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Optimizing Obstetric Care: A Narrative Review of Immediate and Sustained Release Oral Micronized Progesterone

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Abstract

Oral natural micronized progesterone (NMP), commonly administered as immediate-release (IR) soft gelatin capsules, is widely used across reproductive and obstetric indications, offering a patient-friendly alternative to vaginal and parenteral routes. However, conventional IR formulations are limited by variable bioavailability and central nervous system (CNS)-related adverse effects due to first-pass hepatic metabolism. Sustained-release (SR) oral NMP formulations are developed to overcome these limitations. These formulations utilize polymer-based matrices to provide gradual progesterone release over 16-24 hours, resulting in stable serum concentrations, reduced peak-trough fluctuations, once-daily dosing, and improved tolerability. These pharmacokinetic advantages may enhance treatment convenience and adherence, particularly in settings requiring prolonged hormonal support. Clinically, oral NMP-SR plays an important role in luteal phase support (LPS), threatened abortion, recurrent pregnancy loss, and prevention of preterm birth. Evidence from randomized and observational studies indicates that oral NMP SR provides pregnancy outcomes comparable to vaginal progesterone in selected settings, particularly in LPS. In other indications, findings are more heterogeneous; however, available data and real-world experience suggest favourable clinical utility. Across indications, oral NMP-SR formulations appear to offer improved tolerability and dosing convenience. Overall, oral NMP-SR represents a practical and patient-friendly option, offering consistent systemic exposure and improved tolerability across key obstetric indications.

Keywords

Immediate-Release, Luteal Phase Support, Natural Micronized Progesterone, Obstetrics, Oral Progesterone, Sustained-Release, Threatened Miscarriage

Abbreviations

AEs: Adverse Effects; ART: Assisted Reproductive Technology; CNS: Central Nervous System; GABA: γ-aminobutyric acid; GI: Gastrointestinal; IR: Immediate-release; LPS: Luteal Phase Support; NMP: Natural Micronized Progesterone; PTB: Preterm birth; RPL: Recurrent pregnancy loss; SR: Sustained-release

Introduction

Pregnancy loss, including miscarriage and stillbirth, remains a significant global reproductive health concern, often accompanied by stigma and inadequate access to appropriate care in many settings [1]. Globally, miscarriage affects approximately 15% of clinically recognized pregnancies and contributes substantially to maternal morbidity and adverse reproductive outcomes [2]. In parallel, preterm birth (PTB) is a major contributor to adverse perinatal outcomes and remains the leading cause of mortality among children under five years of age worldwide [3], underscoring the need for effective preventive strategies across the continuum of pregnancy care.

Progesterone plays a central role in the establishment and maintenance of pregnancy by regulating endometrial receptivity, facilitating embryo implantation, and maintaining uterine quiescence [4]. Alterations in progesterone signalling or luteal function have been implicated in a spectrum of reproductive disorders, including early pregnancy failure and implantation-related disorders [5–7]. Consequently, progestogen supplementation has been widely investigated as a therapeutic strategy in key obstetric indications. Over the past decade, clinical evidence evaluating progesterone therapy has evolved considerably. Although findings across clinical studies have been heterogeneous, recent meta-analytic evidence suggests that progesterone therapy may improve live birth rates in women at increased risk of pregnancy loss, particularly among those with a history of prior miscarriage [8]. Similarly, progesterone has demonstrated benefit in reducing the risk of recurrent PTB in appropriately selected patients [9]. In the context of assisted reproduction, progesterone remains indispensable for luteal phase support (LPS) to optimize implantation and pregnancy maintenance [10]. Progesterone supplementation may involve the use of natural progesterone or synthetic progestins (such as dydrogesterone); however, these agents differ in their chemical structure, pharmacological properties, and clinical effects. In this context, the present review focuses specifically on oral natural micronized progesterone formulations [11].

Despite its established therapeutic role, optimizing progesterone delivery remains an important clinical consideration [12,13]. The effectiveness of progesterone therapy is influenced by the route of administration, tolerability, and associated pharmacokinetic characteristics [10]. Progesterone can be administered through oral, vaginal, or intramuscular routes, each associated with distinct advantages and limitations [10,14,15]. Vaginal formulations provide targeted uterine delivery but may be associated with local discomfort and variable patient acceptability, whereas intramuscular injections, although effective, are invasive and often associated with pain and reduced compliance. Oral progesterone is often preferred in clinical practice due to its convenient and non-invasive nature and potential for improved treatment acceptability [16]. However, conventional immediate-release (IR) oral natural micronized progesterone soft gelatin capsules are limited by low and variable bioavailability owing to extensive first-pass metabolism, often necessitating repeated dosing and leading to fluctuations in systemic exposure [17]. Also, it is commonly associated with central nervous system (CNS)-related adverse effects (AEs) such as drowsiness and dizziness, largely attributed to neuroactive metabolites [16,18]. These limitations often necessitate multiple daily dosing and may compromise treatment adherence.

To address these limitations, sustained-release (SR) formulations of oral NMP have been developed to provide more consistent pharmacokinetic profiles and simplified dosing schedules [19]. By potentially minimizing peak-trough fluctuations and improving treatment acceptability, such approaches may help address practical challenges associated with conventional progesterone therapy [16]. These pharmacokinetic and tolerability advantages are particularly relevant in clinical scenarios requiring prolonged therapy, where adherence and patient comfort are critical determinants of treatment success [20,21]. Recent pharmaceutical advancements have further optimized oral progesterone delivery through the incorporation of solubilizing technologies designed to enhance drug dissolution and absorption, thereby improving systemic exposure and reducing inter-individual variability [19].

In this context, the present narrative review aims to provide a comprehensive and updated overview of the clinical utility of oral NMP SR formulations in obstetrics. Specifically, it examines the pharmacological rationale, formulation advantages, and emerging clinical evidence supporting its use across key obstetric indications, including threatened miscarriage, prevention of PTB, and LPS, while also highlighting practical considerations for its integration into routine clinical practice.

Progesterone Mechanism of Action and Clinical Uses in Obstetrics and Reproductive Medicine

Progesterone is a key regulatory hormone in female reproductive physiology, exerting its biological effects primarily through activation of nuclear progesterone receptors, including the PR-A and PR-B isoforms, which modulate transcription of genes involved in endometrial differentiation and pregnancy maintenance [4,22]. Progesterone receptor signalling promotes endometrial receptivity, stromal decidualization, and successful embryo implantation, processes that are essential for the establishment of early pregnancy [23]. Disruptions in progesterone signalling pathways have been associated with implantation failure, recurrent pregnancy loss (RPL), and other gestational complications [24,25].

Beyond early pregnancy, progesterone contributes to the maintenance of uterine quiescence by modulating myometrial contractility and suppressing pro-inflammatory pathways within uterine tissues [26]. Alterations in progesterone responsiveness, often described as functional progesterone withdrawal, have been implicated in the initiation of labor, including the premature activation of parturition pathways associated with PTB [27]. These mechanistic insights provide the biological rationale for therapeutic progesterone supplementation in a range of gynecological and obstetric indications.

Clinically, progesterone supplementation is widely utilized in conditions associated with inadequate endogenous progesterone support or increased risk of pregnancy loss. These include luteal phase deficiency, threatened or recurrent miscarriage, assisted reproductive technology (ART) cycles requiring LPS, and prevention of PTB in selected high-risk populations [9,10,28]. The therapeutic effectiveness of progesterone supplementation in these settings has been explored across multiple clinical studies and meta-analyses, supporting its role as an important component of reproductive care [8,12,29].

Pharmacology of Natural Progesterone (NMP)

For therapeutic use, progesterone is available in multiple pharmaceutical forms, including synthetic progestins as well as formulations containing natural progesterone [14,30]. Natural progesterone, which is structurally identical to the endogenous

hormone, is widely utilized in clinical practice owing to its physiological receptor interactions, established clinical role and favorable safety profile across reproductive indications [14]. NMP, being structurally identical to endogenous progesterone, differs from synthetic progestins such as dydrogesterone in terms of chemical structure, receptor interactions, and pharmacokinetic properties, which may influence their clinical effects and tolerability profiles [31,32]

Routes of Administration of Natural Progesterone

The clinical application of natural progesterone, such as its role in supporting endometrial receptivity and maintaining early pregnancy across various reproductive indications [33] is influenced by its physicochemical properties, including high lipophilicity and susceptibility to extensive metabolic inactivation [34]. These characteristics have posed challenges for achieving consistent systemic and tissue exposure through a single mode of delivery [34]. Consequently, multiple routes of administration, including oral, vaginal, and parenteral approaches, have been developed and adopted in clinical practice to optimize pharmacokinetic profiles, therapeutic efficacy, and patient acceptability [33]. These delivery strategies are associated with distinct patterns of systemic progesterone exposure and tissue-level pharmacodynamic responses, reflecting route-dependent differences in absorption kinetics and endometrial effects [33,35].

Oral administration represents a convenient and non-invasive option for delivering natural progesterone in clinical practice, largely owing to its convenience and patient acceptability [33]. The development and clinical introduction of micronized progesterone improved gastrointestinal (GI) absorption and facilitated the attainment of circulating progesterone concentrations consistent with pharmacological activity [34]. Consequently, oral micronized progesterone has been incorporated into therapeutic use across a range of reproductive and endocrine indications as a non-invasive alternative to parenteral and locally administered progesterone preparations [33].

Vaginal administration provides an alternative route, particularly in clinical contexts requiring targeted endometrial support [33,36,37]. This delivery approach has been associated with preferential uterine exposure, often described as a "first uterine pass effect," whereby adequate endometrial transformation may occur despite comparatively lower circulating progesterone concentrations [38]. Vaginal route leads to higher endometrial tissue concentration despite lower serum levels and is widely used in LPS and hormone therapy [38–40]. However, variability in absorption may occur depending on formulation characteristics and dosing regimens [41]. Limitations such as vaginal irritation, discharge, and the requirement for repeated daily applications have also been reported [42]. Randomized evaluation of vaginal formulations has also demonstrated administration-related inconvenience, including medication leakage and interference with sexual activity during treatment cycles [43]. Patient-reported assessments have shown that vaginal progesterone formulations are generally perceived as acceptable, although administration may involve practical handling considerations such as applicator use and local administration requirements [44].

Parenteral administration, particularly intramuscular progesterone, provides sustained systemic exposure due to gradual absorption from oil-based depots and has been widely used in reproductive medicine [33,39,40]. While it may achieve higher serum levels compared with vaginal administration, its use is often influenced by practical considerations such as inconvenience, local pain, and inflammatory reactions at the injection site [33,39,42]. Water-soluble subcutaneous progesterone preparations have emerged as an alternative systemic delivery approach, with comparable efficacy to vaginal progesterone for LPS in assisted reproductive settings [45].

Across these approaches, the choice of route is guided by a balance between pharmacokinetic profile, clinical efficacy, safety considerations, and patient preference. Among these, oral progesterone remains widely used because of its convenience and non-invasive nature. Nevertheless, ensuring reliable systemic progesterone exposure following oral dosing has remained an important consideration in clinical pharmacology [33].

Barriers to Effective Oral Delivery of Natural Progesterone

The oral delivery of natural progesterone is inherently challenged by its physicochemical and pharmacokinetic properties, which limit consistent systemic exposure. Progesterone is highly lipophilic and exhibits poor aqueous solubility [46], resulting in suboptimal dissolution within the GI tract and variable absorption following oral administration [47]. In addition, extensive pre-systemic metabolism in the intestinal mucosa and liver significantly reduces the fraction of unchanged drug reaching the systemic circulation [34].

Pharmacokinetic investigations have demonstrated rapid metabolic clearance of orally administered progesterone in hepatic and intestinal tissues, contributing to low and variable bioavailability [17]. This first-pass metabolism also leads to the formation of neuroactive metabolites, including allopregnanolone, which are associated with CNS effects such as somnolence and dizziness. These limitations have restricted the widespread use of oral progesterone in certain clinical settings, such as LPS, where consistent and sustained progesterone exposure is critical [48–50]. Despite these challenges, the convenience and non-invasive nature of oral administration continue to drive efforts toward improving progesterone delivery through formulation strategies aimed at improving progesterone dissolution, absorption, and systemic delivery.

Pharmaceutical Micronization of Natural Progesterone

To address solubility-related limitations, pharmaceutical micronization was introduced as a formulation strategy to improve the oral bioavailability of progesterone. Micronization reduces drug particle size to the micrometer range, thereby increasing

surface area and enhancing dissolution characteristics. Oral micronized progesterone mediates its therapeutic effects through progesterone receptor-dependent pathways analogous to endogenous hormone activity [51], while pharmaceutical micronization facilitates improved dissolution, GI absorption, and systemic exposure [16,18]. Further improvements have been achieved by suspending micronized progesterone in oil-based vehicles and encapsulating it within soft gelatin capsules, which represent the conventional IR oral progesterone formulation used in clinical practice, enhancing GI absorption and systemic exposure [20]. Pharmacokinetic studies have demonstrated relatively rapid systemic absorption after oral administration of micronized progesterone capsules, with peak plasma concentrations typically observed within a few hours following dosing, reflecting characteristics consistent with IR delivery [52]. These investigations have also shown variability in peak concentration and overall progesterone exposure between different capsule formulations, indicating formulation-dependent differences in absorption and systemic availability [52].

Pharmacokinetic and Clinical Profile

However, micronization does not fully overcome the challenges associated with oral progesterone delivery. Significant first-pass metabolism persists, and variability in systemic exposure remains evident [32,53,54]. Furthermore, conventional micronized progesterone soft gelatin capsule formulations are typically IR, resulting in fluctuating plasma progesterone concentrations and limiting the consistency of therapeutic hormone levels [35,55].

Implications of Oral NMP

Following oral administration, systemic exposure to NMP is influenced by extensive pre-systemic metabolism and metabolic clearance mechanisms, which contribute to variability in circulating progesterone concentrations [17]. Although oral micronized progesterone can achieve serum concentrations comparable to those observed during the luteal phase, considerable inter-individual variability in absorption has been reported [52,56].

IR oral micronized progesterone are characterized by rapid GI absorption, with peak plasma concentrations typically achieved within 2-3 hours and elevated serum levels maintained for approximately 12 hours [50]. Approximately 80% of progesterone is released within the first 4 hours in the upper GI tract. In this region, progesterone undergoes extensive pre-systemic metabolism mediated by 5α-reductase enzyme, which is present in the gut lumen (including gut microbiota), intestinal wall, and liver. This metabolic conversion leads to the formation of pregnane metabolites, including allopregnanolone, which are neuroactive and act on γ-aminobutyric acid (GABA-A) receptors, contributing to central nervous system–related adverse effects such as sedation and dizziness [18,55,57,58]. These pharmacokinetic properties may necessitate divided dosing schedules to maintain therapeutically relevant systemic progesterone concentrations. Additionally, rapid absorption associated with IR formulations may also result in pronounced peak-trough fluctuations in circulating hormone levels across the dosing interval, potentially influencing the consistency of luteal-phase hormonal support [17,21].

Although dose-proportional exposure and elimination half-lives of approximately 16–18 hours have been reported across commonly used dose ranges, clinically meaningful progesterone concentrations may not be consistently maintained throughout the dosing interval, often requiring individualized dosing approaches in clinical practice [50,55]. Systemic exposure may be further influenced by physiological and pharmacokinetic factors such as metabolic clearance and food intake [18,50,55].

Taken together, these pharmacokinetic features highlight the potential for variability in systemic hormone exposure following conventional oral administration. Such considerations have stimulated interest in formulation approaches aimed at achieving more stable progesterone concentrations and improving dosing convenience in clinical practice [20].

Oral Natural Micronized Progesterone

Clinical Positioning of Oral Natural Micronized Progesterone

Clinical practice guidelines recommend progesterone supplementation as standard care for LPS in assisted reproductive treatments, reflecting its established role in optimizing reproductive outcomes [59]. Multiple routes of administration are available, and selection is typically guided by pharmacokinetic characteristics, clinical objectives, tolerability, and patient preference rather than superiority of any single route [33,60].

Micronized natural progesterone is available for oral administration and has been described as convenient to use and a safe and effective alternative to other progesterone formulations in clinical practice [61]. Prescription trend analyses have also suggested increasing clinical use of oral micronized progesterone therapy in pregnancy care settings, reflecting its acceptability and ease of administration [61].

Clinical Use and Limitations of IR Oral NMP

Conventional IR oral NMP formulations are administered as oil-filled soft gelatin capsules designed for IR, with micronization enhancing GI absorption and enabling therapeutic oral use [18,21]. These formulations are available in multiple dosage strengths such as 100 mg, 200 mg, 300 mg, and 400 mg to facilitate individualized dosing in clinical practice [61–63].

In routine clinical practice to support adequate luteal hormone exposure, IR oral NMP is commonly administered in divided daily doses to maintain adequate systemic hormone levels [50,55]. However, such dosing schedules may contribute to treatment burden, especially in settings where progesterone is prescribed alongside multiple supportive therapies [52,61].

Additionally, as outlined in Section 3, oral progesterone is associated with pharmacokinetic variability due to extensive hepatic first-pass metabolism and formulation-dependent differences in absorption [60]. Thus, pharmacokinetic variability and the need for repeated dosing schedules may represent practical challenges for long-term adherence in reproductive indications where consistent hormonal support is required [55]. In addition, metabolite-related CNS effects, including sedation, may influence tolerability in some patients receiving oral progesterone therapy [60]. Taken together, these clinical and pharmacokinetic considerations highlight limitations associated with conventional IR oral progesterone formulations and underscore the need for optimized delivery approaches that provide more consistent systemic exposure and improved dosing convenience.

Sustained-Release Formulation Advances in Oral Progesterone

Rationale for Sustained-Release Oral Progesterone

As discussed in the preceding sections, conventional IR progesterone formulations are associated with pharmacokinetic variability, extensive first-pass metabolism, and the need for divided dosing, which may affect therapeutic consistency and patient adherence. These limitations have driven the development of SR formulations designed to provide more stable systemic progesterone exposure while improving dosing convenience [20,64]. SR formulations offer the advantage of once-daily dosing, minimizing treatment burden while maintaining therapeutic hormone levels over an extended duration [64]. This approach aligns with the clinical need for consistent progesterone exposure in reproductive indications requiring prolonged hormonal support.

Formulation Design and Drug Delivery Characteristics

SR oral progesterone formulations are typically based on hydrophilic matrix systems in which micronized progesterone is embedded within a controlled-release polymeric structure [16,64]. Upon oral administration, the matrix hydrates within the GI tract, allowing gradual and controlled release of progesterone over an extended period [20]. The homogenization process, including micronization, enhances solubility and dissolution rate, thereby improving oral bioavailability [64]. The polymeric matrix dissolves progressively as it transits through the GI tract, releasing micron-sized progesterone particles in a sustained manner [16].

In contrast to immediate-release formulations, SR formulations are designed to modify the site of drug release, with only a limited proportion (~20%) released in the upper GI tract and a larger fraction (~80%) released more distally in the lower GI tract. This shift in drug release reduces early exposure to metabolic enzymes such as 5α-reductase present in the gut lumen, intestinal wall, and liver, thereby minimizing pre-systemic metabolism and contributing to improved systemic availability and more consistent plasma progesterone concentrations, enabling once-daily dosing.

Certain SR formulations have been described as being developed using matrix-based delivery technologies (e.g., EROMAT-based systems), which enable controlled release of progesterone over approximately 16–24 hours [19,65](Figure 1). The "smooth release" pattern avoids rapid drug liberation or dose dumping and supports gradual systemic exposure [20]. Recently, Sun Pharmaceutical Industries Limited has been granted patent for innovation in oral NMP SR formulation. It employs addition of solubilizing agents to improve solubility of lipophilic progesterone in aqueous environment and minimizes dependence on bile salts. Solubilizing agents acting as microboosters offers approximately 3.5-fold higher bioavailability compared with formulations lacking solubilizing agents.

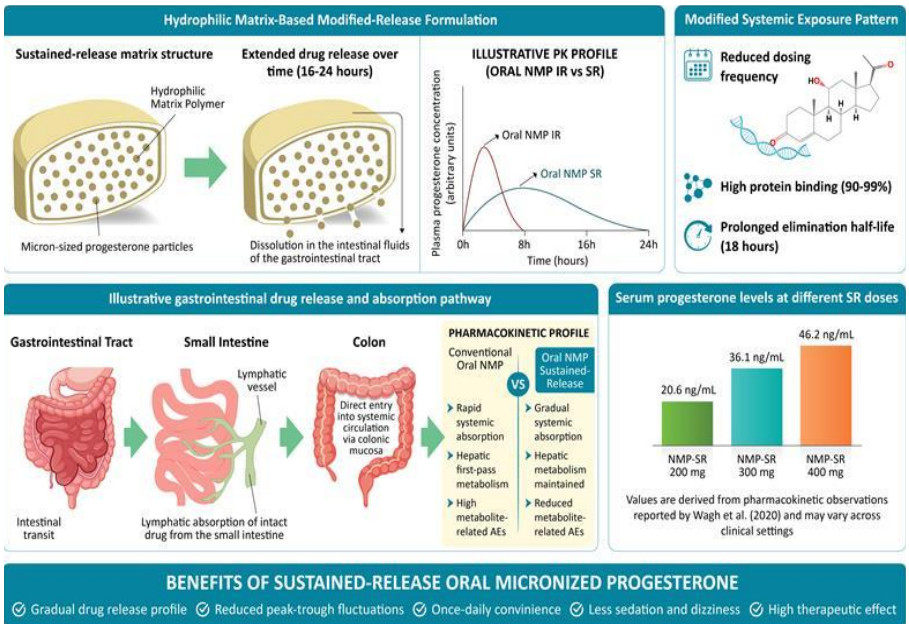

Figure 1: Mechanistic Overview and Pharmacokinetic Profile of a Hydrophilic Matrix-Based Sustained-Release Oral Micronized Progesterone Formulation [19,65]

Pharmacokinetic Advantages of SR Formulations

SR progesterone formulations are characterized by prolonged drug release over 24 hours, resulting in more stable plasma progesterone concentrations compared with IR preparations [16]. These formulations exhibit an extended elimination half-life of approximately 18 hours and high protein binding (90-99%), supporting sustained systemic exposure with once-daily dosing [16,19,61]. Pharmacokinetic evaluations have demonstrated that once-daily administration of NMP-SR for seven days at doses of 200 mg, 300 mg, and 400 mg can achieve mean mid-luteal serum progesterone concentrations of 20.6 ng/mL, 36.1 ng/mL, and 46.2 ng/mL, respectively, consistent with luteal phase physiological ranges [19,65].

The controlled release of progesterone particles during intestinal transit facilitates lymphatic absorption of intact drug from the small intestine, as well as direct entry into systemic circulation via the colonic mucosa [16,19,65]. This pathway partially circumvents hepatic first-pass metabolism, thereby enhancing systemic availability of active drug and reducing the AEs associated with metabolites [16,19].

Clinical and Practical Advantages of SR Oral Progesterone

The pharmacokinetic profile of SR formulations translates into several practical advantages in clinical use. Once-daily dosing reduces treatment burden and may improve patient adherence, particularly in settings requiring prolonged progesterone therapy [20]. The gradual release of progesterone minimizes peak–trough fluctuations in plasma levels, which are typically observed with IR formulations, thereby supporting more consistent hormonal exposure. In addition, reduced peak serum concentrations may contribute to a lower incidence of CNS-related AEs such as sedation and dizziness [20,64]. Prescription trend observations suggest increasing clinical adoption of SR progesterone formulations, with a shift from conventional soft gelatin capsule preparations toward once-daily SR formulations in routine practice [61]. The clinical relevance of oral NMP SR is also reflected in its inclusion in contemporary textbooks including John Studd's Current Progress in Obstetrics and Gynaecology, and Reproductive Immunogenetics: A Molecular and Clinical Overview, where it is described as an effective oral option with improved tolerability and once-daily dosing advantages [66–69].

Addressing Limitations of Conventional Oral Progesterone

By providing controlled drug release, improved bioavailability, and reduced first-pass metabolism, SR oral progesterone formulations address several key limitations associated with conventional IR preparations [16,19,66,69]. The combination of gradual drug release, lymphatic absorption pathways, and sustained systemic exposure enables maintenance of progesterone concentrations within the physiological luteal range, supporting its role as an optimized oral delivery strategy [19,65].

Clinical Applications of Oral NMP

Oral NMP SR is widely used across gynecological and obstetric indications, including threatened or habitual abortion, PTB, luteal phase defect, dysfunctional uterine bleeding, endometriosis, and hormone replacement therapy [63,67,68]. Real-world and consensus-based evidence suggests that oral NMP, including SR formulations with once-daily dosing regimens, is used across multiple obstetric indications; however, the strength of evidence varies across indications, with most robust data in specific settings [70,71]. NMP, including SR formulations, is frequently utilized in the management of high-risk pregnancies in clinical practice, particularly among women with prior PTB, adverse obstetric history, or cervical risk factors, although such observations largely reflect prescribing patterns rather than efficacy outcomes [72–74]. In these settings, oral SR formulations have been incorporated into routine care over extended durations, including use in women with bad obstetric history, RPL, and prior PTB as part of primary or secondary prophylactic strategies [75]. Contemporary textbooks such as Essentials of Medical Pharmacology by K.D. Tripathi and Towards Zero Preterm Delivery Practice by Girija Wagh, along with guideline-based resources including FOGSI ethical evidence-based recommendations for preterm labour, KFOG key practice guidelines, and the FOGSI Perinatology Committee, describe oral oral NMP SR (200–400 mg once daily) as a therapeutic option in LPS during ART, prevention of threatened miscarriage, and in women at risk of preterm birth, including those with a short cervix and those requiring maintenance tocolysis following arrested preterm labour [62,63,66,74,76,77].

Luteal Phase Support

LPS is a cornerstone of ART, necessitated by impaired corpus luteum function following ovarian stimulation and the resulting deficiency in endogenous progesterone [78,79]. The dependence on luteal progesterone secretion persists during early gestation until placental endocrine function becomes sufficient, reinforcing the clinical importance of timely hormonal support [80].

Multiple routes of progesterone administration have been evaluated for LPS. While vaginal progesterone is widely used due to targeted uterine delivery, oral NMP provides a non-invasive and patient-preferred alternative in selected settings [81]. Early studies demonstrated that oral NMP initiated at oocyte retrieval significantly increased serum progesterone concentrations ($P < 0.001$) and prolonged luteal phase duration ($P < 0.05$) compared with unsupplemented IVF cycles [82]. Subsequent comparative trials evaluating oral IR NMP against vaginal formulations have shown comparable pregnancy rates, spontaneous abortion rates, and delivery outcomes, with no statistically significant differences observed between the two routes of administration [49,83], although vaginal progesterone has demonstrated higher implantation rate in a comparative study [49]. A Cochrane meta-analysis incorporating randomized trials across progesterone

regimens confirmed that progesterone supplementation improved clinical pregnancy outcomes versus no treatment, but no consistent superiority of any specific route was established [84]. Data from a large multicenter randomized non-inferiority trial demonstrated that oral NMP at a dose of 400 mg per day achieved ongoing pregnancy rates comparable to vaginal progesterone, with rates of 35.3% and 38.0%, respectively, thereby confirming non-inferiority between the two routes in luteal phase support [85].

Clinical observations demonstrate attainment of mid-luteal progesterone levels within the therapeutic range by Oral NMP SR [86], with additional real-world data suggesting maintenance of these levels alongside improved tolerability and treatment adherence [20]. In an open-label observational study of intrauterine insemination cycles, SR NMP showed comparable LPS to dydrogesterone, with similar serum progesterone levels achieved [66,87]. However, robust comparative trials evaluating reproductive outcomes with SR oral progesterone in ART settings remain limited. Consensus-based evaluations indicate growing clinician preference for SR formulations in LPS settings [88]. Overall, oral micronized progesterone represents a viable alternative for LPS, although route selection continues to depend on clinical context, patient preference, and tolerability.

Threatened Miscarriage and Early Pregnancy Support

Progesterone supplementation is frequently initiated during early pregnancy to support early gestation in women presenting with vaginal bleeding or those considered at increased risk of spontaneous pregnancy loss. However, evidence evaluating oral NMP in threatened miscarriage remains heterogeneous across study designs and patient populations.

Randomized evidence from the TRoMaD trial demonstrated comparable efficacy between oral NMP and dydrogesterone in terms of miscarriage rates and resolution of vaginal bleeding [89]. In contrast, a randomized study reported a significantly higher rate of miscarriage prevention with oral NMP compared to vaginal administration, with rates of 91.8% and 73.5%, respectively ($P = 0.0164$) [90]. Oral NMP SR has also been evaluated in women with threatened abortion, demonstrating comparable pregnancy continuation outcomes to vaginal progesterone [91]. Conversely, prospective comparative data in high-risk pregnancies demonstrated numerically higher patient acceptability with oral progesterone and higher pregnancy continuation rates with vaginal progesterone, although not statistically significant, underscoring variability in route-related clinical responses [92].

Furthermore, in women presenting with first-trimester threatened abortion, short-term treatment with oral NMP was associated with a significantly greater increase in placental volume compared with untreated controls [93]. However, the clinical significance of these findings remains uncertain.

Observational data support the practical use of oral NMP, including SR formulations, in early pregnancy bleeding and high-risk obstetric contexts, particularly in terms of symptom improvement and practical advantages related to dosing convenience and adherence [20]. Historical retrospective clinical experience has also described favourable pregnancy continuation patterns following short-term oral NMP therapy in women with threatened abortion [94]. At a broader level, systematic evaluations of progestogen therapy in miscarriage prevention have demonstrated variability in treatment effects across formulations, routes, and patient populations [95]. Prospective comparative studies in high-risk pregnancies have reported differences in perinatal outcomes between oral and vaginal NMP, underscoring route-dependent variability in clinical response [96].

Recurrent Pregnancy Loss

RPL, defined as the loss of two or more consecutive pregnancies, affects approximately 1-2% of couples and represents a significant clinical challenge, with progesterone deficiency implicated in selected cases [97]. Meta-analytic evidence from randomized trials suggests that progestogen therapy may reduce the risk of miscarriage in women with RPL (risk ratio 0.73, 95% confidence interval 0.54–1.00) and may be associated with a modest improvement in live birth rates [95]. Large randomized trials evaluating progesterone therapy in early pregnancy have demonstrated improved outcomes in women with a history of RPL, particularly in those presenting with early pregnancy bleeding [98].

Emerging evidence also suggests an immunomodulatory role of oral NMP in women with RPL, with favorable modulation of cytokine profiles and lower abortion rates reported compared to untreated groups [99]. In observational clinical settings, oral NMP SR has been utilized in women with RPL, including those with unexplained etiology. Reported cohorts have included women with ≥2 prior pregnancy losses, in whom oral NMP SR was commonly administered at doses of approximately 200–300 mg daily. Pregnancy follow-up in these cohorts extended to later gestational time points, providing insights into real-world patterns of use [19,75].

Prevention of Preterm Birth

PTB remains a leading cause of neonatal morbidity and mortality worldwide, with short cervical length (≤25 mm) and prior PTB being key risk factors [100–102]. Progesterone plays a key role in maintaining uterine quiescence and cervical integrity throughout pregnancy, and disruption of progesterone-mediated pathways has been implicated in the initiation of preterm labor [9]. Accordingly, oral NMP therapy is recommended for the prevention of PTB in at-risk singleton pregnancies, particularly in women with a prior history of preterm delivery or a short cervix [74,103–105]. In women

with a short cervix, a recognized risk factor for PTB, oral NMP has shown outcomes comparable to cervical cerclage in terms of PTB and neonatal parameters [106].

Available clinical evidence for oral progesterone in PTB prevention remains more limited compared with vaginal formulations [107]. Randomized evidence has demonstrated a significant reduction in PTB rates with oral NMP compared with placebo,-as indicated by lower rates of preterm delivery (39.2% vs 59.5%; P = 0.002), significantly prolonged gestational age at delivery (36.1 vs 34.0 weeks; P < 0.001), and reduced early PTB risk (RR 0.20; 95% CI 0.05–0.73) [108]. Similarly, a randomized study demonstrated a statistically significant reduction in spontaneous preterm delivery (relative risk 0.7; 95% confidence interval 0.54–0.92; P = 0.01), along with a significant prolongation of gestational age at birth (35.4 vs 33.9 weeks; P = 0.01) [109]. Additional studies have similarly reported reduced risk of spontaneous PTB and prolongation of gestation with oral NMP [110]. Improvements in neonatal outcomes, including higher birth weight and reduced rates of neonatal intensive care unit admission, have also been reported [108–110]. However, evidence remains limited by smaller sample sizes and heterogeneity in study design, and some studies have not demonstrated statistically significant benefits [111]. In addition to its prophylactic use, oral NMP has also been evaluated in women presenting with symptoms suggestive of preterm labor, where it has been used as part of clinical management alongside other approaches [112]. However, more favorable gestational age at delivery and neonatal outcomes with vaginal progesterone compared with oral administration were reported in women presenting with symptoms suggestive of preterm labour [113]. Its use as maintenance therapy following arrested preterm labour has demonstrated flexibility in administration without compromising maternal or neonatal outcomes, and has been further associated with significant prolongation of latency to delivery, with a mean duration of 33.29 days compared to 23.07 days in the placebo control group, along with a reduction in PTB rates from 58% to 33% (P<0.05), and improved neonatal outcomes including higher birth weight when evaluated as maintenance tocolysis in randomized settings [114]. Additional evidence indicates that oral NMP allows flexibility in dosing without compromising maternal or neonatal outcomes [115], with further support from clinical practice guidance and real-world data supporting its use as maintenance therapy in women with arrested preterm labour [74,76]Oral NMP SR formulations offer practical advantages such as once-daily dosing and improve treatment adherence, but clinical outcome data specific to PTB prevention remain limited [16,19,20]. In mixed high-risk populations, including women with threatened abortion and those at risk of preterm labour, SR oral progesterone has been assessed alongside vaginal formulations in clinical settings [116].

Safety and Tolerability of Oral Natural Micronized Progesterone

Immediate-Release Oral NMP

In LPS settings, oral NMP shows acceptable tolerability, but with a higher incidence of CNS-related symptoms (notably drowsiness) compared with vaginal progesterone. Other systemic effects (e.g., irritability, decreased libido, dyspareunia) are more frequent with oral use, whereas vaginal formulations are associated with local irritation [49,83,85]. Overall safety profiles are comparable across routes, with predominantly mild AEs and no significant differences in primary outcomes; however, heterogeneity in reporting limits definitive comparisons [84,85].

In women with threatened miscarriage, oral NMP has been generally well tolerated, with only occasional reports of mild AEs such as headache and dizziness [94]. Comparative data further indicate that CNS-related symptoms, particularly drowsiness, may occur more frequently with oral NMP IR than with other oral progestogens such as dydrogesterone [89]. However, pharmacovigilance analyses have identified a signal of increased reporting of birth defects, including hypospadias and congenital heart defects, with dydrogesterone exposure [117,118]. Oral NMP has been associated with significantly lower rates of preterm birth (11.8% vs 44.2%; P < 0.001) and low birth weight (15.3% vs 33.7%; P = 0.007), and higher birth weight (3324.58 ± 546.15 g vs 2734.76 ± 784.42 g; P < 0.001) and gestational age (38.77 ± 1.79 vs 35.68 ± 4.07 weeks; P<0.001) compared with dydrogesterone [11]. An ongoing multicentric randomized controlled trial is currently evaluating oral NMP versus dydrogesterone in threatened miscarriage, highlighting the need for robust comparative evidence [119].

In PTB prevention, oral NMP is not associated with an increased risk of major maternal complications, including gestational hypertension, postpartum hemorrhage, or infections [109]. Reported AE remain predominantly mild e.g., somnolence, dizziness, vaginal dryness, and occasional GI symptoms, with no treatment discontinuations in most studies [108,111]. Meta-analyses and observational data similarly indicate a higher frequency of mild CNS and mucosal symptoms versus placebo, but no serious AEs or clear attribution of adverse maternal outcomes to oral progesterone use has been established [41,110,112].

In women with a short cervix, NMP has demonstrated comparable maternal and neonatal safety outcomes to cervical cerclage, with no significant differences in obstetric or neonatal complications [106].

Sustained-Release Oral NMP

Oral NMP SR has been associated with improved tolerability, likely due to reduced first-pass hepatic metabolism and more stable systemic exposure [120]. Across clinical settings, including LPS and high-risk pregnancies, AEs with Oral NMP SR formulations are infrequent and predominantly mild, with relatively lower rates of CNS-related symptoms such as drowsiness or dizziness and occasional GI disturbances, and no reports of serious AEs or treatment-related hospitalizations [75,121]. In LPS settings, tolerability is good, with minimal next-day somnolence and only isolated

mild AEs [86,87]. In women with RPL receiving oral NMP SR, no major safety concerns or serious adverse events requiring treatment discontinuation have been reported in observational studies [75]. Real-world and surveillance data also support a low AE burden with once-daily SR dosing in women receiving treatment for reproductive and high-risk pregnancy indications [75,121].

Comparative evidence suggests that SR formulations may offer improved tolerability and a lower burden of CNS-related AEs compared with IR preparations, consistent with their pharmacokinetic profile, although direct comparative evidence remains limited [19,20].

Future Perspectives

SR formulations have improved the pharmacokinetic profile and convenience of oral micronized progesterone; however, variability in absorption and systemic exposure remains a challenge. Future efforts should focus on advanced formulation strategies such as optimized polymer matrices and lipid-based delivery systems to enhance bioavailability and achieve more predictable drug delivery. Equally important is the need for robust comparative and real-world evidence to better define the role of IR and SR formulations across key obstetric indications such as LPS, threatened miscarriage, and prevention of PTB. Standardized endpoints and head-to-head studies will be critical in guiding clinical practice. Overall, continued innovation in drug delivery, along with stronger clinical evidence, is expected to further optimize the use of oral micronized progesterone as a convenient and effective option in obstetric care.

Conclusion

Oral NMP remains a valuable therapeutic option across reproductive and obstetric indications, offering the advantages of ease of administration and patient acceptability. While IR formulations are effective, their use is limited by pharmacokinetic variability and CNS-related AEs associated with fluctuating systemic exposure. Oral SR formulations represent a promising advancement, addressing key limitations of IR preparations by providing more consistent systemic hormone levels, reduced peak–trough fluctuations, and improved tolerability. The convenience of once-daily dosing further enhances treatment adherence, particularly in clinical settings requiring prolonged progesterone support. Clinically, oral NMP SR plays a key role in LPS, threatened abortion, RPL, and prevention of PTB, where progesterone supplementation is integral to improving pregnancy outcomes. Emerging evidence and real-world data suggest that SR formulations offer practical advantages across these indications, particularly in terms of dosing convenience and tolerability. Overall, oral NMP SR represents a clinically relevant and patient-friendly optimization of progesterone therapy, with the potential to enhance adherence and consistency of treatment across key obstetric indications. Future large-scale, well-designed trials are warranted to establish definitive efficacy, safety, and positioning of oral SR progesterone in clinical practice.

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Competing Interests

The authors declare no conflicts of interest.

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