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The Use of Supplemental Progesterone in Preventing Preterm Birth in High-Risk Women: A Critical Review of the Literature

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THE USE OF SUPPLEMENTAL PROGESTERONE IN PREVENTING PRETERM BIRTH IN HIGH-RISK WOMEN: A CRITICAL REVIEW OF THE LITERATURE

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Abstract

Background: Twelve percent of births in the United States occur before 37 weeks of gestation and therefore are considered preterm births (Norwitz, 2015). While the ability to identify women at risk for preterm birth has improved dramatically over the past three decades, the application of primary and secondary interventions has failed to reduce the incidence of preterm delivery, which has actually been on the rise (Norwitz, 2015). Preterm birth is a phenomenon that needs to be reduced not only in the United States, but also across the world.

Purpose: To determine to what extent the use of supplemental progesterone in pregnancy can aid in preventing preterm labor, and more importantly preterm birth, in women who are at a high-risk for preterm birth.

Results: Twenty articles were identified for review and appraised using the John Hopkins Research Evidence Appraisal Tool. The major findings of the reviewed literature concluded that the use of progestational agents is an effective measure in preventing preterm birth and improving neonatal outcomes.

Conclusion: By reducing the rate of preterm birth, there is potential to reduce many other linked outcomes such as neonatal outcomes and costs related to premature delivery complications. Progestational agents are an effective measure in preventing preterm birth in high-risk women. Screening women for preterm birth risk factors early in their antenatal care is an appropriate primary prevention technique. The use of progestational agents in high-risk women is an appropriate secondary prevention technique that has shown many benefits.

Implications for Research and Practice: There is a need for further research focusing specifically on multiple gestation pregnancies and pregnancies with known fetal anomalies and the use of progestational agents. Significant research has focused on singleton gestation pregnancies and pregnancies with known fetal anomalies excluded from these research studies. Additionally, further research needs to be conducted on optimal administration route, timing of administration, and studies investigating cost-effectiveness.

Keywords: progesterone, preterm birth, pregnancy, preterm labor, prevention, and short cervix.

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Chapter I: Introduction

Preterm birth is defined as the 'delivery of an infant between 20 and 37 weeks of gestation and is the greatest contributor to infant death and a leading cause of long-term neurological disabilities in children (Centers for Disease Control and Prevention, 2015; The American Congress of Obstetricians and Gynecologists, 2015). The risk of mortality and morbidity strongly correlates with birth weight and the gestational age at the time of delivery with the highest risk being early gestational age (Mackenzie, Walker, Armson, & Hannah, 2006). In addition to the potential health consequences of preterm birth, the cost of premature infants needing the neonatal intensive care unit (NICU) or long-term care is enormous and overwhelming (Mackenzie, Walker, Armson, & Hannah, 2006). Unfortunately, the reality is that twelve percent of births in the United States occur before 37 weeks of gestation and therefore are considered preterm births (Norwitz, 2015). Preterm birth is a phenomenon that needs to be reduced not only in the United States, but across the world.

Throughout history, researchers and providers have focused on active management (tertiary prevention) of preterm labor (regular contractions of the uterus resulting in cervical change that start before 37 weeks of pregnancy) in preventing preterm birth (ACOG, 2015). These efforts to delay delivery in women presenting with acute preterm labor have been largely unsuccessful (Norwitz, 2015). While the ability to identify women at risk for preterm birth has improved dramatically over the past three decades, the application of primary and secondary interventions has failed to reduce the incidence of preterm delivery, which has actually been on the rise (Norwitz, 2015).

Statement of Purpose

The intent of this critical appraisal of the literature is to determine to what extent the use of supplemental progesterone in pregnancy can aid in preventing preterm labor, and more importantly preterm birth, in women who are at a high-risk for preterm birth. By developing an evidenced-based method for primary prevention of preterm labor and birth, maternal and neonatal outcomes have the potential to improve exponentially.

Need for Critical Review of a Nurse-Midwifery Problem

Healthy People has developed a set of science-based, 10-year national objectives for improving the health of all Americans (Office of Disease Prevention and Health Promotion, 2016). A vast majority of these objectives focus on maternal, infant, and child health. Pertinent Healthy People 2020 objectives include MICH-1 reduce the rate of fetal and infant deaths, MICH-8 reduce low birth weight (LBW) and very low birth weight (VLBW), and finally, MICH-9 reduce preterm births (ODPHP, 2016). Developing a research-supported method to aid in primary and secondary prevention of preterm birth would contribute to the success of these Healthy People 2020 goals and improve maternal and neonatal outcomes not only nationally, but worldwide.

The first randomized controlled trial of progestational agents for the prevention of preterm birth in high-risk women was published in 1970 by Paperink (Mackenzie, Walker, Armson, & Hannah, 2006). The evidence on the use of supplemental progesterone in preventing preterm labor and preterm birth is a relatively new phenomenon in medicine that has been identified as a mechanism to potentially reduce the risk of spontaneous preterm birth in a variety of high-risk populations (Norwitz, 2015). While supplemental progesterone is currently used in medical practice in an effort to reduce the incidence of preterm birth, there is a significant disconnect in the

appropriate timing, route, and dose of treatment. Over the past decade, there have been numerous research studies to attempt to identify these factors and a critical review of the literature is needed to analyze the data as a whole and determine the most appropriate treatment plan, if any.

Significance to Nurse-Midwifery

Nurse-midwives are on the forefront for providing exceptional prenatal care and identifying women at risk for pregnancy complications. At every visit, especially the first visit, the nurse-midwife is assessing the women's history and clinical picture. Identifying women at risk for certain complications such as preterm birth is crucial. If a nurse-midwife is able to prevent even one preterm birth, he/she is potentially saving a life. The art and science of nurse-midwifery are characterized by hallmarks including incorporation of scientific evidence into clinical practice, health promotion, disease prevention, and health education, and care to vulnerable populations- to name a few (American College of Nurse-Midwives, 2012). By understanding the potential impact of supplemental progesterone therapy, nurse-midwives will better serve these hallmarks of nurse-midwifery and the patients that may benefit from secondary intervention.

Conceptual Model

The conceptual model selected for this critical appraisal is Betty Neuman's Systems Model (Petiprin, 2015). A systems perspective requires the nurse-midwife to not only view the interaction of the subsystems within the system but also the effect that each subsystem on the other subsystems (Reed, 1993). In other words, the Systems Model focuses on the response of the patient system to stressors and the use of primary, secondary, and tertiary nursing prevention, intervention, attainment, and maintenance of

patient system wellness (Petiprin, 2015). This model is applicable to primary, secondary, and tertiary prevention of preterm birth and the potential effects that progesterone has on patient system wellness.

The Neuman's Systems Model has basic beliefs, called assumptions, which are necessary to understand when using the Neuman Model. The following assumptions are found in the Neuman model (Neuman, 1989, pp. 21-22, 77; Reed, 1993 pp. 5-7).

1. Though each individual client or group as a client system is unique, each system is a composite of common known factors or innate characteristics within a normal, given range of response contained within a basic structure.
2. Many, known, unknown, and universal and environmental stressors exist. Each differs in its potential for disturbing a client's usual stability level, or normal line of defense. The particular interrelationships of client variables - physiological, psychological, sociocultural, developmental, and spiritual - at any point in time can affect the degree to which a client is protected by flexible line of defense against possible reaction to a single stressor or combination of stressors.
3. Each individual client/client system, over time, has evolved a normal range of response to the environment that is referred to as a normal line of defense, or usual wellness/stability state.
4. When the cushioning, accordion-like effect of the flexible line of defense is no longer capable of protecting the client/client system against an environmental stressor, the stressor breaks through the normal line of

defense. The interrelationships of variables - physiological, psychological, sociocultural, developmental, and spiritual - determine the nature and degree of the system reaction or possible reaction to the stressor invasion.

5. The client, whether in a state of wellness or illness, is a dynamic composite of the interrelationships of variables - physiological, psychological, sociocultural, developmental, and spiritual. Wellness is on a continuum of available energy to support the system in its optimal state.
6. Implicit within each client system is a set of internal resistance factors, known as lines of resistance (resources), which function to stabilize and return the client to the usual wellness state (normal line of defense) or possible to a higher level of stability following an environmental stressor reaction.
7. Primary prevention relates to general knowledge that is applied in client assessment and intervention in identification and reduction or mitigation of risk factors associated with environmental stressors to prevent possible stressor reaction.
8. Secondary prevention relates to symptomatology following a reaction to stressors appropriate ranking of intervention priorities, and treatment to reduce their noxious effects.
9. Tertiary prevention relates to the adjustive processes taking place as reconstitution begins and maintenance factors move the client back in a circular manner toward primary prevention.
10. The client is in dynamic constant energy exchange with the environment.

Figure 1.1 depicts Neuman's Systems Model. The circle surrounded by the series of concentric rings graphically represents the client. The rings are known as the basic structure and serve as a protective structure for the client and to help maintain a stable state (Reed, 1993). The outer ring is known as the flexible line of defense (FLD) and is the outer boundary of the client that protects the normal line of defense or usual state of wellness of the client (Reed, 1993). The FLD is ultimately the first line of defense in response to stressors from the environment (Reed, 1993). An example of a stressor in regards to the research question may be a history of preterm birth or a sonographically short cervix. The next ring is known as the normal line of defense (NLD) and represents the client's usual state of wellness (Reed, 1993). And finally, lines of resistance (LR) are the closest mechanism and function as a protectant for the basic structure's integrity (Reed, 1993). When these lines of defense and resistance are effective, the system is able to reconstitute and return to a steady state and when they are ineffective, death or illness of the system may occur (Reed, 1993).

Physiological, psychological, sociocultural, developmental, and spiritual variables have an influence on the system (Reed, 1993). Another positive or negative influence on the system includes both internal and external environmental stress factors (Reed, 1993). These environmental factors are further divided into internal, external, and created.

The internal environment (intrapersonal) "consists of all forces or interactive influences internal to or contained solely within boundaries of the client" (Neuman, 1989, pp. 31; Reed, 1993, pp. 11). This forms as the result of relationships among the subsystems of the client (Reed, 1993). The external environment consists of intrapersonal or extrapersonal influences (Reed, 1993). These influences include interaction of the

client with another person such as a work colleague, family member, or healthcare team member (Reed, 1993). The created environment is the client's attempt to create a safe setting for functioning (Reed, 1993). In particular, this created environment is developed by the client if the client perceives a threat to the basic structure and function of the system (Reed, 1993).

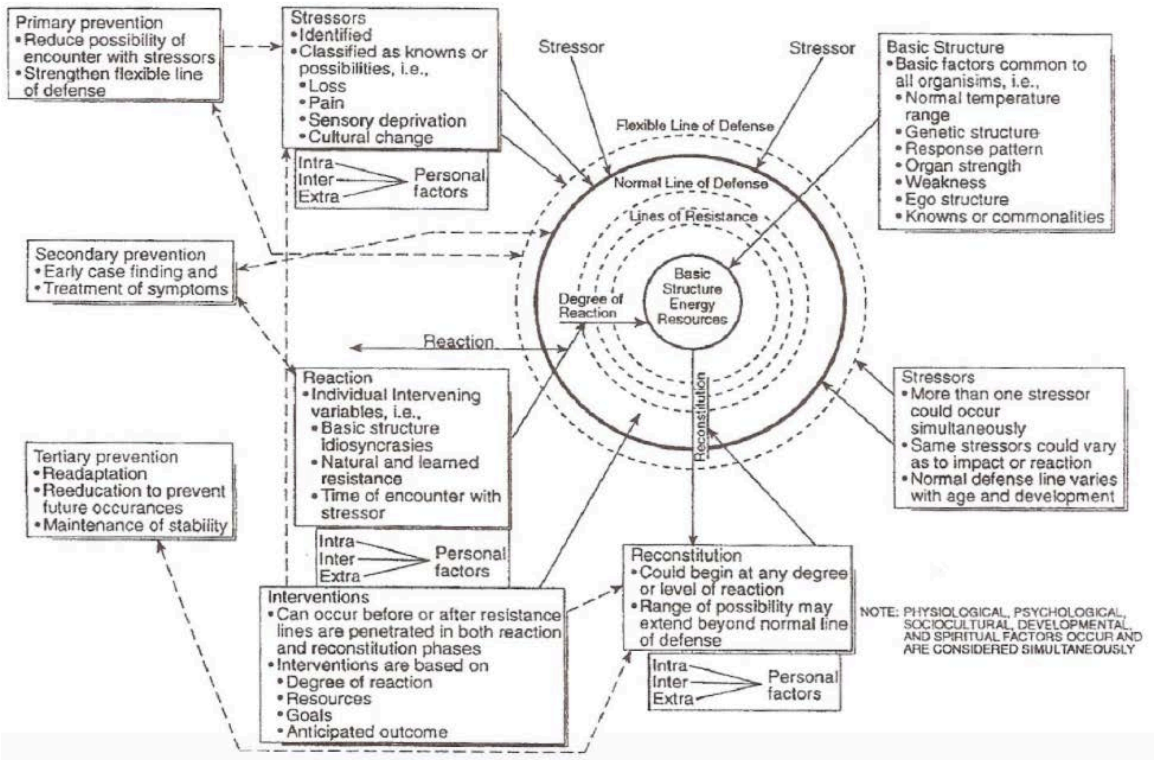
In every environment, there are stressors that have the potential to cause disequilibrium. These stressors can be divided into intrapersonal, interpersonal, and extrapersonal stressors. The stressor's effect on the client is dependent on the strength of the stressor, the number of stressors present at any given time, and the ability of the client to protect against the stressor (Reed, 1993). In the Neuman Model, health and wellness are considered the same (Reed, 1993). Wellness occurs when system needs are fully met and the client is healthy. Obviously, the reverse is true as well - when there are unmet needs, wellness is reduced.

The nursing goal is to keep the client well and stable by integrating appropriate interventions (Reed, 1993). There are three levels of prevention used to attain, maintain and retain wellness - primary, secondary, and tertiary (Reed, 1993). Primary prevention is aimed at decreasing risk factors and increasing the FLD's ability to withstand environmental stressors (Reed, 1993). Secondary prevention comes into effect when the NLD is disrupted. It is aimed at strengthening at protecting the basic structure and strengthening the LR (Reed, 1993). Tertiary prevention focuses on helping treating the client in order to promote a healthy return to a wellness state (Reed, 1993).

Until recently, preterm birth has largely focused on the tertiary level of prevention to delay delivery in women presenting with acute preterm labor (Norwitz, 2015). The

rates of preterm labor, preterm birth, and complications in relation to these factors result in suffering. Women may be at risk for preterm birth if they have a personal history of previous spontaneous preterm birth or have a sonographically identified short cervix. By identifying women at risk for preterm birth early in their pregnancies, nurse-midwives will be utilizing primary prevention and by determining and implementing the safest method of progesterone supplementation in high-risk women in an effort to avoid preterm birth nurse-midwives will be encompassing secondary prevention. By acting upon these assessments, the provider will have a better chance of being successful in keeping the client and the fetus in a state of wellness and health. Prevention as intervention is the basis of health promotion and needs to encompass primary, secondary, and tertiary prevention in order to be successful.

Figure 1.1: Neuman's Systems Model Diagram



(Harris County District Hospital, n.d.)

Summary

As healthcare, midwifery, and medicine continue to evolve, we must make a cognizant effort to remain up-to-date on current research. The use of progesterone supplementation in pregnant women with a high-risk for preterm birth is growing. There is evidence supporting the use of progesterone; however, there is still inconsistent information on the preferred route, dosing, diagnostic criteria and timing of administration. This chapter described the consequences of preterm labor and birth and the need for primary and secondary prevention strategies, the need for a critical review of the literature, the significant to nurse-midwifery, and the conceptual model supporting the review.

Chapter 2 describes the strategies used for appraisal of the literature including databases, search terms, inclusion and exclusion criteria, a summary of the number and types of research selected for this critical review, and criteria for evaluating research studies. Chapter 3 provides a breakdown of the review and analysis of the evidence and includes a synthesis of major findings in the form of a matrix as well as strengths and weakness of the research studies. Chapter 4 concludes with a synthesis of the literature answering the research question, current trends, and gaps in the literature, implications for nurse-midwifery, recommendations for further nursing research, and application and integration of the identified conceptual model.

Chapter II: Methods

This chapter will discuss the search methods used in this critical appraisal of the literature. Studies related to the prevention of preterm birth in high-risk women by utilizing the use of progesterone were included. This chapter describes the search strategies to identify research studies that answer the research question, strategies used to evaluate the research, explanation of inclusion and exclusion criteria, and the number and types of studies found in the literature review. Finally, the evaluation process for determining the level and quality of the evidence in the research studies will be explained.

Search Strategies Used to Identify Research Studies

The purpose of this critical appraisal of the literature is to determine if the use of progesterone in high-risk singleton pregnancies reduces the risk of preterm labor and birth. An initial search was conducted utilizing a basic general search of several EBSCO databases with scholarly articles including Academic Search Premier, AgeLine, Alt HealthWatch, Database of Abstracts of Reviews of Effects, EBSCO MegaFILE, ERIC, Family & Society Studies Worldwide, GreenFILE, MasterFILE Premier, MLA International Bibliography, Music Index, New Testament Abstracts, Old Testament Abstracts, Philosopher's Index, Professional Development Collection, PsycINFO, Teacher Reference Center, and Business Source Premier through the Bethel University library using a combination of the following key words: progesterone, preterm birth, pregnancy, preterm labor, progesterone, prophylactic progesterone, prevention, high-risk, premature, early labor, and short cervix.

Strategies Used to Evaluate the Research

The John Hopkins Nursing Evidence-Based Practice: Model and Guidelines by Deerholt & Dang (2012) were used to evaluate the research studies in this critical appraisal of the literature. The John Hopkins Research Evidence Appraisal Tool allowed the research studies to be critiqued based on the level and quality of the evidence (Deerholt & Dang, 2012). The evidence was categorized from level I-IV according to the John Hopkins Research Evidence Appraisal Tool (Deerholt & Dang, 2012). Level I research studies include experimental studies that are randomized controlled trials (RCT), and systematic reviews of RCTs with or without a meta-analysis. Level II research studies include quasi-experimental studies and systemic reviews that include RCTs and quasi-experimental studies with or without meta-analysis. Level III research studies are non-experimental studies, qualitative studies, or a combination of RCTs, quasi-experimental and non-experimental studies with or without meta-analysis. Level IV studies include opinions of respected authorities, clinical practice guidelines, or expert committee/consensus panels based on scientific evidence (Deerholt & Dang, 2012).

Research studies are considered 'high quality' if the results obtained are generalizable, have a sufficient sample size, design, adequate control, and definitive conclusions. If the study has reasonably consistent results, a sufficient sample size, design, moderate control, and fairly definitive conclusions, it is then considered 'good quality'. And finally, research studies are categorized as 'low quality' if there is little evidence with inconsistent results, insufficient sample size for the study, and if conclusions are unable to be drawn from the results (Deerholt & Dang, 2012). The studies were further analyzed based on their purpose, sample, design, measurement,

results, conclusions, and recommendations. The data were then organized in the form of a Matrix (Table 1).

Criteria for Including or Excluding Research Studies

Experimental, quasi-experimental, and non-experimental research studies of all qualities were included in the matrix. Many of the studies in the initial search were excluded because their content did not relate to the purpose of the review or pertain to the research question. All ages, routes of medication administration, formulations, and timing of medication administration were included. Singleton pregnancies were included and multi-gestation pregnancies were omitted for the sake of data analysis but if the study included data on singleton pregnancies as well, it was included. Only studies written in English were included.

Number and Types of Studies Selected for the Review

A total of 748 studies were evaluated in the initial selection. Abstracts were reviewed and many studies that did not pertain to the research question were immediately omitted. The remaining studies were organized according to original research, literature review, meta-analysis, and expert opinion. The studies were also sorted according to the type of research. In addition, the references within the research studies were analyzed yielding additional pertinent literature for review.

Ultimately, 20 articles were chosen for the final review and compiled into matrices. 10 of these studies were 'high quality' and 10 of these studies were 'good quality'. Table 1 summarizes the studies that were included in the final review in an organized matter. The matrix was developed using the headings: citation, purpose,

sample, design, measurement, results/conclusions, recommendations, and level/quality. The matrix was then sorted alphabetically by author.

Summary

The use of progesterone for preterm birth prophylaxis in high-risk mothers is not well understood in terms of route, timing, appropriate use, and duration of use which, presented a need for a critical appraisal of the literature. There is a need for analysis of the evidence to determine these items as well as analyze neonatal outcomes. The Matrix (table 1) includes 20 studies that provide a thorough evaluation of the evidence. This chapter summarized the search and evaluation strategies used for this critical appraisal of the literature.

Chapter III: Literature and Analysis

Chapter Three synthesizes the major findings of the literature review as it pertains to the use of progesterone to prevent preterm birth. Strengths and weaknesses of the selected research studies will be discussed. The articles are organized in a matrix, which has been alphabetized by author for ease of use for the reader.

Synthesis of Matrix

The matrix was created as a tool to organize the selected research studies. Organization in this manner allows for an easier identification of trends in the research studies. Twenty studies were selected for the final matrix. The following headings were utilized in every matrix entry: citation, purpose, sample, design, measurement, results/conclusions, recommendations, and level/quality. After organizing and examining the studies, the findings were synthesized and implications for practice were identified.

Synthesis of Major Findings

Effectiveness of Placebo and Progestational Agents

One of the most important measures of the critical appraisal was to determine if the use of progestational agents was effective in preventing preterm birth. In the studies identified for review, researchers often determined effectiveness by comparing effectiveness of progestational agents with placebo agents.

The research for this review that investigated the effectiveness of progestational agents dated back until 2003. There were two research articles published in 2003 that were included in this literature review. The first study by Meis et al. (2003) provided statistically significant results that treatment with progestational agents significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3% in the

progesterone group vs. 54.9% in the placebo group; relative risk, 0.66 [95% confidence interval, 0.54 to 0.81]), 35 weeks of gestation (incidence, 20.6% vs. 30.7%; relative risk, 0.67 [95% confidence interval, 0.48 to 0.93]), and 32 weeks of gestation (11.4% vs. 19.6%; relative risk, 0.58 [95% confidence interval, 0.37 to 0.91]). This was further confirmed by a second study in 2003 by Da Fonesca, Bittar, Carvalho, and Zugaib in which a placebo and progestational agents were utilized in 142 cases. In this study, 72 women received progesterone and 70 received a placebo (Da Fonesca et al., 2003). Of the 142 cases in the study, there were a total of 30 preterm births or a preterm birth rate of 21.1% (Da Fonesca et al., 2003). The study concluded that there were differences in uterine activity between the progesterone and placebo (23.6% vs. 54.3%, respectively; $p < .05$). and in preterm birth rates between the progesterone and placebo groups (13.8% vs. 28.5%, respectively; $p < .05$) as more women were delivered before 34 weeks in the placebo group than in the progesterone group (Da Fonesca et al., 2003). Once again, the use of progestational agents was supported by this study.

Moving forward in time, a study by Sanchez-Ramos, Kaunitz, and Delke (2005) also compared patients who received a placebo agent to women who received progestational agents. This study found that the women who received progestational agents had lower rates of preterm delivery (Sanchez-Ramos, Kaunitz, & Delke, 2005). This was confirmed in additional studies by Dodd, Crowther, Cincotta, Flenady, and Robinson (2005) Mackenzie, Walker, Armson, and Hannah (2006). Both studies resulted in similar outcomes of a significant reduction in delivery at less than 37 weeks with the use of progestational agents. Once again, the research findings were supported by Fonesca, Celik, Parra, Singh, and Nicolaides (2007) when their study suggested that

spontaneous delivery before 34 weeks of gestation was less frequent in their progesterone group in comparison to the placebo group.

As the research progressed throughout the years, results remained quite consistent supporting the use of progestational agents in preventing preterm birth. Cetingoz, Cam, Sakalli, Karateke, Celik, and Sancak (2011) determined that there was once again a statistically significant difference in the rate of preterm birth between the placebo and progesterone groups. More women delivered before 37 weeks of gestation in the placebo group than in the progesterone group, therefore supporting the use of progestational agents (Cetingoz et al., 2011). The use of progesterone also resulted in a reduction in the preterm births before 34 weeks of gestation (Cetingoz et a., 2011).

A large study by Hassan et al. (2011) compared vaginal progesterone gel with a placebo agent. The results revealed that women allocated to receive vaginal gel progesterone without a history of preterm birth had a lower rate of preterm birth before 35, 33, and 28 weeks than did those allocated to placebo group (Hassan et al., 2011). However, it is important to note that the reduction in the rate of preterm birth in women with a prior history of preterm birth between 20 and 35 weeks of gestation did not reach statistical significance (Hassan et al., 2011). Ultimately, the administration of vaginal progesterone gel to women with a sonographic short cervix in the mid-trimester was found to be associated with a 45% reduction in the rate of preterm birth before 33 weeks of gestation (Hassan et al., 2011). And finally, in a study by Conde-Agudelo et al. (2013), direct comparison results determined that both vaginal progesterone and cerclage were associated with significant reductions in the risk of pre-term birth at less than 32 weeks of gestation compared to placebo/no cerclage (relative risk 0.47, 95% confidence interval

0.24 to 0.91, four RCTs for vaginal progesterone compared with placebo; relative risk 0.66, 95% confidence interval 0.48 to 0.91, five RCTs for cerclage compared with no cerclage).

There were only a few articles that did not fully support the use of progestational agents in preventing preterm birth. The first study was completed by O'Brien el al. (2007), which determined that the use of progesterone did not decrease the frequency of preterm birth at less than or equal to 32 weeks of gestation. Berghella et al. (2010) conducted a second study, which determined that in 300 women, progestational agents had no effect on preterm birth at less than 35 weeks of gestation in women with ($p = 0.64$) or without cerclage ($p = 0.51$). However, this study did conclude that preterm birth at less than 24 weeks of gestation (odds ratio, 0.08) was significantly lower for those with progestational agents and no cerclage (Berghella et al., 2010).

Route of Administration

Determining the optimal route for progesterone administration is important. Currently, there are vaginal, oral, and intramuscular routes of progesterone agent administration. Two studies from the identified studies investigated the optimal route of progesterone administration. In terms of identifying the optimal route of administration, it is important to take into consideration effectiveness and adverse effects.

Velez Edwards et al. (2013) performed a systemic review and meta-analysis by drug route of 27 randomized trials. Across all of the studies analyzed, all routes (oral, vaginal, and intramuscular) were identified as effective in reducing preterm birth in singleton pregnancies (Intramuscular risk ratio 0.77, 95% Bayesian credible interval: 0.69-0.87; vaginal risk ratio 0.80, 95% Bayesian credible interval: 0.69-0.91; oral risk

ratio 0.66, 95% Bayesian credible interval: 0.47-0.84) (Velez Edwards et al., 2013). Vaginal and intramuscular progesterone were both effective in reducing neonatal deaths in singleton pregnancies (Velez Edwards et al., 2013). This study suggests that the oral route is not the optimal route of administration.

Maher, Abelaziz, Ellaithy, and Bazeed (2013) completed a randomized trial to analyze the use of vaginal and intramuscular progesterone. This study revealed that vaginal progesterone was associated with a lower percentage of deliveries before 34 weeks in comparison to the intramuscular route of administration ($p = 0.02$) (Maher et al., 2013). The same outcome was seen when deliveries between 28 and 32 weeks of gestation were analyzed ($p = 0.04$) (Maher et al., 2013). As far as deliveries at other gestational ages, there were no statistically significant differences between the routes of delivery (Maher et al., 2013).

In the study by Maher et al. (2013), adverse effects were reported higher in the intramuscular group than the vaginal group. In their study, 14.1% of patients in the intramuscular group reported adverse effects compared to only 7.5% in the vaginal group ($p = 0.017$) (Maher et al., 2013).

Cost-Effectiveness

An important consideration to address regarding the use of progesterone for preventing preterm birth is determining whether this strategy promotes cost-effectiveness. Two of the studies reviewed identified cost-effectiveness as an outcome measure. It must be determined what the appropriate screening technique is and when progesterone should be initiated to be most effective and cost-effective.

Cahill et al. (2010) identified that universal sonographic screening for cervical length and treatment with vaginal progesterone was the most cost-effective strategy and was the best choice among three alternatives. The three alternatives were cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone, risk-based treatment with 17-OHP-C without screening, and no screening or treatment (Cahill et al., 2010). Universal screening represented savings of $1339 ($8323 vs $9664), when compared with treatment with 17-OHP-C, and led to a reduction of 95,920 preterm births annually in the United States (Cahill et al., 2010).

Pizzi, Seligman, Baxter, Jutkowitz, and Berghella (2014) analyzed a well-known trial known as the PREGNANT trial for the cost effectiveness of the use of vaginal progesterone 8% gel in reducing the likelihood of preterm birth among women with a short cervix. Researches analyzed the costs and cost effectiveness of vaginal progesterone gel versus placebo. The estimated cost per mother was US $23,079 for vaginal progesterone gel and US $36,436 for the placebo (Pizzi et al., 2014). The cost-effectiveness model showed a savings of US $24,071 per preterm birth averted with vaginal progesterone gel (Pizzi et al., 2014). As you can see, vaginal progesterone gel realized cost savings and cost effectiveness in 79% of simulations (Pizzi et al., 2014).

According to Petrini et al. (2005), if all eligible women receive progestational preventative therapy, 9,870 preterm births may have been prevented, which is an astonishing amount and would have a significant reduction in costs. If the progestational agent were restricted to women with a history of a previous spontaneous very preterm birth, 2,163 preterm births may have been prevented (Petrini et al., 2005).

Effect on the Neonatal Outcomes

It is well-known that preterm birth has an effect on a neonate. There are often higher rates of neonatal death, neonatal complications, NICU admissions, and lower birth weights to neonates born at earlier gestations or prematurely. Because of this, it is important to analyze if the use of progesterone not only prevents preterm birth but if there is also an effect on neonatal outcomes. There was an overwhelming amount of research on this; in the critical appraisal, numerous studies that addressed neonatal outcomes were located.

The use of progestational agents to prevent preterm birth was found to be statistically associated with decreased neonatal morbidity (Sotiriadis, Papatheodorou & Markydimas, 2012; Fonesca et al., 2007; Rai et al. 2009), perinatal death (Berghella et al., 2010; Rode et al., 2009), respiratory distress syndrome (Rode et al., 2009; Hassan et al., 2011), necrotizing enterocolitis (Rode et al., 2009; Meis et al., 2003), intraventricular hemorrhage (Dodd et al., 2005; Meis et al., 2003), need for supplemental oxygen (Meis et al., 2003), neonatal intensive care unit (NICU) admissions (Sotiriadis, Papatheodorou & Markydimas, 2012), NICU length of stay (Rai et al., 2009) and higher APGAR scores (Rai et al., 2009).

One factor that has a significantly associated with some of these complications is the infant's weight at birth. If progestational agents have the potential to decrease the rate of premature births, the average birth weight is likely to rise. There is a statistically significant reduction of infants born with low birth weights when receiving progestational agents (Sanchez- Ramos, Kaunitz, & Delke, 2005; Tita & Rouse, 2009; Dodd et al., 2005; Rai et al., 2009; Hassan et al., 2011).

Some studies however did not have statistically significant results between the progestational group and the placebo groups. Rode et al. (2009) concluded that the risk of admission for preterm labor, antenatal corticosteroid therapy, and tocolytic therapy is not decreased in women who are treated prophylactically with progesterone. Sanchez-Ramos, Kaunitz, and Delke (2005) had similar results in that there were no differences in rates of hospital admissions for threatened preterm labor or perinatal mortality. Some studies determined that there was no difference between the groups in infant morbidity or mortality rates or other maternal or neonatal outcome measures (O'Brien et al., 2007; Mackenzie et al., 2006; Cetingoz et al., 2011).

Strengths and Weaknesses

The strengths and weaknesses of the articles selected for the critical appraisal of the literature were evaluated using the Johns Hopkins Research Evidence Appraisal Tool (Dearholt & Dang, 2012). Only evidence graded 'high' or 'good' according to the Quality Rating Scheme for Evidence as described in Dearholt and Dang (2012) was included in the critical appraisal. There were 16 level I studies, one level II study, and three level III studies included in the critical appraisal. Weaknesses include occasionally less than ideal sample sizes and the need for further research in larger studies including diverse populations and high-risk populations. An additional weakness with this critical appraisal is that only two studies were identified that addressed the route of administration of progestational agents. Additional studies on route of administration would have strengthened the critical review.

Summary

The matrix consists of 20 critically appraised articles that examine the use of progestational agents in preventing preterm birth. Cost effectiveness, route, and neonatal outcomes were also evaluated. The John Hopkins Research Evidence Appraisal Tool was used to appraise the quality and evidence level of every article included in the matrix. All of the articles met established criteria for 'high' or 'good' quality literature. Limitations, strengths, and implications for practice were identified within the matrix. A major focus of the appraised literature is the use of progestational agents in preventing preterm birth. Although a few studies found no differences in the use of progestational agents in preventing preterm birth, the majority of studies showed that this method was indeed effective in this outcome. The use of progestational agents in high-risk women is secondary prevention that is cost effective and improves neonatal outcomes. There is need for further research focusing specifically on the appropriate conditions of use and route.

Chapter IV: Discussion

This chapter is based on a discussion of the critical appraisal of the literature. Current trends, gaps, future research topics, and application and integration of the theoretical framework will be discussed. This discussion is based on the original research question addressed: to what extent can the use of supplemental progesterone in pregnancy aid in preventing preterm labor, and more importantly preterm birth, in women who are at a high-risk for preterm birth? The John Hopkins Research Evidence Appraisal Tool was used to appraise 20 scholarly articles related to this topic. The findings were then evaluated and synthesized to identify trends and gaps in the literature and identify implications for changes as well as future research topics. Betty Neuman's Systems Model was applied to the concept of screening women for their risk of preterm labor and birth and implementing a preventative measure such as progesterone when appropriate.

Effectiveness of Placebo and Progestational Agents

The use of progestational agents has been recognized as an appropriate method in preventing preterm birth in women with a history of preterm birth or have an identified sonographic short cervix. Multiple studies included in the matrix are supportive of the use of progestational agents in preventing preterm birth and found a significant decrease in births at less than 37 weeks of gestation. In fact, the only two studies that lacked evidence to support the use of progestational agents were the studies by O'Brien el al. (2007) and Berghella et al. (2010). The repetitive findings supportive of progestational agents were reviewed in multiple Level I studies of good or high quality based on the John Hopkins Research Evidence Appraisal Tool. The consistency present in these results provides

evidence and support for the use of progestational agents in preventing preterm labor and birth in high-risk women.

It does need to be recognized that multiple gestation pregnancies and documented known fetal anomalies were not included in this critical appraisal. It also needs to be noted that many of the studies used different gestational ages in their outcome measures making conclusions more difficult to generalize in this critical appraisal.

The studies by O'Brien el al. (2007) and Berghella et al. (2010) that did not show significant evidence to support the use of progestational agents in preventing preterm birth were both Level I studies. Although the quality of evidence was rated as good through the Johns Hopkins Research Evidence Appraisal Tool, the lack of additional research supporting similar and consistent results weakens the argument of implementing a change in practice based on these two studies alone. Instead, the overwhelming amount of evidence supporting the use of progestational agents is apparent and practice changes would better be supported from these reproducible studies.

Route of Administration

Unfortunately, only two studies identified in this critical appraisal investigated the optimal route of progesterone administration making it difficult to identify trends. Velez Edwards et al. (2013) found that vaginal and intramuscular progesterone were both effective in reducing neonatal deaths in singleton pregnancies (Velez Edwards et al., 2013). And most importantly, this study suggests that the oral route is not the optimal route of administration (Velez Edwards et al., 2013). This leaves the potential optimal route choice of delivery between intramuscular and vaginal routes.

Maher, Abelaziz, Ellaithy, and Bazeed (2013) completed a randomized trial to analyze the use of vaginal and intramuscular progesterone. This study revealed that vaginal progesterone was associated with a lower percentage of deliveries before 28, 32, and 34 weeks of gestation than the intramuscular route of administration (Maher et al., 2013). This study also identified that there are more adverse effects reported in the intramuscular group in comparison to the vaginal group (Maher et al., 2013). This suggests that the vaginal route may be the preferred route.

Despite the results of these two studies, there are significant gaps in research given that there are only two studies investigating administration routes. Although the quality of evidence was rated as good through the Johns Hopkins Research Evidence Appraisal Tool, the lack of additional research supporting similar and consistent results weakens the argument of implementing a change in practice based on these two studies alone

Cost-Effectiveness

Only three of the studies reviewed identified cost-effectiveness as an outcome measure making it difficult to identify significant trends in the literature. Cahill et al. (2010) identified that universal sonographic screening for cervical length and treatment with vaginal progesterone was the most cost-effective strategy and was the best choice as opposed to cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone, risk-based treatment with 17-OHP-C without screening, and no screening or treatment (Cahill et al., 2010). Universal screening represented savings of $1,339, when compared with treatment with 17-OHP-C, and led to a reduction of 95,920 preterm births annually in the United States (Cahill et al., 2010).

Additionally, Pizzi, Seligman, Baxter, Jutkowitz, and Berghella (2014) analyzed a well-known trial known as the PREGNANT trial for the cost effectiveness of the use of vaginal progesterone 8% gel in reducing the likelihood of preterm birth among women with a short cervix. The cost-effectiveness model showed a significant savings of US $24,071 per preterm birth averted with vaginal progesterone gel (Pizzi et al., 2014). According to Petrini et al. (2005), if all eligible women receive progestational preventative therapy, 9,870 preterm births may have been prevented, which is an astonishing amount and in turn would have a significant reduction in costs. If the progestational agent were restricted to women with a history of a previous spontaneous very preterm birth, only 2,163 preterm births may have been prevented (Petrini et al., 2005).

Despite the results of these three studies, there are significant gaps in research given that there are only three studies investigating administration routes. The quality of evidence was rated as high and good through the Johns Hopkins Research Evidence Appraisal Tool. However, the studies by Cahill et al. (2010) and Petrini et al. (2005) were identified as Level III studies leaving Pizzi et al. (2014) as the only Level I study addressing this outcome. The lack of Level I studies and additional research supporting similar and consistent results weakens the argument of implementing a change in practice based on these three studies alone.

Effect on the Neonatal Outcomes

The use of progestational agents in high-risk women has been recognized as an appropriate method in preventing preterm birth as well as a method that has a positive effect on neonatal outcomes. The use of progestational agents to prevent preterm birth

was found to be statistically associated with decreased neonatal morbidity (Sotiriadis, Papatheodorou & Markydimas, 2012; Fonesca et al., 2007; Rai et al. 2009), perinatal death (Berghella et al., 2010; Rode et al., 2009), respiratory distress syndrome (Rode et al., 2009; Hassan et al., 2011), necrotizing enterocolitis (Rode et al., 2009; Meis et al., 2003), intraventricular hemorrhage (Dodd et al., 2005; Meis et al., 2003), need for supplemental oxygen (Meis et al., 2003), neonatal intensive care unit (NICU) admissions (Sotiriadis, Papatheodorou & Markydimas, 2012), NICU length of stay (Rai et al., 2009), higher birth weights (Sanchez- Ramos, Kaunitz, & Delke, 2005; Tita & Rouse, 2009; Dodd et al., 2005; Rai et al., 2009; Hassan et al., 2011), and higher APGAR scores (Rai et al., 2009).

Some studies however did not have statistically significant results between the progestational group and the placebo groups. However, these results generally did not focus on neonatal outcomes but rather focused on preterm labor, hospital admissions, antenatal corticosteroid therapy, and tocolytic therapy (Rode et al., 2009; Sanchez-Ramos, Kaunitz, & Delke, 2005). Other studies showed that there was no difference between the groups in infant morbidity or mortality rates or other maternal or neonatal outcome measures meaning they were not better or worse (O'Brien et al., 2007; Mackenzie et al., 2006; Cetingoz et al., 2011).

The evidence that was identified in regards to the use of progestational agents having a positive effect on neonatal outcomes is overwhelming. The quality of evidence was rated as high and good through the Johns Hopkins Research Evidence Appraisal Tool and despite some studies identifying no significant effects on the outcome measures, no studies identified that the use of progesterone caused harm on neonatal outcomes.

Future Research

There is a need for further research focusing specifically on multiple gestation pregnancies and pregnancies with known fetal anomalies and the use of progestational agents. Significant research has focused on singleton gestation pregnancies and pregnancies with known fetal anomalies excluded from these research studies. Additionally, further research needs to be conducted in regards to optimal administration route and timing of administration. The lack of studies investigating cost-effectiveness and route of administration necessitates further studies.

Application and Integration of Theoretical Framework

Betty Neuman's Systems Theory supports the nursing goal to keep the client well and stable by integrating appropriate interventions (Reed, 1993). There are three levels of prevention used to attain, maintain, and retain wellness - primary, secondary, and tertiary (Reed, 1993). Primary prevention is aimed at decreasing risk factors and increasing the FLD's ability to withstand environmental stressors, secondary prevention comes into effect when the NLD is disrupted and it is aimed at strengthening at protecting the basic structure and strengthening the LR, and finally tertiary prevention focuses on helping treating the client in order to promote a healthy return to a wellness state (Reed, 1993).

Until recently, preterm birth has largely focused on the tertiary level of prevention to delay delivery in women presenting with acute preterm labor (Norwitz, 2015). The rates of preterm labor, preterm birth, and complications in relation to these factors were contributing to suffering and it is necessary to intervene sooner with primary or secondary prevention strategies to improve these outcomes.

Women may be at risk for preterm birth if they have a personal history of previous spontaneous preterm birth or have a sonographically identified short cervix. By identifying women at risk for preterm birth early in their pregnancies we will be utilizing primary prevention and by determining and implementing the safest method of progesterone supplementation in high-risk women in an effort to avoid preterm birth we will be encompassing secondary prevention. By acting upon these assessments, the provider will have a better chance of being successful in keeping the client and the fetus in a state of wellness and health. Prevention as intervention is the basis of health promotion and we need to to encompass primary, secondary, and tertiary prevention in order to be successful.

Conclusion

The major findings of this critical review emphasize the benefits of the use of progestational agents in reducing preterm birth and neonatal outcomes. The literature supports the use of progestational agents in women at a high-risk for preterm labor or preterm birth. By reducing the rate of preterm birth, there is potential to reduce many other linked outcomes such as neonatal outcomes and costs related to premature delivery complications. Nurse leaders have the ability and responsibility to discuss a woman's risk factors and obstetrical history at antenatal visits to determine their risk for preterm delivery. By identifying those at risk early on, strategies such as prophylactic progesterone administration may be implemented in those identified as appropriate candidates. Betty Neuman's Systems theory provides a theoretical framework to improve nursing practice for those at risk for preterm birth by identifying the benefits of primary, secondary, and tertiary interventions. The nursing body of knowledge can be

strengthened through further research focused on route and timing of administration, cost-effectiveness, and investigating the potential effects on multiple gestation pregnancies and pregnancies with known fetal anomalies as these factors were not addressed fully in this literature review.

References

American College of Nurse Midwives (2012). *Core competencies for basic midwifery practice*. Retrieved from http://midwife.org/ACNM/files/ACNMLibraryData/UPLOADFILENAME/000000000050/Core%20Comptencies%20Dec%202012.pdf

Berghella, V., Figueroa, D., Szychowski, J. M., Owen, J., Hankins, G. D., Iams, J. D., & ... Guzman, E. R. (2010). 17-alpha-hydroxyprogesterone caproate for the prevention of preterm birth in women with prior preterm birth and a short cervical length. *American Journal of Obstetrics & Gynecology*, *202*(4), 351.e1-351.e6. doi:10.1016/j.ajog.2010.02.019

Cahill, A. G., Odibo, A. O., Caughey, A. B., Stamilio, D. M., Hassan, S. S., Macones, G. A., & Romero, R. (2010). Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: A decision and economic analysis. *American Journal of Obstetrics & Gynecology*, *202*(6), 548.e1-548.e8. doi:10.1016/j.ajog.2009.12.005

Centers for Disease Control and Prevention (2015). *Preterm birth.* Retrieved from http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm

Cetingoz, E., Cam, C., Sakallı, M., Karateke, A., Celik, C., & Sancak, A. (2011). Progesterone effects on preterm birth in high-risk pregnancies: A randomized placebo-controlled trial. *Archives of Gynecology & Obstetrics*, *283*(3), 423-429. doi:10.1007/s00404-009-1351-2

Conde-Agudelo, A., Romero, R., Nicolaides, K., Chaiworapongsa, T., O'Brien, J. M., Cetingoz, E., & ... Hassan, S. S. (2013). Vaginal progesterone vs cervical cerclage

for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: A systematic review and indirect comparison meta-analysis. *American Journal of Obstetrics & Gynecology, 208*(1), 42.e1. doi:10.1016/j.ajog.2012.10.877

Da Fonseca, E. B., Bittar, R. E., Carvalho, M. H., & Zugaib, M. (2003). 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. *American Journal of Obstetrics & Gynecology*, *188*(2), 419.

Dearholt, S.L., & Dang, D. (Eds.). (2012). *John Hopkins nursing evidence-based practice: Model and guidelines* (2nd ed.). Indianapolis, IN: Sigma Theta Tau International.

Dodd, J. M., Crowther, C. A., Cincotta, R., Flenady, V., & Robinson, J. S. (2005). Progesterone supplementation for preventing preterm birth: A systematic review and meta-analysis. *Acta Obstetricia Et Gynecologica Scandinavica*, *84*(6), 526-533. doi:10.1111/j.0001-6349.2005.00835.x

Fonseca, E. B., Celik, E., Parra, M., Singh, M., & Nicolaides, K. H. (2007). Progesterone and the risk of preterm birth among women with a short cervix. *New England Journal of Medicine*, *357*(5), 462-469. doi:10.1056/NEJMoa067815

Harris County District Hospital (n.d). *Betty Neuman model.* Retrieved from http://www.stti.iupui.edu/pp07/congress10/johnson_o.pdf

Hassan, S. S., Romero, R., Vidyadhari, D., Fusey, S., Baxter, J. K., Khandelwal, M., & ... Manchulenko, D. (2011). Vaginal progesterone reduces the rate of preterm birth

in women with a sonographic short cervix: A multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound in Obstetrics & Gynecology*, *38*(1), 18-31. doi:10.1002/uog.9017

Mackenzie, R., Walker, M., Armson, A., & Hannah, M. E. (2006). Progesterone for the prevention of preterm birth among women at increased risk: A systematic review and meta-analysis of randomized controlled trials. *American Journal of Obstetrics & Gynecology*, *194*(5), 1234-1242. doi:10.1016/j.ajog.2005.06.049

Maher, M. A., Abdelaziz, A., Ellaithy, M., & Bazeed, M. F. (2013). Prevention of preterm birth: A randomized trial of vaginal compared with intramuscular progesterone. *Acta Obstetricia Et Gynecologica Scandinavica*, *92*(2), 215-222. doi:10.1111/aogs.12017

Meis, P. J., Klebanoff, M., Thom, E., Dombrowski, M. P., Sibai, B., Moawad, A. H., & ... Thorp, J. M. (2003). Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *New England Journal of Medicine*, *348*(24), 2379-2385. doi:10.1056/NEJMoa035140

Neuman, B. (1989). *The Neuman systems model* (2nd ed.). Norwalk, CT: Appleton & Lange.

Norwitz, E.R. (2015). *Prevention of spontaneous preterm birth.* Retrieved from http://www.uptodate.com/contents/prevention-of-spontaneous-preterm-birth?source=search_result&search=progesterone+in+pregnancy&selectedTitle=6%7E150

Norwitz, E.R. (2015). *Progesterone supplementation to reduce the risk of spontaneous preterm birth.* Retrieved from http://www.uptodate.com/contents/progesterone-

supplementation-to-reduce-the-risk-of-spontaneous-preterm-birth?source=see_link

O'Brien, J. M., Adair, C. D., Lewis, D. F., Hall, D. R., Defranco, E. A., Fusey, S., & ... Newton, E. (2007). Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound in Obstetrics & Gynecology*, *30*(5), 687-696. doi:10.1002/uog.5158

Office of Disease Prevention and Health Promotion (2016). *About healthy people.* Retrieved from http://www.healthypeople.gov/2020/About-Healthy-People

Office of Disease Prevention and Health Promotion (2016). *Maternal, infant, and child health.* Retrieved from http://www.healthypeople.gov/2020/topics-objectives/topic/maternal-infant-and-child-health/objectives

Petiprin, A. (2015). *Systems theory.* Retrieved from http://www.nursing-theory.org/theories-and-models/neuman-systems-model.php

Petrini, J. R., Callaghan, W. M., Klebanoff, M., Green, N. S., Lackritz, E. M., Howse, J. L., & ... Damus, K. (2005). Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. *Obstetrics & Gynecology*, *105*(2), 267-272. doi:10.1097/01.AOG.0000150560.24297.4f

Pizzi, L., Seligman, N., Baxter, J., Jutkowitz, E., & Berghella, V. (2014). Cost and cost effectiveness of vaginal progesterone gel in reducing preterm birth: An economic analysis of the PREGNANT trial. *Pharmacoeconomics*, *32*(5), 467-478. doi:10.1007/s40273-014-0133-2

Rai, P., Rajaram, S., Goel, N., Ayalur Gopalakrishnan, R., Agarwal, R., & Mehta, S. (2009). Oral micronized progesterone for prevention of preterm birth. *International Journal of Gynecology & Obstetrics*, *104*(1), 40-43. doi:10.1016/j.ijgo.2008.08.029

Reed, K. S. (1993). *Betty Neuman: The Neuman systems model*. Newberry Park, CA: Sage Publications.

Rode, L., Langhoff-Roos, J., Andersson, C., Dinesen, J., Hammerum, M. S., Mohapeloa, H., & Tabor, A. (2009). Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies. *Acta Obstetricia Et Gynecologica Scandinavica*, *88*(11), 1180-1189. doi:10.3109/00016340903280982

Sanchez-Ramos, L., Kaunitz, A. M., & Delke, I. (2005). Progestational agents to prevent preterm birth: A meta-analysis of randomized-controlled trials. *Obstetrics & Gynecology*, *105*(2), 273-279. doi:10.1097/01.AOG.0000150559.59531.b2

Sotiriadis, A., Papatheodorou, S., & Makrydimas, G. (2012). Perinatal outcome in women treated with progesterone for the prevention of preterm birth: A meta-analysis. *Ultrasound in Obstetrics & Gynecology*, *40*(3), 257-266. doi:10.1002/uog.11178

The American Congress of Obstetricians and Gynecologists (2015). *Preterm (premature) labor and birth.* Retrieved from http://www.acog.org/Patients/FAQs/Preterm-Premature-Labor-and-Birth#what

Tita, A. N., & Rouse, D. J. (2009). Progesterone for preterm birth prevention: an evolving intervention. *American Journal of Obstetrics & Gynecology*, *200*(3), 219-224. doi:10.1016/j.ajog.2008.12.035

Velez Edwards, D., Likis, F., Andrews, J., Woodworth, A., Jerome, R., Fonnesbeck, C., & ... Hartmann, K. (2013). Progestogens for preterm birth prevention: A systematic review and meta-analysis by drug route. *Archives of Gynecology & Obstetrics*, *287*(6), 1059-1066. doi:10.1007/s00404-013-2789-9

Table 1

Critical Appraisal Matrix

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Berghella, V., Figueroa, D., Szychowski, J. M., Owen, J., Hankins, G. D., Iams, J. D., & ... Guzman, E. R. (2010). 17-alpha-hydroxyprogesterone caproate for the prevention of preterm birth in women with prior preterm birth and a short cervical length. *American Journal of Obstetrics & Gynecology*, *202*(4), 351.e1-351.e6. doi:10.1016/j.ajog.2010.02.019 Level I/Good	To estimate the effect of 17P for prevention of preterm birth in women with prior spontaneous preterm birth, cervical length <25 mm, with and without ultrasound-indicated cerclage.	15 US clinical centers from January 2003 to November 2007. Exclusion criteria was fetal anomaly, planned history-indicated cerclage, and clinically significant maternal-fetal complications. Inclusion criteria was singleton gestations, prior spontaneous preterm birth (17-33+6 weeks), and short cervical length < 25 mm measured between 16-22+6 weeks. 300 women were analyzed. Of these 300 women, 148 were randomized to cerclage and 152 were randomized to no cerclage.	The study conducted secondary analysis of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development was conducted sponsored randomized trial evaluating cerclage for women with singleton gestations, prior spontaneous preterm birth (17-33+6 weeks), and short cervical length < 25 mm measured between 16-22+6 weeks.	The primary outcome of this secondary analysis was preterm birth < 35 weeks. Secondary outcomes included birth < 7 days from randomization; preterm birth <24, <28, <32, and <37 weeks; and perinatal death. The primary outcome and other categorical variables were compared with x^2 tests and, where appropriate, the Fisher exact test. Continuous variables were analyzed using the t test and Wilcoxon rank sum test where appropriate. Differences in time to birth were assessed with Kaplan-Meier curves and the log rank test. Multivariable logistic regression and Cox proportional hazard models were considered possible cofounders for outcomes of preterm birth <35 weeks and time of birth, respectively. An alpha level of <0.05 was used to represent statistical significance	In 300 women, 17P had no effect on preterm birth <35 weeks in either cerclage or no-cerclage groups. Only preterm birth <24 weeks and perinatal death were significantly lower for those with 17P in the no-cerclage group.	17P had no additional benefit for prevention of preterm birth in women who had prior spontaneous preterm birth and got ultrasound-indicated cerclage for cervical length <25 mm. In women who did not get cerclage, 17P reduced pre-viable birth and perinatal mortality.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Cahill, A. G., Odibo, A. O., Caughey, A. B., Stamilio, D. M., Hassan, S. S., Macones, G. A., & Romero, R. (2010). Universal cervical length screening and treatment with vaginal progesterone to prevent preterm birth: A decision and economic analysis. *American Journal of Obstetrics & Gynecology*, *202*(6), 548.e1-548.e8. doi:10.1016/j.ajog.2009.12.005 Level III/High	To estimate which strategy is most cost-effective for the prevention of preterm birth and associated morbidity.	A MEDLINE and PubMed literature search was conducted using the key words 'preterm birth, premature birth, preterm labor, short cervix, and progesterone' and searched for pertinent references in identified bibliographies. The search was restricted to human subject data that was published in the English language in the last 14 years. Exclusions were any case reports or series, meta-analyses, or review articles. Studies without control groups were included only for prevalence estimates of rare events.	A decision analytic model was designed to compare 4 strategies: (1) the strategy of universal screening of cervical length with transvaginal ultrasound at the time of routine anatomic survey and treatment with daily vaginal progesterone for women with a short cervix, (2) cervical length screening for women at increased risk for preterm birth (i.e., previous spontaneous preterm birth) and treatment with vaginal progesterone for women with a cervical length $\leq$ 1 mm, (3) no cervical length and treatment with 17- OHP- C based on obstetric history, and (4) no screening or treatment. Decision analytic and cost-effectiveness analyses to estimate which of 4 strategies was superior based on quality-adjusted life-years, cost in US dollars, and number of preterm births prevented.	Probability and utility point estimates were calculated as the sample size-weighted means of estimates from the included studies; their ranges were defined by the extreme low and high values reported in the literature. For estimates derived from a single source, a range was defined by 95% CI that was calculated from binomial distribution. Cost estimates were derived from the literature and, when unavailable, from local sources based on Medicaid reimbursement rates. When local estimates were used, charges were multiplied by a cost-charge ratio of 0.6 as an approximation to third-party reimbursements. Base-case cost effectiveness analysis was performed that compared strategies 1-3 with each other and with strategy 4. A threshold of $100,000 was considered cost-effective. Sensitivity analyses, threshold analyses, and Monte Carlo simulation were used.	Universal sonographic screening for cervical length and treatment with vaginal progesterone was the most cost-effective strategy and was the dominant choice over 3 alternatives: cervical length screening for women at increased risk for preterm birth and treatment with vaginal progesterone; risk-based treatment with 17-OHP-C without screening; no screening or treatment. Universal screening represented savings of $1339 ($8323 vs $9664), when compared with treatment with 17-OHP-C, and led to a reduction of 95,920 preterm births annually in the United States.	Universal sonographic screening for short cervical length and treatment with vaginal progesterone appears to be cost-effective and yields the greatest reduction in preterm birth at <34 weeks' gestation.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Cetingoz, E., Cam, C., Sakallı, M., Karateke, A., Celik, C., & Sancak, A. (2011). Progesterone effects on preterm birth in high-risk pregnancies: A randomized placebo-controlled trial. *Archives of Gynecology & Obstetrics*, *283*(3), 423-429. doi:10.1007/s00404-009-1351-2 Level I/High	To evaluate whether the prophylactic administration of vaginal progesterone would reduce the preterm birth rate in high-risk population including singleton and twin pregnancies.	This study included a sample of women from the Department of Obstetrics and Gynecology Clinic of Zeynep Kamil Women and Children Diseases Education and Research Hospital in Isstanbul from December 2004 to February 2007. 150 high-risk pregnancies were analyzed. Risk groups included prior spontaneous preterm birth, twin pregnancy, and uterine malformation.	Randomized, double blind, placebo controlled study. Micronized progesterone or placebo (100 mg) was administered daily by vaginal suppository between 24 and 34 weeks of gestation.	The primary outcome measure was the ratio of preterm delivery with both the progesterone and placebo groups. The secondary outcome measures included the frequency of delivery <34 weeks and the frequency of preterm labor and neonatal outcomes. Analysis was performed according to intention-to-treat principle. The x^2 test or Fisher exact test were used for categoric variables. The two-tailed student t test was used for continuous variables. A p value of 0.05 was considered significant.	There was a statistically significant difference in the rate of preterm labor between placebo and progesterone groups. More women delivered before 37 weeks in the placebo group than in the progesterone group. Administering progesterone also reduced preterm birth before 34 weeks of gestation. There was no significant difference in neonatal death between placebo and progesterone groups.	Prophylactic vaginal progesterone reduced the rate of preterm labor and preterm delivery in high-risk pregnancies. Additional studies will need to study large population to confirm progesterone effects in multiple pregnancies and pregnancies with uterine malformation, and to evaluate neonatal effects of progesterone therapy in high-risk pregnancies.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/ Conclusion	Recommendations
Conde-Agudelo, A., Romero, R., Nicolaides, K., Chaiworapongsa, T., O'Brien, J. M., Cetingoz, E., & ... Hassan, S. S. (2013). Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: A systematic review and indirect comparison meta-analysis. *American Journal Of Obstetrics & Gynecology, 208*(1), 42.e1. doi:10.1016/j.ajog.2012.10.877 Level I/Good	To compare vaginal progesterone and cervical cerclage directly for the prevention of preterm birth in women with a sonographic short cervix (<25 mm) in the mid-trimester, singleton gestation, and a history of previous spontaneous preterm birth.	MEDLINE, EMBASE, CINAHL, and LILACS (all from inception to October 31, 2012), the Cochrane Central Register of Controlled Trials & ISI Web of Science (1960 to October 31, 2012), research registers of ongoing trials, and Google scholar were searched using a combination of keywords and text words related to progesterone, cervical cerclage, short cervix, and preterm birth. Congress proceedings of international society meetings of maternal-fetal reproductive medicine and international meetings on preterm birth, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also searched. Experts in the field were contacted to identify further studies. Quasi-randomized studies were excluded. Randomized controlled trials in which asymptomatic women with a sonographic short cervix (cervical length, <25 mm) in the mid-trimester, singleton gestation, and previous spontaneous preterm birth at <37 weeks of gestation were allocated randomly to receive vaginal progesterone vs placebo/no treatment or cerclage vs no cerclage for prevention of preterm birth were included. Trials were included if the primary aim of the study was to (1) prevent preterm birth in women with such characteristics; or (2) prevent preterm birth in women with other characteristics, but outcomes were available for patients with a pre-randomization cervical length <25 mm in the mid trimester, singleton gestation, and previous preterm birth. All published studies that were deemed suitable were retrieved and reviewed independently by 2 authors to determine inclusion. 9 randomized control trials were included (662 women). Sample sizes ranged from six to 301 women. Four studies were of vaginal progesterone versus placebo (158 women) and 5 evaluated cerclage vs no cerclage (504 women).	This study was a systematic review with adjusted indirect meta-analysis of randomized controlled trials. It was conducted based on a prospectively prepared protocol and is reported with the use of the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines for meta-analyses of randomized controlled trials and suggested guidelines for IPD and indirect meta-analyses. The Cochrane risk of bias tool was used to evaluate bias in the following areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Two reviewers independently assessed risk of bias. Intention-to-treat data from two previous individual patient data meta-analyses were extracted in order to calculate risk ratios. Both pair-wise direct comparisons, and indirect comparisons were performed. For the direct comparisons, a fixed-effect model was used if there was no evidence of substantial heterogeneity; otherwise a random effects model was used. The number-needed-to-treat was also calculated. Publication bias was assessed using funnel plots and the Egger test.	The primary outcome measures were preterm birth <32 weeks of gestation and composite perinatal morbidity and mortality (defined as the occurrence of any of the following events: respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal mortality). Secondary outcome measures included preterm birth at <37, <35, and <28 weeks of gestation, respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, neonatal sepsis, bronchopulmonary dysplasia, or perinatal mortality, a composite neonatal morbidity outcome, birthweight <1500 g and <2500g, and admission to the NICU.	Direct comparisons results displayed that both vaginal progesterone and cerclage were associated with significant reductions in the risk of pre-term birth at less than 32 weeks of gestation and composite perinatal morbidity and mortality compared to placebo/no cerclage. On the other hand, the indirect comparisons revealed that there were no significant differences between vaginal progesterone and cerclage for any outcome measures.	Both vaginal progesterone and cerclage significantly reduce the risk of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation and previous preterm birth. Indirect comparisons indicated equal efficacy. Selection of the optimal treatment needs to consider adverse events, cost, and patient/clinician preferences. Medical treatment with vaginal progesterone could decrease the risks associated with anesthesia and a surgical procedure; therefore, it is important to disclose the availability of a non-surgical therapeutic choice to patients with a history of preterm birth and a short cervix. The authors estimated that any future trial which directly compared progesterone with cerclage would need to recruit around 800 patients.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Da Fonseca, E. B., Bittar, R. E., Carvalho, M. H., & Zugaib, M. (2003). 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. *American Journal Of Obstetrics & Gynecology*, *188*(2), 419. Level I/Good	To evaluate the effect of prophylactic vaginal progesterone in decreasing preterm birth rate in a high-risk population.	The study was performed in the Obstetrics Clinic, at Hospital das Clinicas, University of Sao Paulo Medical School, a tertiary medical center, in Brazil. Women at high risk for preterm delivery were considered to be those in the presence of at least one previous spontaneous preterm birth, prophylactic cervical cerclage, and uterine malformation. Multiple gestation and fetal malformations were excluded. Among the women who sought high-risk prenatal care, 257 asymptomatic high-risk singleton pregnant women for preterm delivery were followed from February 2, 1996 to March 30, 2001. Fifteen patients were lost to follow-up or withdrew from the study. Therefore the data analyses 142 high-risk singleton pregnancies.	This study was a randomized, double-blind, placebo-controlled trial in which progesterone (100 mg) or placebo was administered daily by vaginal suppository and all patients underwent uterine contraction monitoring with an external tocodynamometer once a week for 60 minutes, between 24 and 34 weeks' gestation. A positive test was considered when there were four or more contractions per hour before the 30th week of gestation and from 30 weeks onward, 6 or more contractions per hour. Preterm labor was defined as two or more regular uterine contractions every 10 minutes, recorded by external tocodynamometer, associated with cervical changes, represented by a dilation of more than 2 cm, or the presence of progressive dilation or effacement of the cervix. A preterm delivery was defined as birth before 37 weeks of pregnancy.	Progesterone (n = 72) and placebo (n = 70) groups were compared for epidemiologic characteristics, uterine contraction frequency, and incidence of preterm birth. Data were compared by x^2 analysis and Fisher exact test. The two-tailed Student t test was used for continuous variables and the Wilcoxon rank sum test was used for interval variables. Kaplan-Meier survival analysis was used to determine the relationship between the administration of prophylactic vaginal progesterone and preterm birth. The long-rank x^2 test was used to compare the differences in the generated survival curves. A *P* value of .05 was considered significant.	Of 142 cases, there were 30 preterm births (preterm birth rate of 21.1%). Differences in uterine activity were found between the progesterone and placebo groups and in preterm birth between progesterone and placebo. More women were delivered before 34 weeks in the placebo group than in the progesterone group.	This study indicates that the prophylactic use of natural progesterone may be associated with the decrease of uterine contractions. However, the lower incidence of preterm delivery in the progesterone group cannot be explained by these findings because uterine activity was only assessed weekly for just one hour. This study strongly suggests that, by administering vagina natural progesterone in pregnant women with high risk for preterm delivery, it is possible to decrease the frequency of preterm birth. However, multi-center randomized clinical trials with other risk factors are required to confirm these results.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Dodd, J. M., Crowther, C. A., Cincotta, R., Flenady, V., & Robinson, J. S. (2005). Progesterone supplementation for preventing preterm birth: A systematic review and meta-analysis. *Acta Obstetricia Et Gynecologica Scandinavica*, *84*(6), 526-533. doi:10.1111/j.0001-6349.2005.00835.x Level II/Good	To assess the role of progesterone in preterm birth prevention by using the best available evidence form the current, randomized, controlled trial literature.	Types of studies included were published randomized, controlled trials in which progesterone (either intramuscular or vaginal administration) was compared with placebo or no treatment. Quasi-randomized studies were included. The types of participants in these studies were women with a singleton pregnancy in which progesterone was administered for the prevention of preterm birth. The types of outcomes measured were adverse outcomes for the infant/child and the woman as well as the costs of health care. Seven randomized controlled trials were identified that met this criteria.	A MEDLINE search (from 1966 to the present; date of last search January 2005) were performed-using the key words progesterone, pregnancy, preterm birth, preterm labor, and randomized controlled tria0 in order to identify randomized, controlled trials in which progesterone (either intramuscular or vaginal administration) was compared with placebo or no treatment. Data was extracted and meta-analyses were performed.	Meta-analyses were performed by using relative risks (RR) and 95% confidence intervals for binary outcomes, and weighted mean differences for continuous outcomes. Planned subgroup analyses were by means of dose and frequency of progesterone administration and mode of administration (intramuscular versus vaginal). Sensitivity analyses were performed in order to take account of any differences in use, only in women considered to be at 'high' risk for preterm birth, and study quality. The outcomes measured were preterm birth (<37 weeks), birthweight <2.5kg, perinatal death, stillbirth, neonatal death, respiratory distress syndrome, ventilatory support, intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus, sepsis, and retinopathy of prematurity.	Women who received progesterone were statistically significantly less likely to give birth before 37 weeks, to have an infant with birth weight of <2.5 kg, or to have an infant diagnosed with intraventricular hemorrhage.	For progesterone supplementation to be advocated for women at the risk of preterm birth, the prolongation of gestation demonstrated in this meta-analysis must translate into improved infant outcomes, including a reduction in mortality. There is currently insufficient information to allow recommendations regarding the optimal dose, route, and timing of administration of progesterone supplementation. Further large trials are required in order to provide reliable information on the maternal outcomes including side-effects associated with treatment, maternal views, preferences for care, and satisfaction with care.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Fonseca, E. B., Celik, E., Parra, M., Singh, M., & Nicolaides, K. H. (2007). Progesterone and the risk of preterm birth among women with a short cervix. *New England Journal Of Medicine*, *357*(5), 462-469. doi:10.1056/NEJMoa067815 Level I/High	To evaluate the effect of vaginal progesterone on the incidence of spontaneous early preterm delivery in asymptomatic women found at routine mid-trimester screening to have a short cervix.	The study was conducted from September 2003 to May 2006 in five maternity hospitals around London. All women with singleton or twin pregnancies who were undergoing routine ultrasonography at 20 to 25 weeks of gestation for examination of fetal anatomy or growth were given the option of transvaginal ultrasonographic measurement of cervical length as a predictor of spontaneous early preterm delivery. The exclusion criteria were major fetal abnormalities, painful regular uterine contractions, a history of ruptured membranes, or a cervical cerclage. Women with a cervical length of 15 mm or less were invited to take part in this study. 413 women qualified for this study but 250 women agreed to participate.	The study was a multi-center, randomized, double-blind, placebo-controlled trial. The 250 women who agreed to participate in the trial were randomly assigned to receive vaginal progesterone (200 mg each night) or placebo from 24 to 33+6 weeks of gestation.	The primary outcome was spontaneous delivery before 34 weeks. The secondary outcome measures were birth weight, fetal or neonatal death, major adverse outcomes before discharge form the hospital (intraventricular hemorrhage, respiratory distress syndrome, retinopathy of prematurity, or necrotizing enterocolitis), and need for neonatal special care (admission to the NICU, ventilation, phototherapy, treatment for proven or suspected sepsis, or blood transfusion). The analysis was performed according to the intention-to-treat principle. Baseline data for the progesterone and placebo groups were summarized by the median and interquartile range. Comparisons between groups were performed with the use of the Mann-Whitney U test. Univariate comparisons of dichotomous data were performed with the use of Fisher's exact test. Effect modification was assessed with the use of the Mantel-Haenszel test for homogeneity. Multivariable analysis was performed by logistic regression. The risk of spontaneous preterm birth from randomization until 34 weeks was assessed using Kaplan-Meier analysis. Hazard ratios were estimated with the use of the Cox proportional-hazards model, with a formal test of the proportional-hazards assumption. Logistic regression was used to assess the risk of adverse events in the offspring.	Spontaneous delivery before 34 weeks of gestation was less frequent in the progesterone group than in the placebo group. Progesterone was associated with a nonsignificant reduction in neonatal morbidity. There were no serious adverse events associated with the use of progesterone. In conclusion, in women with a short cervix, treatment with progesterone is a method to reduce the rate of spontaneous early preterm delivery.	The article states that the American College of Obstetrics and Gynecologists Committee on Obstetric Practice recommends that women who have had a previous preterm delivery should be considered for treatment with progesterone in a subsequent pregnancy but notes that the ideal formulation, optimal route of delivery, and long-term safety of progesterone remain unknown. Although in this trial progesterone proved effective in reducing spontaneous preterm birth in women with cervical lengths less than 15 mm, it should be noted that less than one third of the women who had spontaneous preterm delivery met this criterion. Future randomized trials should investigate the effectiveness of progesterone in other high-risk populations. The findings of this study provide support for a strategy of routine screening of pregnant women by ultrasonographic measurement of cervical length and the prophylactic administration of progesterone to those with a short cervix.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Hassan, S. S., Romero, R., Vidyadhari, D., Fusey, S., Baxter, J. K., Khandelwal, M., & ... Manchulenko, D. (2011). Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: A multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound In Obstetrics & Gynecology*, *38*(1), 18-31. doi:10.1002/uog.9017 Level I/High	To determine the efficacy and safety of using micronized vaginal progesterone gel to reduce the risk of preterm birth (before 33 weeks) and associated neonatal complications in asymptomatic women with a mid-trimester sonographic short cervix.	44 centers in 10 countries. Included 465 women with singleton pregnancies between 19+0 to 23+6 weeks of gestation that had transvaginal sonographic short cervical lengths (10-20mm) but were asymptomatic (no signs or symptoms of preterm labor). Of these 458 women, 16% had a history of a previous preterm birth between 20 and 35 weeks of gestation.	Multi-center, randomized, double-blind, placebo-controlled trial. Subjects were allocated randomly to receive vaginal progesterone gel or placebo beginning at 20 to 23+6 weeks. Randomization sequence was stratified by center and history of a previous preterm birth. Women self administered the drug once daily in the morning. The women were instructed to return to study center every 2 weeks. The study drug was continued until 36+6 weeks' gestational age, rupture of membranes or delivery, whichever occurred first.	The primary outcome of this study was preterm birth before 33 weeks of gestation. The key secondary outcomes were neonatal morbidity, including respiratory distress syndrome, bronchopulmonary dysplasia, Grade III or IV intraventricular hemorrhage, periventricular leukomalacia, proven sepsis, necrotizing enterocolitis, and perinatal mortality (fetal death or neonatal death). Other pre-specified secondary outcomes included preterm birth before 28, 35, and 37 weeks of gestation, neonatal length, weight and head circumference at birth and incidence of congenital abnormalities. And finally, the frequency of adverse events related to treatment was also assessed. The primary endpoint of the study, preterm birth before 33 weeks, was analyzed using the Cochran-Mantel-Haenszel (CMH) test. Analysis of the primary efficacy endpoint was also performed using multivariable logistic regression, in which the following variables were included: treatment group, poled study site, risk strata, gestational age at first dose, maternal age, cervical length, body mass index, and race. RR with 95% CI was used as the measure of effect. The CMH test was also used for the analysis of the ordinal composite scores in which a modified ranking procedure (modified ridits) was used to calculate the sum of the expected values for each of the ordinal categories for each of the treatment groups. The ranking procedure is equivalent to non-parametric van Elteren scores. The RR for the primary endpoint was calculated unadjusted, partially adjusted (for pooled study and risk strata), as well as fully adjusted using multivariable logistic regression.	Of 465 women randomized, seven were lost to follow-up, & 458 (vaginal progesterone gel, n = 235; placebo, n = 223) were included in the analysis. The results revealed that women allocated to receive vaginal gel progesterone without a history of preterm birth had a lower rate of preterm birth before 33 weeks than did those allocated to placebo. However, the reduction in the rate of preterm birth in women with a prior history of preterm birth between 20 and 35 weeks of gestation did not reach statistical significance. Vaginal progesterone was also associated with a significant reduction in the rate of preterm birth before 28 weeks & 35 weeks, respiratory distress syndrome, any neonatal morbidity or mortality event, & birth weight < 1500 g. There were no differences in the incidence of treatment-related adverse events between the two groups. The administration of vaginal progesterone gel to women with a sonographic short cervix in the mid-trimester is associated with a 45% reduction in the rate of preterm birth before 33 weeks of gestation with improved neonatal outcome.	To date, no intervention in an asymptomatic patient with a risk factor has demonstrated both a reduction in preterm birth and an improvement in infant outcome, without a safety signal. The results of this trial indicate that a combined approach, in which transvaginal sonographic cervical length is used to identify patients at risk for preterm delivery, followed by the administration of vaginal progesterone gel from the mid-trimester of pregnancy until term, reduces the rate of both preterm birth before 33 weeks of gestation and respiratory distress syndrome, the most common complication of preterm neonates. The main implication of this study for clinical practice is that universal screening of women with transvaginal sonography to measure cervical length in the mid-trimester to identify patients at risk can now be coupled with the use of vaginal progesterone gel to reduce the frequency of preterm birth and improve neonatal outcomes. Additional studies are necessary to determine if treatment of women with a short cervix in the early second trimester may further reduce the rate of preterm delivery.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Mackenzie, R., Walker, M., Armson, A., & Hannah, M. E. (2006). Progesterone for the prevention of preterm birth among women at increased risk: A systematic review and meta-analysis of randomized controlled trials. *American Journal Of Obstetrics & Gynecology*, *194*(5), 1234-1242. doi:10.1016/j.ajog.2005.06.049 Level I/Good	To determine whether progestational agents, initiated in the second trimester or pregnancy, reduce the risk of delivery less than 37 weeks, among women at increased risk of spontaneous preterm birth.	Three trials were eligible for inclusion.	A systemic review and meta-analysis was done. Medline, pre-Medline, EMBASE, and Cochrane Central Register of Controlled Trials were searched. RCTs with less than 20% lost follow-up were included.	The primary outcome was delivery less than 37 weeks' gestation. Secondary outcomes included delivery before 35, 34, and 32 weeks' gestation, birth weight less than 2500 g, birth weight less than 1500 g, spontaneous abortion or perinatal death, measures of serious neonatal morbidity, and congenital abnormalities. The relative risk and 95% CI for dichotomous variables and weighted mean difference and 95% CI for continuous variables, with the use of the DerSimonian and Laird random-effects model was done.	There was a significant reduction in risk delivery less than 37 weeks with progestational agents. There was no significant effect on perinatal mortality or serious neonatal morbidity.	Progestational agents, initiated in the second trimester of pregnancy, may reduce the risk of delivery less than 37 weeks' gestation, among women at increased risk of spontaneous preterm birth, but the effect on neonatal outcome is uncertain. Larger randomized controlled trials are required to determine whether this treatment reduces perinatal mortality or serious neonatal morbidity.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Maher, M. A., Abdelaziz, A., Ellaithy, M., & Bazeed, M. F. (2013). Prevention of preterm birth: A randomized trial of vaginal compared with intramuscular progesterone. *Acta Obstetricia Et Gynecologica Scandinavica*, *92*(2), 215-222. doi:10.1111/aogs.12017 Level I/Good	To aim of this study was to assess the efficacy and tolerability of vaginal compared with intramuscular progesterone in reducing the rate of recurrent preterm birth before 34 weeks gestation.	The study was conducted at Armed Forces Hospital Southern Region, Khamis Mushyat, Kingdom of Saudi Arabia. Eligibility criteria for this study included women of any age, any parity, with singleton pregnancies, a gestation between 14 and 18 weeks, and a previous history of one or more mid-trimester preterm births, or cerclage suture inserted in a previous pregnancy but not in the current pregnancy. Exclusion criteria included fetal anomaly or loss, advanced cervical dilation, membranes bulging into the vagina in asymptomatic women, history of ruptured membranes, short cervix (<25 mm measured between 14 and 18 weeks gestation), or significant funneling(>25%), women who planned to undergo cervical cerclage or who already had cerclage inserted at another hospital, major chronic medical disorder (such as chronic hypertension, chronic renal disease, or progestational diabetes mellitus, because these conditions would increase the risk of preterm birth and potentially confound the primary study outcome), multiple gestational pregnancies, and any contraindication for progesterone therapy (known active liver disease or active thromboembolism). Of the 547 women eligible for the study, 518 women consented to participate.	The study was conducted as a prospective, randomized, non-blinded and non-placebo controlled trial. The participants underwent simple randomization using a computer-generated random list. The women were randomized to receive either 90 mg of vaginal progesterone gel once daily (n= 262) or 250 mg of intramuscular progesterone weekly (n= 265). Treatment began between 14 and 18 weeks gestation and continued until 36 complete weeks of gestation, delivery, or the occurrence of premature rupture of membranes or preterm birth.	The primary outcome measure was delivery before 34 weeks of gestation. The secondary outcome measures were preterm birth between 34 to 37 weeks of gestation and neonatal outcomes including birthweight, neonatal death, and the need for admission to the NICU. Student's t-test was used for quantitative data.	When all deliveries before 34 weeks of gestation were compared between the groups, vaginal progesterone was associated with a lower percentage of deliveries than the intramuscular preparation. This association was also observed between 28 and 32 weeks of gestation. No statistically significant difference was observed between the groups regarding delivers at other weeks of gestation. Adverse effects were reported in 14.1% of patients in the intramuscular group and in 7.5% of patients in the vaginal group. The intramuscular group showed a significantly higher rate of neonatal intensive care unit admission than the vaginal progesterone group. More data from different populations are needed to support the results.	The use of vaginal progesterone over intramuscular progesterone administration shows a reduction in recurrent preterm births and fewer adverse effects. Given that prophylactic intervention to prevent preterm birth entails a long duration of progesterone administration, less invasive forms of administration are preferred. Further data regarding the optimal route, dose, or duration of progesterone is still lacking, and it remains unknown whether there is a dose-response relation between progesterone and its action to reduce preterm birth. More research regarding the mechanisms of progesterone and cerclage in preterm birth may help clinicians to understand how these two interventions can be used together.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Meis, P. J., Klebanoff, M., Thom, E., Dombrowski, M. P., Sibai, B., Moawad, A. H., & ... Thorp, J. M. (2003). Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *New England Journal Of Medicine*, *348*(24), 2379-2385. doi:10.1056/NEJMoa035140 Level I/High	To test the effectiveness of 17P as compared with placebo in the prevention of recurrent preterm delivery.	The sample for this study was collected throughout 19 clinical centers. Women presenting to these centers for prenatal care were screened for eligibility to participate in the trial; criteria for eligibility included a history of spontaneous preterm delivery in a previous pregnancy and a current pregnancy between 15 weeks and 20+3 gestation. Exclusion criteria included multifetal gestation, known fetal anomaly progesterone or heparin treatment during the current pregnancy, current or planned cervical cerclage, hypertension requiring medication, a seizure disorder, or a plan to deliver elsewhere. 463 women consented to participate in the study. There were 310 women in the progesterone group and 153 women in the placebo group.	This was a double-blind, placebo-controlled trial. The women were randomly assigned by a central data center in a 2:1 ratio, to receive either weekly injections of 250 mg of 17P or weekly injections of an inert oil placebo; injections were continued until delivery or to 36 weeks gestation.	The primary outcome was preterm delivery before 37 weeks of gestation. Analysis was performed according to the intention-to-treat principle. Continuous variables were compared with the use of the Wilcoxon rank-sum test, and categorical variables were compared with the use of the chi-square or Fisher's exact test. Prolongation of pregnancy was assessed by life-table methods, with the duration considered being that between the time of randomization and the time a woman gave birth, was lost to follow-up, or reached 40 weeks of gestation, which ever came first. Curves for event free survival were estimated to account for differing durations of gestation at entry, and were tested with the log-rank test.	Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation, delivery at less than 35 weeks gestation, and delivery at less than 32 weeks gestation. Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage and need for supplemental oxygen.	Weekly injections of 17P resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
O'Brien, J. M., Adair, C. D., Lewis, D. F., Hall, D. R., Defranco, E. A., Fusey, S., & ... Newton, E. (2007). Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound In Obstetrics & Gynecology*, *30*(5), 687-696. doi:10.1002/uog.5158 Level I/Good	To determine whether prophylactic administration of vaginal progesterone reduces the risk of preterm birth in women with a history of spontaneous preterm birth.	The study included 659 pregnant women with a history of spontaneous preterm birth between 18+0 and 22+6 weeks of gestation. The women were eligible for the trial if they were between 18 and 45 years of age with a n estimated gestational age between 16+0 and 22+6 weeks, and had a history of spontaneous singleton preterm birth between 20+0 and 35+0 weeks of gestation in the immediately preceding pregnancy, confirmed by review of medical records.	This study was a randomized, double-blind, placebo-controlled, multinational trial. The patients were assigned randomly to once-daily treatment with either progesterone vaginal gel or placebo until either delivery, 37 weeks' gestation or development of preterm rupture of membranes.	The primary outcome was preterm birth at ≤32 weeks of gestation and to assess the efficacy and safety of progesterone vaginal gel compared with placebo. The trial was analyzed using an intent-to-treat strategy. Baseline characteristics and outcome data were compared between treatment groups using chi-square or Fisher's exact test for categorical variables and using ANOVA for continuous variables. The duration of pregnancy in the placebo and intervention groups was evaluated using survival analysis (life-table analysis and the Kaplan-Meier method). A P-value of <0.05 was considered statistically significant.	Progesterone did not decrease the frequency of preterm birth at ≤32 weeks. There was no difference between the groups with respect to the mean gestational age at delivery, infant morbidity or mortality or other maternal or neonatal outcome measures.	Prophylactic treatment with vaginal progesterone did not reduce the frequency of recurrent preterm birth (≤32 weeks) in women with a history of spontaneous preterm birth. The effect of progesterone administration in patients at high risk for preterm delivery as determined by methods other than history alone (e.g. sonographic cervical length) requires further investigation.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Petrini, J. R., Callaghan, W. M., Klebanoff, M., Green, N. S., Lackritz, E. M., Howse, J. L., & ... Damus, K. (2005). Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. *Obstetrics & Gynecology*, *105*(2), 267-272. doi:10.1097/01.AOG.0000150560.24297.4f Level III/High	To understand the potential national effect of 17P preventive therapy on preterm birth rates	The study defines "17P eligible" as singleton births to multiparous women with onset of prenatal care within the first 4 months of pregnancy with a history of spontaneous birth. Preterm birth is defined as less than 37 completed weeks of gestation and very preterm as less than 32 completed weeks. Spontaneous birth is defined as a non-induced vaginal delivery. To estimate the number of pregnant women in the United States who would be eligible for 17P preventive therapy, the 2002 United States natality (birth certificate) file from the National Center of Health Statistics, Centers for Disease and Prevention. This database includes information on all live births in the nation. Studies have indicated, however, that reporting of a woman's history of a prior preterm birth on the birth certificate may not be complete and may underestimate the true occurrence of this event. To address this potential limitation, the data from longitudinal birth certificate files from New Jersey and Missouri were also analyzed for the rates of prior preterm birth and recurrence of spontaneous preterm birth. Based on the 2002 United States natality data, the number of births to multiparous women with single gestation was 2,313,718. From this number, the estimated number of women who did not meet the 16-20 weeks' prenatal care entry period was subtracted. The resultant 2,037,292 births represent those women who initiated care early enough to have been candidates for 17P therapy. The New Jersey and Missouri databases identified women who met the inclusion criteria in the same fashion. The averaged rates from the 2 states were 8.7% for prior preterm birth and 1.3% for prior very preterm birth.	Estimated the number of singleton preterm births delivered to women with a history of prior spontaneous preterm birth who accessed prenatal care within the first 4 months gestation by analyzing the sample.	Using 2002 national birth certificate data, augmented by vital statistics from 2 states, the estimated number of singleton births delivered to women eligible for 17P through both a history of spontaneous preterm birth and prenatal care onset within the first 4 months of pregnancy.	According to this study's calculations, if 17P 9,870 preterm births, might have been prevented if eligible women received 17P preventive therapy. If 17P use were restricted to women with a history of a previous spontaneous very preterm birth, 2,163 preterm births might have been prevented. Among the smaller cohort of 2,037,292 spontaneous singleton births to multiparous women with onset of prenatal care during the first 4 months of pregnancy, regardless of history of preterm birth, universal use of 17P would have reduced the preterm birth rate in this cohort from 9.4% to 8.5%, reflecting an estimated 11% reduction, or an absolute difference of 0.9%, $P < .001$.	The use of 17P could reduce preterm birth among eligible women, but would likely have a modest effect on the national preterm birth rate. Additional research is urgently needed to identify other populations who might benefit from 17P evaluate new methods for early detection of women at risk, and develop additional prevention strategies.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Pizzi, L., Seligman, N., Baxter, J., Jutkowitz, E., & Berghella, V. (2014). Cost and cost effectiveness of vaginal progesterone gel in reducing preterm birth: An economic analysis of the PREGNANT trial. *Pharmacoeconomics*, *32*(5), 467-478. doi:10.1007/s40273-014-0133-2 Level I/High	To calculate the costs and cost effectiveness of VP gel versus placebo using decision analytic models informed by PREGNANT patient-level data.	The PREGNANT trial enrolled 459 pregnant women with a cervical length of 10-22 mm and randomized them to either VP 8% gel or placebo.	An economic analysis of the PREGNANT study was done. The PREGNANT study was a randomized, multi-center, clinical trial that investigated the safety and effectiveness of VP gel to decrease the incidence of PTB among women with a short cervix, with or without a history of preterm birth. Used a cost model to estimate the total cost of treatment per mother and a cost-effectiveness model to estimate the cost per PTB averted with VP gel versus placebo. Cost consumptions were based on 2010 US healthcare services reimbursements. The cost model was validated against patient-level data. Sensitivity analyses were used to test the robustness of the cost-effectiveness model.	The primary measure was determining the total cost per mother treated with VP gel in PREGNANT. Secondary measures were cost effectiveness of VP gel in terms of cost per preterm birth averted.	The estimated cost per mother was $US23,079 for VP gel and $US36,436 for placebo. The cost-effectiveness model showed a savings of $US24,071 per preterm birth averted with VP gel. VP gel realized cost savings and cost effectiveness in 79% of simulations.	Based on the findings from PREGNANT, VP gel was associated with cost savings and cost effectiveness compared with placebo. Future trials designed to include cost metrics are needed to better understand the value of VP.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Rai, P., Rajaram, S., Goel, N., Ayalur Gopalakrishnan, R., Agarwal, R., & Mehta, S. (2009). Oral micronized progesterone for prevention of preterm birth. *International Journal of Gynecology & Obstetrics*, *104*(1), 40-43. doi:10.1016/j.ijgo.2008.08.029 Level I/Good	To evaluate oral micronized progesterone (OMP) to prevent preterm birth (PTB).	The sample of women was collected in the Department of Obstetrics and Gynecology at the University College of Medical Science and Guru Teg Bahadur Hospital, Delhi, between January 2005 and December 2006. Inclusion criteria for the study were asymptomatic women aged between 18 and 35 years who were between 18 and 24 weeks of pregnancy, with a history of at least 1 spontaneous preterm delivery (between 20 weeks and 36+6 weeks of gestation) with a singleton live pregnancy. Women with first trimester bleeding, premature rupture of membranes, multiple pregnancy, fetal anomalies, or active liver disease were excluded from the trial. A total of 150 women with at least one PTB met the inclusion criteria.	A randomized, double-blind, placebo-controlled trial in which the study participants received 100 mg of OMP or placebo twice a day from recruitment (18-24 weeks) until 36 weeks or delivery.	Statistical analysis was done using the x^2 test for quantitative variables Fisher exact test for quantitative variables (small sample size), independent sample t test to compare qualitative with quantitative variables, and Mann-Whitney test to compare qualitative with quantitative variables (for non-normalized data).	PTB occurred in 29 women in the OMP group compared with 44 in the control group. Mean gestational age at delivery was higher in the OMP group. Fewer PTB occurred between 28 and 31+6 weeks of gestation in the OMP group. Neonatal age at delivery, birth weight, NICU stay, and Apgar scores were more favorable in the OMP group, and fewer neonatal deaths occurred.	OMP reduced the risk of PTB between 28 and 31+6 weeks of gestation, NICU admissions, and neonatal morbidity and mortality in high risk patients. Although there were favorable results in the OMP group, the study was limited to a single hospital which is a huge limitation. Extended follow-up is needed to determine whether the drug exerts any long-term adverse effects. A large multi-center study with a higher number of patients and a longer follow-up is needed to confirm its efficacy and safety.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Rode, L., Langhoff-Roos, J., Andersson, C., Dinesen, J., Hammerum, M. S., Mohapeloa, H., & Tabor, A. (2009). Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies. *Acta Obstetricia Et Gynecologica Scandinavica*, *88*(11), 1180-1189. doi:10.3109/00016340903280982 Level I/High	To provide an update on the preventive effect of progesterone on preterm birth in singleton pregnancies.	A search in the PubMed, Embase, and Cochrane database was performed using the keywords: pregnancy, progesterone, preterm birth/preterm delivery, preterm labor, controlled trial, and randomized controlled trial. Inclusion criteria was intramuscular, vaginal, or oral progesterone starting treatment during the second trimester of pregnancy in singleton pregnancies. Two new randomized controlled trials of women with previous preterm birth were added to the four analyzed in the 2006 Cochrane review, and the meta-analysis was done on all six studies.	A meta-analysis was performed on randomized trials including singleton pregnancies with previous preterm birth.	The trials were compared and results were reported as RRs with the corresponding 95% CI using the fixed effect model. Risk differences were reported as the risk in the placebo groups minus the risk in the progesterone groups.	In women with a singleton pregnancy and previous preterm delivery, progesterone reduces the rates of preterm delivery before 32 weeks, perinatal death, as well as respiratory distress syndrome, and necrotizing enterocolitis in the newborn. The risk of admission for preterm labor, antenatal corticosteroid therapy, and tocolytic therapy is not decreased in women who are treated prophylactically with progesterone. Women with a short cervix or preterm labor may also benefit from progesterone, but further evidence is needed to support such recommendations.	Based on previously published meta-analyses of data on women with a singleton pregnancy and a history of preterm birth, progesterone seems to have a beneficial effect on pregnancy length and some secondary neonatal outcomes. Inclusion of the most recent studies in a meta-analysis even shows that infant survival is significantly increased in the progesterone group compared to the placebo group. The strengthening of evidence should be considered in obstetric practice. Follow up studies should focus on possible metabolic complications in the mother or the offspring as an observational study has shown that there is an association between progesterone treatment and the risk of developing gestational diabetes.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Sanchez-Ramos, L., Kaunitz, A. M., & Delke, I. (2005). Progestational agents to prevent preterm birth: A meta-analysis of randomized-controlled trials. *Obstetrics & Gynecology*, *105*(2), 273-279. doi:10.1097/01.AOG.0000150559.59531.b2 Level I/High	To perform an updated systematic review with meta-analysis to further elucidate the efficacy of progestational agents for the prevention of preterm births in patients at elevated risk.	Computerized databased, references in published studies, and textbook chapters in all languages were used to identify RCTs evaluating the use of progestational agents for the prevention of preterm births in women at elevated risk. RCT's that compared progestational agents with placebo for patients at risk for preterm birth and evaluated at least one of the following: delivery before 37 weeks of gestation, birth weight less than 2,500 g, threatened preterm labor, RDS, and perinatal mortality. Ten studies met inclusion criteria for this review. A total of 1,339 subjects were enrolled in these ten trials.	Meta-analysis of RCTs.	The primary outcomes assessed were preterm delivery and perinatal mortality. For each study with binary outcomes, and odds ratio with 95% CI was calculated for selected outcomes. Homogeneity was tested across the studies. Estimates of odds ratios for dichotomous outcomes were calculated using fixed effects (Mantel Haenszel) and random effects (DerSimonian and Laird) models. Number needed to treat was calculated for outcomes showing significant benefit from the use of progestational agents. To determine the combinability of individual studies, a formal test of heterogeneity by using the Mantel-Haenszel method was done.	Compared with women allocated to receive placebo, those who received progestational agents had lower rates of preterm delivery. Similar results were noted when comparing patients who were specifically treated with 17P. Additionally, subjects allocated to receive 17P had lower rates of birth weights less than 2,500 g. No differences in rates of hospital admissions for threatened preterm labor or perinatal mortality were noted for subjects receiving progestational agents in general or for those receiving only 17P specifically.	The use of progestational agents and 17P reduced the incidence of preterm birth and low birth weight outcomes. Substantially less data supports the efficacy of progestational agents in the prevention of preterm births among patients with multiple gestations compared with singletons. More research is needed in the area.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Sotiriadis, A., Papatheodorou, S., & Makrydimas, G. (2012). Perinatal outcome in women treated with progesterone for the prevention of preterm birth: A meta-analysis. *Ultrasound in Obstetrics & Gynecology*, *40*(3), 257-266. doi:10.1002/uog.11178 Level I/Good	To quantify the effect on perinatal outcome in women treated with progesterone for the prevention of preterm birth	A search was done for literature (last update December 2011) for clinical trials in which progesterone was given for prevention of preterm birth in pregnant women at risk compared to placebo. MEDLINE and SCOPUS searches used combinations of the terms 'progesterone' and 'preterm'. Inclusion criteria: RCT's; progesterone vs placebo for the prevention of preterm birth in women at risk; women with singleton pregnancy at risk for preterm birth owing to previous history or short cervix during the second trimester or multiple pregnancies. Studies were excluded if there was no adequate randomization or no placebo group, the administration of progesterone was done in women with symptoms of preterm labor, bleeding, or rupture of membranes, or if they did not provide data on neonatal outcomes. Sixteen studies were included in the meta-analysis.	This study was a meta-analysis of RCT's. Data extraction and study quality assessment were independently performed by two authors in case of disagreement a consensus was reached after discussion between the two authors or after evaluation by a third author. The CONSORT statement was used for addressing the reporting quality of the RCTs included in the meta-analysis. The risk of bias in the randomized trials was assessed with the 'Risk-of-bias' tool from the Cochrane Collaboration.	The primary outcome was the rate of neonatal mortality, meaning the number of deaths from birth to under the age of 28 days, and perinatal mortality. Secondary outcomes were rates of perinatal complications (respiratory distress syndrome, grade III/IV intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and retinopathy), admission to the NICU, and composite adverse outcomes (the presence of any perinatal morbidity or mortality). Comparisons were made using the risk ratio and the number needed to treat was calculated. The random effects models (DerSimonian and Laird) were used for data synthesis.	For singleton pregnancies, progesterone reduced the rates of neonatal death, NICU admission, and composite adverse outcome. No favorable effect was observed in multiple gestation pregnancies.	The next step after testing the effects of progesterone treatment on the rates of preterm birth and immediate perinatal complications is to examine its impact on the longer-term neurodevelopment of treated children.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Tita, A. N., & Rouse, D. J. (2009). Progesterone for preterm birth prevention: an evolving intervention. *American Journal of Obstetrics & Gynecology*, *200*(3), 219-224. doi:10.1016/j.ajog.2008.12.035 Level III/High	To present a concise review of more recent data (since 2000) on progesterone use specifically for preterm birth prevention focusing on pharmacologic options, specific clinical indication, and expected benefits.	Of a total of 17 reports identified, there were 8 clinical trials, 6 meta-analyses, and 3 reports of national recommendations or guidelines.	A search was conducted of the entire PubMed database (January 2000-October 2008) using the key words "progesterone" and "preterm". A total of 240 abstracts were reviewed to identify all relevant clinical trials or meta-analyses of clinical trials evaluating the effect of antenatal maternal use of progesterone on the risk of preterm birth. A bibliographic review was then conducted of the selected reports.	After the sample was selected, relevant pharmacologic data on progesterone formulation (type, dose, route, side effects) and pregnancy outcome by risk group under study was abstracted. An analytic approach was applied to the synthesis of the data from these reports (i.e., analyzed observed similarities and/or differences without conducting additional meta-analyses). RR and 95% CI for pertinent outcomes were obtained either from the reports or, when not available, calculated form the reported data.	The reviewed data strongly suggests that prophylactic use of progesterone leads to significant reductions in the measures of preterm birth and low birth weight.	Additional research is needed to clarify if progesterone may benefit neonatal morbidity and mortality. Additional research is also needed in the areas of identifying risk groups, and superior route of administration and dose.

Citation and Level/Quality	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations
Velez Edwards, D., Likis, F., Andrews, J., Woodworth, A., Jerome, R., Fonnesbeck, C., & ... Hartmann, K. (2013). Progestogens for preterm birth prevention: A systematic review and meta-analysis by drug route. *Archives of Gynecology & Obstetrics*, *287*(6), 1059-1066. doi:10.1007/s00404-013-2789-9 Level I/Good	To systematically review the effectiveness of intramuscular (IM), vaginal, or oral progestogens for preterm birth and neonatal death prevention.	The databases MEDLINE and EMBASE for English language articles published from January 1966 to January 2013 were searched. Controlled vocabulary terms served as the foundation of the search, complimented by additional keyword phrases to represent the myriad ways in which progestogens and preterm labor are referred to in the clinical literature. The references of the included articles were also hand-searched to identify studies. Randomized controlled trials with 20 or more women were included in order to have adequate power for statistical analysis. All formulations and drug delivery routes were included. Analyses were limited to only major indications for progestogen treatment that include prior preterm births, preterm labor, short cervix, and multiple gestations. 27 randomized trials were identified with data for Bayesian meta-analysis.	A Bayesian meta-analysis was conducted to provide aggregate estimates of the effectiveness of progestogen treatment for preventing preterm birth and reducing neonatal death.	The primary outcomes extracted from articles were preterm birth [less than 33 (singleton with short cervix), 34 (multiples and singleton with short cervix), 35 (multiples), and 37 (singleton) weeks' gestation] and neonatal death.	Across all studies, only vaginal and oral routes were effective at reducing preterm births. However, when analyses were limited to only single births, all routes were effective in reducing preterm birth. Only IM progestogen was effective at reducing neonatal deaths. Vaginal progestogen was effective in reducing neonatal deaths when limited to singleton births.	All progestogen routes reduce preterm births but not neonatal deaths. The overall strength of the evidence was insufficient or low supporting the need for future studies that directly compare progestogen delivery routes.