseudohermaphrodism. J Clin Endocrinol Metab. 1958 Jun;18(6):559-85. X-3
319. Wiseman RA and Dodds-Smith IC. Cardiovascular birth defects and antenatal exposure to female sex hormones: a reevaluation of some base data. Teratology. 1984 Dec;30(3):359-70. X-2, X-3
320. Wolfrum R, Bordasch C, Holweg J, et al. Prognostic value of combined assay of total estrogen and pregnanediol in 24 hour urine. Experience with 500 pregnancies in an endocrine surveillance program during the second trimester. J Perinat Med. 1977;5(3):133-44. X-3, X-4

321. Wu WX, Ma XH, Zhang Q, et al. Characterization of two labor-induced genes, DSCR1 and TCTE1L, in the pregnant ovine myometrium. J Endocrinol. 2003 Jul;178(1):117-26. X-2
322. Yalom ID, Green R and Fisk N. Prenatal exposure to female hormones. Effect on psychosexual development in boys. Arch Gen Psychiatry. 1973 Apr;28(4):554-61. X-3, X-4
323. Yan R, Fokina V, Hankins GD, et al. The effect of esterases on 17alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol. 2008 Feb;198(2):229 e1-5. X-3
324. Yan R, Nanovskaya TN, Zharikova OL, et al. Metabolism of 17alpha-hydroxyprogesterone caproate by hepatic and placental microsomes of human and baboons. Biochem Pharmacol. 2008 May 1;75(9):1848-57. X-3
325. Ylikorkala O, Kauppila A, Tuimala R, et al. Effects of intravenous isoxsuprine and ritodrine, with and without concomitant dexamethasone, on fetoplacental and pituitary hormones and cyclic adenosine monophosphate during late pregnancy. Am J Obstet Gynecol. 1978 Feb 1;130(3):302-6. X-3
326. Yokoyama M, Hinode D, Masuda K, et al. Effect of female sex hormones on Campylobacter rectus and human gingival fibroblasts. Oral Microbiol Immunol. 2005 Aug;20(4):239-43. X-3
327. Youssef RE, Ledingham MA, Bollapragada SS, et al. The role of toll-like receptors (TLR-2 and -4) and triggering receptor expressed on myeloid cells 1 (TREM-1) in human term and preterm labor. Reprod Sci. 2009 Sep;16(9):843-56. X-3
328. Zaremba W, Grunert E and Aurich JE. Prophylaxis of respiratory distress syndrome in premature calves by administration of dexamethasone or a prostaglandin F2 alpha analogue to their dams before parturition. Am J Vet Res. 1997 Apr;58(4):404-7. X-2, X-3
329. Zicari A, Ticconi C, Realacci M, et al. Hormonal regulation of cytokine release by human fetal membranes at term gestation: effects of oxytocin, hydrocortisone and progesterone on tumour necrosis factor-alpha and transforming growth factor-beta 1 output. J Reprod Immunol. 2002 Jul-Aug;56(1-2):123-36. X-3
330. Zuspan FP. Premature labor: its management and therapy. J Reprod Med. 1972 Sep;9(3):93-118. X-1, X-3, X-4