Review

DOI: 10.4274/anajog.galenos.2025.07279

Anat J Obstet Gynecol Res 2025;2(3):99-110

The Role of Dydrogesterone in the Management of Threatened Miscarriage: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Threatened miscarriage affects approximately 20% of pregnancies and results in pregnancy loss in around half. Progesterone therapy is the most commonly applied pharmacological approach. The efficacy and safety of dydrogesterone were systematically evaluated and compared with micronized/vaginal progesterone for management of threatened miscarriage using analysis of randomized controlled trials (RCTs). Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, RCTs published between January 1, 1980, and September 1, 2025, were screened. The inclusion criteria comprised patients diagnosed with threatened miscarriage in the first trimester, use of dydrogesterone or micronized/vaginal progesterone as intervention, and placebo or conservative approach as comparator. Twelve RCTs involving around 6000 participants were included. Miscarriage rates across the studies ranged from 10% to 33.3%. Large-scale, placebo-controlled studies did not show a significant improvement in live birth rate with vaginal/micronized progesterone compared to placebo (e.g., 20% vs. 22% miscarriage rate, $p>0.05$). Similarly, dydrogesterone did not provide significant superiority compared to placebo in large trials (12.8% vs. 14.3%, $p=0.772$). However, smaller studies reported a significant reduction in miscarriage rates compared to conservative approach (e.g., 12.5% vs. 28.4%, $p<0.05$). Some studies showed that dydrogesterone was associated with earlier cessation of vaginal bleeding, while vaginal progesterone reduced pain and uterine contractions. Adverse events were uncommon but sedation occurred more frequently with vaginal or micronized progesterone. Although pharmacovigilance data have suggested possible associations of dydrogesterone with hypospadias and congenital heart anomalies, no such relationship was confirmed in RCTs. RCT evidence regarding progesterone support in threatened miscarriage is heterogeneous and does not demonstrate a consistent effect in increasing live birth in the general population. While dydrogesterone has advantages for symptom control and practical ease of use, its effect on live birth is no different from other management strategies. Progesterone therapy should be individualized considering patient risk profile and clinical characteristics. Future biomarker-guided RCTs with robust methodology may help resolvie uncertainties and defining the specific subgroups that would benefit from personalized treatment.

Keywords: Dydrogesterone, progesteron, miscarriage

INTRODUCTION

Vaginal bleeding that may be accompanied by pelvic pain without cervical dilation before the 20th week of pregnancy is termed threatened miscarriage.[1] Threatened miscarriage affects approximately 20% of pregnancies and miscarriage occurs in approximately half of affected pregnancies.[2,3]

In cases of threatened miscarriage, bed rest, avoidance of sexual intercourse, or a wait-and-see approach may be applied, while the main treatment option is progesterone. Progesterone deficiency in early pregnancy has been reported to lead to miscarriage.[4] Progesterone has a critical role in the continuation of pregnancy. In the luteal phase, it induces secretory changes in the endometrium that facilitate implantation and support early pregnancy.[5] Progesterone plays a role in supporting immune tolerance throughout pregnancy and in the relaxation of uterine smooth muscles.[6,7] Based on these clinical findings, many studies have investigated the efficacy and safety of progesterone in cases of threatened miscarriage, but the results have been inconsistent.[8-11] Oral micronized progesterone has

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Received: 07.10.2025 **Accepted:** 29.11.2025 **Publication Date:** 26.01.2026

Cite this article as: Hansu K, Özer A, Bakkaloğlu İ. The role of dydrogesterone in the management of threatened miscarriage: a systematic review of randomized controlled trials. Anat J Obstet Gynecol Res. 2025;2(3):99-110

low bioavailability and is associated with side effects such as drowsiness, while vaginal progesterone may be difficult to administer in women with bleeding and impaired absorption when bleeding is substantial.[12]

Dydrogesterone is an orally administered progestin with a profile similar to physiological progesterone. High bioavailability, high selectivity, and administration at lower doses prevent the occurrence of progestogenic side effects.[13] A recent study suggested an association between dydrogesterone used in early pregnancy and congenital defects.[14] The present review will examine the role of dydrogesterone in pregnancies under threat of miscarriage based on randomized controlled trials (RCTs).

METHODS

For this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. The protocol for this systematic review was not prospectively registered. However, to ensure transparency and minimize bias, the review process strictly adhered to the PRISMA checklist, and all eligibility criteria and data extraction procedures were defined a priori. Studies conducted with oral micronized progesterone, vaginal micronized progesterone, and dydrogesterone were systematically collected.

Inclusion Criteria

Studies conducted between January 1, 1980, and September 1, 2025, were included according to the population, intervention, comparison, outcome, and study design (PICOS) framework, as follows; (1) Population - women diagnosed with threatened miscarriage in the first trimester (vaginal bleeding and/or pelvic pain + viable pregnancy confirmed by ultrasonography); (2) Intervention - oral micronized progesterone, vaginal micronized progesterone, or dydrogesterone supplementation; (3) Comparison - comparison of dydrogesterone or micronized progesterone with placebo (inert capsules) or conservative management (observation-only/standard care) controls; comparison of vaginal micronized progesterone with oral micronized progesterone or placebo; comparison of oral micronized progesterone with placebo (4); Outcome measure - miscarriage before the 20th week of pregnancy, ongoing pregnancy after the 20th week of pregnancy, or live birth rates (5); Study design - compilation of RCTs conducted on the effects of dydrogesterone, oral micronized progesterone, and vaginal micronized progesterone on threatened miscarriages.

Exclusion Criteria

Non-randomized studies, reviews and meta-analyses, case reports, animal experiments, studies conducted for luteal support in IVF/ assisted reproductive techniques (ART) cycles, and studies conducted with indications other than threatened miscarriage.

Information Sources

Information was obtained from online databases such as Web of Science, PubMed, Cochrane, Embase, and Google Scholar.

Search

A search strategy containing appropriate keywords was created to identify relevant studies in electronic databases and was applied to access articles. Search terms included a combination of medical subject headings (MeSH) and free-text keywords related to progesterone, dydrogesterone, and threatened miscarriage. Boolean operators (AND, OR) were used to refine the results. The full electronic search strategy for PubMed is presented in Supplementary Appendix 1. Manual search (back referencing) was performed in the reference section to find possible articles that automatic search could not find. We also searched clinical trial registries (ClinicalTrials.gov, WHO, International Clinical Trials Registry Platform) to identify ongoing or unpublished trials, but no completed trials meeting the inclusion criteria were found. Gray literature was excluded as per the exclusion criteria.

Study Selection

The screening process was conducted independently by two reviewers to select relevant articles for systematic review. The initial search identified 1245 articles (Figure 1). Then, 315 duplicate articles were removed. In the second step, 930 articles were screened and evaluated for eligibility for the study. Of these, 780 articles were excluded for reasons such as inability to access full text and lack of relevance to the subject. Of the remaining 150 articles examined, 137 were excluded because they were not RCTs. Consequently, a total of 12 RCTs were included in this review-comprising 7 studies on dydrogesterone and 5 on micronized progesterone-as detailed in Table 1.

Data Collection Process

An Excel spreadsheet was used for the data extraction process covering the basic study characteristics described in the data elements subsection. Data extraction and verification were performed by two reviewers. In cases of disagreement, consensus was reached through discussions.

Data Elements

The following data were extracted: Author, year of publication, country, sample size, study design, intervention regimen and dose, comparison group, and primary outcome measures were extracted through a standard form.

Quality Assessment

The methodological quality of included RCTs was evaluated using the Cochrane risk of bias 2 (RoB 2) tool. Randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and other potential sources of bias were examined.

Data Synthesis

The primary outcome measure was determined as the miscarriage rate occurring before the 20th week of pregnancy. Secondary outcome measures were ongoing pregnancy after the 20th week of pregnancy, live birth, and maternal and fetal side effects. The feasibility of a meta-analysis was assessed

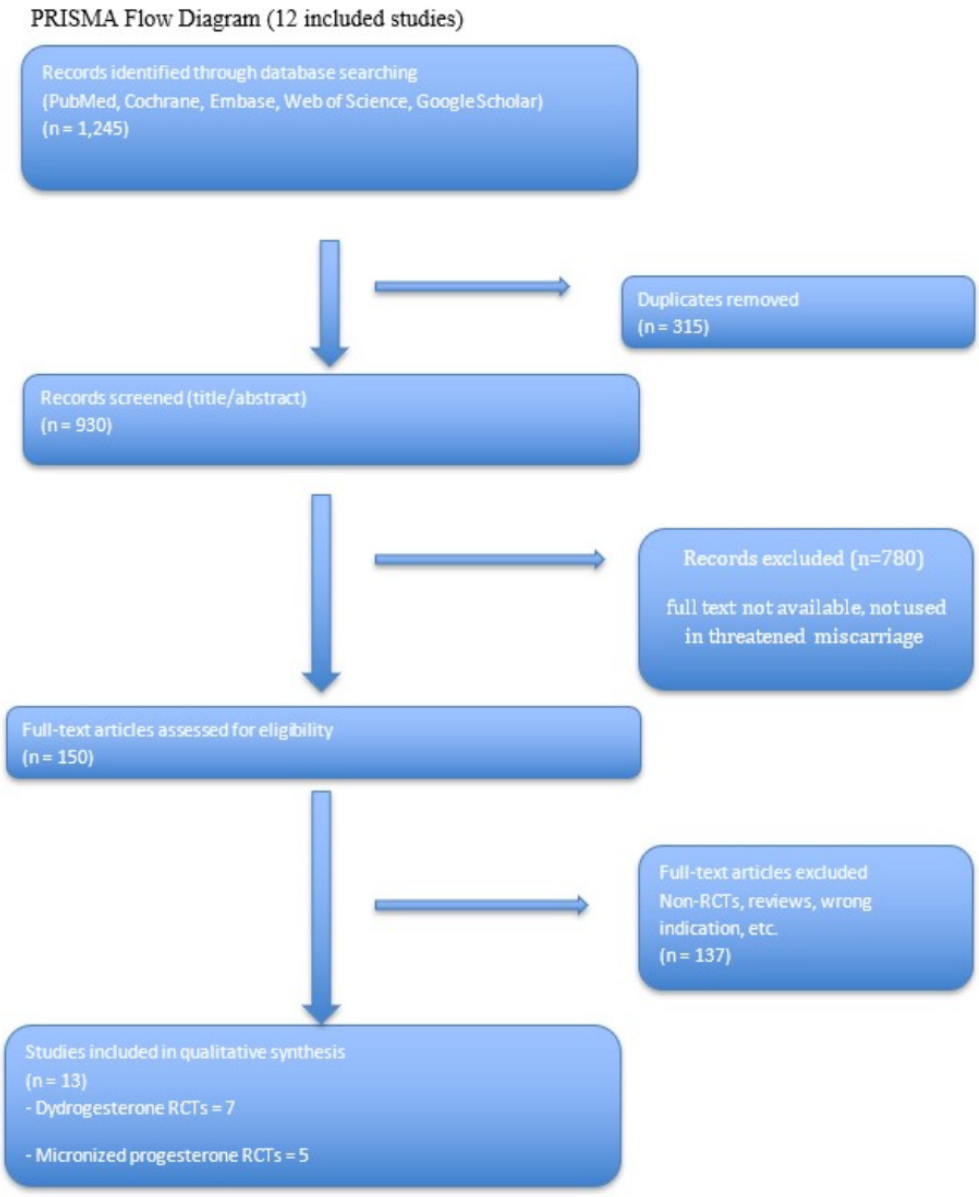


Figure 1. PRISMA flow diagram (12 included studies)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs: Randomized controlled trials

based on clinical and methodological homogeneity. Specifically, we evaluated the similarity of participants, intervention protocols (dose and route), comparator groups (placebo vs. conservative), and outcome definitions across studies. Due to substantial diversity observed in these domains, a quantitative synthesis was deemed inappropriate to avoid misleading results, and a narrative synthesis was conducted. The risk of bias assessment (RoB 2) was primarily used to guide the interpretation of the findings. Studies judged to have a high risk of bias were discussed cautiously, although none were formally excluded, reflecting the heterogeneous nature of the available evidence.

RESULTS

Included studies opted for different forms of control. Six studies used placebo (Chan et al.,[11] Kuptarak and Phupong[15],

Table 1. RCT findings

Study	Patient number	Group/dose	Miscarriage rate	Statistics	Comment
Chan et al.[11]	406	DYD 40 mg stat +10 mg ×3/day vs. placebo	12.8% vs. 14.3%	RR 0.897, $p=0.772$	Not significant
Kuptarak and Phupong[15]	100	DYD 20 mg/day vs. placebo	10% vs. 14%	$p=0.538$	Not significant
El-Zibdeh and Yousef[16]	146	DYD 10 mg ×2 vs. conservative	17.5% vs. 25%	$p<0.05$	In favor of DYD
Pandian[17]	191	DYD 40 mg loading +10 mg x2/day vs. conservative	12.5% vs. 28.4%	$p<0.05$	In favor of DYD
Siew et al.[18]	118	DYD 10 mg x2/day vs. MP 200 mg x2/day	15.2% vs. 10.2%	$p=0.581$	Not significant
Kale et al.[19]	200	DYD 30 mg vs. 600 mg/day VMP	30% vs. 25%	$p=0.5267$	Not significant
Kumar and Chandersheikhar[20]	90	DYD 10 mg x2/day vs. omp 200 x2/day	11% vs. 11%	Ns	Not significant
McLindon et al.[21] (STOP trial)	278	VMP 400 mg vs. placebo	14.7% vs. 15.8%	0.805	Not significant
Coomarasamy et al.[10]	4153	VMP 400 mg/day vs. placebo	20% vs. 22%	Ns	Not significant
Alimohamadi et al.[22]	160	VMP 400 mg/day vs. placebo	16.9% vs. 14%	Ns	Not significant
Yassaee et al.[9]	60	VMP 400 mg/day vs. placebo	20% vs. 33.3%	$p=0.243$	Not significant
Gerhard et al.[23]	56	VMP 25 mg x2/day vs. placebo	11% vs. 19%	$p>0.05$	Not significant

DYD: Dydrogesterone, VMP: Vaginal micronized progesterone, RCT: Randomized controlled trial

McLindon et al.[21], Coomarasamy et al.[10], Alimohamadi et al.[22], Gerhard et al.[23]), while three studies utilized conservative management/observation only (El-Zibdeh and Yousef[16], Pandian[17], Yassaee et al.[9]) as the comparator.

Regarding the comparison between dydrogesterone and placebo, a double-blind study conducted by Chan et al.[11] in Hong Kong included 406 women. Participants had pregnancies with viable embryos at 6-10 weeks with vaginal bleeding. The intervention group received 10 mg dydrogesterone three times daily after an initial dose of 40 mg. The miscarriage rate was 12.8% in the dydrogesterone group and 14.3% in the placebo group (RR 0.897, $p=0.772$). Live birth rate was also similar (81.3% vs. 83.3%). While the strength of the study is the sample size, its limitation is its focus on low-risk patient profile.

In a double-blind RCT conducted by Kuptarak and Phupong[15] in Thailand, 100 patients were included, 50 women were treated with 20 mg dydrogesterone and the other 50 women with placebo. Women who were at 6-12 weeks of pregnancy and in whom a viable embryo was detected were included in the study. The rate of reaching the 20th week of pregnancy was 90% in the dydrogesterone group and 86% in the placebo group ($p=0.538$).

In a trial comparing dydrogesterone with conservative management reported by El-Zibdeh and Yousef[16] in Jordan, 146 patients were evaluated. The study group consisted of women who had previously miscarried and presented with bleeding. The miscarriage rate was 17.5% in the group receiving dydrogesterone, while it was 25% in the control group receiving conservative care ($p<0.05$).[16] The study suggests that dydrogesterone may reduce the miscarriage rate.

In a study conducted by Pandian[17] in Malaysia, 191 patients without a history of recurrent miscarriage were included. The included patients were divided into two groups, the miscarriage rate was 12.5% in the group receiving dydrogesterone and 28.4% in the conservative follow-up group.[17] The ongoing pregnancy rate was significantly higher in favor of dydrogesterone (87.5% vs. 71.6%; $p<0.05$).

A study conducted in Singapore with 118 patients directly compared micronized progesterone and dydrogesterone in threatened miscarriage. No difference was observed between the groups using micronized progesterone and dydrogesterone in terms of miscarriage rate and resolution of vaginal bleeding, but drowsiness was reported to be significantly more common in the group using micronized progesterone.[18] In subgroup analysis according to serum progesterone levels, in women with low progesterone levels, the miscarriage rate was found to be significantly higher, regardless of treatment type.

In a study conducted in India by Kale et al.[19] 200 pregnant women who presented with risk of miscarriage before the 12th week of pregnancy and had previously had >2 miscarriages were included in the study. One hundred pregnant women were assigned to the dydrogesterone group and 100 to the vaginal progesterone group.[19] The women in the dydrogesterone group were given 30 mg/day oral dydrogesterone, and the pregnant women in the progesterone group were given 600 mg/day vaginal progesterone. The time required for cessation of bleeding was significantly shorter in the dydrogesterone group compared to the progesterone group ($p<0.0001$). Furthermore, the number of pregnancies reaching the 24th week was higher in the dydrogesterone group, but the difference was not significant.

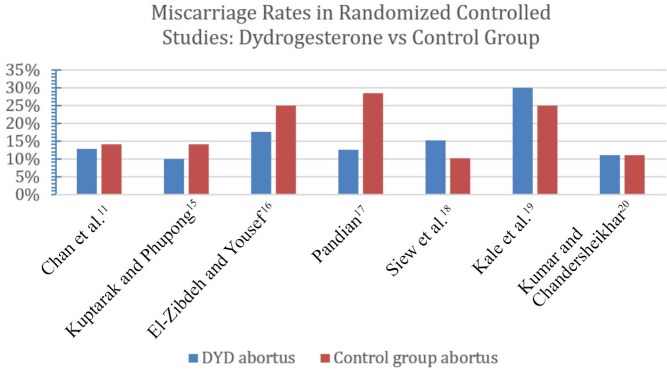
In a small RCT conducted by Kumar and Chandersheikhar[20] in India, 84 patients were included. One group was given 20 mg/day oral dydrogesterone while the other group was given 400 mg/day oral progesterone.[20] Although there was no significant difference between the groups in terms of miscarriage, bleeding ceased earlier in the dydrogesterone group.

Finally, concerning the efficacy of micronized/vaginal progesterone versus placebo, the STOP Trial conducted in Australia compared vaginal progesterone with placebo and 278 pregnant women at <10 weeks were included. However, the study was terminated because miscarriage rates (14.7% vs. 15.8%, $p=0.805$) and live birth rates were similar.[21]

In a study conducted with 836 patients by Coomarasamy et al.[10] to measure the effect of progesterone in recurrent pregnancy losses, it was reported that there was no significant difference in miscarriage and live birth rates (20% vs. 22%) between the group using oral progesterone and the control group.[10]

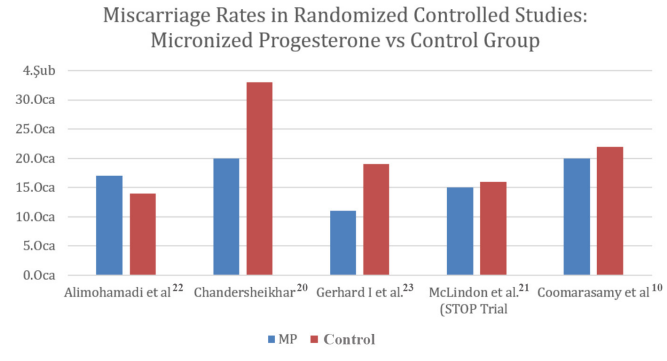
In another single-center RCT conducted in Iran, pregnant women at <20 weeks with threatened miscarriage were included. One group was given 400 mg/day vaginal progesterone while the control group was given placebo.[8] It was reported that there was no difference between the progesterone group and the control group in terms of miscarriage (16.9% vs. 14%), preterm birth, birth weight, and week of delivery.

Another study was conducted in Iran by Yassaee et al.[9] with 60 patients. Of these 30 patients were given 400 mg/day vaginal progesterone while the control group was followed without treatment.[9] The miscarriage rate between the two groups was not different ($p=0.243$).



Graph 1. Miscarriage rates in randomized controlled studies: dydrogesteron vs. control group

DYD: Dydrogesterone



Graph 2. Miscarriage rates in randomized controlled studies: micronized progesterone vs. control group

In a small-scale RCT conducted by Gerhard et al.[23] in Germany, 56 patients were included. Although the study, with its methodological limitations, suggested that vaginal progesterone may be useful in threatened miscarriage, the difference with the control group was not significant.

In terms of safety outcomes, none of the included RCTs explicitly reported cases of hypospadias or congenital heart anomalies in the dydrogesterone or control groups. Maternal adverse events were generally mild; however, drowsiness was reported significantly more frequently in groups treated with micronized progesterone compared to dydrogesterone.

Miscarriage Rates: Visual Comparison

The miscarriage rates in dydrogesterone and control groups are compared graphically in Graphic 1 and Graphic 2.

DISCUSSION

In this systematic review, the efficacy and safety of dydrogesterone and micronized/vaginal progesterone in threatened miscarriage were compared with placebo or conservative approach. In the included RCTs, miscarriage before the 20th week or ongoing pregnancy/live birth rates at ≥24 weeks were mostly used as primary endpoints; secondarily, the duration of improvement of bleeding and pain, side effects, and (in some studies) cytokine profile were evaluated.

When live birth or continuation of pregnancy was evaluated, the superiority of vaginal/micronized progesterone over placebo was not been consistently demonstrated in large and methodologically strong studies.[10,21] When RCTs showing that dydrogesterone was not superior to placebo and studies signaling in favor of dydrogesterone against conservative follow-up are evaluated together, the evidence of efficacy appears heterogeneous. This heterogeneity is thought to arise from differences in patient selection, initial gestational week, timing of treatment initiation, dose/duration, and primary endpoint definitions and the wide time span (1980-2025) of the included studies, which reflects evolving diagnostic and clinical practices.

Some studies showed that bleeding and pain improved more rapidly with dydrogesterone or vaginal/micronized progesterone. However, symptomatic improvement did not reflect a general increase in live birth rates.

Dydrogesterone may have practical advantages with high oral bioavailability, selectivity, and lower sedation profile. However, there was no consistent evidence for increased live birth rate. A similar result was found for vaginal/micronized progesterone. In clinical practice, this suggests that precise definition of indication and the correct combination of timing-dose-duration are important.

Serious adverse events were rare in the included RCTs; both drugs appeared safe for short-term use. Sedation was more frequently reported with vaginal/micronized progesterone. Dydrogesterone is an orally administered active progestin and previous studies have shown that dydrogesterone treatment reduced the risk of miscarriage.[16,24] There is not much research on the relationship between dydrogesterone and adverse pregnancy outcomes. A 2009 review summarized 28 reported

cases of various congenital birth defects; musculoskeletal defects and complex birth defects were the most common types, followed by masculinization, genitourinary defects, neural tube defects, and eye defects.[25] The data did not provide evidence for an association between congenital malformations and dydrogesterone use. In the vigibase study conducted by Henry et al.[14] in 2025, although attention was drawn to the increase in hypospadias and congenital heart anomalies in children of pregnant women using dydrogesterone, the fact that no causality could be established and that the study was only conducted on patients using dydrogesterone for ART should not be ignored even if it is not a proven side effect of dydrogesterone. However, no such association was reported in the RCTs conducted with dydrogesterone that we have examined. However, this highlights the necessity of conducting RCTs with large cohorts on this subject.

In a study conducted by Li et al.[26], exposure to maternal progesterone in the first trimester was found not to increase the frequency of adverse pregnancy outcomes after maternal age and comorbidities were adjusted for. Thus, studies conducted on prevention of threatened miscarriage suggest an importance for, drowsiness and decreased perception caused by progesterone rather than birth defects should be considered.

Study Limitations

Limitations of evidence include high heterogeneity among studies, sample differences, lack of blinding in some studies, and diversity in primary endpoint definitions.

We believe that the clinical implications are that there is no convincing evidence for routine progesterone support to most women with threatened miscarriage. However, individualized use in selected subgroups may be beneficial.

CONCLUSION

RCT evidence regarding progesterone support in threatened miscarriage is mixed and does not demonstrate a consistent effect in increasing live birth. Dydrogesterone may offer advantages for symptom control and ease of use. However, benefits such as increased live birth rate may be limited to selected subgroups. In light of current data, progesterone should be considered in an individualized manner taking into account patient-centered risk profile and symptoms, rther than being prescribed routinely. New, well-designed, biomarker-guided RCTs with adequate power are necessary to define which patients truly benefit and if there are any adverse fetal effects of dydrogesterone.

Footnotes

Author Contributions

Surgical and Medical Practices: K.H., A.Ö., İ.B., Concept: A.Ö., Design: K.H., A.Ö., Data Collection And Processing: K.H., İ.B., Analysis And Interpretation: K.H., A.Ö., Literature Search: K.H., İ.B., Writing: K.H., İ.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Supplementary Appendix 1: Search strategy (PubMed)

Search date: September 1-5, 2025 **Database:** PubMed

Search string: [“abortion, threatened”(MeSH)] OR [“threatened miscarriage”(title/abstract)] OR [“threatened abortion” (title/abstract)] OR [“vaginal bleeding”(title/abstract)] AND [“dydrogesterone”(MeSH)] OR [“dydrogesterone”(title/abstract)] OR [“Progesterone”(MeSH)] OR [“micronized progesterone”(title/abstract)] OR [“vaginal progesterone”(title/abstract)] OR [“oral progesterone”(title/abstract)]

Explanation of terms:

- **MeSH terms:** Controlled vocabulary (e.g., “abortion, threatened”, “dydrogesterone”).
- **Title/abstract:** Keywords searched within the title or abstract of the articles.
- **Boolean operators:**

OR: Used to combine synonyms (e.g., threatened miscarriage OR threatened abortion).

AND: Used to combine the condition (threatened miscarriage) with the intervention (progesterone/dydrogesterone).