



Threatened miscarriage and recurrent miscarriage: Expert opinions on progesterone therapy and treatment challenges

Düşük tehdidi ve tekrarlayan düşük: Progesteron tedavisine ilişkin uzman görüşleri ve tedavi zorlukları

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Abstract

It is crucial to gain a better understanding of threatened and recurrent miscarriages, including the existing knowledge and unknowns, as well as to discuss medical approaches and assess the situation. These issues are outstanding problems, causing significant physical and emotional burdens on women and their families, not only in Turkey but also worldwide. This article aims to explore the topic of miscarriages, including the implications, challenges, and potential therapeutic approaches in Turkey. Nineteen statements were presented to 6 Turkish perinatologists and obstetricians and gynecologists to evaluate the management of threatened and recurrent miscarriage and to compare the results with literature recommendations in an expert opinion meeting. Turkish perinatologists and obstetricians & gynecologists provided their responses using a 5-point Likert scale and discussed every statement. Progesterone use, particularly oral dydrogesterone, was supported by most of the experts. Opinions varied on the preference for dydrogesterone in recurrent miscarriage treatment. Experts unanimously agreed on the efficacy and safety of dydrogesterone and its recommendation in guidelines for threatened and recurrent miscarriage. Regarding progesterone therapy, vaginal progesterone was not associated with an increased rate of live births. Side effects of vaginal and oral micronized progesterone were acknowledged, and compliance with oral progesterone treatment was generally agreed upon. Dydrogesterone activity and effectiveness in threatened miscarriage received positive responses, while opinions on its effectiveness in recurrent miscarriage were divided. The loading dose of dydrogesterone and the practice of checking blood progesterone levels had different opinions among experts. This manuscript provides valuable insights in the management of threatened and recurrent miscarriages, highlighting the role of progesterone therapy, specifically dydrogesterone, and the need for adherence to relevant guidelines. Further research and a national Turkish guideline are warranted to address areas of uncertainty and optimize the management of these conditions.

Keywords: Threatened miscarriage, recurrent miscarriage, progesterone, treatment, diagnosis

Öz

Düşük tehdidi ve tekrarlayan düşüklerin daha iyi anlaşılması, mevcut bilgi ve bilinmezliklerin incelenmesi, tıbbi yaklaşımların tartışılması ve durumun değerlendirilmesi son derece önemlidir. Bu durum, sadece Türkiye’de değil, aynı zamanda tüm dünyadaki kadınlar ve aileleri üzerinde önemli fiziksel ve duygusal yükler yaratan önemli sorunlardır. Bu makale, Türkiye’de düşük konusunu, sonuçlarını, zorluklarını ve potansiyel terapötik yaklaşımları araştırmayı amaçlamaktadır. Uzman görüşleri ile düşük tehdidi ve tekrarlayan düşük yönetimi ve literatür önerilerini değerlendirmek amacıyla 6 Türk perinatolog ve kadın hastalıkları & doğum uzmanına 19 önerme sunulmuş ve uzman görüş toplantısında sonuçlar 5 puanlık Likert ölçeği kullanılarak değerlendirilmiştir. Türk perinatolog ve kadın hastalıkları & doğum uzmanları, her önermeyi ayrı ayrı değerlendirmiş ve tartışmışlardır. Uzmanların cevapları daha sonra analiz edilmiştir. Özellikle oral didrogesteron dahil progesteron kullanımı, uzmanların çoğunluğu tarafından desteklenmiştir. Ancak,

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didrogesteronun tekrarlayan düşük tedavisindeki yeri konusunda görüşler farklılık göstermiştir. Uzmanlar, didrogesteronun etkinliği ve güvenliliği ile düşük tehdidi ve tekrarlayan düşük tedavisinde kılavuzlardaki önerilerle aynı fikirde olmuşlardır. Vajinal progesteronun canlı doğum oranında artışla ilişkilendirilmediği görülmüştür. Vajinal ve oral mikronize progesteronun yan etkileri ve oral progesteron tedavisine daha iyi uyum sağlandığı genel olarak kabul görmüştür. Didrogesteronun düşük tehdidindeki etkinliği olumlu değerlendirilmiş, ancak tekrarlayan düşükteki etkinliği konusunda farklı görüşler belirtilmiştir. Didrogesteronun yükleme dozu şeklinde kullanımı ve kan progesteron seviyelerinin kontrolü konusundaki uygulamalar arasında farklı görüşler vardır. Bu yazı, düşük tehdidi ve tekrarlayan düşük yönetimi konusunda, progesteron tedavisinin, özellikle didrogesteronun rolünü ve ilgili kılavuzlara uyumunu vurgulayan değerli görüşler sunmaktadır. Belirsizlik alanlarını ele almak ve bu durumların yönetimini optimize etmek için daha fazla araştırma ve ulusal bir kılavuz gerekmektedir.

Anahtar Kelimeler: Düşük tehdidi, tekrarlayan düşük, progesteron, tedavi, tanı

Introduction

Miscarriage, defined as the loss of a spontaneous pregnancy before 20 weeks of gestation, can occur due to various reasons such as chromosomal anomalies, implantation dysfunction, and clinical complications^(1,2). Despite advancements in the prevention and management of clinical miscarriages, it remains a significant concern for healthcare professionals.

The most common complication of early pregnancy is threatened miscarriage, characterized by vaginal bleeding with or without abdominal cramps. It is estimated to occur in approximately 20% of pregnancies before the 20th week of gestation⁽³⁾. Recurrent miscarriage is typically defined as the occurrence of three or more consecutive documented pregnancy failures before 20 weeks of development⁽⁴⁾. However, according to the European Society of Human Reproduction and Embryology (ESHRE), recurrent miscarriage is defined as two or more consecutive pregnancy losses confirmed by ultrasound or histopathology. Nevertheless, only about 5% of women who conceive experience two consecutive miscarriages, and only 1% undergo three or more miscarriages⁽⁵⁾.

Progesterone, known as the “pregnancy hormone,” plays a crucial role in early pregnancy by preparing the endometrium for implantation and maintaining the gestational sac in the uterus⁽⁶⁾. Low levels of serum progesterone have been associated with threatened miscarriage. Progesterone is commonly used worldwide as the standard treatment for threatened miscarriage. Progesterone promotes muscle protein synthesis in the uterus, increases sensitivity to prostaglandin and estrogen, and prevents premature contractions of the myometrium⁽⁷⁾.

Progesterone can be administered orally, intramuscularly, or as a vaginal suppository. Oral administration ensures maximum compliance, but the effectiveness of oral progesterone varies⁽⁸⁾. A Cochrane review in 2018 found that oral progesterone “probably reduces miscarriage rates” compared with no treatment, but the evidence from the included trials was of moderate quality⁽⁴⁾. In a study conducted by Abrar et al.⁽⁹⁾, the effectiveness of oral versus vaginal progesterone was compared in terms of the absence of vaginal bleeding and the continuation of pregnancy beyond the 20th week. They found that the oral progesterone group had an efficacy of 90%, compared to 71% in the vaginal progesterone group.

Threatened miscarriage and recurrent miscarriage impose substantial physical and emotional burdens on women and

their families. The aim of this manuscript is to explore the topic of threatened and recurrent miscarriages and discuss the implications, challenges, and potential therapeutic approaches in Turkey. Expert opinions from medical specialists in the field have been consulted to provide valuable insights into this subject.

Materials and Methods

This manuscript is an expert opinion approach in the evaluation of the management of threatened miscarriage and recurrent miscarriage by Turkish perinatologists and obstetricians and gynecologists and comparing the results with the recommendations of the literature. Six opinion leaders with studies/publications on miscarriage were invited to the expert opinion meeting. Relevant guidelines and literature approaches were provided to the experts prior to the meeting. During the expert opinion meeting, a total of 19 statements were presented to 6 Turkish perinatologists and obstetricians and gynecologists, who provided their responses using a 5-point Likert scale. There were 19 statements (Table 1), and the experts responded to the statements with “Strongly Agree”, “Agree”, “Undecided”, “Disagree” and “Strongly Disagree” options. Experts answered and discussed all the statements with an independent moderator, and all the discussions were turned into a final report.

Results and Key Findings

The experts discussed 19 statements. The key findings of this expert opinion meeting are summarized in Table 2.

Discussion

This manuscript offers valuable insights into the real-world management of threatened and recurrent miscarriages in Turkey, providing information on the diagnostic and treatment approaches by Turkish perinatologists and obstetricians and gynecologists. The results demonstrate a high level of awareness and adherence to international guidelines and recommendations, reflecting the commitment of Turkish perinatologists and obstetricians and gynecologists to deliver optimal care for women with threatened miscarriage and recurrent miscarriage.

Experts highlight the influence of ethnicity on pregnancy outcomes, emphasizing that different ethnic groups in

Table 1. Statements

The prevalence of threatened miscarriage in Turkey is similar to the global prevalence.
The prevalence of recurrent miscarriage in Turkey is similar to the global prevalence.
Traditional methods, such as bed rest, are still effective in the treatment of threatened miscarriage and recurrent miscarriage.
Progestogen use is recommended in pregnant women experiencing threatened miscarriage.
It is recommended to investigate the cause of recurrent miscarriage in pregnant women.
In pregnant women experiencing idiopathic recurrent miscarriage, progestogen use is recommended to support the luteal phase.
In pregnant women experiencing idiopathic recurrent miscarriage, progesterone use is recommended in the first trimester.
In pregnant women experiencing idiopathic recurrent miscarriage, natural micronized progesterone treatment is not recommended in the first trimester.
Vaginal progesterone does not increase the rate of live births in recurrent miscarriage.
In the vaginal use of progesterone for threatened miscarriages, there are potential side effects such as discharge, irritation, itching etc.
Due to its sedative and hypnotic effects, oral micronized progesterone has a higher incidence of dizziness and drowsiness.
The oral use of progestogens enhances the compliance of the pregnant woman with the treatment.
While dydrogesterone exhibits progestogenic activity through strong progesterone receptors, its effects on androgen, glucocorticoid, and mineralocorticoid receptors are negligible/insignificant.
Dydrogesterone is effective in the treatment of threatened miscarriage.
Dydrogesterone is effective in the treatment of recurrent miscarriage.
Dydrogesterone treatment should be started with an initial loading dose in threatened miscarriage
Based on the studies, dydrogesterone is a safe treatment option.
According to ESHRE, the European Progestogen Club, Russia, and China guidelines, dydrogesterone is recommended for the treatment of threatened miscarriage and recurrent miscarriage.
It is recommended to check the blood progesterone level in cases of threatened miscarriage.

Turkey may experience variations in preterm birth rates⁽¹⁰⁾. While the overall preterm birth rate in Turkey is reported to be around 1-2%, it can vary significantly and reach up to 5% based on different studies. Additionally, the prevalence rate of miscarriage in Turkey is estimated to be 13.5%, with approximately 168,000 reported cases based on data from the Turkish Statistical Institute⁽¹¹⁾.

Recurrent miscarriage, defined as the loss of three or more consecutive pregnancies, affects approximately 1% to 3% of women, although some definitions consider two or more failed pregnancies^(12,13). The condition is more common in sexually active couples and poses a higher risk for women over 35 years of age⁽¹⁴⁾. Experts acknowledge the challenges in diagnosing recurrent miscarriages, particularly in distinguishing between actual miscarriages and pregnancies with fetal heartbeats seen on ultrasound or those with initially high β -HCG levels that later decline. Different criteria are used to define recurrent miscarriage, with the World Health Organization⁽¹⁵⁾ requiring three miscarriages confirmed histopathologically/ultrasonographically and ESHRE⁽⁵⁾ considering two consecutive miscarriages with positive β -HCG results. Experts emphasize the importance of considering additional factors beyond β -HCG levels when diagnosing recurrent miscarriages. Experts also mention that gestational weeks are also an important factor, and some doctors diagnose miscarriage as early as 5 weeks of gestation, while others consider a loss at 19 weeks as a miscarriage.

Regarding the treatment of threatened and recurrent miscarriages, traditional methods such as bed rest are considered ineffective by most of experts⁽¹⁶⁾. However, 83.34% of experts advocate the use of progestogens, citing the role of progesterone in preparing the endometrium and preventing endometrial defects that may contribute to miscarriage. Progesterone therapy, specifically oral dydrogesterone, is supported by most experts due to its minimal side effects and effectiveness in preventing miscarriages. Investigating the causes of miscarriage in cases of recurrent miscarriage is unanimously agreed upon by experts^(17,18).

Experts emphasize the importance of administering progesterone and providing appropriate bed rest and treatment in cases of threatened miscarriage. They strongly recommend the use of progesterone therapy due to the absence of observed side effects or adverse outcomes, indicating its safety and efficacy.

Regarding recurrent miscarriage, experts unanimously agree on the significance of investigating the underlying causes. In cases of idiopathic recurrent miscarriage, progestogen's use agents to support the luteal phase is recommended. However, there are differing opinions among experts regarding the preference for dydrogesterone and the overall importance of progesterone therapy for recurrent miscarriages. Some experts argue that dydrogesterone has minimal side effects and higher effectiveness compared with other options. However, one expert expresses skepticism about the proven benefits of progesterone therapy in such cases. It is noted that progesterone therapy is administered to exclude uterine septum or anomalies and to mitigate the impact of immunological factors. Experts report variations in the diagnostic rate of idiopathic recurrent miscarriages among competent physicians, highlighting the need for a differentiated evaluation of these cases. The importance of progesterone support in in vitro fertilization is also mentioned. Genetic factors,

Table 2. Key Findings

The prevalence of threatened miscarriage in Turkey similar to global prevalence: 33.33% of the experts responded with “Strongly Agree” and 66.67% responded with “Agree”.
The prevalence of recurrent miscarriage in Turkey similar to global prevalence: 6.67% of the experts responded with “Strongly Agree”, 50% responded with “Agree”, and 33.33% responded with “Undecided”.
Traditional methods effectiveness: 33.33% of the experts responded with “Agree”, 16.67% responded with “Disagree”, and 50% responded with “Strongly Disagree”.
Progestogen use in threatened miscarriage: 66.67% of the experts responded with “Strongly Agree”, 16.67% responded with “Agree”, and 16.67% responded with “Disagree”.
The cause of recurrent miscarriage investigation: 66.67% of the experts responded with “Strongly Agree”, and 33.33% responded with “Agree”.
Progesterone use in the first trimester in idiopathic recurrent miscarriage: 66.67% of the experts responded with “Strongly Agree”, and 33.33% responded with “Agree”.
Progesterone use in the first trimester in idiopathic recurrent miscarriage: 16.67% of the experts responded with “Strongly Agree”, 50% responded with “Agree”, 16.67% responded with “Undecided”, and 16.67% responded with “Disagree”.
Natural micronized progesterone treatment is not recommended in idiopathic recurrent miscarriage: 33.33% of the experts responded with “Agree”, 50% responded with “Disagree”, and 16.67% responded with “Strongly Disagree”.
Vaginal progesterone: 100% of the experts agree that the use of vaginal progesterone does not increase the rate of live births.
Vaginal progesterone side effects: 33.33% of the experts responded with “Strongly Agree”, 50% responded with “Agree”, and 16.67% responded with “Disagree”.
Oral micronized progesterone side effects: The experts, with 50% stating “Strongly Agree” and 50% stating “Agree”, expressed their consensus.
The compliance treatment with oral progesterone: 33.33% of the experts stated “Strongly Agree” while 66.67% stated “Agree”, indicating their consensus. The statements refers to the evaluation of vaginal, intramuscular, subcutaneous, and oral use.
Dydrogesterone strong activity on progesterone receptors: 33.33% of the experts responded with “Strongly Agree”, while 66.67% responded with “Agree”.
Effectivity of dydrogesterone in threatened miscarriage: 33.33% of the experts responded “Strongly Agree”, 50% responded “Agree”, and 16.67% responded “Undecided”.
Effectivity of dydrogesterone in recurrent miscarriage: 83.33% of the experts responded “Agree”, and 16.67% responded “Disagree”.
Loading dose of dydrogesterone use in threatened miscarriage: 16.67% of the experts responded “Agree”, 66.67% responded “Undecided”, and 16.67% responded “Strongly Disagree”.
Dydrogesterone safety: The experts reported that dydrogesterone is a safe treatment option, with 50% responding “Strongly Agree” and 50% responding “Agree”.
The recommendation of dydrogesterone in guidelines: The experts confirmed that in guidelines, dydrogesterone is recommended for threatened miscarriage and recurrent miscarriage treatment, with 16.67% responding “Strongly Agree” and 83.33% responding “Agree”.
Checking the blood progesterone level in threatened miscarriage: 33.33% of the experts responded “Agree”, 50% responded “Disagree”, and 16.67% responded “Strongly Disagree”.

structural anomalies, thrombophilia, and other endocrine causes are evaluated in cases of recurrent miscarriages, whereas idiopathic cases are reported to be less common.

Negative publications concerning medroxyprogesterone acetate (MPA) suggest that it should not be considered in the same category as dydrogesterone⁽¹⁹⁾. Overall, the experts’ opinion highlighted the importance of progesterone therapy in threatened miscarriage and recurrent miscarriage, with considerations for individual cases, potential causes, and treatment options.

According to experts, guidelines indicate that micronized progesterone is considered ineffective for pregnant women

with recurrent miscarriage, and recent studies have shown no significant difference in its effectiveness⁽²⁰⁾. MPA has been excluded, and it is stated that any form of progesterone is effective. Experts comment that the desired effect of progesterone is primarily local, and although micronized progesterone lacks a specific vaginal indication, its ability to be used vaginally provides a psychological indication and is perceived as superior by some individuals.

Regarding the treatment of recurrent miscarriages, experts state that vaginal progesterone has lower efficacy compared with oral dydrogesterone, suggesting the need to consider a systemic effect. They reference a study by Lee et al.⁽²¹⁾ in 2017

titled “The Influence of Oral Dydrogesterone and Vaginal Progesterone on Threatened Abortion: A Systematic Review and Meta-Analysis,” which highlights the effectiveness of progesterone therapy, especially oral dydrogesterone, in preventing miscarriages in women with threatened abortion. They underlined that the vaginal form of progesterone is less effective. Furthermore, the experts unanimously agree that the statement “Vaginal progesterone does not increase the live birth rate in recurrent miscarriages” is supported by all experts with a 100% agreement rate. They state that vaginal administration of progesterone can cause discomfort in patients and should not be recommended if there is vaginal bleeding. The presence of vaginal bleeding increases the risk of infection and may serve as a contraindication; thus, oral treatment can be considered. In cases of vaginal bleeding, experts emphasize to completely discontinue vaginal progesterone application, as it will have no effect.

It is noted that oral micronized progesterone, due to its sedative and hypnotic effects, has a higher incidence of dizziness and drowsiness⁽²²⁾.

The experts’ opinion highlights the varying efficacy of different forms of progesterone, with oral dydrogesterone considered more effective for recurrent miscarriages compared to vaginal progesterone. They emphasize the importance of individual considerations, potential contraindications, and the need for further research in this field. Progesterone can be administered orally, intramuscularly, or as a vaginal suppository⁽²³⁾. An oral administration of progesterone ensures maximum compliance although its efficacy has shown varying results. A Cochrane review conducted in 2018 found that oral progesterone “probably reduces the rates of miscarriage” (relative risk 0.57, 95% confidence interval 0.38-0.85) compared with no treatment, although all included studies were noted to have moderate quality evidence⁽⁴⁾. In another study by Abrar et al.⁽⁹⁾, the effectiveness of oral and vaginal progesterone was observed in terms of absence of vaginal bleeding and the ability of the pregnancy to progress beyond the 20th week. They noted that the oral progesterone group had an efficacy rate of 90% compared to 71% in the vaginal progesterone group. The experts clarified that the statement evaluated the effectiveness of different administration routes of progestogens compared with oral use. All experts unanimously agreed that an oral administration of progestogens improves compliance in pregnant women with the treatment.

Regarding the efficacy of dydrogesterone in the treatment of threatened miscarriage and recurrent miscarriage, 83.33% of the experts agree that the molecule is effective, while 16.67% express uncertainty due to the lack of conclusive evidence in the literature⁽²⁴⁾. Some studies in the literature support the claim that dydrogesterone has beneficial effects on maintaining pregnancy in women with threatened miscarriage and recurrent miscarriage, as suggested by the majority of experts⁽²⁵⁻²⁷⁾.

In the statement suggesting the use of an initial loading dose of dydrogesterone for treating threatened miscarriage, 66.67% of the experts expressed indecision. They provided various explanations for this uncertainty. One expert emphasized the variability of progesterone dosages and the need for a standardized definition of a loading dose, highlighting the lack of sufficient evidence in this regard. Another expert shared their clinical practice of using a loading dose with dydrogesterone, but acknowledged the absence of a standardized definition for such a dose. The third expert confirmed the absence of a loading dose in their practice and mentioned the existence of oral loading studies, but noted the lack of clear information regarding specific products and dosages⁽²⁸⁾.

Regarding the need to check blood progesterone levels in cases of threatened miscarriage, 66.67% of the experts stated that it is unnecessary. The experts held different opinions on this matter. They generally agreed that while measuring progesterone levels is feasible as a research topic, it is not meaningful or practical in the clinical setting. They highlighted the risks associated with delaying treatment or referring patients to other doctors while waiting for test results, especially in cases of bleeding. One expert suggested that measuring progesterone levels could be considered if it provides prognostic information, but emphasized that this test is not practical or cost-effective. Given the limited alternatives for miscarriage management, initiating treatment without measuring progesterone levels was deemed necessary. Experts noted that progesterone levels could potentially provide insights into prognosis and indicate the effectiveness of medication in target-oriented treatment. However, the mechanisms underlying changes in interplacental shift and progesterone secretion capacity remain poorly understood. All experts unanimously reported that dydrogesterone is a safe treatment option. They referred to the guidelines of reputable organizations such as ESHRE, the European Progestogen Club, Russia, and China, which recommend dydrogesterone for the treatment of threatened and recurrent miscarriages.

In summary, the experts’ opinion reflects their indecision regarding the use of an initial loading dose of dydrogesterone for threatened miscarriage and the need to check blood progesterone levels in such cases. They highlight the lack of standardized definitions and sufficient evidence in these areas in Turkey. While they recognize the potential benefits of measuring progesterone levels as a prognostic indicator, they emphasize the practical challenges and risks associated with delayed treatment. Overall, experts unanimously agree on the safety of dydrogesterone and its recommendation in the treatment of threatened and recurrent miscarriages according to relevant guidelines.

Conclusion

This manuscript reflects a high level of awareness among Turkish perinatologists and obstetricians and gynecologists regarding international guidelines and their commitment to

providing optimal care for women with these conditions. Experts acknowledge the influence of ethnicity on pregnancy outcomes and highlight the variability of preterm birth rates and the frequency of miscarriages in Turkey. They emphasize the challenges in diagnosing recurrent miscarriages. Experts consider the use of progestogens, especially oral dydrogesterone, in the treatment of threatened and recurrent miscarriages. However, there are differing opinions on the preference for dydrogesterone and the overall importance of progesterone therapy for recurrent miscarriages. The experts propose the need to investigate the underlying causes of recurrent miscarriage and highlight the importance of individual evaluations and potential contraindications in selecting appropriate treatment options. They underline the differences in efficacy among different forms of progesterone and suggest that oral dydrogesterone is a more effective option for recurrent miscarriages compared with vaginal progesterone. Overall, experts unanimously agree on the safety of dydrogesterone and its recommendation in the treatment of threatened and recurrent miscarriages according to relevant guidelines. Experts concluded that population - based research regarding miscarriage should be conducted because of the lack of data in Turkiye, and a national guideline is needed to address areas of uncertainty and optimize the management of threatened and recurrent miscarriage in clinical practice.

Key findings

- The results demonstrate a high level of awareness and adherence to international guidelines and recommendations, reflecting the commitment of Turkish perinatologists and obstetricians and gynecologists to deliver optimal care for women with threatened miscarriage and recurrent miscarriage.
 - Oral dydrogesterone is a more effective option for recurrent miscarriage than vaginal progesterone.
 - Experts unanimously agree on the safety of dydrogesterone and its recommendation in the treatment of threatened and recurrent miscarriage according to relevant guidelines.
 - The experts agreed that there is a lack of data in the Turkish literature. A population-based study in Turkiye regarding miscarriage should be conducted.
 - It has been highlighted that a Turkish guideline regarding threatened miscarriage and recurrent miscarriage should be prepared.
- These key findings highlight the benefits and effectiveness of different forms of progesterone in miscarriage. These expert opinions emphasize the importance of progesterone administration in threatened miscarriage and recurrent threatened miscarriage, the significance of progesterone levels in predicting risk and guiding treatment. Further research is needed to enhance our understanding of these relationships and optimize progesterone therapy in clinical practice.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: S.C.D., A.G., H.T., C.Ç., H.G.P., Ç.G., Design: S.C.D., A.G., H.T., C.Ç., H.G.P., Ç.G., Data Collection or Processing: S.C.D., A.G., H.T., C.Ç., H.G.P., Ç.G., Analysis or Interpretation: S.C.D., A.G., H.T., C.Ç., H.G.P., Ç.G., Literature Search: S.C.D., A.G., H.T., C.Ç., H.G.P., Ç.G., Writing: S.C.D., A.G., H.T., C.Ç., H.G.P., Ç.G.

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References

1. Zegers-Hochschild F, Adamson GD, De MJ, Ishihara O, Mansour R, Nygren K, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology. *Fertil Steril* 2009;92:1520-4.
2. Macklon NS, Geraedts JP, Fauser BC. Conception to ongoing pregnancy: the 'black box' of early pregnancy loss. *Hum Reprod Update* 2002;8:333-43.
3. National Guideline Alliance (UK). Ectopic pregnancy and miscarriage: diagnosis and initial management. London: National Institute for Health and Care Excellence (UK); 2019. Available at: www.nice.org.uk/guidance/ng126. [Access date: 10 July 2023]
4. Wahabi HA, Fayed AA, Esmaeil SA, Bahkali KH. Progestogen for treating threatened miscarriage. *Cochrane Database Syst Rev* 2018;8:CD005943.
5. ESHRE Guideline Group on RPL; Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. *Hum Reprod Open* 2023;2023:hoad002.
6. Di Renzo GC, Giardina I, Clerici G, Brillo E, Gerli S. Progesterone in normal and pathological pregnancy. *Horm Mol Biol Clin Investig* 2016;27:35-48.
7. Taraborrelli S. Physiology, production and action of progesterone. *Acta Obstet Gynecol Scand* 2015;94:8-16.
8. Practice Committee of the American Society for Reproductive Medicine. Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. *Fertil Steril* 2008;89:789-92.
9. Abrar S, Abrar T, Tahir M, Sayyed E. Efficacy of oral with vaginal progesterone in the treatment of threatened miscarriage in first trimester. *J Med Sci* 2017;25:407-10.
10. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* 2012;379:2162-72.
11. <https://data.tuik.gov.tr/Bulten/Index?p=Birth-Statistics-2021-45547>. [Access date: 02 July 2023]
12. Rai R, Regan L. Recurrent miscarriage. *Lancet* 2006;368:601-11.
13. Carrington B, Sacks G, Regan L. Recurrent miscarriage: pathophysiology and outcome. *Curr Opin Obstet Gynecol* 2005;17:591-7.
14. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. *Fertil Steril* 2008;90:560.

15. WHO. Recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14 1976. *Acta Obstet Gynecol Scand* 1977;56:247-53.
16. Aleman A, Althabe F, Belizán J, Bergel E. Bed rest during pregnancy for preventing miscarriage. *Cochrane Database Syst Rev* 2005;2005:CD003576.
17. Li TC, Spuijbroek MD, Tuckerman E, Anstie B, Loxley M, Laird S. Endocrinological and endometrial factors in recurrent miscarriage. *BJOG* 2000;107:1471-9.
18. Li TC, Tuckerman EM, Laird SM. Endometrial factors in recurrent miscarriage. *Hum Reprod Update* 2002;8:43-52.
19. Dianat S, Fox E, Ahrens KA, Upadhyay UD, Zlidar VM, Gallo MF, et al. Side Effects and Health Benefits of Depot Medroxyprogesterone Acetate: A Systematic Review. *Obstet Gynecol* 2019;133:332-41.
20. Jevé YB, Davies W. Evidence-based management of recurrent miscarriages. *J Hum Reprod Sci* 2014;7:159-69.
21. 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;2017:3616875.
22. Kolatorova L, Vitku J, Suchopar J, Hill M, Parizek A. Progesterone: A Steroid with Wide Range of Effects in Physiology as Well as Human Medicine. *Int J Mol Sci* 2022;23:7989.
23. Parveen R, Khakwani M, Tabassum S, Masood S. Oral versus Vaginal Micronized Progesterone for the Treatment of Threatened Miscarriage. *Pak J Med Sci* 2021;37:628-32.
24. Stute P. Dydrogesterone indications beyond menopausal hormone therapy: An evidence review and woman's journey. *Gynecol Endocrinol* 2021;37:683-8.
25. Kalinka J, Szekeres-Bartho J. The impact of dydrogesterone supplementation on hormonal profile and progesterone-induced blocking factor concentrations in women with threatened abortion. *Am J Reprod Immunol* 2005;53:166-71.
26. Pandian RU. Dydrogesterone in threatened miscarriage: a Malaysian experience. *Maturitas* 2009;65(Suppl 1):S47-50.
27. Haas DM, Ramsey PS. Progestogen for preventing miscarriage. *Cochrane Database Syst Rev* 2013;31:CD003511. Update in: *Cochrane Database Syst Rev* 2018;08;10:CD003511
28. https://titck.gov.tr/storage/Archive/2020/kubKtAttachments/temizkub_8ebe4ad7-5b9a-4806-aff1-78fee4f3c1d4.pdf [Access date: 06 June 2023]