International Journal of Community Medicine and Public Health
Altaiam AA et al. Int J Community Med Public Health. 2025 Oct;12(10):4774-4781
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20253284

Review Article

Progesterone therapy in the prevention of pregnancy loss

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Received: 02 September 2025
Revised: 15 September 2025
Accepted: 17 September 2025

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ABSTRACT

Pregnancy loss, including early miscarriage and recurrent pregnancy loss (RPL), is a significant concern in reproductive health. Progesterone, a key steroid hormone, plays a critical role in preparing the endometrium, modulating immune tolerance, and maintaining uterine quiescence. This narrative review explores the current evidence on the mechanisms of progesterone action, its clinical efficacy in preventing pregnancy loss, available routes of administration, international guideline recommendations, and emerging therapeutic strategies. Randomized controlled trials (RCTs) notably the progesterone in spontaneous miscarriage (PRISM) and progesterone in recurrent miscarriage (PROMISE) studies-have demonstrated mixed results, with benefits more apparent in women with a history of RPL and those experiencing early pregnancy bleeding. These findings are supported by recent meta-analyses, which suggest that treatment success may depend on proper patient selection and timing of intervention. Among administration methods, vaginal progesterone remains the preferred route due to its targeted endometrial effects and reduced systemic side effects. However, oral dydrogesterone, a synthetic progestin, has shown potential in improving patient adherence. Recommendations from major clinical guidelines including those from the National Institute for Health and Care Excellence (NICE), the American College of Obstetricians and Gynecologists (ACOG), and the International Federation of Gynecology and Obstetrics (FIGO)-differ slightly based on interpretation of available data and individualized care approaches. Emerging directions include novel synthetic progestins with enhanced receptor specificity, combination regimens incorporating progesterone with surgical or immunologic therapies, and biomarker-guided approaches involving serum progesterone and progesterone-induced blocking factor (PIBF) levels. Advances in genetic and molecular profiling offer further potential for personalized medicine. Further research is warranted to refine patient selection, establish standardized protocols, and ultimately improve pregnancy outcomes

Keywords: Pregnancy loss, Recurrent miscarriages, Progesterone therapy

INTRODUCTION

The term pregnancy loss includes early miscarriage and recurrent pregnancy loss (RPL), which constitutes an emerging public health issue in reproductive medicine. Globally, pregnancy loss is a major reproductive health burden. According to the World Health Organization (WHO), approximately 10-15% of clinically recognized pregnancies result in miscarriage, with the actual rate potentially higher due to underreporting and losses before clinical recognition.[1] RPL affects about 1-2% of couples attempting to conceive.[2] The global burden is disproportionately higher in low- and middle-income countries (LMICs), where limited access to reproductive health services, high rates of untreated maternal infections, and nutritional deficiencies contribute to poorer outcomes.[3,4] Additionally, early miscarriage accounts for more than 80% of all pregnancy losses, most of which occur before 12 weeks of gestation.[5] Early pregnancy loss is described as the spontaneous termination of a nonviable intrauterine pregnancy in the initial 12 weeks of gestation. Early miscarriage is estimated to occur in about 10% of clinically recognized pregnancies, with the vast majority occurring during the first trimester.[6] LMICs experience a

much higher incidence due to limited healthcare access and nutritional deficiencies.[7] About 1% of couples trying to conceive are affected by RPL, characterized by two or more consecutive miscarriages.[8] Progesterone, a steroid hormone produced primarily by the corpus luteum and later by the placenta, plays a central role in establishing and maintaining pregnancy. Its key functions include preparing the endometrium for embryo implantation, modulating maternal immune tolerance to the fetus, and maintaining uterine quiescence.[9] Progesterone promotes decidualization of endometrial stromal cells to support implantation and suppresses maternal immune rejection of the semi-allogeneic fetus by enhancing regulatory T-cell differentiation and inhibiting natural killer cell activity. It also reduces uterine smooth muscle contractility, thereby lowering the risk of miscarriage and preterm labor.[10,11] Therapeutic intervention using exogenous progesterone has been widely studied for miscarriage prevention, particularly in women with a history of RPL or early pregnancy bleeding.[12] Notably, two major randomized controlled trials (RCTs)-the progesterone in recurrent miscarriage (PROMISE) trial and the progesterone in spontaneous miscarriage (PRISM) trial-investigated its efficacy. The PROMISE trial, which enrolled women with unexplained RPL, found no significant improvement in live birth rates with vaginal progesterone compared to placebo.[11] In contrast, the PRISM trial showed a modest benefit in live birth rates for women with early pregnancy bleeding who had a history of pregnancy loss.[13]

This narrative review was conducted through a comprehensive search of English-language, peer-reviewed literature using major biomedical databases including PubMed, MEDLINE, and the Cochrane Library. The search covered publications from 2000 to 2024 and focused on studies evaluating the role of progesterone in preventing pregnancy loss.

Inclusion criteria comprised human studies published in English that addressed the use of progesterone in the context of early pregnancy loss or recurrent pregnancy loss (RPL). Eligible sources included randomized controlled trials (RCTs), systematic reviews, meta-analyses, clinical guidelines, and original research articles. Special emphasis was placed on guidelines from authoritative bodies such as the National Institute for Health and Care Excellence (NICE), the American College of Obstetricians and Gynecologists (ACOG), and the International Federation of Gynecology and Obstetrics (FIGO). Studies were excluded if they did not directly assess progesterone in relation to pregnancy loss or if they were non-human, non-English, or focused on unrelated gynecological conditions. Given the heterogeneity in study designs, populations, and outcomes, a narrative review approach was employed to qualitatively assess and summarize the current evidence. The review aimed to highlight key findings related to progesterone's mechanisms of action, clinical efficacy, administration routes, guideline recommendations, and emerging treatment strategies.

REVIEW

Mechanisms of action of progesterone in pregnancy maintenance

As described in Figure 1, progesterone combines with progesterone receptor A (PR-A) and progesterone receptor B (PR-B), both of which regulate the expression of genes important to successful reproduction.[14] During the luteal phase of the monthly cycle, progesterone causes the endometrium to switch from a proliferative to a secretory phase, which supports embryo implantation.[15] During this process, known as decidualization, the endometrial stromal cells are changed in such a way that they will secrete hormones like prolactin and insulin-like growth factor-binding protein 1 (IGFBP-1) that allow for embryonic implantation and growth of the placenta.[10,15,16] In the endometrium, progesterone suppresses estrogen receptor alpha (ERα) so that while estrogen drives growth, it is downregulated in a balanced way, keeping the uterus ready for the embryo.[17]

Progesterone, besides aiding the endometrium in functioning properly, has immune-boosting effects for preventing fetal rejection. By causing a shift from T helper 1 (Th1) to T helper 2 (Th2) type of cytokines, it contributes to regulating the mother's immune system, thus helping reduce pregnancy risks associated with extreme inflammation.[18] Natural killer (NK) cells, including uterine natural killer (uNK) cells, which comprise a significant percentage of the decidual cell population during early pregnancy, are modulated by progesterone.[9] Progesterone-induced blocking factor (PIBF), responsible for mediating progesterone's immune regulation effect, produces interleukin-10 (IL-10) and downregulates NK cell activity to protect the fetus from the mother's immune response.[19]

During pregnancy, progesterone is crucial in maintaining myometrial quiescence. It downregulates the expression of contraction-associated proteins, thereby decreasing myometrial responsiveness to stimulatory factors and suppressing uterine contractility. This action is mediated by PR-B, which promotes transcription of genes that induce uterine relaxation.[14] With advancing pregnancy, a functional withdrawal of progesterone activity-determined by changes in PR isoform expression and local progesterone metabolism-contributes to labor onset.[20]

Clinical evidence for progesterone use in preventing pregnancy loss

Numerous randomized controlled trials (RCTs) have examined the effectiveness of progesterone in preventing miscarriages. In the PRISM study, a major multicenter RCT, Coomarasamy et al investigated whether vaginal progesterone (400 mg twice a day) reduces risk in women who report with early pregnancy bleeding. Live birth rates were not significantly different between the progesterone and placebo groups in the overall population. A subgroup analysis nevertheless suggested there may be a benefit in

women with three or more previous miscarriages, with a live birth rate of 72% in the progesterone group compared with 57% in the placebo group (relative rate, 1.28; 95% CI, 1.08 to 1.51; p=0.004).[21] Additionally, the PROMISE (Progesterone in Recurrent Miscarriage) study assessed the impact of progesterone treatment administered during the first trimester in women with unexplained RPL. Progesterone did not improve live birth rates compared to placebo (rates of 65.8% and 63.3%, respectively [relative rate, 1.04; 95% CI, 0.94 to 1.15]).[22]

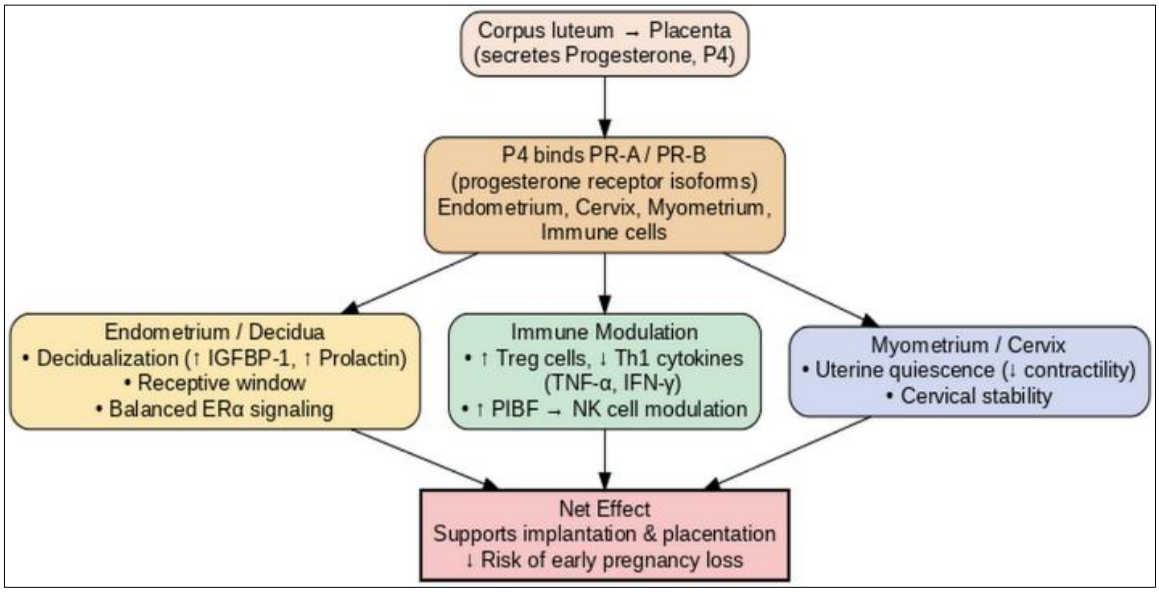

Figure 1: Mechanism of action of progesterone in preventing pregnancy loss.

PR A/PR B (progesterone receptor isoform A/isoform B), IGFBP 1 (insulin like growth factor binding protein 1), ERα (estrogen receptor alpha), T-reg (regulatory T) cells, Th1 (T helper 1) cytokines, TNF α (tumor necrosis factor alpha), IFN γ (interferon gamma)

A meta-analysis of many progestogens for avoiding miscarriages was conducted by Devall et al. Using data from multiple RCTs, the analysis found that in women who have threatened or frequent miscarriages, progestogens likely have little to no effect on the live birth rate. In women with a history of one or more previous miscarriages and early pregnancy bleeding, however, vaginal micronized progesterone resulted in a higher live birth rate than placebo.[23] The use of dydrogesterone in cases of threatened miscarriage was reviewed in another systematic review and meta-analysis by Wang et al. Dydrogesterone was found to significantly decrease the risk of miscarriage versus placebo (RR 0.49, 95% CI 0.33 to 0.75). However, the authors concluded that progesterone agents are effective and reduce the incidence of miscarriage in threatened miscarriage, and dydrogesterone appears more significant than natural progesterone in this effect.[24]

Specific populations that may benefit from progesterone therapy have been explored in subgroup analyses. For example, the PRISM study found that progesterone supplementation dramatically boosted live birth rates for women with early pregnancy blood loss and a history of three or more losses. On the other hand, women who had never had a miscarriage before did not significantly benefit.[25] The supportive treatment for ongoing pregnancy (STOP) trial by McLindon et al, which examined the use of vaginal progesterone in women who were at risk of miscarriage, did not show a statistically significant increase in live birth rates in the general population. However, the study concluded that progesterone could be beneficial for women with threatened miscarriage, regardless of the previous miscarriage, and more research is needed.[26]

Table 1: Key randomized evidence and reviews - progesterone for miscarriage prevention.

Study (year)	Design and population	Regimen versus control	Primary outcome	Key result	Bottom line
PRISM (2019)	Multicenter RCT; women with threatened miscarriage (early pregnancy bleeding)	Vaginal micronized progesterone 400 mg twice daily (BID) for 16 weeks versus placebo	Live birth ≥34 weeks	72% versus 57% (RR 1.28; 95% CI 1.08–1.51; p=0.004)	No overall benefit; clinically meaningful benefit for women with bleeding plus prior losses (strongest when ≥3 prior).[21]

Continued.

Study (year)	Design and population	Regimen versus control	Primary outcome	Key result	Bottom line
PROMISE (2015)	Multicenter RCT; unexplained RPL with ≥3 prior miscarriages; no bleeding requirement	Vaginal micronized progesterone 400 mg BID from positive test to 12 weeks versus placebo	Live birth ≥24 weeks	65.8% versus 63.3% (RR 1.04; 95% CI 0.94–1.15) — not significant	Routine first-trimester progesterone not beneficial in unexplained RPL without current bleeding.[22]
Cochrane network meta-analysis (NMA) (Devall et al)	NMA pooling RCTs in threatened miscarriage and RPL	Various progestogens versus placebo/no treatment	Live birth	Overall probably little/no difference; vaginal micronized progesterone increases live birth in women with bleeding + ≥1 prior miscarriage; little/no effect when no prior losses	Supports phenotype-specific use: benefit when bleeding + prior loss; otherwise minimal effect.[23]
Wang 2019 (systematic review and meta-analysis)	Threatened miscarriage	Dydrogesterone versus placebo	Miscarriage	RR 0.49 (95% CI 0.33–0.75) — fewer miscarriages with dydrogesterone; authors note limitations	Signals benefit of dydrogesterone in threatened miscarriage; heterogeneity/limitations warrant caution.[24]
STOP trial (McLindon 2023)	Single-centre RCT; women with threatened miscarriage	Vaginal progesterone 400 mg nightly to 12 weeks versus placebo	Live birth	No increase in live birth; trial stopped for futility at interim analysis	No overall benefit for general threatened-miscarriage population; further targeted research needed.[26]

RCT=randomized controlled trial, RPL=recurrent pregnancy loss, BID=twice daily, RR=relative risk (also called relative rate), CI=confidence interval, PRISM=progesterone in spontaneous miscarriage trial, PROMISE=progesterone in recurrent miscarriage trial, STOP=supportive treatment for ongoing pregnancy trial, NMA=network meta-analysis

ROUTES OF ADMINISTRATION AND FORMULATIONS

The route of administration is the most important factor in determining the efficacy, pharmacokinetics, side effect profile, and patient compliance of progesterone therapy. Vaginal administration of progesterone bypasses hepatic metabolism to reach higher local concentrations at the endometrial level, promoting implantation and maintenance of early pregnancy.[27] Vaginal progesterone is available in several formulations, including gels, suppositories, and tablets. Although this route is very effective, it can be associated with local irritation and discharge, leading to poor patient adherence.[28] Natural micronized progesterone (NMP) has low bioavailability as it is extensively metabolized by the liver when taken orally, necessitating large therapeutic doses.[29] This route, as described by Memi et al carries systemic side effects, such as drowsiness and dizziness, due to the production of neuroactive metabolites. These limitations have been overcome with the development of an oral form of synthetic retroprogesterone and dydrogesterone. Oral dydrogesterone is effective in decreasing rates of miscarriage in women with threatened miscarriage.[30] A meta-analysis found that oral dydrogesterone significantly reduced the risk of miscarriage compared to natural progesterone (RR 0.49, 95% CI 0.33 to 0.75).[24] Oral administration also has the advantage of better patient compliance and ease of use.[30] Traditionally used in assisted reproductive technologies, intramuscular (IM) injection of progesterone in oil can generate high serum concentrations.[31] However, IM injection is associated with discomfort, injection site reactions, and lower patient satisfaction.[32] Although IM progesterone results in higher serum levels, it 4 of 8 does not necessarily provide higher efficacy compared to other routes.[33]

CLINICAL GUIDELINES AND RECOMMENDATIONS FOR PROGESTERONE USE

Progesterone treatment for preventing miscarriage has been evaluated by major health organizations. As described in Table 2, In November 2021, National Institute for Health and Care Excellence (NICE) in the United Kingdom updated its guidelines and suggested the use of vaginal micronized progesterone (400 mg twice daily) in women with an intrauterine pregnancy, confirmed by ultrasound, who have a history of one or more prior miscarriages and who present with vaginal bleeding.[34] Treatment is continued until 30 weeks of gestation.[35] The recommendation is based on the evidence from the PRISM trial, which showed a modest but statistically significant increase in the live birth rate for this population.[25] The American College of Obstetricians and Gynecologists (ACOG), in its Practice Bulletin No. 200, includes

guidance for the use of progesterone to prevent miscarriage. Progesterone therapy in the first trimester may be beneficial in women who have had at least three prior pregnancy losses, according to ACOG.[6] Guidance for the use of progestogens in the prevention of recurrent preterm birth has also been provided. In its April 2023 Practice Advisory, ACOG stated that intramuscular 17-alpha hydroxyprogesterone caproate (17-OHPC) is not recommended for the primary prevention of preterm birth in patients with a history of spontaneous preterm birth. However, vaginal progesterone may be considered for patients with a history of preterm birth, singleton gestation, and a shortened cervix.[36] The International Federation of Gynecology and Obstetrics (FIGO) released Good Practice Recommendations in 2023 regarding the use of progesterone in the management of recurrent first-trimester miscarriage.[37] FIGO found no conclusive evidence that progesterone supplementation improves live births in women with unexplained RPL. Thus, routine use is not recommended for this group. However, FIGO acknowledged that progesterone appears essential for maintaining a healthy pregnancy and emphasized the need for further research to identify subgroups who may benefit from supplementation.[37]

Table 2: Comparative summary of NICE, ACOG, and FIGO clinical guidelines on progesterone use.

Aspect	NICE (UK)	ACOG (USA)	FIGO
Target population	Women with vaginal bleeding in early pregnancy and ≥1 previous miscarriage, with intrauterine pregnancy confirmed on ultrasound	Addresses early pregnancy loss broadly; for prevention, evidence for progestins in threatened miscarriage is inconclusive. Notes women with ≥3 prior losses may benefit from first-trimester progesterone	Women with recurrent first-trimester miscarriage (often unexplained); global good-practice focus rather than a single uniform population definition
Recommendation	Offer vaginal micronised progesterone 400 mg twice daily to eligible women; if fetal heartbeat is confirmed, continue to 16 completed weeks	Do not recommend routine progestin for threatened miscarriage; consider first-trimester progesterone for women with ≥3 prior losses	Acknowledge potential benefits; recommend further research; no clear guidance for routine use in unexplained recurrent miscarriage
Evidence basis	Recommendation driven by PRISM trial and evidence review showing a benefit limited to bleeding + prior loss; no benefit with bleeding without prior loss or prior loss without current bleeding	Summaries (Cochrane and others) indicate mixed/limited evidence for threatened miscarriage; possible benefit in women with ≥3 prior losses (evidence not definitive)	Narrative synthesis of available trials and reviews; concludes evidence is mixed and insufficient for routine empiric therapy in unexplained recurrent miscarriage
Route of administration	Vaginal micronised progesterone	Not specified (varies by clinical judgement; not routinely advised)	Not specified (document focuses on practice considerations and research needs)
Duration of treatment	Until 16 weeks' gestation if fetal heartbeat is seen	Not specified	Not specified
Clinical considerations	Requires ultrasound-confirmed intrauterine pregnancy; recommendation is phenotype-specific (bleeding + prior loss only)	Emphasizes individualized care; routine preventative measures for threatened miscarriage are not supported by conclusive evidence	Encourages standardized definitions, research, and individualized counseling; highlights gaps requiring high-quality RCTs

NICE-National Institute for Health and Care Excellence, UK-United Kingdom, ACOG-International Federation of Gynecology and Obstetrics, USA-United states of America, FIGO-International Federation of Gynecology and Obstetrics, PRISM-Progesterone in recurrent miscarriage randomized trial

CLINICAL DECISION ALGORITHM - USE OF PROGESTERONE IN EARLY PREGNANCY SCOPE

When to consider vaginal micronized progesterone for miscarriage prevention, based on NICE 5 of 8 (National Institute for Health and Care Excellence) guidance and major randomized evidence.

Early pregnancy (up to 13 weeks)

During the initial assessment, check stability, pain, and bleeding, and review obstetric history (including prior miscarriages); then perform TVUS with quantitative hCG to confirm intrauterine pregnancy, and if pregnancy of unknown location or ectopic pregnancy is suspected, manage as per protocol without initiating progesterone.

According to NICE criteria, women with early pregnancy bleeding, at least one prior miscarriage, and a confirmed intrauterine pregnancy should be offered vaginal micronized progesterone 400 mg twice daily (continued to 16 weeks if a fetal heartbeat is seen, or until a repeat scan within 14 days clarifies viability), while progesterone should not be routinely given for bleeding without prior miscarriage or for recurrent pregnancy loss without current bleeding.

All women should be followed up as per local early pregnancy loss pathways, with reassessment of symptoms and viability; progesterone should be discontinued if the pregnancy is non-viable or at 16 weeks if viable, and counseling should emphasize that evidence shows no overall benefit in all-comers with bleeding, but a possible benefit in those with bleeding plus prior miscarriage, especially three or more.

EMERGING THERAPIES AND FUTURE DIRECTIONS

Advancements in reproductive medicine have led to the development of novel therapeutic strategies aimed at preventing pregnancy loss. Below are some emerging therapies.

Novel progesterone analogs

Recent research has focused on developing synthetic progestins with improved bioavailability and receptor specificity. For instance, Nestorone® (NES) is a novel progestin designed to have a high affinity for the progesterone receptor (PR) and minimal androgenic or estrogenic activity. It has been shown that NES has powerful progestational effects and could be a promising candidate for nonoral contraception and possibly also for pregnancy maintenance therapies.[38] Selective progesterone receptor modulators (SPRMs), agents that interact with PR as both agonists and antagonists have also been developed. These compounds offer the possibility of more precise modulation of progesterone signaling, which may be helpful in cases of recurrent pregnancy loss (RPL).[39]

Biomarker-guided therapy

Identifying and utilizing biomarkers to direct progesterone therapy is one of the most promising developments in personalized reproductive medicine. Serum progesterone levels have been studied as potential biomarkers to predict pregnancy outcomes.[40] For instance, the risk of miscarriage in women with threatened miscarriage has been associated with serum progesterone levels below 12 mg/ml.[41] Furthermore, the role of progesterone-induced blocking factor (PIBF), a protein regulated by progesterone-has been investigated as a biomarker for pregnancy viability. Elevated PIBF levels have been linked with successful pregnancies, and PIBF could therefore support monitoring and tailoring of progesterone therapy.[42]

Limitations

This narrative review is subject to several limitations. First, as a non-systematic review, it does not include a comprehensive meta-analysis or a formal risk of bias assessment, which may limit the objectivity of evidence synthesis. Second, while the literature search was structured and targeted high-quality sources, the inclusion of only English-language articles may have excluded relevant studies published in other languages. Third, given the heterogeneity in study populations, progesterone formulations, dosing regimens, and outcome measures across the included studies, direct comparison of findings remains challenging. Additionally, some of the emerging therapies and biomarker-guided approaches discussed are based on preliminary or limited evidence and require further validation through large-scale, well-designed randomized controlled trials. These limitations should be considered when interpreting the findings and clinical implications of this review.

CONCLUSIONS

The use of progesterone therapy is essential to prevent pregnancy loss among women with early pregnancy loss or recurrent miscarriages. Evidence supports its benefit in certain groups, yet outcomes vary in the general population. Synthetic progestins and biomarker-guided approaches are leading the way towards more personalized treatments. Additional therapies could improve outcomes, including cervical cerclage, immunomodulation, and other agents combined with progesterone. Further research should focus on refining patient selection, maximizing dosing regimens and validating predictive biomarkers for effective tailoring of interventions. Clear evidence-based protocols will provide hope to many women affected by significantly increasing treatment success and reducing miscarriage rates globally.

Funding: No funding sources
Conflict of interest: No conflict of interest
Ethical approval: Not required

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Cite this article as: Altaiam AA, Almomani JR. Progesterone therapy in the prevention of pregnancy loss. Int J Community Med Public Health 2025;12:4774-81.