

REVIEW ARTICLE

Progestogen therapy in threatened miscarriage and unexplained recurrent pregnancy loss: Recommendations by the Thai interest group

Kiattisak Kongwattanakul¹  | Phudit Jatavan² | Olarik Musigavong³ |
Savitree Pranpanus⁴ | Lingling Salang⁵  | Chonthicha Satirapod⁶ | Somsin Petyim⁷ |
Boonchai Uerpairojkit⁸ 

¹Maternal Fetal Medicine Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

²Maternal and Fetal Medicine Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Thailand

³Chaophya Abhaibhubejhr Hospital, Prachinburi, Thailand

⁴Department of Obstetrics and Gynecology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand

⁵Reproductive Medicine Unit, Obstetrics and Gynecology Department, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

⁶Reproductive Endocrinology and Infertility Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

⁷Reproductive Biology and Infertility Unit, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

⁸Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Correspondence

Boonchai Uerpairojkit, Division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.
Email: boonchaiu59@gmail.com

Funding information

Abbott Laboratories Ltd., Bangkok, Thailand

Abstract

Aim: Threatened miscarriage and unexplained recurrent pregnancy loss (RPL) pose significant physical and psychological challenges for women and their families globally. The lack of local guidelines and variations in recommendations by existing guidelines result in inconsistent management of these conditions in Thailand. The Thai interest group aims to provide recommendations to healthcare providers for the use of progesterone supplementation in women experiencing threatened miscarriage and unexplained RPL.

Methods: Existing guidelines and relevant studies were reviewed to explore the role of oral, vaginal, and injectable progestogens. In the present evidence-based recommendations, the Thai interest group delineated effective diagnostic and therapeutic strategies for managing patients with threatened miscarriages and unexplained RPL.

Results: Treatment initiation for unexplained RPL is recommended after experiencing two or more pregnancy losses, regardless of consecutive occurrences. Oral progestogen (dydrogesterone) is recommended for the management of both threatened miscarriage and unexplained RPL. Exceeding 200 mg of micronized vaginal progesterone (MVP) per intake is not advisable for threatened miscarriage or preventing recurrent miscarriage because of luteal phase insufficiency. Treatment with intramuscular injection progestin should be continued at a dosage of 250 mg twice weekly for several weeks. Additionally, patient experiences and safety concerns related to MVP and injectable progestogens are discussed.

Conclusion: These inaugural evidence-based Thai recommendations can be applied in regional healthcare settings for improved outcomes in threatened miscarriage and unexplained RPL. Further research is needed to better understand the epidemiology and etiology of these conditions in Thailand.

KEYWORDS

progesterone, progestogen, recommendations, recurrent pregnancy loss, threatened miscarriage

INTRODUCTION

Threatened miscarriage is the most common complication in early pregnancy and is characterized by vaginal bleeding through a closed cervical os with or without abdominal pain. It is estimated to occur in approximately 15% to 20% of pregnancies before the 20th week of gestation, and 20% to 25% of cases eventually progress to spontaneous miscarriage.^{1–4} The prevalence varies across Asian countries, with reported rates of 8.3% to 11.5%.^{5,6}

Recurrent pregnancy loss (RPL), defined as three consecutive pregnancy losses before 20 weeks from the last menstrual period, affects 1% to 2% of women.^{7,8} Estimating its prevalence is challenging due to diverse patient populations and varied guidelines.⁹ Clinically confirmed recurrent miscarriages range from 0.8% to 1.4%, increasing to 2% to 3% with biochemical losses.^{8,10} The mean incidence of RPL in pregnant women was 0.65% in Sweden.¹¹ The prevalence was 15.34% in Nigeria,¹² and it varied between 5% and 12% in Asia.^{13,14} RPL prevalence in Thailand is unknown. The cause remains unexplained in 50% to 75% of RPL cases.^{15,16} Each additional miscarriage increases the risk by nearly 10%, reaching 42% in women with ≥ 3 previous miscarriages.¹⁷

The etiology of threatened miscarriage and RPL is complicated and multifactorial. Commonly accepted risk factors include chromosomal abnormalities, uterine structural anomalies, maternal thrombophilic disorders, immunological dysfunction, and endocrine disorders (including insufficient progesterone levels). Maternal age and obesity, previous history of miscarriage, infectious agents, lifestyle factors, and environmental exposure act as additional risk factors.^{2,9,16,18–21} The miscarriages due to aneuploidy occur randomly and do not increase the risk of a subsequent miscarriage. However, euploid miscarriages are more commonly diagnosed with an increasing number of previous miscarriages.²²

Luteal phase defect (LPD), associated with progesterone insufficiency in early pregnancy, is considered a potential cause of miscarriage.^{2,23} LPD is recognized as a contributing factor to euploid miscarriages, and its prevalence may rise with previous miscarriages.^{22,24} Sadekova et al.²⁵ diagnosed LPD more frequently in women with recurrent miscarriage than in fertile women without gynecological diseases. A significantly lower expression of vascular endothelial growth factor mRNA in LPD endometrium suggests an association with angiogenic abnormalities, leading to placental insufficiency and pregnancy complications. Causes of LPD include impaired corpus luteum function, inadequate endometrial response to estradiol and progesterone²⁶ and insufficient placentation or trophoblast function.²⁷ Threatened miscarriage and RPL impose substantial physical and psychological burdens on women and their families.³ Threatened miscarriage is associated with significant anxiety and depressive symptoms.²⁸ RPL increases the risk of obstetric complications, long-term

cardiovascular issues, post-traumatic stress, anxiety, and depression.^{17,29–31} Miscarriage can also have social impact, resulting in a lower birth rate, reduced workforce, and fewer taxpayers, thereby limiting government resources for national progress.^{32–35}

Role of progesterone in early pregnancy

Progesterone and estradiol secretion by the corpus luteum, and placental human chorionic gonadotropin production are pivotal endocrine events in early pregnancy.³⁶ The luteo-placental shift, occurring between weeks 6 and 8, with completion by weeks 10 to 11, marks the transition of progesterone production from the corpus luteum to the placenta.^{26,36–38} Progesterone is essential for establishing and maintaining early pregnancy,^{26,39–41} preparing the endometrium for blastocyst implantation, sustaining decidualization, suppressing uterine contractility, and controlling cervical competence.^{26,42} Moreover, progesterone promotes maternal immune tolerance to the fetal semi-allograft by modulating cytokine expression, favoring anti-inflammatory Th2 cytokines (e.g., interleukin-4, -6, and -10) over proinflammatory Th1 cytokines (e.g., interferon- γ , tumor necrosis factor- α).^{43–46}

Given its well-documented physiological role in early pregnancy, progesterone treatment (oral, intramuscular, or vaginal suppository) has been evaluated, and the data suggest that it prevents miscarriage.^{2,3} Target populations for progesterone therapy include women at higher overall risk of miscarriage, particularly those with potential pathologies such as LPD.²² High-risk women, identified by early pregnancy bleeding and ≥ 1 previous miscarriage(s), may benefit from vaginal progesterone treatment, given that the risk of future miscarriage increases with each prior miscarriage.²²

Rationale of interest group recommendation and problem statement

Thailand lacks local guidelines for managing threatened miscarriage and unexplained RPL, leading to inconsistent clinical practices. International guidelines vary, and these may not be applicable in the Thai context. Moreover, Thailand has experienced a significant decline in birth rates, decreasing by 40% from 2012 to 2022. Population projections suggest a potential reduction from 66 to 33 million by 2083, posing challenges to the workforce, productivity, and key sectors. Childbirth promotion is now a national priority, prompting government initiatives.⁴⁷ Therefore, tailored recommendations are urgently needed for obstetrics and gynecology practice in Thailand. We present a comprehensive approach to managing threatened and recurrent miscarriages, addressing therapeutic options in the Thai setting.

Scope of interest group recommendation

Purpose

These evidence-based recommendations by the Thai interest group aim to standardize and provide guidance for the use of progesterone supplementation in women with threatened miscarriage and unexplained RPL in Thailand.

Target audience/user groups

The recommendations are directed toward multiple stakeholders with the intent to ensure effective treatment outcomes in women with threatened miscarriage and unexplained RPL. The target audience includes health-care providers who are qualified to manage pregnant women: maternal-fetal medicine specialists, obstetricians, general practitioners, advanced practice clinicians, and nurses.

Definitions/terminologies

The definitions of RPL vary across different guidelines, as shown in Table S1, Supporting Information. The Thai interest group defines recurrent miscarriage as ≥ 2 clinical pregnancy losses before 20 weeks, regardless of whether or not they are consecutive. The group believes that defining RPL as ≥ 2 pregnancy losses will facilitate research, shared decision-making, and psychological support for couples.

METHODS

A group of eight experts in obstetrics and gynecology from various institutions in Thailand, each with at least 15 years of recognized academic and clinical experience, was convened to support the development of this manuscript. Members were selected based on their expertise in early pregnancy care and contributed to identifying relevant literature, interpreting the clinical significance of the evidence, and ensuring its applicability to the Thai context.

A comprehensive literature search was conducted across two biomedical databases, PubMed and Embase, as well as gray literature sources like Google Scholar, spanning from August 2013 to August 2023. The search strategy employed a combination of keywords including: “threatened miscarriage,” “recurrent pregnancy loss,” “recurrent miscarriage,” “recurrent spontaneous miscarriage,” “repeated miscarriage,” “habitual abortion,” “unexplained recurrent pregnancy loss,” “unexplained recurrent miscarriage,” “hydroxyprogesterone caproate,” “poluton,” “hydroxyprogesterone,” “micronized vaginal

progesterone,” “micronized progesterone,” “progestogen,” “progestagen,” “gestogen,” “gestagen,” “progestin,” “dydrogesterone,” “preimplantation genetic screening,” “preimplantation genetic diagnosis,” and “treatment.” Articles, including randomized studies, systematic reviews and meta-analyses, network meta-analyses, recommendations, and guidelines published in English were included. Non-English publications, narrative reviews, letters, case reports, editorials, and studies focusing on other therapeutics were excluded.

Diagnostic and investigation tests for threatened miscarriage and unexplained recurrent pregnancy loss

Recommendation for diagnosis and investigations in threatened miscarriage

Vaginal bleeding is common in early pregnancy, affecting nearly 25% of women,⁴⁸ often indicating miscarriage ($\sim 20\%$ of recognized pregnancies).⁴⁹

After confirming pregnancy with positive beta-human chorionic gonadotropin in urine or serum, transabdominal pelvic ultrasound and/or transvaginal ultrasound (TVUS) are recommended (Figure 1). TVUS locates the pregnancy by assessing the intrauterine (IU) gestational sac (GS), with the presence of a yolk sac indicating an IU pregnancy. A crown-rump length (CRL) of ≥ 7 mm without fetal heartbeat suggests miscarriage.^{50,51} A CRL of < 7 mm prompts a repeat TVUS in 7 to 10 days to confirm viability. A mean sac diameter (MSD) of ≥ 25 mm without visible fetal pole (FP) indicates a missed miscarriage; an MSD < 25 mm may suggest early gestation, warranting repeat TVUS in 7 to 10 days.^{50,51} Absence of IU GS suggests ectopic pregnancy if an extrauterine GS or adnexal mass is present, while a diagnosis of complete miscarriage relies on clinical history and evidence of conception (IU GS or clinically observed products of conception [POC]). Visibility of POC on TVUS suggests an incomplete miscarriage; absence of POC observation indicates pregnancy of an unknown location.⁴⁹

In Rh-negative prevalent regions, assessing blood group and antibody status is crucial for anti-D immunoprophylaxis to prevent maternal sensitization and reduce Rh-D incompatibility risk in subsequent pregnancies.^{49,52} However, Thailand’s Rh-negative prevalence is low ($\sim 0.3\%$).^{53,54}

Recommendation for diagnosis and investigations in recurrent pregnancy loss

Recommendations for RPL vary across guidelines. The American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology suggest diagnosis after ≥ 2 pregnancy losses,^{8,55} while Royal College of Obstetricians and Gynecologists

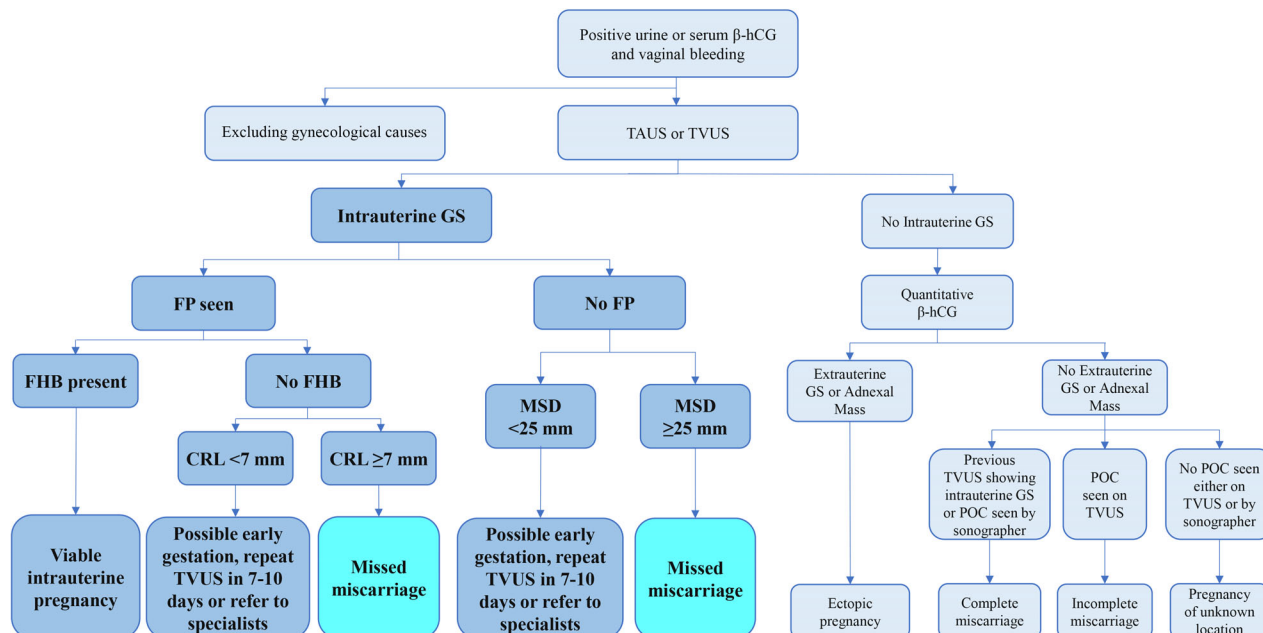


FIGURE 1 Investigation and differential diagnosis for bleeding in early pregnancy. β -hCG, beta-human chorionic gonadotropin; CRL, crown-rump length; FHB, fetal heartbeat; FP, fetal pole; GS, gestational sac; MSD, mean sac diameter; POC, products of conception; TAUS, transabdominal ultrasound; TVUS, transvaginal ultrasound.

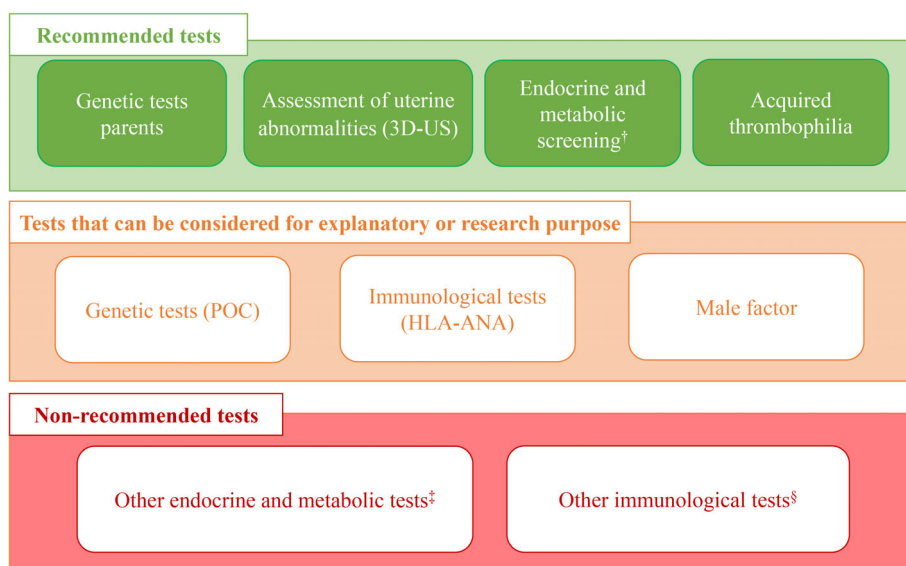


FIGURE 2 Recommendations for diagnostic investigations in women/couples with recurrent pregnancy loss. [†]Thyroid (TSH, TPO antibodies and T4), 75-g OGTT, prolactin concentration. [‡]AMH, androgens, vitamin D, luteinizing hormone, and hyperhomocysteinemia. [§]Human leukocyte antigen (HLA-DR or other classical HLA genes), anti-HY antibodies, cytokine and cytokine polymorphism, NK cells of either peripheral blood or endometrial tissue, and anti-HLA antibodies. 3D-US, three-dimensional ultrasound; AMH, anti-Müllerian hormone; ESHRE, European Society of Human Reproduction and Embryology; HLA, human leukocyte antigen; HLA-ANA, human leukocyte antigen-antinuclear antibody; HLA-DR, human leukocyte antigen-DR isotype; HY, male-specific minor histocompatibility; NK, natural killer; OGTT, oral glucose tolerance test; POC, products of conception; T4, Thyroxine; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

guidelines set the diagnostic threshold at ≥ 3 losses.⁵⁶ Identifying the underlying causes and therapeutic targets is crucial, prompting recommended investigations for all cases of RPL.⁸ Figure 2 outlines diagnostic recommendations for RPL investigations.

A comprehensive assessment is strongly advised for all RPL cases, covering medical and family history, uterine abnormalities, endocrine factors, and antiphospholipid syndrome (anticardiolipin antibody, lupus anticoagulants, $\beta 2$ glycoprotein I antibodies). Reviewing patient history

TABLE 1 Summary of guideline recommendations for the management and treatment of threatened miscarriage.

Guidelines/expert opinions	Recommendations/statements
FOGSI position statement 2015 ⁵⁷	• MVP: 400 mg/day till bleeding stops • Oral dydrogesterone: 40-mg loading dose followed by 20–30 mg/day till 7 days after the bleeding stops
RANZCOG guidelines 2018 ⁵⁸	• Progesterogen supplementation until the second trimester in women presenting with a clinical diagnosis of threatened miscarriage may reduce the rate of spontaneous miscarriage and may be considered
NICE guidelines 2023 ⁵¹	• Advise a woman with a confirmed intrauterine pregnancy with a fetal heartbeat who presents with vaginal bleeding but has no history of previous miscarriage, that ◦ if her bleeding gets worse, or persists beyond 14 days, she should return for further assessment ◦ if the bleeding stops, she should start or continue routine antenatal care • Offer MVP 400 mg BID to women with an intrauterine pregnancy confirmed by a scan, if they have vaginal bleeding and have previously had a miscarriage • If a fetal heartbeat is confirmed, continue progesterone until 16 completed weeks of pregnancy • Rationale for the recommendation: There was good evidence that 400 mg BID of MVP increases the number of live births in women with early pregnancy bleeding and a previous miscarriage. There was no evidence of benefit for any other preparations or doses of progesterone, so the committee made a recommendation for research
Saudi Arabian guidelines 2019 ⁵⁹	• Oral dydrogesterone should be offered ◦ Manufacturer dosage: 40-mg loading, then 30 mg/day until symptoms (bleeding) remit ◦ If symptoms persist/recur, increase the dose by 10 mg TID. Maintain effective dose for 1 week after symptoms have ceased and then gradually reduce the dose. Immediately resume treatment at an effective dose, if symptoms recur • Available evidence is insufficient to recommend the use of vaginal and injectable progestogens
Malaysian guidelines 2020 ⁶⁰	• In women with no previous miscarriage, initiate oral dydrogesterone 10 mg BID at diagnosis and continue until 1 week after bleeding has stopped ◦ MVP is not recommended • In women with a history of ≥ 1 previous miscarriage, micronized progesterone 400 mg BID per vagina/rectal or dydrogesterone 10 mg BID from the onset of bleeding up to 16 weeks of pregnancy may be considered
Turkish Expert Opinion 2023 ³	• Progesterone use, especially the efficacy of oral dydrogesterone, was supported by 83.33% of the experts • Safety of dydrogesterone and its recommendation for the treatment of threatened miscarriage according to relevant guidelines was unanimously agreed • Indecision was expressed regarding the initial loading dose of dydrogesterone for treating threatened miscarriage

Abbreviations: BID, twice daily; FOGSI, Federation of Obstetric and Gynecological Societies of India; MVP, micronized vaginal progesterone; NICE, National Institute for Health and Care Excellence; RANZCOG, Royal Australian and New Zealand College of Obstetricians and Gynecologists; TID, three times a day.

aids in tailoring diagnostic investigations. Three-dimensional ultrasound is preferred for assessing uterine anomalies, with two-dimensional (2D) ultrasound acceptable depending on expertise.^{8,48}

In Thailand, 2D ultrasound is suitable for screening uterine anomalies when performed by trained professionals. Thyroid screening may be considered based on test availability. Genetic analysis of embryos or parents, immunological tests (human leukocyte antigen-antinuclear antibody), and sperm DNA fragmentation are mainly for research due to weak associations with RPL. For genetic analysis of pregnancy tissue, array-based comparative genomic hybridization is recommended. Other metabolic and hormonal tests (anti-Müllerian hormone, androgens, vitamin D, luteinizing hormone, hyperhomocysteinemia) lack evidence of associations with RPL.⁸

TREATMENT

Progestogen therapy in threatened miscarriage

Recommendations proposed by various national and international clinical guidelines for the use of

progestogens in the treatment of threatened miscarriage are summarized in Table 1.

The role of oral, vaginal, and injectable progestogens in the treatment of threatened miscarriage has been investigated in several studies and systematic reviews (Table 2).

Role of dydrogesterone (oral progestogen)

The beneficial effects of dydrogesterone in threatened miscarriage have been evaluated in several clinical trials. In pregnant women with threatened miscarriage at <13 weeks of gestation, the pregnancy success rate (viable pregnancies at 20 weeks) was significantly higher in the dydrogesterone group compared with conservative treatment (95.9% vs. 86.3%; $p = 0.037$).⁶¹ Similarly, among women experiencing vaginal bleeding up to 16 weeks of pregnancy, significantly higher pregnancy success rates were noted with dydrogesterone treatment versus conservative management (87.5% vs. 71.6%); along with a significantly lower miscarriage rate in the dydrogesterone group ($p < 0.05$ for both).⁵ A randomized controlled trial (RCT) conducted in pregnant women

TABLE 2 Characteristics and outcomes of studies using progesterone therapy in threatened miscarriage and unexplained recurrent pregnancy loss.

Study reference	Study location	Study design	Patient population (no. of patients)	Intervention versus control (no. of patients or %)	Key findings or outcomes
Progesterone therapy in patients with threatened miscarriage					
Omar et al. 2005 ⁶¹	NA	Prospective, open study	Pregnant women with threatened miscarriage at <13 weeks gestation (without a history of recurrent miscarriage; $N = 154$)	- Dydrogesterone (40-mg stat, followed by 10 mg BID until the bleeding stopped; $n = 74$) versus conservative management with bed rest and folic acid ($n = 80$) - Women in the treatment group were also recommended bed rest and received folic acid	Significantly higher pregnancy success rate (viable pregnancies at 20 weeks) in the dydrogesterone treatment group than in the conservative management group (95.9% vs. 86.3%; OR 3.773; 95% CI 1.009 to 14.108; $p = 0.037$)
Pandian 2009 ⁵	Malaysia	Prospective, open, randomized study	Women with vaginal bleeding up to week 16 of pregnancy ($N = 191$)	Dydrogesterone (40-mg stat, followed by 10 mg BID; $n = 96$) treatment continued until 16 weeks of gestation versus conservative management with bed rest ($n = 95$)	- Significantly higher success rate of pregnancy (continuation of pregnancy beyond 20 weeks) in the dydrogesterone group than in the control group (87.5% vs. 71.6%; $p < 0.05$) - Significantly lowered miscarriages in the dydrogesterone group compared with the control group (12.5% vs. 28.4%; $p < 0.05$; OR 0.36; 95% CI 0.172 to 0.756) - No between-group differences in the incidence of cesarean section and complications such as placenta previa, antepartum hemorrhage, preterm labor (28–36 weeks), pregnancy-induced hypertension or low-birth-weight (<2500 g) babies
El-Zibdeh and Yousef 2009 ⁶²	Jordan	RCT	Pregnant women with mild or moderate vaginal bleeding during the first trimester of pregnancy ($N = 146$)	- Oral dydrogesterone (10 mg BID [continued until 1 week after the bleeding had stopped]; $n = 86$) versus no treatment ($n = 60$) - All women received standard supportive care; including iron, folic acid and multivitamin supplements; and recommended bed rest	- Significantly lowered miscarriage incidence in the dydrogesterone group than in the untreated group (17.5% vs. 25%; $p \leq 0.05$) - No significant differences between the groups regarding pregnancy complications or congenital abnormalities
Chan et al. 2021 ⁶³	Hong Kong	Randomized, double-blind, controlled study	Women presenting with vaginal bleeding during the first trimester ($N = 406$)	Oral dydrogesterone (40 mg orally, followed by 10 mg orally TID [in accordance with the prescription instruction]; $n = 203$) versus placebo ($n = 203$)	- Miscarriage rates before 20 weeks of gestation were similar in the progestogen and placebo groups (12.8% vs. 14.3%; RR 0.897; 95% CI 0.548 to 1.467; $p = 0.772$) - Live birth rate was also comparable between the progestogen group (81.3%) and the placebo group (83.3%; $p = 0.697$) - Safety profile was similar between both groups
Siew et al. 2018 ⁶⁴	Singapore	Prospective, parallel-group, open-label, single-center, RCT	Patients with threatened miscarriage (single intrauterine pregnancy at 6–10 weeks of gestational age and vaginal bleeding; $N = 141$)	Oral micronized progesterone (200 mg BID for 2 weeks; $n = 59$) versus oral dydrogesterone (10 mg BID for 2 weeks; $n = 59$)	- Comparable miscarriage rates and extent of bleeding between the treatment groups - Significantly greater number of women treated with micronized progesterone experienced drowsiness compared with dydrogesterone (34 vs. 17; $p = 0.003$)
Carp 2012 ⁶⁵	-	Systematic review and meta-analysis of 5 RCTs	Pregnant women with threatened miscarriage ($N = 660$)	Oral dydrogesterone ($n = 335$) versus standard of care (placebo or bed rest; $n = 325$)	- Miscarriage rate was reduced to 13% (44/335) with the administration of dydrogesterone compared with 24% (78/325) in the control group (absolute reduction: 11%) - Dydrogesterone administration was associated with a significant 47%

TABLE 2 (Continued)

Study reference	Study location	Study design	Patient population (no. of patients)	Intervention versus control (no. of patients or %)	Key findings or outcomes
Lee et al. 2017 ⁶⁶	-	Systematic review and meta-analysis of 9 RCTs	Pregnant women experiencing threatened abortion (<i>N</i> = 913)	Oral dydrogesterone (<i>n</i> = 322); vaginal progesterone (<i>n</i> = 213) vs. placebo or conservative treatment (<i>n</i> = 378)	reduction in the odds of miscarrying (OR 0.47; 95% CI 0.31 to 0.7) - Significantly reduced miscarriage incidence in the oral dydrogesterone group than in the control group (11.7% vs. 22.6%; OR 0.43; 95% CI 0.26 to 0.71; <i>p</i> = 0.001; <i>I</i>² 0%; trials 3; low-quality evidence) - Lower miscarriage incidence in the vaginal progesterone group than in the control group; however, this difference was not statistically significant (15.4% vs. 20.3%; <i>P</i> = 0.30; <i>I</i>² 0%; trials 4; high-quality evidence)
Wahabi et al. 2018 ²	-	Cochrane review and meta-analysis of 7 RCTs	Pregnant women, with threatened miscarriage ≤23 weeks and who had a confirmed viable pregnancy (<i>N</i> = 696)	Oral progestogen (<i>n</i> = 218) versus no treatment (<i>n</i> = 190) Vaginal progesterone (<i>n</i> = 143) versus placebo (<i>n</i> = 145)	- Oral progestogen probably reduces the miscarriage rate compared with no treatment (RR 0.57; 95% CI 0.38 to 0.85; trials: 3; moderate-quality evidence) - Vaginal progesterone probably has little or no effect in reducing the miscarriage rate compared with placebo (RR 0.75; 95% CI 0.47 to 1.21; trials 4; moderate-quality evidence)
Wang et al. 2019 ⁶⁷	-	Meta-analysis of 8 RCTs	Pregnant women with threatened miscarriage (<i>N</i> = 845)	Progesterone (<i>n</i> = 437) versus placebo or no treatment (<i>n</i> = 408)	- Pooled data showed that the progesterone group had a lower risk of miscarriage (RR 0.64; 95% CI 0.48 to 0.85) compared with those receiving a placebo or no treatment - Dydrogesterone showed a lower risk of miscarriage (RR 0.49; 95% CI 0.33 to 0.75) than natural progesterone (RR 0.69; 95% CI 0.40 to 1.19) - Oral route had a reduced risk of miscarriage (RR 0.55; 95% CI 0.38 to 0.79) compared with vaginal administration (RR 0.58; 95% CI 0.28 to 1.21)
Li et al. 2020 ⁶⁸	-	Meta-analysis of 10 RCTs	Women with threatened miscarriage (any episode of vaginal bleeding within 24 weeks of gestation; <i>N</i> = 5056)	Oral progesterone; vaginal progesterone versus placebo or no treatment	- Oral progesterone increased the incidence of live birth (RR 1.17; 95% CI 1.04 to 1.31; <i>p</i> = 0.008; <i>I</i>² 0%; low-quality evidence), whereas there was no significant difference with the use of vaginal progesterone (RR 1.04; 95% CI 1.00 to 1.08; <i>p</i> = 0.07; <i>I</i>² 0%; moderate-quality evidence) - Risk of miscarriage was reduced only with the use of oral progestogen (RR 0.58; 95% CI 0.42 to 0.80; low-quality evidence) and not with vaginal progesterone (RR 0.90; 95% CI 0.80 to 1.01; moderate-quality evidence)
Zhao et al. 2022 ⁶⁹	-	Network meta-analysis of 59 RCTs (in Chinese or English)	Pregnant women with threatened miscarriage at or <28 weeks, (<i>N</i> = 10 424)	Vaginal progesterone; oral dydrogesterone; oral micronized progesterone; intramuscular progesterone versus placebo	Risk of miscarriage was the lowest with oral dydrogesterone (SUCRA 100.0%), followed by vaginal progesterone (SUCRA 67.9%)
Coomarasamy et al. 2019 ⁷⁰	United Kingdom	Multicenter, randomized, double-blind, placebo-	Women with vaginal bleeding in early pregnancy (<i>N</i> = 4153)	MVP suppository (400-mg progesterone, BID, through 16 weeks of gestation; <i>n</i> = 2079) versus placebo (<i>n</i> = 2074)	Incidence of live births after at least 34 weeks of gestation was 75% (1513/2025) in the progesterone group and 72% (1459/2013) in the placebo group

(Continues)

TABLE 2 (Continued)

Study reference	Study location	Study design	Patient population (no. of patients)	Intervention versus control (no. of patients or %)	Key findings or outcomes
		controlled trial			(relative rate 1.03; 95% CI 1.00 to 1.07; $p = 0.08$)
McLindon et al. 2023 ⁷¹	Australia	Single-center, double-blinded, placebo-controlled RCT	Pregnant women under 10 weeks gestation, experiencing a threatened miscarriage ($N = 278$)	Vaginal pessaries (400-mg progesterone nightly until 12 weeks of gestation or earlier if the pregnancy ended before 12 weeks; $n = 139$) versus placebo ($n = 139$)	- No significant difference between the groups in the incidence of miscarriage or stillbirth - Similar rates of live birth in the progesterone (82.4%) and placebo groups (84.2%; RR 0.98; 95% CI 0.88 to 1.09; $p = 0.683$) - No significant differences in the rates of miscarriage, subgroup analysis of live birth for history of miscarriage and perinatal outcomes
Devall et al. 2021 ⁷²	-	Network meta-analysis of 7 RCTs	Women at risk of miscarriage (threatened miscarriage: Early vaginal bleeding during the first trimester [12 weeks] of pregnancy or a history of recurrent miscarriage [as defined by the trialists]; $N = 5682$)	14 treatment arms: MVP: 21% (3 arms); dydrogesterone: 21% (3 arms); oral micronized progesterone: 7% (1 arm); 17-OHPC: 7% (1 arm); matched placebo: 43% (6 arms)	- Little or no improvement in live birth rate with MVP versus placebo in women with no previous miscarriages and early pregnancy bleeding (RR 0.99; 95% CI 0.95 to 1.04; trials 2; $n = 2261$; high-certainty evidence) - Increased the live birth rate with MVP compared with placebo in women with ≥ 1 previous miscarriage and early pregnancy bleeding (RR 1.08; 95% CI 1.02 to 1.14; trials 2; $n = 1829$; high-certainty evidence)
Beigi et al. 2016 ⁷³	Iran	Balanced, randomized, double-blind, single-center, controlled clinical trial	Pregnant women with threatened miscarriage at <34 weeks gestational age ($N = 190$)	Vaginal progesterone suppository (400 mg/day [every night to the end of week 34 of gestation]; $n = 95$) versus 17-OHPC (250-mg intramuscular injection/week; $n = 95$)	No significant difference in risk of preterm labor (<34 weeks) between the two groups (RR 1.31; 95% CI 0.47 to 3.66; $p = 0.59$)
Progesterone therapy in patients with unexplained RPL					
Saccone et al. 2017 ⁷⁴	-	Systematic review and meta-analysis of 10 trials	Women with a history of unexplained recurrent miscarriage ($N = 1586$)	Progestogens (including natural P and synthetic progestins; $n = 802$) versus placebo or no treatment ($n = 784$)	- Pooled data showed that women randomized to the progestogens group in the first trimester and before 16 weeks had a lower risk of recurrent miscarriage (RR 0.72; 95% CI 0.53 to 0.97) and higher live birth rate (RR 1.07; 95% CI 1.02 to 1.15) compared with those in the control group - Subgroup analysis of oral progestogens (RR 0.61; 95% CI 0.38 to 0.98), intramuscular progestogens (RR 0.54; 95% CI 0.29 to 0.94) and synthetic progestogens (RR 0.35; 95% CI 0.23 to 0.52), all agreed with the overall analysis - Subgroup analyses of intramuscular 17-OHPC (either dose scale or 500 mg/week) and of oral dydrogesterone (either 2×5-mg tablet TID or 10-mg BID) both agreed with the overall analysis (RR 0.69; 95% CI 0.35 to 0.88; and RR 0.47; 95% CI 0.30 to 0.73; respectively)
Haas et al. 2019 ²³	-	Cochrane review and meta-analysis of 12 RCTs	Women with unexplained recurrent miscarriage unclear etiology ($N = 1856$)	Progestogens (natural or synthetic) versus placebo or no treatment	- Progestogen supplementation may reduce the miscarriage rate compared with placebo/control (27.5% vs. 20.1%; average RR 0.73; 95% CI 0.54 to 1.00; $p = 0.10$; I^2 38%; trials 10; $n = 1684$; moderate-quality evidence) - No subgroup differences based on the route of administration of the progestogen

TABLE 2 (Continued)

Study reference	Study location	Study design	Patient population (no. of patients)	Intervention versus control (no. of patients or %)	Key findings or outcomes
El-Zibdeh 2005 ⁷⁵	Jordan	Prospective, randomized, controlled study	Women with a history of recurrent, unexplained spontaneous abortion ($N = 180$)	Oral dydrogesterone (10 mg BID [continued until 12th gestational week]; $n = 82$); intramuscular hCG (5000 IU every 4 days; $n = 50$) versus no additional treatment ($n = 48$) All women received standard supportive care, including multivitamin supplements and recommended bed rest	as indicated by the subgroup interaction test (test for subgroup differences: $p = 0.27$; I^2 24.7%) • Abortions were significantly less common in the dydrogesterone group (13.4%) than in the control group (29%; $p = 0.028$) • No significant differences between the groups for obstetric complications and delivery details
Carp 2015 ⁷⁶	-	Systematic review and meta-analysis of 3 studies	Women with recurrent miscarriage ($N = 509$)	Dydrogesterone vs. standard supportive care (placebo or bed rest)	• Miscarriage rate of 23% (55/234) in control women was reduced to 10.5% (29/275) after dydrogesterone administration (absolute reduction: 12.5%) • Significant reduction of 29% in the odds of miscarriage with dydrogesterone compared with standard care (OR 0.29; CI 0.13 to 0.65)
Coomarasamy et al. 2015 ⁷⁷	United Kingdom and Netherlands	Multicenter, double-blind, placebo-controlled, randomized trial	Women with unexplained recurrent miscarriage (defined as ≥ 3 consecutive or non-consecutive losses of pregnancy in the first trimester; $N = 836$)	MVP suppositories (400 mg of micronized progesterone BID through 12 completed weeks of gestation or earlier if an ectopic pregnancy was diagnosed or miscarriage occurred before 12 weeks; $n = 404$) versus placebo ($n = 432$)	• No significant difference in the rate of live births after 24 completed weeks of gestation between the progesterone group (65.8%; 262/398) and the placebo group (63.3%; 271/428 [RR 1.04; 95% CI 0.94 to 1.15; rate difference 2.5% points; 95% CI -4.0 to 9.0]) • Rates of clinical pregnancy (at 6 to 8 weeks), ongoing pregnancy (at 12 weeks), ectopic pregnancy, miscarriage, stillbirth, and neonatal outcomes, as well as in the median gestational age at miscarriage were similar in the 2 groups

Abbreviations: 17-OHPC, 17 α -hydroxyprogesterone caproate; BID, twice daily; CI, confidence interval; hCG, human chorionic gonadotrophin; MVP, micronized vaginal progesterone; NA, not available; OR, odds ratio; RCT, randomized controlled trial or randomized clinical trial; RPL, recurrent pregnancy loss; RR, risk ratio or relative risk; SUCRA, surface under the cumulative ranking area; TID, three times a day; TVUS, transvaginal ultrasound.

with mild or moderate vaginal bleeding during the first trimester of pregnancy showed that the incidence of miscarriage was significantly lower in the dydrogesterone group compared with the untreated group (17.5% vs. 25%; $p \leq 0.05$).⁶² In another RCT comparing oral progestogen (dydrogesterone 40 mg, followed by 10 mg three times a day) with placebo in women presenting with threatened miscarriage in the first trimester, the primary outcome was miscarriage rate.⁶³ The use of oral progestogen did not reduce the miscarriage or improve the live birth rates. Several limitations may have influenced these findings, including the sample size ($N = 406$); though larger than in previous trials, it was inadequate to demonstrate a small difference in miscarriage rates; multiple pregnancies were included, which increased the miscarriage risk. Additionally, the live birth rate in this study was notably high (over 80%; progestogen group vs. placebo group: 81.3% vs. 83.3%) compared to rates

reported in other major trials, such as the PROMISE trial (live birth rate $\sim 63\%$). This unusually high baseline live birth rate may have limited the ability to detect a statistically significant difference between the treatment and placebo groups.⁶³ There were no significant differences between the groups for obstetrical complications such as incidence of cesarean section, placenta previa, preterm labor, antepartum hemorrhage, pregnancy-induced hypertension, or low-birth-weight babies.^{5,62,63}

Further, an open-label RCT in women presenting with threatened miscarriage demonstrated that the extent of bleeding during days 4 to 10 and subsequent miscarriage rates were comparable between the oral dydrogesterone and micronized progesterone treatment groups.⁶⁴

Four meta-analyses of RCTs demonstrated the efficacy of oral progestogen (dydrogesterone) in reducing miscarriage rates among women with threatened miscarriage. Dydrogesterone administration was associated

with a 47% reduction in the odds of miscarriage, compared with standard care, indicating a real treatment effect (absolute reduction in miscarriage rate: 11%).⁶⁵ Miscarriage incidences were significantly lower with oral dydrogesterone versus the control group (11.7% vs. 22.6%; $p = 0.001$), while vaginal progesterone did not show a significant reduction.⁶⁶ Oral progestogen reduced the miscarriage rate versus no treatment (risk ratio [RR] 0.57; 95% confidence interval [CI] 0.38 to 0.85), while vaginal progesterone probably had little or no effect when compared with placebo.² Furthermore, treatment with dydrogesterone demonstrated a reduced risk of miscarriage than natural progesterone, and the oral route exhibited a lower risk of miscarriage, compared with vaginal administration.⁶⁷

A recent meta-analysis investigating the improvement in the incidence of live birth with progesterone therapy versus placebo or no treatment reported that oral progestogen increased the incidence of live birth (RR 1.17; 95% CI 1.04 to 1.31; $p = 0.008$); while there was no significant difference with the use of vaginal progesterone (RR 1.04; 95% CI 1.00 to 1.08; $p = 0.07$). Moreover, the risk of miscarriage was reduced only with oral progestogen and not with vaginal progesterone.⁶⁸ Furthermore, in a recent network meta-analysis of 59 RCTs, oral dydrogesterone demonstrated the lowest risk of miscarriage, followed by vaginal progesterone in the treatment of threatened miscarriage.⁶⁹

A meta-analysis by Katalinic et al.⁷⁸ suggested using dydrogesterone for the prevention of miscarriages with no unwarranted safety concerns. The study showed no significant increase in the risk of congenital abnormalities with the use of dydrogesterone during the first trimester (pooled RR 0.96; 95% CI 0.57 to 1.62; RCTs 6), confirming previous conclusions of no causal association between fetal abnormalities and dydrogesterone use. Consistently, another recent meta-analysis provided evidence that the use of dydrogesterone during the first trimester poses no additional risk for congenital anomalies beyond the rate expected for all progestogens or environmental and genetic factors.⁷⁸

Role of micronized vaginal progesterone

The PRISM trial, a large RCT conducted at 48 UK hospitals, found no benefit of progesterone in the first trimester for women with early pregnancy bleeding. Live birth rates at ≥ 34 weeks were similar between the micronized vaginal progesterone (MVP) and placebo groups (75% vs. 72%; $p = 0.08$). Authors cautioned against generalizing PRISM's vaginal progesterone results to other administration routes due to molecular differences.⁷⁰ A recent placebo-controlled trial also showed no benefit of vaginal progesterone over placebo for live birth rate, miscarriage rates, live births stratified by miscarriage history, or obstetric outcomes in threatened miscarriage.⁷¹ In a

recent meta-analysis, MVP was found to increase live birth rates compared with placebo in women with ≥ 1 previous miscarriage and early pregnancy bleeding (RR 1.08; 95% CI 1.02 to 1.14; high-certainty evidence).⁷²

Role of 17 α -hydroxyprogesterone caproate (injectable progestogen)

Few studies have evaluated injectable progestogens for threatened miscarriage. A single-center RCT comparing vaginal progesterone with 17 α -hydroxyprogesterone caproate (17-OHPC) found no significant differences in preterm labor risk in women with threatened abortion at < 34 weeks of gestation.⁷³ Injectable progestogens for luteal-phase support, preterm birth, and pregnancy complications have been studied more thoroughly.^{79–82}

Concerns regarding the safety of 17-OHPC include an increased risk of gestational diabetes mellitus (GDM). A retrospective study demonstrated a significantly higher GDM incidence in women receiving 17-OHPC prophylaxis for the prevention of recurrent preterm birth compared with controls (12.9% vs. 4.9%; $p < 0.001$), prompting early GDM screening.⁸³ Egerman et al.⁸⁴ reported that early 17-OHPC initiation may increase GDM risk in obese pregnant women aged ≥ 35 years. Further clinical trials are needed to assess the efficacy and safety of 17-OHPC in women with threatened miscarriage.

While multiple studies and meta-analyses support the use of oral progestogen (dydrogesterone) in threatened miscarriage, findings remain inconsistent due to variability in study design, patient populations, dosing regimens, and outcome measures. Available evidence suggests a potential benefit of oral progestogen, while the role of vaginal and injectable formulations remains less conclusive.

Progestogen therapy in unexplained recurrent pregnancy loss

Recommendations for the use of progestogens in the treatment of unexplained RPL by various clinical guidelines are included in Table 3.

Studies have assessed the benefits of using various progestogens (oral, vaginal, and injectable) in the treatment of unexplained RPL (Table 2). A meta-analysis by Saccone et al.⁷⁴ (trials 10; $N = 1586$) reported that progestogen therapy reduced the incidence of miscarriages and seemed to be safe in women with a history of unexplained recurrent miscarriages during the first trimester of pregnancy. However, natural progesterone was not associated with a lower risk of recurrent miscarriage (RR 0.94; 95% CI 0.77 to 1.13). Similarly, another meta-analysis suggested that progestogen supplementation

TABLE 3 Summary of guidelines for the management and treatment of recurrent pregnancy loss.

Guidelines	Recommendations/statements
Saudi Arabian guidelines 2019 ⁵⁹	- Oral dydrogesterone should be offered - Manufacturer dosage of 10–20 mg/day, until the 20th week of pregnancy - Treatment should preferably start before conception - If symptoms of threatened miscarriage occur during treatment, continue the therapy as stated for that indication - Available evidence is not enough to recommend the use of vaginal and injectable progestogens
Malaysian guidelines 2020 ⁶⁰	- Consider progesterone therapy in women with unexplained recurrent miscarriages as it potentially reduces the rate of miscarriage - There is some evidence that oral dydrogesterone if initiated when fetal heart activity is confirmed is effective - Initiate oral dydrogesterone 20 mg OD once the pregnancy is diagnosed for up to 20 weeks of gestation - Vaginal progesterone is unlikely to be of benefit in women with unexplained RPL in women without bleeding in early pregnancy
ESHRE guideline 2022 ⁸	- Vaginal progesterone may improve live birth rate in women with ≥ 3 pregnancy losses and vaginal blood loss in a subsequent pregnancy - There is some evidence that oral dydrogesterone initiated when fetal heart action can be confirmed may be effective, but more trials are needed
German (DGGG), Austrian (OEGGG) and Swiss (SGGG) Societies of Gynecology and Obstetrics guideline 2022 ⁸⁵	- Treatment with natural micronized progesterone or with synthetic progestogens in the first trimester of pregnancy to prevent miscarriage is recommended for women with idiopathic recurrent miscarriage. - Natural micronized progesterone administered vaginally should be provided until the 16th week of gestation
RCOG guidelines 2023 ⁵⁶	- Routine progesterone supplementation should be used with caution in asymptomatic women with unexplained recurrent miscarriage - Progestogen supplementation should be considered in women with recurrent miscarriage who present with bleeding in early pregnancy (e.g., 400-mg MVP BID at the time of bleeding until 16 weeks of gestation)
FIGO Good Practice Recommendations 2023 ⁸⁶	- Oral progesterone[†] supplementation during pregnancy can be considered as there seems to be some beneficial impact on first-trimester recurrent miscarriage - Prescribing a daily dose of 20-mg oral progesterone would appear to be optimal; however, the limitations of published trials and the paucity of studies in this regard should be taken into consideration - Commencing natural vaginal progesterone at positive pregnancy test is not recommended in asymptomatic women with a history of unexplained recurrent miscarriage - Vaginal progesterone supplementation during pregnancy is not recommended as there is no beneficial impact on first-trimester recurrent miscarriage - Injectable progesterone supplementation during pregnancy is not recommended as there is no beneficial impact on first-trimester recurrent miscarriage. It is the authors' view that injectable progesterone may not be considered in low-resource settings due to cost and storage requirements
Ireland guidelines 2023 ⁸⁷	In women with ≥ 3 consecutive miscarriages immediately preceding their current pregnancy, empiric vaginal progestogen administration of 400 mg BID may be of some potential benefit

Abbreviations: BID, twice daily; DGGG, German Society of Gynecology and Obstetrics; ESHRE, European Society of Human Reproduction and Embryology; FIGO, International Federation of Gynecology and Obstetrics; MVP, micronized vaginal progesterone; OD, once daily; OEGGG, Austrian Society of Gynecology and Obstetrics; RCOG, Royal College of Obstetricians and Gynecologists; RPL, recurrent pregnancy loss; SGGG, Swiss Society of Gynecology and Obstetrics.

[†]Oral progesterone refers to oral dydrogesterone. The recommendation is based on the prospective, randomized, controlled study conducted by El-Zibdeh⁷⁵ in women with a history of recurrent, unexplained spontaneous miscarriage.

may reduce the miscarriage rate compared with placebo/no treatment in women with recurrent miscarriage of unclear etiology (27.5% vs. 20.1%; average RR 0.73; 95% CI 0.54 to 1.00; trials 10; $n = 1684$; moderate-quality evidence).²³

Role of dydrogesterone (oral progestogen)

A randomized study of women with a history of recurrent unexplained spontaneous abortion showed that hormonal support with dydrogesterone until the 12th week of gestation increased the chances of a successful pregnancy in these patients. Abortions were significantly less common in the dydrogesterone group than in the control group

(13.4% vs. 29%; $p = 0.028$).⁷⁵ Bashiri et al.⁸⁸ demonstrated a significant positive association of dydrogesterone treatment with live birth rates (adjusted odds ratio 1.592; 95% CI 1.051 to 2.413; $p = 0.028$).

A meta-analysis of three studies demonstrated that dydrogesterone effectively prevents miscarriages in women with a history of unexplained recurrent miscarriages. The odds of miscarriage were reduced by 29% with dydrogesterone treatment compared with standard care, indicating a real treatment effect.⁷⁶ Two meta-analyses by Katalinic et al.^{78,89} found no association between the use of dydrogesterone during the first trimester and congenital anomalies, offering reassurance regarding the safety profile of dydrogesterone in women with RPL. Few studies have reported side effects such as drowsiness and nausea/

TABLE 4 Summary of the recommendations for the use of progestogens in the management of threatened miscarriage and unexplained recurrent pregnancy loss.

	Oral progestogen	Micronized vaginal progesterone	Injection progestin
Posology	- Threatened miscarriage: An initial dose of up to 40 mg of dydrogesterone may be given, followed by 10 mg every 8 h until symptoms remit - Recurrent miscarriage: 10 mg twice daily until the 12th week of pregnancy¹⁰⁸ - Note: For recurrent miscarriage, oral progestogen should be administered when fetal heartbeat is detected^{8,60}	- Threatened miscarriage or prevention of recurrent miscarriage due to luteal phase insufficiency: The recommended dosage is from 200 to 400 mg/day in two divided doses until the 12th week of pregnancy¹⁰⁹ - Dosage should never exceed 200 mg per intake - Note: MVP should be provided to women with a history of ≥ 3 previous miscarriages and first-trimester bleeding^{8,22,87}	- Threatened miscarriage: 500 mg intramuscular 2–3 times weekly until bleeding ceases - Recurrent miscarriage: 250–500 mg intramuscular at weekly intervals - Treatment must be continued with 250 mg intramuscular twice weekly for several weeks¹¹⁰
Key consideration points	- Alleviating patient burden with reduced hospital visits compared with injectables - Convenient administration route with appropriate bloodstream drug levels^{93,94}	- For threatened miscarriage or prevention of recurrent miscarriage due to luteal phase insufficiency, oral micronized progesterone is not recommended¹⁰⁹ - Vaginal administration during bleeding might cause discomfort for patients - Vaginal discharge^{93,94,111} - Patients conceiving through ART may find it uncomfortable to switch from vaginal to oral administration of the same drug	- Painful injections and potential dermal inflammation/infections, including sterile abscesses at the injection site (progestogen in oil injection)^{105,112–114} - Patient burden: weekly hospital visits for drug administration^{107,115}
Safety concerns	No additional risk of congenital anomalies after the first trimester⁷⁰	NA	GDM⁸³
Reimbursement status	NLEM category D	NLEM category D (solely for preterm indication)	Non-NLEM

Abbreviations: ART, assisted reproductive technology; GDM, gestational diabetes mellitus; MIMS, Monthly Index of Medical Specialities; MVP, micronized vaginal progesterone; NA, not available/not applicable; NLEM, National List of Essential Medicines.

vomiting with dydrogesterone use.^{90–92} However, these symptoms could more likely be due to early pregnancy than to the use of dydrogesterone.⁶⁵

Role of micronized vaginal progesterone

The progesterone in recurrent miscarriages (PROMISE) trial evaluating the influence of MVP suppositories in women with a history of unexplained recurrent miscarriages failed to show any benefit in improving the pregnancy and neonatal outcomes during the first trimester of pregnancy.⁷⁷ Furthermore, there were no significant differences between the MVP and placebo groups in live birth rates after 24 weeks of gestation (RR 1.04; 95% CI 0.94 to 1.15; $p = 0.45$). However, the prespecified and post hoc subgroup analyses of the PROMISE trial suggested a greater benefit of MVP in those with a higher number of prior miscarriages.²² Furthermore, the prespecified subgroup analysis of the PRISM trial by the number of previous miscarriages demonstrated a greater benefit with MVP for the subgroup of women with ≥ 3 previous miscarriages and current pregnancy bleeding; the live birth rate was significantly higher with progesterone compared with placebo (% difference: 14.1%; RR

1.28, 95% CI 1.08 to 1.51; $p_{\text{interaction}} = 0.007$).²² The subgroup findings of the PRISM trial met all 11 criteria of credibility, suggesting a high plausibility of this subgroup effect.

Adverse events such as vaginal irritation and discharge occur commonly with vaginal progesterone.^{93,94} Not all patients may accept the vaginal route due to inconvenience and discomfort, leading to reduced satisfaction.^{93,95–97} Consideration of these side effects and patient preference based on convenience and tolerability before the administration of vaginal progesterone can help improve patient satisfaction and compliance, resulting in improved clinical outcomes.

Role of 17 α -hydroxyprogesterone caproate (injectable progestogen)

Synthetic progestogen 17-OHPC has been used historically in pregnant women for the prevention of preterm birth and miscarriages.^{98–104}

The meta-analysis by Saccone et al.⁷⁴ showed that synthetic progestogens, including weekly intramuscular 17-OHPC (RR 0.54; 95% CI 0.29 to 0.94), but not natural P were associated with a reduced risk of recurrent

miscarriage in women with a history of unexplained recurrent miscarriage. The analysis included three studies assessing intramuscular 17-OHPC. Two studies used a dosage of 500 mg/week,^{99,102} whereas the third study used a dosing scale of 250 to 500 mg depending on the gestation week.⁹⁸ Subgroup analyses of intramuscular 17-OHPC (either dose scale or 500 mg/week) were consistent with the overall analysis. Further, Haas et al.²³ also identified the same three trials for meta-analysis^{98,99,102} to compare intramuscular 17-OHPC with placebo. However, the RCT by Reijnders et al.¹⁰² that included women with RPL among all the recruited women did not report outcomes separately for this group; hence, it was not considered in the meta-analysis. For the two included trials, there was no clear difference in miscarriages between the intramuscular progestogen group and placebo group (average RR 0.63; 95% CI 0.30 to 1.30; $n = 80$).²³

The most common adverse events leading to the discontinuation of 17-OHPC treatment are injection site pain/swelling and urticaria.¹⁰⁵ Common barriers to 17-OHPC therapy adherence include injection site pain, inconvenience due to the intramuscular route of administration, frequency and length of clinic visits, and inadequate awareness regarding 17-OHPC.^{106,107}

In women with unexplained RPL, oral dydrogesterone has shown promising potential to improve pregnancy outcomes, based on the limited available evidence. While MVP and injectable progestogens have also been evaluated, their effectiveness remains less clear, with evidence primarily limited to specific subgroups. Further large-scale trials are needed to strengthen clinical guidance.

Based on the available guidelines and literature evidence, the recommendations developed to guide the use of progestogen therapies for the management of threatened miscarriage and unexplained RPL in Thailand are outlined in Table 4. Oral dydrogesterone appears to offer potential benefit, with initiation recommended after confirmation of fetal viability in cases of recurrent miscarriage. MVP may be considered in women presenting with first-trimester vaginal bleeding who have a history of ≥ 3 previous miscarriages.

CONCLUSION

Managing threatened miscarriages and unexplained RPL in Thailand poses a significant challenge, largely due to the limited availability of comprehensive regional data. The proposed recommendations constitute the inaugural regional consensus guidelines for administering progestosterone therapy to women experiencing threatened miscarriage and unexplained RPL in Thailand. The Thai interest group underscores the importance of timely and effective diagnostic and therapeutic approaches in addressing these patient populations. Treatment strategies for unexplained RPL are advantageous and may necessitate adaptation based on individual clinical

contexts. Initiation of treatment for unexplained RPL is deemed appropriate following the ≥ 2 pregnancy losses, irrespective of their sequential nature. Oral progestogen (dydrogesterone) is recommended for the management of both threatened miscarriage and unexplained RPL. In women with RPL, initiation of oral dydrogesterone is advised after confirmation of fetal viability. MVP is not recommended as a general treatment for threatened miscarriage. Treatment with MVP may be considered in specific subgroups, such as women presenting with first-trimester vaginal bleeding and a history of ≥ 3 previous miscarriages. A single dose of MVP exceeding 200 mg is not advisable due to concerns regarding luteal phase insufficiency. These evidence-driven recommendations serve as valuable tools to aid regional healthcare providers in optimizing patient management decisions. Furthermore, additional research endeavors are indispensable for augmenting our comprehension of the epidemiology and etiology of threatened miscarriage and unexplained RPL in the Thai context.

AUTHOR CONTRIBUTIONS

Kiattisak Kongwattanakul: Conceptualization; methodology; formal analysis; data curation; investigation; writing – original draft; writing – review and editing; validation; visualization; project administration. **Phudit Jatanvan:** Conceptualization; methodology; formal analysis; writing – original draft; data curation; investigation; validation; visualization. **Olarik Musigavong:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; formal analysis; data curation. **Savitree Pranpanus:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; formal analysis; data curation. **Lingling Salang:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; formal analysis; data curation. **Chonthicha Satirapod:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; formal analysis; data curation. **Somsin Petyim:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; formal analysis; data curation. **Boonchai Uerpair-ojkit:** Conceptualization; methodology; formal analysis; data curation; writing – original draft; writing – review and editing; investigation; validation; visualization; project administration; supervision.

ACKNOWLEDGMENTS

This study was funded by the Abbott Laboratories Ltd., Bangkok, Thailand. The authors would like to thank Neetu Menghani, PhD, and Vijay Kadasi, MSc, ISMPP-CMPP, Indegene Limited, Bengaluru, India for providing the medical writing and editorial support for this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Kiattisak Kongwattanakul  <https://orcid.org/0000-0001-5062-7328>

Lingling Salang  <https://orcid.org/0000-0001-6101-5589>

Boonchai Uerpairojkit  <https://orcid.org/0009-0008-5956-8262>

REFERENCES

- Kouk LJ, Neo GH, Malhotra R, Allen JC, Beh ST, Kouk LJ, et al. A prospective study of risk factors for first trimester miscarriage in Asian women with threatened miscarriage. *Singapore Med J*. 2013;54(8):425–31.
- Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. *Cochrane Database Syst Rev*. 2018;8(8):CD005943.
- Demir SC, Gedikbaşı A, Timur H, Çetin C, Pala HG, Gülümser Ç. Threatened miscarriage and recurrent miscarriage: expert opinions on progesterone therapy and treatment challenges. *Turk J Obstet Gynecol*. 2023;20(3):242–8.
- Xie H, Zhang A, Mou X, He T, Li J, Wang CC, et al. Chinese herbal medicine for threatened miscarriage: an updated systematic review and meta-analysis. *Front Pharmacol*. 2023;14:1083746.
- Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. *Maturitas*. 2009;65(SUPPL 1):S47–50.
- Hassan W, Abu-Helalah M, Salam A, Elhakim A, Bayazeed H, Latif S, et al. Incidence of early pregnancy bleeding in the eastern region of Saudi Arabia. *Int J Reprod Contracept Obstet Gynecol*. 2016;5:1392–9.
- Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy. *Rev Obstet Gynecol*. 2009;2(2):76–83.
- European Society of Human Reproduction and Embryology (ESHRE) guideline development group. Recurrent pregnancy loss. Update. 2022 Available from: <https://www.eshre.eu/guidelines-and-legal/guidelines/recurrent-pregnancy-loss>. Accessed 21 February 2024
- Cao C, Bai S, Zhang J, Sun X, Meng A, Chen H. Understanding recurrent pregnancy loss: recent advances on its etiology, clinical diagnosis, and management. *Med Rev*. 2023;2(6):570–89.
- Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage. *BMC Med*. 2013; 11(1):154.
- Rasmak Roepke E, Matthiesen L, Rylance R, Christiansen OB. Is the incidence of recurrent pregnancy loss increasing? A retrospective register-based study in Sweden. *Acta Obstet Gynecol Scand*. 2017;96(11):1365–72.
- Eleje GU, Ugwu EO, Igbojike EP, Malachy DE, Nwankwo EU, Ugboaja JO, et al. Prevalence and associated factors of recurrent pregnancy loss in Nigeria according to different national and international criteria (ASRM/ESHRE vs. WHO/RCOG). *Front Reprod Health*. 2023;5:1049711.
- Ayadurai T, Muniandy S, Omar SZ. Thrombophilia investigation in Malaysian women with recurrent pregnancy loss. *J Obstet Gynaecol Res*. 2009;35(6):1061–8.
- Patki A, Chauhan N. An epidemiology study to determine the prevalence and risk factors associated with recurrent spontaneous miscarriage in India. *J Obstet Gynaecol India*. 2016;66(5):310–5.
- Hong Li Y, Marren A. Recurrent pregnancy loss: a summary of international evidence-based guidelines and practice. *Aust J Gen Pract*. 2018;47(7):432–6.
- Turesheva A, Aimagambetova G, Ukybassova T, Marat A, Kanabekova P, Kaldyulova L, et al. Recurrent pregnancy loss etiology, risk factors, diagnosis, and management. Fresh look into a full box. *J Clin Med*. 2023;12(12):4074.
- Quenby S, Gallos ID, Dhillon-Smith RK, Podsek M, Stephenson MD, Fisher J, et al. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. *Lancet*. 2021;397(10285):1658–67.
- Hahn KA, Hatch EE, Rothman KJ, Mikkelsen EM, Brogly SB, Sørensen HT, et al. Body size and risk of spontaneous abortion among danish pregnancy planners. *Paediatr Perinat Epidemiol*. 2014;28(5):412–23.
- Krieg SA, Shahine LK, Lathi RB. Environmental exposure to endocrine-disrupting chemicals and miscarriage. *Fertil Steril*. 2016;106(4):941–7.
- Lu L, Li J, Zhou Y, Ma H, Hu M. Complementary and alternative medicine for threatened miscarriage: advantages and risks. *Evid Based Complement Alternat Med*. 2021;2021:1–26.
- Zhang Y, Yan X, Tan J, Tan J, Liu C, Yang P, et al. Exposure of reproductive-aged women to multiple metals and its associations with unexplained recurrent miscarriage. *Toxics*. 2023;11(10):830.
- Coomarasamy A, Devall AJ, Brosens JJ, Quenby S, Stephenson MD, Sierra S, et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. *Am J Obstet Gynecol*. 2020;223(2):167–76.
- Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. *Cochrane Database Syst Rev*. 2019;2019(11):CD003511.
- Duane M, Schliep K, Porucznik CA, Najmabadi S, Stanford JB. Does a short luteal phase correlate with an increased risk of miscarriage? A cohort study. *BMC Pregnancy Childbirth*. 2022; 22(1):922.
- Sadekova ON, Nikitina LA, Rashidov TN, Voloschuk IN, Samokhodskaya LM, Demidova EM, et al. Luteal phase defect is associated with impaired VEGF mRNA expression in the secretory phase endometrium. *Reprod Biol*. 2015;15(1):65–8.
- Ku CW, Zhang X, Zhang VRY, Allen JC, Tan NS, Østbye T, et al. Gestational age-specific normative values and determinants of serum progesterone through the first trimester of pregnancy. *Sci Rep*. 2021;11(1):4161.
- Schindler AE. First trimester endocrinology: consequences for diagnosis and treatment of pregnancy failure. *Gynecol Endocrinol*. 2004;18(1):51–7.
- Zhu CS, Tan TC, Chen HY, Malhotra R, Allen JC, Østbye T. Threatened miscarriage and depressive and anxiety symptoms among women and partners in early pregnancy. *J Affect Disord*. 2018;237:1–9.
- Farren J, Jalmbrant M, Falconieri N, Mitchell-Jones N, Bobdiwala S, Al-Memar M, et al. Posttraumatic stress, anxiety and depression following miscarriage and ectopic pregnancy: a multicenter, prospective, cohort study. *Am J Obstet Gynecol*. 2020;222(4):367.e1–367.e22.
- Wu CQ, Nichols K, Carwana M, Cormier N, Maratta C. Preterm birth after recurrent pregnancy loss: a systematic review and meta-analysis. *Fertil Steril*. 2022;117(4):811–9.
- Kuhlmann E, Scharli P, Schick M, Ditzel B, Langer L, Strowitzki T, et al. The posttraumatic impact of recurrent pregnancy loss in both women and men. *Geburtshilfe Frauenheilkd*. 2023;83(1):88–96.
- Nargund G. Declining birth rate in developed countries: a radical policy re-think is required. *Facts Views Vis Obgyn*. 2009;1(3): 191–3.
- Tamhankar VA, Liu B, Yan J, Li TC. A comparison of pattern of pregnancy loss in women with infertility undergoing IVF and women with unexplained recurrent miscarriages who conceive spontaneously. *Obstet Gynecol Int*. 2015;2015:1–6.
- Song JE, Ahn JA, Lee SK, Roh EH. Factors related to low birth rate among married women in Korea. *PLoS One*. 2018;13(3): e0194597.

35. The Nation. Declining birthrates will see Thailand's population drop by half in next 60 years. The Nation, 01 November. 2023. Available from: <https://www.nationthailand.com/thailand/general/40032444>. Accessed 21 February 2024
36. Shah D, Nagarajan N. Luteal insufficiency in first trimester. *Indian J Endocrinol Metab.* 2013;17(1):44–9.
37. Csapo AI, Pulkkinen MO, Ruttner B, Sauvage JP, Wiest WG. The significance of the human corpus luteum in pregnancy maintenance. I. Preliminary studies. *Am J Obstet Gynecol.* 1972;112(8):1061–7.
38. Csapo AI, Pulkkinen MO, Wiest WG. Effects of luteectomy and progesterone replacement therapy in early pregnant patients. *Am J Obstet Gynecol.* 1973;115(6):759–65.
39. Arck P, Hansen PJ, Mulac Jericevic B, Piccinni M, Szekeres-Bartho J. Progesterone during pregnancy: endocrine-immune cross talk in mammalian species and the role of stress. *Am J Reprod Immunol.* 2007;58(3):268–79.
40. Hizli D, Köşüş N, Köşüş A, Kasap B, Kafali H, Turhan NÖ. First-trimester reference ranges for decidual thickness and its relation to progesterone levels. *J Perinat Med.* 2012;40(5):521–5.
41. Ku CW, Allen JC Jr, Lek SM, Chia ML, Tan NS, Tan TC. Serum progesterone distribution in normal pregnancies compared to pregnancies complicated by threatened miscarriage from 5 to 13 weeks gestation: a prospective cohort study. *BMC Pregnancy Childbirth.* 2018;18(1):360.
42. Arck PC, Rütke M, Rose M, Szekeres-Bartho J, Douglas AJ, Pritsch M, et al. Early risk factors for miscarriage: a prospective cohort study in pregnant women. *Reprod Biomed Online.* 2008;17(1):101–13.
43. Raghupathy R, Al Mutawa E, Makhseed M, Azizieh F, Szekeres-Bartho J. Modulation of cytokine production by dydrogesterone in lymphocytes from women with recurrent miscarriage. *BJOG.* 2005;112(8):1096–101.
44. Raghupathy R, Al-Mutawa E, Al-Azemi M, Makhseed M, Azizieh F, Szekeres-Bartho J. Progesterone-induced blocking factor (PIBF) modulates cytokine production by lymphocytes from women with recurrent miscarriage or preterm delivery. *J Reprod Immunol.* 2009;80(1–2):91–9.
45. Raghupathy R, Szekeres-Bartho J. Progesterone: a unique hormone with immunomodulatory roles in pregnancy. *Int J Mol Sci.* 2022;23(3):1333.
46. Hudić I, Szekeres-Bartho J, Fatušić Z, Stray-Pedersen B, Dizdarević-Hudić L, Latifić A, et al. Dydrogesterone supplementation in women with threatened preterm delivery—the impact on cytokine profile, hormone profile, and progesterone-induced blocking factor. *J Reprod Immunol.* 2011;92(1–2):103–7.
47. Promchertchoo P. IN FOCUS: record-low births, ageing society could halve Thailand's 66m population, but it's not a done deal yet. CNA. 2023 Available from: <https://www.channelnewsasia.com/asia/thailand-low-birth-rate-elderly-population-demographic-disruption-3991311>. Accessed 21 February 2024
48. Hendriks E, MacNaughton H, MacKenzie MC. First trimester bleeding: evaluation and management. *Am Fam Physician.* 2019;99(3):166–74.
49. South Australian Perinatal Practice Guideline. Bleeding in early pregnancy ectopic pregnancy, miscarriage & PUL. 2023 Available from: https://www.sahealth.sa.gov.au/wps/wcm/connect/fead0f004ee4554cb7ecbdf150ce4f37/Bleeding+in+Early+Pregnancy_PPG_v1_3.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-fead0f004ee4554cb7ecbdf150ce4f37-otj-Oyl. Accessed 21 February 2024
50. Mizia K, Campbell Westerway S, Robertson M, Parry E, Paoletti D, Perry D, et al. Guidelines for the performance of the first trimester ultrasound. *Australas J Ultrasound Med.* 2018;21(3):179–82.
51. National Institute of Health and Care Excellence (NICE). Ectopic pregnancy and miscarriage: diagnosis and initial management. Guideline. 2019 Available from: 17 April 2019. Last updated: 23 August 2023. Available from: <https://www.nice.org.uk/guidance/ng126/resources/ectopic-pregnancy-and-miscarriage-diagnosis-and-initial-management-pdf-66141662244037>. Accessed 21 February 2024
52. Costumbrado J, Mansour T, Ghassemzadeh S. Rh Incompatibility. In StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK459353/>. Accessed 21 February 2024.
53. Puangsricharern A, Suksawat S. Prevalence of rh negative pregnant women who attended the antenatal clinic and delivered in Rajavithi hospital: 2000–2005. *J Med Assoc Thai.* 2007;90(8):1491–4.
54. Anuphun T, Srichai S, Sudwila Y, Jenwitheesuk K, Phunikhom K. ABO and rhesus blood group distribution in blood donors. *Srinagarind Med J.* 2018;33(5):138–41.
55. Practice Committee of the American Society for reproductive medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril.* 2012;98(5):1103–11.
56. Regan L, Rai R, Saravolos S, Li TC. Recurrent MiscarriageGreen-top guideline No. 17. *BJOG.* 2023;130(12):e9–e39.
57. Patki A, Pandit SN. FOGSI position statement on the use of progestogens. 2015 Available from: <https://www.fogsi.org/wp-content/uploads/2015/11/Progesterone-position-paper-Oct-2015.pdf>. Accessed 21 February 2024
58. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Progesterone support of the luteal phase and in the first trimester. 2018 Available from: <https://rancog.edu.au/wp-content/uploads/2022/05/Progesterone-Support-of-the-Luteal-Phase-and-in-the-First-Trimester.pdf>. Accessed 21 February 2024
59. Arab H, Alharbi AJ, Oraif A, Sagr E, Al Madani H, Abduljabbar H, et al. The role of progestogens in threatened and idiopathic recurrent miscarriage. *Int J Women's Health.* 2019;11:589–96.
60. Sinthamoney E, Voon HY, Hamdan M, Bhaskaran V, Nagandla K, Syed Aznal SS, et al. Progestogens in the management of miscarriage and preterm labour. *Obstetrical and Gynaecological Society of Malaysia.* 2020 Available from: <https://www.ogsm.org.my/docs/Clinical-Practice-Guidelines-on-Miscarriage-Management.pdf>. Accessed 21 February 2024
61. Omar MH, Mashita MK, Lim PS, Jamil MA. Dydrogesterone in threatened abortion: pregnancy outcome. *J Steroid Biochem Mol Biol.* 2005;97(5):421–5.
62. El-Zibdeh MY, Yousef LT. Dydrogesterone support in threatened miscarriage. *Maturitas.* 2009;65(Suppl 1):S43–6.
63. Chan DMK, Cheung KW, Ko JKY, Yung SSF, Lai SF, Lam MT, et al. Use of oral progestogen in women with threatened miscarriage in the first trimester: a randomized double-blind controlled trial. *Hum Reprod.* 2021;36(3):587–95.
64. Siew JYS, Allen JC, Hui CY, Ku CW, Malhotra R, Østbye T, et al. The randomised controlled trial of micronised progesterone and dydrogesterone (TRoMaD) for threatened miscarriage. *Eur J Obstet Gynecol Reprod Biol.* 2018;228:319–24.
65. Carp H. A systematic review of dydrogesterone for the treatment of threatened miscarriage. *Gynecol Endocrinol.* 2012;28(12):983–90.
66. Lee HJ, Park TC, Kim JH, Norwitz E, Lee B. The influence of oral dydrogesterone and vaginal progesterone on threatened abortion: a systematic review and meta-analysis. *Biomed Res Int.* 2017;2017:1–10.
67. Wang X, Luo Q, Bai W. Efficacy of progesterone on threatened miscarriage: difference in drug types. *J Obstet Gynaecol Res.* 2019;45(4):794–802.
68. Li L, Zhang Y, Tan H, Bai Y, Fang F, Faramand A, et al. Effect of progestogen for women with threatened miscarriage: a systematic review and meta-analysis. *BJOG.* 2020;127(9):1055–63.
69. Zhao H, He W, Yang Z. A pairwise and network meta-analysis comparing the efficacy and safety of progestogens in threatened abortion. *Int J Gynaecol Obstet.* 2022;156(3):383–93.

70. Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med*. 2019;380(19):1815–24.
71. McLindon LA, James G, Beckmann MM, Bertolone J, Mahomed K, Vane M, et al. Progesterone for women with threatened miscarriage (STOP trial): a placebo-controlled randomized clinical trial. *Hum Reprod*. 2023;38(4):560–8.
72. Devall AJ, Papadopoulou A, Podsek M, Haas DM, Price MJ, Coomarasamy A, et al. Progestogens for preventing miscarriage: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;4(4):CD013792.
73. Beigi A, Esmailzadeh A, Pirjani R. Comparison of risk of preterm labor between vaginal progesterone and 17-alpha-hydroxyprogesterone caproate in women with threatened abortion: a randomized clinical trial. *Int J Fertil Steril*. 2016;10(2):162–8.
74. Saccone G, Schoen C, Franasia JM, Scott RT, Berghella V. Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials. *Fertil Steril*. 2017;107(2):430–438.e3.
75. El-Zibdeh MY. Dydrogesterone in the reduction of recurrent spontaneous abortion. *J Steroid Biochem Mol Biol*. 2005;97(5):431–4.
76. Carp H. A systematic review of dydrogesterone for the treatment of recurrent miscarriage. *Gynecol Endocrinol*. 2015;31(6):422–30.
77. Coomarasamy A, Williams H, Truchanowicz E, Seed PT, Small R, Quenby S, et al. A randomized trial of progesterone in women with recurrent miscarriages. *N Engl J Med*. 2015;373(22):2141–8.
78. Katalinic A, Noftz MR, Garcia-Velasco JA, Shulman LP, van den Anker JN, Strauss JF III. No additional risk of congenital anomalies after first-trimester dydrogesterone use: a systematic review and meta-analysis. *Hum Reprod Open*. 2024;2024(1):hoae004.
79. Duan L, Yan D, Zeng W, Yang X, Wei Q. Effect of progesterone treatment due to threatened abortion in early pregnancy for obstetric and perinatal outcomes. *Early Hum Dev*. 2010;86(1):41–3.
80. Satir F, Toptas T, Inel M, Erman-Akar M, Taskin O. Comparison of intravaginal progesterone gel and intramuscular 17- α -hydroxyprogesterone caproate in luteal phase support. *Exp Ther Med*. 2013;5(6):1740–4.
81. Haghighi L, Rashidi M, Najmi Z, Homam H, Hashemi N, Mobasser A, et al. Comparison of intramuscular progesterone with oral nifedipine for treating threatened preterm labor: a randomized controlled trial. *Med J Islam Repub Iran*. 2017;31(1):327–31.
82. Seshadri S, Odia R, Ozturk O, Saab W, AlChami A, Gonzalez XV, et al. A comparative analysis of outcomes between two different intramuscular progesterone preparations in women undergoing frozen embryo transfer cycles. *J Reprod Infertil*. 2022;23(1):46–53.
83. Rebarber A, Istwan NB, Russo-Stieglitz K, Cleary-Goldman J, Rhea DJ, Stanziano GJ, et al. Increased incidence of gestational diabetes in women receiving prophylactic 17 α -hydroxyprogesterone caproate for prevention of recurrent preterm delivery. *Diabetes Care*. 2007;30(9):2277–80.
84. Egerman R, Ramsey R, Istwan N, Rhea D, Stanziano G. Maternal characteristics influencing the development of gestational diabetes in obese women receiving 17-alpha-hydroxyprogesterone caproate. *J Obstet Gynecol*. 2014;2014:1–4.
85. Toth B, Bohlmann M, Hancke K, Kuon R, Nawroth F, Von Otte S, et al. Recurrent miscarriage: diagnostic and therapeutic procedures guideline of the DGGG, OEGGG and SGGG (S2k-level, AWMF registry no. 015/050, May 2022). *Geburtshilfe Frauenheilkd*. 2023;83(1):49–78.
86. Shehata H, Elfrituri A, Doumouchsis SK, Zini ME, Ali A, Jan H, et al. FIGO good practice recommendations on the use of progesterone in the management of recurrent first-trimester miscarriage. *Int J Gynaecol Obstet*. 2023;161(S1):3–16.
87. Linehan L, Hennessy M, Khalid A, Whelan J, O'Donoghue K. National clinical practice guideline: recurrent miscarriage. National Women and Infants Health Programme and The Institute of Obstetricians and Gynaecologists. January 2023. Available from: <https://www.hse.ie/eng/about/who/acute-hospitals-division/woman-infants/clinical-guidelines/recurrent-miscarriage.pdf>. Accessed 21 February 2024.
88. Bashiri A, Galperin G, Zeadna A, Baumfeld Y, Wainstock T. Increased live birth rate with dydrogesterone among patients with recurrent pregnancy loss regardless of other treatments. *J Clin Med*. 2023;12(5):1967.
89. Katalinic A, Shulman LP, Strauss JF, Garcia-Velasco JA, van den Anker JN. A critical appraisal of safety data on dydrogesterone for the support of early pregnancy: a scoping review and meta-analysis. *Reprod Biomed Online*. 2022;45(2):365–73.
90. Pelinescu-Oniciu D. Subchorionic hemorrhage treatment with dydrogesterone. *Gynecol Endocrinol*. 2007;23(Suppl 1):77–81.
91. Salehpour S, Tamimi M, Saharkhiz N. Comparison of oral dydrogesterone with suppository vaginal progesterone for luteal-phase support in in vitro fertilization (IVF): a randomized clinical trial. *Iran J Reprod Med*. 2013;11(11):913–8.
92. Gellé P, Schaeffer P. Apropos of the use of dydrogesterone in gynecology and obstetrics; clinical experience. *Bull Fed Soc Gynecol Obstet Lang Fr*. 1965;17(4):369–70.
93. Chakravarty BN, Shirazee HH, Dam P, Goswami SK, Chatterjee R, Ghosh S. Oral dydrogesterone versus intravaginal micronised progesterone as luteal phase support in assisted reproductive technology (ART) cycles: results of a randomised study. *J Steroid Biochem Mol Biol*. 2005;97(5):416–20.
94. Tomic V, Tomic J, Klaić DZ, Kasum M, Kuna K. Oral dydrogesterone versus vaginal progesterone gel in the luteal phase support: randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol*. 2015;186:49–53.
95. Ghosh S, Chattopadhyay R, Goswami S, Chaudhury K, Chakravarty B, Ganesh A. Assessment of sub-endometrial blood flow parameters following dydrogesterone and micronized vaginal progesterone administration in women with idiopathic recurrent miscarriage: a pilot study. *J Obstet Gynaecol Res*. 2014;40(7):1871–6.
96. Tournaye H, Sukhikh GT, Kahler E, Griesinger G. A phase III randomized controlled trial comparing the efficacy, safety and tolerability of oral dydrogesterone versus micronized vaginal progesterone for luteal support in in vitro fertilization. *Hum Reprod*. 2017;32(5):1019–27.
97. Colombo C, Pistoljevic-Kristiansen N, Saupstad M, Bergenheim SJ, Spangmose AL, Klajnbard A, et al. Does luteal phase progesterone supplementation affect physical and psychosocial well-being among women undergoing modified natural cycle-FET? A sub-study of a randomized controlled trial. *Hum Reprod*. 2023;38(10):1970–80.
98. Shearman RP, Garrett WJ. Double-blind study of effect of 17-hydroxyprogesterone caproate on abortion rate. *BMJ*. 1963;1(5326):292–5.
99. Levine L. Habitual abortion. A controlled study of progestational therapy. *West J Surg Obstet Gynecol*. 1964;72:30–6.
100. Johnson JWC, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α -hydroxyprogesterone caproate in the prevention of premature labor. *N Engl J Med*. 1975;293(14):675–80.
101. Yemini M, Borenstein R, Dreazen E, Apelman Z, Mogilner BM, Kessler I, et al. Prevention of premature labor by 17 α -hydroxyprogesterone caproate. *Am J Obstet Gynecol*. 1985;151(5):574–7.
102. Reijnders FJ, Thomas CM, Doesburg WH, Rolland R, Eskes TK. Endocrine effects of 17 alpha-hydroxyprogesterone caproate during early pregnancy: a double-blind clinical trial. *Br J Obstet Gynaecol*. 1988;95(5):462–8.

103. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med*. 2003; 348(24):2379–85.
104. Saghafi N, Khadem N, Mohajeri T, Shakeri MT. Efficacy of 17 α -hydroxyprogesterone caproate in prevention of preterm delivery. *J Obstet Gynaecol Res*. 2011;37(10):1342–5.
105. Sibai B, Saade GR, Das AF, Gudeman J. Safety review of hydroxyprogesterone caproate in women with a history of spontaneous preterm birth. *J Perinatol*. 2021;41(4):718–25.
106. Garcia SM, Kellom KS, Boelig RC, Wang X, Matone M. Patient and provider perspectives on acceptability, access, and adherence to 17-alpha-hydroxyprogesterone caproate for preterm birth prevention. *Womens Health Rep (New Rochelle)*. 2021;2(1):295–304.
107. Kalata M, Teter K, Wagner L, Swarr V, Witzeman K. Understanding barriers to uptake of 17 alpha-hydroxyprogesterone caproate (17-OHP) in women with history of preterm birth. *J Matern Fetal Neonatal Med*. 2021;34(4):541–6.
108. Duphaston Prescribing Information MIMS Thailand. Available from: <https://www.mims.com/thailand/drug/info/duphaston?type=full>. Accessed 21 February 2024
109. Utrogestan Prescribing Information MIMS Thailand. Available from: <https://www.mims.com/thailand/drug/info/utrogestan/dosage>. Accessed 21 February 2024
110. Proluton Depot Prescribing Information MIMS Thailand. Available from: <https://www.mims.com/thailand/drug/info/proluton%20depot>. Accessed 21 February 2024
111. Heine P, Sellar L, Whitten S, Bajaj P. A questionnaire-based audit to assess overall experience and convenience among patients using vaginal progesterone tablets (Lutigest[®]) for luteal phase support during IVF treatment. *Patient Relat Outcome Meas*. 2017;8:169–79.
112. Propst AM, Hill JA, Ginsburg ES, Hurwitz S, Politch J, Yanushpolsky EH. A randomized study comparing crinone 8% and intramuscular progesterone supplementation in in vitro fertilization-embryo transfer cycles. *Fertil Steril*. 2001;76(6): 1144–9.
113. Vaisbuch E, Leong M, Shoham Z. Progesterone support in IVF: is evidence-based medicine translated to clinical practice? A worldwide web-based survey. *Reprod Biomed Online*. 2012;25(2): 139–45.
114. Thangaraju P, Varthya SB, Shanmugam PST, Sree Sudha TY, Mittal C. Hydroxyprogesterone caproate for preterm birth: a situational analysis from the Indian perspective. *Gynecol Obstet Clin Med*. 2021;1(3):144–7.
115. Dashti S, Eftekhari M. Luteal-phase support in assisted reproductive technology: an ongoing challenge. *Int J Reprod Biomed*. 2021; 19(9):761–72.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kongwattanakul K, Jatavan P, Musigavong O, Pranpanus S, Salang L, Satirapod C, et al. Progesterone therapy in threatened miscarriage and unexplained recurrent pregnancy loss: Recommendations by the Thai interest group. *J Obstet Gynaecol Res*. 2025;51(8): e70038. <https://doi.org/10.1111/jog.70038>