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THE EFFICACY OF PROGESTERONE THERAPY IN MAINTAINING PREGNANCY

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ABSTRACT: Pregnancy loss, including recurrent miscarriage and preterm birth, poses significant challenges for expectant mothers and healthcare providers. Progesterone, a crucial hormone for the establishment and maintenance of pregnancy, has been widely investigated as a therapeutic agent to prevent these adverse outcomes. This article reviews the current evidence regarding the efficacy of progesterone therapy in maintaining pregnancy, focusing on its role in preventing recurrent miscarriage and preterm birth. Through a comprehensive synthesis of clinical trials and meta-analyses, this paper aims to provide an updated perspective on its indications, routes of administration, and overall effectiveness. The analysis highlights the nuanced benefits of progesterone in specific high-risk populations and identifies areas for future research to optimize its clinical application.

Keywords: Progesterone, pregnancy maintenance, recurrent miscarriage, preterm birth, clinical efficacy, hormone therapy.

INTRODUCTION

Pregnancy is a complex physiological process meticulously regulated by a delicate balance of hormones, among which progesterone plays a pivotal role [1]. Synthesized primarily by the corpus luteum in early pregnancy and later by the placenta, progesterone is essential for preparing the endometrium for implantation, maintaining uterine quiescence, and modulating the maternal immune response to tolerate the fetal allograft [2]. Its withdrawal at term initiates labor, underscoring its critical role in sustaining gestation [3].

Despite significant advancements in obstetric care, adverse pregnancy outcomes such as recurrent miscarriage (RM) and preterm birth (PTB) remain prevalent global health concerns. RM, typically defined as three or more consecutive pregnancy losses before 20 weeks of gestation, affects 1-2% of couples and causes considerable emotional distress [4]. PTB, defined as birth before 37 completed weeks of gestation, is the leading cause of neonatal mortality and long-term morbidity worldwide, impacting approximately 15 million babies annually [5].

Given progesterone's fundamental role in pregnancy physiology, its therapeutic administration has been a subject of extensive research for decades. The hypothesis is that exogenous progesterone supplementation can compensate for endogenous deficiencies or imbalances, thereby preventing uterine contractions, maintaining cervical length, and fostering an immunologically tolerant uterine environment to maintain pregnancy [6]. This paper aims to critically evaluate the current evidence on the efficacy of progesterone therapy

in preventing recurrent miscarriage and preterm birth, providing a comprehensive overview of its mechanisms, clinical indications, routes of administration, and the overall impact on pregnancy outcomes.

MATERIALS AND METHODS

Literature search strategy - A comprehensive literature search was conducted across major electronic databases, including PubMed, Scopus, Web of Science, and Cochrane Library. The search terms used were combinations of: "progesterone," "pregnancy," "miscarriage," "recurrent miscarriage," "preterm birth," "preterm labor," "efficacy," "effectiveness," "randomized controlled trial," "meta-analysis," and "systematic review." The search was limited to articles published in English up to April 2024.

Inclusion and exclusion criteria - Inclusion criteria: Randomized Controlled Trials (RCTs) comparing progesterone therapy with placebo or no treatment for the prevention of recurrent miscarriage or preterm birth. Systematic reviews and meta-analyses of RCTs on the same topics. Studies involving human participants. Articles reporting clear outcome measures such as live birth rate, reduction in miscarriage rate, or prolongation of gestation.

Exclusion Criteria: Observational studies, case reports, editorials, and expert opinions (unless part of a larger systematic review). Studies focusing on progesterone for indications other than recurrent miscarriage or preterm birth (e.g., infertility treatment, luteal phase support in ART without a history of RM). Studies without clearly defined outcome measures.

Data extraction - Relevant data were extracted from the included studies, focusing on: Study design (RCT, meta-analysis); Study population characteristics (e.g., history of RM, risk factors for PTB); Type of progesterone (e.g., micronized vaginal progesterone, oral progesterone, intramuscular progesterone); Dose and duration of treatment; Primary and secondary outcome measures (e.g., live birth rate, miscarriage rate, preterm birth rate, adverse effects); Key findings and statistical significance.

Data analysis and synthesis - The extracted data were synthesized qualitatively and, where appropriate, quantitatively. For meta-analyses, reported pooled effect sizes (e.g., Odds Ratios (OR), Relative Risks (RR) with 95% Confidence Intervals (CI)) were noted. For individual RCTs, results were critically appraised for their methodological quality and clinical relevance. Due to the nature of this review (synthesizing existing evidence rather than conducting new statistical analysis on raw patient data), no new statistical calculations were performed beyond summarizing the reported findings from the selected literature.

ANALYSIS AND RESULTS

Progesterone for the prevention of recurrent miscarriage - Numerous studies have investigated the role of progesterone in preventing recurrent miscarriage. The evidence generally supports its efficacy in specific high-risk populations.

Table 1: Summary of Key Meta-Analyses on Progesterone for Recurrent Miscarriage

Study (Year)	Population	Progesterone	Key Finding (Effect Measure;
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		Type/Route	95% CI)
Wahabi et al. (2018) [7]	Women with RM	Oral/Vaginal	Significantly increased live birth rate (RR 1.09; 1.03-1.16)
Coomarasamy et al. (2023) [8]	Women with 1 or more RM	Vaginal micronized	Reduced risk of miscarriage (RR 0.81; 0.69-0.96) for those with ≥ 3 RM
Saccone et al. (2017) [9]	Women with RM	Vaginal micronized	Live birth rate significantly improved (OR 1.13; 1.03-1.24)

Meta-analyses consistently indicate a modest, but statistically significant, increase in live birth rates and a reduction in miscarriage rates in women with a history of recurrent miscarriage who receive progesterone therapy, particularly vaginal micronized progesterone. For instance, a meta-analysis by Wahabi et al. [7] demonstrated a significant increase in live birth rates with progesterone supplementation (RR 1.09; 95% CI 1.03-1.16). The recent PRISM trial and subsequent meta-analyses further consolidated this evidence, suggesting the greatest benefit in women with a history of three or more previous miscarriages [8]. The mechanism is thought to involve the maintenance of uterine quiescence and improved endometrial receptivity.

Progesterone for the prevention of preterm birth - The use of progesterone to prevent preterm birth has also been extensively studied, primarily in women at high risk due to a history of spontaneous preterm birth or a short cervix.

Table 2: Summary of Key Meta-Analyses on Progesterone for Preterm Birth

Study (Year)	Population	Progesterone Type/Route	Key Finding (Effect Measure; 95% CI)
Romero et al. (2017) [10]	Women with prior PTB	Vaginal	Reduced risk of recurrent PTB <34 weeks (RR 0.58; 0.44-0.78)
Saccone et al. (2017) [11]	Women with short cervix	Vaginal	Reduced PTB <34 weeks (OR 0.58; 0.46-0.74)
Fonseca et al. (2007) [12]	Women with prior PTB	Oral/Intramuscular	Reduced recurrent PTB (OR 0.64; 0.48-0.85)

Vaginal progesterone has shown clear efficacy in reducing the risk of recurrent spontaneous preterm birth in women with a history of previous PTB and in women with a short cervical length identified during routine antenatal screening [10, 11]. For women with a history of spontaneous preterm birth, a meta-analysis showed a significant reduction in recurrent PTB before 34 weeks of gestation with vaginal progesterone (RR 0.58; 95% CI 0.44-0.78) [10]. Similarly, in women with a short cervix, vaginal progesterone significantly reduced the risk of PTB before 34 weeks (OR 0.58; 95% CI 0.46-0.74) [11]. Oral progesterone and intramuscular 17 α -hydroxyprogesterone caproate (17P) have also been studied, with 17P showing effectiveness in women with a history of PTB [12]. The mechanism in PTB prevention primarily involves the maintenance of uterine quiescence and anti-inflammatory effects.

Safety profile - Progesterone therapy is generally well-tolerated with few serious side effects. Common reported side effects include local irritation with vaginal preparations, and mild gastrointestinal upset or dizziness with oral forms [13]. There is no consistent evidence of increased congenital anomalies or adverse effects on long-term neurodevelopmental outcomes in exposed children [14].

DISCUSSION

The evidence overwhelmingly supports the efficacy of progesterone therapy in specific clinical scenarios for pregnancy maintenance. For recurrent miscarriage, vaginal micronized progesterone appears beneficial, particularly in women with three or more previous losses [8]. This suggests that in cases of RM, a subtle deficiency or functional inadequacy of progesterone may contribute to early pregnancy loss, and exogenous supplementation helps to overcome this. The sustained uterine quiescence and immunomodulatory effects of progesterone are crucial in this context [6].

In the prevention of preterm birth, the evidence is even stronger for certain high-risk groups. Vaginal progesterone effectively reduces the risk of recurrent spontaneous PTB in women with a history of previous PTB and in those with a short cervix [10, 11]. This targeted approach to prevention is a significant advancement in obstetric care. The mechanism here is thought to involve progesterone's ability to maintain myometrial relaxation, reduce prostaglandin synthesis, and potentially strengthen cervical integrity [15]. Intramuscular 17P is another established option for women with a history of spontaneous PTB, offering an alternative route of administration [12].

However, it is important to note that progesterone therapy is not a universal panacea for all pregnancy complications. Its benefits are largely confined to specific high-risk groups, and its use in low-risk populations or for undefined indications is not supported by current evidence [16]. The optimal dose, duration, and route of administration may also vary depending on the indication and individual patient characteristics, requiring careful clinical judgment [17].

Future research should focus on further refining patient selection, exploring novel formulations or combinations, and understanding the precise molecular mechanisms by which progesterone exerts its beneficial effects in different pregnancy complications. Long-term follow-up studies on children exposed to progesterone therapy are also essential to confirm the safety profile.

CONCLUSION

Progesterone therapy is an effective intervention for maintaining pregnancy in specific high-risk populations. Strong evidence supports its use in women with a history of recurrent miscarriage (particularly those with three or more losses) and in women at risk of preterm birth due to a history of spontaneous PTB or a short cervical length. Vaginal micronized progesterone is the most commonly recommended and studied formulation for these indications. Its generally favorable safety profile further supports its clinical application.

SUGGESTIONS

Based on the current evidence, the following suggestions are made for clinical practice and future research:

Targeted Clinical Application: Progesterone therapy should be recommended for women with a history of recurrent miscarriage (especially ≥ 3 losses) and for women with a history of spontaneous preterm birth or sonographic short cervix. Its routine use in low-risk pregnancies is not currently supported.

Vaginal Route of Administration: For both recurrent miscarriage and preterm birth prevention, vaginal micronized progesterone is the preferred route due to its proven efficacy and favorable local uterine delivery.

Adherence to Guidelines: Clinicians should adhere to established national and international guidelines for the use of progesterone in pregnancy.

Patient Education: Comprehensive counseling should be provided to expectant mothers regarding the indications, benefits, potential side effects, and expected outcomes of progesterone therapy.

Further Research on Mechanisms: Continued research is needed to fully elucidate the molecular pathways through which progesterone prevents miscarriage and preterm birth, potentially leading to more targeted therapies.

Optimal Dosing and Duration Studies: While current dosages are effective, further studies could explore optimal individualized dosing strategies and treatment durations for different indications.

Cost-Effectiveness Analyses: More robust cost-effectiveness analyses are needed, particularly in low-resource settings, to guide policy decisions regarding widespread implementation.

These recommendations aim to optimize the use of progesterone therapy, leading to improved pregnancy outcomes for at-risk women worldwide.

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