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REVIEW ARTICLE

A review of the effect of progesterone use on early pregnancy bleeding, threatened abortion and recurrent pregnancy loss

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Abstract

Threatened abortion and miscarriage are prevalent complications in early pregnancy, affecting approximately 5-22% of all pregnancies [1]. These conditions can result in significant psychological and physiological distress for pregnant individuals, adversely impacting their mental and social well-being. The etiopathogenesis of bleeding in early pregnancy and threatened abortion remains incompletely understood, as it may arise from various underlying mechanisms.

Threatened abortion is defined as a clinical condition characterized by vaginal bleeding, the presence of fetal cardiac activity, and a closed cervix. It represents the most common non-traumatic cause of vaginal bleeding during the first trimester. The bleeding is hypothesized to result from disruptions in the decidual vasculature at the maternal-fetal interface. While this disruption is not always detectable with ultrasonography, it may occasionally present as a subchorionic hematoma. Notably, when subchorionic bleeding exceeds 25% of the gestational sac volume, the risk of pregnancy loss significantly increases [2].

The management of miscarriage, threatened abortion, and recurrent pregnancy loss remains challenging due to the multifactorial and often unclear etiologies. Progesterone and its derivatives are frequently employed in therapeutic protocols; however, the optimal type and mode of administration remain subjects of ongoing investigation. Progestogens exhibit variability in their pharmacological potency, mechanisms of action, and routes of administration. Both natural and synthetic progestogens are utilized in clinical practice.

This review aims to critically evaluate the efficacy, administration methods, duration, and clinical outcomes associated with progestogen use in the management of early pregnancy bleeding, threatened abortion, and recurrent pregnancy loss.

Keywords: Early pregnancy bleeding; threatened abortion; miscarriage; progesterone

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Progestins

Progesterone is a pivotal steroid hormone with essential roles in human physiology, particularly in the maintenance of pregnancy. It also serves as a critical metabolic precursor in the biosynthesis of other endogenous steroids, including corticosteroids. Progesterone, a naturally occurring hormone, was first introduced as a pharmaceutical agent in 1934 [3]. In clinical practice, it has been utilized for contraception, hormone replacement therapy, prevention of preterm birth, and the management of miscarriage.

During pregnancy, progesterone is indispensable for maintaining gestational integrity. In the first eight weeks of gestation, progesterone is exclusively synthesized by the corpus luteum. Following placentation, between the 8th and 12th weeks, progesterone production is shared equally between the corpus luteum and the placenta. After the 12th week, the placenta becomes the predominant source of progesterone synthesis.

Progestogens encompass both endogenous progesterone and synthetic compounds with progesterone-like activity. These agents are classified into two categories: natural progesterone, synthesized endogenously, and synthetic progesterone analogs. Progestogens exert their effects by binding to progesterone receptors, thereby modulating various physiological processes. Progesterone, the most critical progestogen for pregnancy maintenance, is essential for immunomodulation, inhibition of myometrial contractility, and enhancement of endometrial receptivity.

Insufficient secretion of human chorionic gonadotropin (hCG) during the implantation phase can lead to corpus luteum insufficiency, reduced progesterone levels, and subsequent pregnancy loss. Studies have demonstrated that surgical removal of the corpus luteum prior to placental development invariably results in miscarriage [3].

Adequate progesterone levels during the luteal phase are critical for endometrial maturation and successful implantation. Luteal phase defects, characterized by insufficient progesterone secretion, are associated with early pregnancy loss [4]. A 2015 meta-analysis demonstrated that progesterone supplementation during the luteal phase significantly improves pregnancy outcomes, including live birth rates [5].

Serum progesterone levels have been investigated as a prognostic marker in pregnancies complicated by threatened abortion. Women with serum progesterone levels below 90.62 nmol/L were found to have a significantly higher risk of miscarriage [6]. Furthermore, low progesterone levels during the first trimester have been strongly associated with an increased likelihood of pregnancy loss [7]. Consequently, progesterone supplementation has been extensively studied for its potential to prevent recurrent pregnancy loss and early pregnancy bleeding [8].

Progesterone can be administered via oral, intramuscular, or vaginal routes. Oral administration is subject to first-pass metabolism in the liver, which may reduce its bioavailability. In contrast, intramuscular and vaginal administration bypass hepatic metabolism, allowing higher concentrations to reach the endometrial tissue. Vaginal administration is often preferred due to its localized effect and favorable pharmacokinetic profile [9].

Progestogens are broadly categorized into natural and synthetic forms. Micronized progesterone, a natural form, is associated with side effects such as androgenic activity, agitation, fatigue, and fluid retention [10]. Didrogesterone, a synthetic progestogen, is administered orally and is frequently compared with micronized progesterone in terms of efficacy for managing recurrent pregnancy loss and threatened abortion.

Miscarriage

Miscarriage is defined as the spontaneous loss of pregnancy before 22 weeks of gestation, often accompanied by vaginal bleeding and pelvic pain. Threatened abortion refers to vaginal bleeding and pelvic pain in the presence of a viable fetus and a closed cervical canal [11].

A study reported a miscarriage rate of 19.7%, excluding cases of unwanted pregnancy loss [12]. Risk factors for miscarriage include advanced maternal age, immunological abnormalities (e.g., antiphospholipid syndrome), hormonal imbalances, and environmental exposures. Maternal diabetes and polycystic ovary syndrome are also significant risk factors. One study identified 27 years as the maternal age associated with the lowest miscarriage risk, with the risk increasing fourfold after three consecutive miscarriages [13]. Recurrent miscarriages are often linked to parental chromosomal abnormalities and genetic factors [14].

The majority of miscarriages occur within the first 12 weeks of gestation, with the risk declining significantly after 14 weeks [15]. In cases of early pregnancy bleeding, advancing gestational age is generally associated with a more favorable prognosis. Women with a history of bleeding during their first pregnancy are at an increased risk of experiencing bleeding in subsequent pregnancies [16].

Recurrent miscarriage, defined as three or more consecutive pregnancy losses, has been the focus of numerous studies investigating the role of progesterone supplementation in improving pregnancy outcomes [17].

Progesterone use in miscarriages

Early pregnancy management involves biochemical confirmation of pregnancy and ultrasonographic monitoring of fetal cardiac activity. In cases of vaginal bleeding, the type of miscarriage should be determined based on cervical status and fetal viability. Pregnancies with a closed cervical canal and positive fetal cardiac activity are classified as threatened abortion.

Miscarriage has profound psychological and physical consequences for affected individuals. Severe bleeding in early pregnancy may also pose significant maternal morbidity and mortality risks. Studies have demonstrated that miscarriage is associated with increased rates of depression, anger, and sleep disturbances [18].

Numerous clinical trials and meta-analyses have evaluated the efficacy of various progesterone formulations in reducing miscarriage rates. A 2017 meta-analysis compared vaginal micronized progesterone and oral didrogesterone with conservative management or placebo in patients with threatened abortion. Both treatments were associated with reduced miscarriage rates, with oral didrogesterone demonstrating a statistically significant advantage [19].

Further studies, including the PROMISE and PRISM trials, have highlighted the potential of progesterone to improve live birth rates, particularly in women with a history of recurrent miscarriage or early pregnancy bleeding [20].

In a meta-analysis conducted in 2021, the use of oral dydrogesterone, placebo, and vaginal micronized progesterone was compared in women with threatened abortion. The study demonstrated that oral dydrogesterone significantly reduced miscarriage rates compared to the other groups [21].

A study conducted in 2022 showed that the use of 200 mg micronized progesterone twice daily for two weeks had similar efficacy in preventing miscarriage as 10 mg dydrogesterone administered twice daily. However, the same study reported that patients using oral micronized progesterone experienced more side effects, such as drowsiness and dizziness [22].

In another study conducted on pregnant women with threatened abortion during the first 12 weeks, the use of 10 mg dydrogesterone twice daily was compared with 200 mg oral micronized progesterone twice daily. It was found that dydrogesterone was more effective in reducing vaginal bleeding and alleviating lower abdominal pain compared to micronized progesterone [23].

Two large controlled studies on the use of progesterone in early pregnancy demonstrated that 400 mcg of micronized progesterone could reduce early pregnancy loss and increase live birth rates [20]. The effects of progesterone on miscarriage prevention were systematically analyzed, and it was concluded that progesterone is particularly beneficial for women with threatened abortion [17].

Another meta-analysis found that the use of progesterone in women with recurrent pregnancy loss and threatened abortion may have little to no benefit on live birth rate [17]. However, among progestogens, the use of vaginal micronized progesterone was shown to be more effective in increasing live birth rates [17]. The same meta-analysis indicated that there was insufficient data to evaluate the efficacy of 17-α-hydroxyprogesterone caproate (17-OHPC) or oral micronized progesterone in recurrent pregnancy loss [17].

The efficacy of 17-OHPC in preventing recurrent preterm births was evaluated in the PROLONG study and other analyses involving a total of 2,221 patients. The findings indicated that 17-OHPC did not significantly reduce preterm birth rates. The study emphasized that there is insufficient evidence to support the use of 17-OHPC for this purpose [24].

Additionally, the use of 17-OHPC in miscarriage prevention was found to be ineffective, as it did not significantly reduce miscarriage risk. A study also suggested that exposure to 17-OHPC during the first trimester may be associated with an increased risk of cancer in offspring. It was reported that as the number of 17-OHPC injections increased during the first trimester, the risk of cancer in exposed fetuses also increased. Specifically, the risks of colorectal, prostate, and pediatric brain cancers were found to be higher in those exposed to 17-OHPC during the first trimester compared to those who were not exposed [25, 26].

Given these findings, caution is advised when considering the use of 17-OHPC in early pregnancy. Due to insufficient evidence supporting its efficacy in reducing preterm birth risk, the U.S. Food and Drug Administration (FDA) withdrew its approval for the use of 17-OHPC for this indication on April 5, 2023 [26]. For these reasons, 17-OHPC should not be used in cases of threatened abortion.

Progesterone is also used to reduce miscarriage risk and increase live birth rates in cases of recurrent pregnancy loss and luteal phase defects. A meta-analysis has shown that the use of progesterone in women with recurrent pregnancy loss can reduce miscarriage rates [27].

The role of progesterone in reducing miscarriage rates and its effects in assisted reproductive technologies have been discussed. Progesterone has been emphasized as an important hormone for maintaining pregnancy continuity [1].

Studies have also shown that the use of 400 mg micronized progesterone in recurrent pregnancy loss may reduce the risk of miscarriage [20].

Conclusion

Progesterone supplementation in cases of threatened abortion, early pregnancy bleeding, and recurrent pregnancy loss has demonstrated potential in reducing miscarriage risk. While didrogesterone appears to be more effective in certain scenarios, both natural and synthetic progesterone formulations are viable options.

Although micronized progesterone has shown promise in recurrent pregnancy loss, further large-scale studies are required to establish definitive conclusions. Clinicians should tailor progesterone therapy based on the patient's obstetric history, clinical findings, and ultrasonographic evaluation.

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