Guideline / Kılavuz

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PERİDER-TJOD joint review on threatened abortion and guideline for its treatment

PERİDER-TJOD düşük tehdidi ve tedavisi kılavuzu

Süleyman Cansun Demir[1], İbrahim Polat[2], Dilek Şahin[3], Ali Gedikbaşı[4], Cihan Çetin[5], Hakan Timur[6], Atakan Tanaçan[3]

[1]*Çukurova University Faculty of Medicine, Department of Gynecology and Obstetrics, Division of Perinatology, Adana, Türkiye*

[2]*Başakşehir Çam ve Sakura City Hospital, Clinic of Gynecology and Obstetrics, Perinatology Unit, İstanbul, Türkiye*

[3]*Ankara Bilkent City Hospital, Clinic of Gynecology and Obstetrics, Perinatology Unit, Ankara, Türkiye*

[4]*Private Practice, İstanbul, Türkiye*

[5]*Bahçeşehir University Faculty of Medicine, Department of Gynecology and Obstetrics, Division of Perinatology, İstanbul, Türkiye*

[6]*Ordu University Gynecology and Children's Hospital, Clinic of Gynecology and Obstetrics, Perinatology Unit, Ordu, Türkiye*

Abstract

Objective: Although there are several guidelines in the literature on "recurrent abortion", there is no comprehensive guideline on "threatened abortion". The overall purpose of this guideline is to provide healthcare providers with the best available evidence for examination and treatment of pregnant women with threatened abortion.

Materials and Methods: The scope of the guideline and the first version of the questions were prepared by the Perinatology and High Risk Pregnancies Association (PERİDER) guideline development group in January 2024. Meetings were held to discuss key questions and redefine them. A final list of 8 key questions was created. Keywords were defined for each question and ranked in order of importance and used in searches for all English-language publications in PubMed/Medline and Cochrane libraries. These databases were thoroughly scanned for publications that were published until February 1, 2024. Literature reviews were conducted as an iterative process. In the first step, systematic reviews and meta-analyses were collected. If no results were found, the research was expanded to randomized controlled trials and then to cohort studies and case reports, following the hierarchy of evidence levels.

Results: This guideline was presented to the board of directors of the Turkish Gynecology and Obstetrics Society (TJOD). With their suggestions, guideline was finalized, and it was decided to be published as a joint guideline of PERİDER-TJOD.

Conclusion: This guideline provides an overview of threatened abortion and the recommended treatments. In addition, by recognizing the deficiencies in the literature, suggestions were made regarding research that could help clinicians' decisions in the future.

Keywords: Threatened abortion, progesterone, threatened miscarriage

Öz

Amaç: Literatürde "tekrarlayan düşük" ile ilgili çok sayıda kılavuz bulunmakla birlikte, "düşük tehdidi" ile ilgili kapsamlı bir kılavuz bulunmamaktadır. Bu kılavuzun genel amacı, sağlık hizmeti sağlayıcılarına düşük tehdidinde muayene ve tedavi için mevcut en iyi kanıtları sağlamaktır.

Gereç ve Yöntemler: Kılavuzun kapsamı ve soruların ilk versiyonu Ocak 2024'te Perinatoloji ve Riskli Gebelikler Derneği (PERİDER) kılavuz geliştirme grubu tarafından hazırlandı. Temel soruların tartışılması ve yeniden tanımlanması için toplantılar yapıldı ve 8 sorudan oluşan son liste oluşturuldu. Her soru için anahtar kelimeler belirlenerek önem sırasına göre sıralandı ve PubMed/Medline ve Cochrane kütüphanelerindeki tüm İngilizce yayınlar için yapılan aramalarda kullanıldı. Bu veri tabanları, 1 Şubat 2024 tarihine kadar yayımlanan yayınlar için kapsamlı bir şekilde tarandı. Literatür taramaları

PRECIS: The overall purpose of this guideline is to provide healthcare providers with the best available evidence for examination and treatment of pregnant women with threatened abortion.

Corresponding Author/Sorumlu Yazar: Prof. MD, Süleyman Cansun Demir, Çukurova University Faculty of Medicine, Department of Gynecology and Obstetrics, Division of Perinatology, Adana, Türkiye

E-mail: cansundemir@gmail.com **ORCID ID:** orcid.org/0000-0001-8331-9559

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yinelemeli bir süreç olarak yürütüldü. İlk adımda, sistematik derlemeler ve meta-analizler incelendi. Sonuç bulunamazsa, araştırma randomize kontrollü çalışmalara ve daha sonra kanıt düzeyi hiyerarşisini takip ederek kohort çalışmalarına ve olgu raporlarına kadar genişletildi.

Bulgular: Bu kılavuz hazırlanarak Türk Jinekoloji ve Obstetrik Derneği (TJOD) yönetim kuruluna sunuldu. Onların da önerileri ile kılavuza son şekli verildi ve PERİDER-TJOD ortak kılavuzu olarak yayınlandı.

Sonuç: Bu kılavuz, düşük tehdidine ve önerilen tedavilere genel bir bakış sunmaktadır. Ayrıca literatürdeki eksiklikler fark edilerek, gelecekte klinisyenlerin kararlarına yardımcı olabilecek araştırmalara ilişkin önerilerde de bulunulmuştur.

Anahtar Kelimeler: Düşük tehdidi, progesteron, gebelik kaybı

Disclaimer

As Perinatology and High Risk Pregnancies Association (*Perinatoloji ve Riskli Gebelikler Derneği* - PERİDER), we developed the current clinical practice guideline to provide clinical recommendations in Türkiye, and the world to improve the quality of healthcare delivery to patients with threatened abortion. This guide represents the views of PERİDER obtained after careful consideration of the scientific evidence available at the time of its preparation. Due to the lack of sufficient scientific evidence on some issues, a consensus has been reached among the relevant PERİDER members. The purpose of clinical practice guidelines is to assist healthcare professionals in day-to-day clinical decisions regarding the appropriate and effective care of their patients. However, adherence to these clinical practice guidelines does not guarantee a successful or specific outcome or establish a standard of care. Clinical practice guidelines do not override the clinical judgment of the healthcare professional in the diagnosis and treatment of patients. Healthcare professionals should make their decisions on a case-by-case basis, using their own knowledge and skills and clinical reasoning. They should take into account the situation, circumstances, and wishes of each patient, and consult with the patient or, as appropriate, her guardian.

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About the Guideline

Although there are several guidelines in the literature on the recurrent abortion, there is no comprehensive guideline on "threatened abortion", so as PERİDER, we decided to prepare this guideline in 2024. The guideline development group selected from PERİDER determined the questions that needed to be answered in the guideline. They did a thorough literature review and created a guideline by reaching a consensus through regular meetings.

This guideline, prepared by PERİDER, was presented to the board of directors of the Turkish Gynecology and Obstetrics Society (*Türk Jinekoloji ve Obstetrik Derneği* - TJOD). With their suggestions, the guideline was finalized, and it was decided to be published as a joint guideline between PERİDER and TJOD.

The overall purpose of this guideline is to provide healthcare providers with the best available evidence for examination and treatment of pregnant women with threatened abortion.

This guideline provides an overview of threatened abortion and the recommended treatments. In addition, by recognizing the deficiencies in the literature, suggestions were made regarding research, that could help clinicians' decisions in the future.

This guideline is presented in two parts. In the first section, basic concepts and definitions regarding threatened abortion are summarized. Several up-to-date references have been used in the compilation of this part. In the second part, the main clinical questions, comprehensive literature data, and recommendations, especially for the treatment of threatened abortion, are included.

The scope of the guideline and the first version of the questions were prepared by the PERİDER guideline development group in January 2024. Guideline development group meetings were held to discuss key questions and redefine them. As a result of the meetings, a final list of 8 key questions was created. Keywords were defined for each question, ranked in order of importance, and used in searches for all English-language publications in PubMed/Medline and Cochrane libraries. These databases were thoroughly scanned for publications up to February 1, 2023. Literature reviews were conducted as an iterative process. In the first step, systematic reviews and meta-analyses were collected. If no results were found, the research was expanded to randomized controlled trials and then to cohort studies and case reports, following the hierarchy of evidence levels.

Part 1: Basic Concepts

What is miscarriage?

Miscarriage (Spontaneous Abortion) is the loss of pregnancy up to the 20th week of pregnancy. The World Health Organization also considers the loss of a fetus weighing less than 500 grams as an abortion. The most important symptoms in abortion are bleeding and pain; therefore, abortion can be mistaken for ectopic pregnancy or molar pregnancy[1].

What is threatened abortion?

Threatened abortion is bleeding in early pregnancy with no evidence of pregnancy loss[1].

What are the types of abortion?

Anembryonic pregnancy: It is a pregnancy that is not viable with the presence of a gestational sac without an embryo or yolk sac. In the past, the term "***blighted ovum***" was also used.

Recurrent pregnancy loss: It is the loss of two or more spontaneous pregnancies.

Septic abortion: A spontaneous or provoked abortion associated with a uterine infection.

Incomplete abortion: It is the presence of products of conception in the uterus after the diagnosis of pregnancy loss.

Inevitable abortion (abortus incipiens): Occurs when the abortion cannot be prevented as the cervix is open, accompanied by bleeding and pain. It is an old term that is not used much today.

Missed abortion: It is the loss of a fetus without symptoms. It can also be called asymptomatic pregnancy loss[2].

What is the frequency of threatened abortion in the world and in Türkiye?

Threatened abortion is an important cause of early pregnancy bleeding. Implantation bleeding, cervical lesions, and ectopic pregnancy should be kept in mind in the differential diagnosis of bleeding in the first trimester.

Although the studies are heterogeneous, in one study bleeding in the first trimester was observed in approximately 25% of pregnant women. In the same study, the rate of pregnancy loss was observed as 12% in pregnant women with bleeding in the first trimester[3]. In another observational study, bleeding was observed in 21% of pregnant women before 20 weeks of pregnancy and pregnancy loss was observed in 50% of this group[4].

There is no comprehensive epidemiological study on the incidence of threatened abortion in Türkiye.

What are the risk factors for threatened abortion?

Maternal Age: The risk of miscarriage varies with maternal age. There is a strong correlation between advanced maternal age (>35 years) and fetal chromosomal abnormalities[5]. Risk of miscarriage increases with advanced maternal age, and adolescent pregnancies are also a risk factor.

Paternal Age: The risk of pregnancy loss increases in advanced paternal age. However, this risk rate is lower than that of maternal age[6].

Previous pregnancy loss: Previous pregnancy loss increases the risk of loss in subsequent pregnancies. In one study the number of pregnant women with a history of at least one pregnancy loss was reported to be higher[7].

Maternal diseases: These are factors whose effects decrease when they are well controlled.

1. Some systemic infections (malaria, brucellosis, CMV, and HIV, travel sickness, influenza virus) and bacterial vaginosis increase the risk of miscarriage[8].
2. Pregnancy loss increases in case of diabetes, hypo/hyperthyroidism, obesity and chronic stress[9].
3. In women who become pregnant in the presence of an intrauterine device (IUD), the rate of miscarriage increases if the IUD is not removed[9].

Substance use: Smoking, alcohol, and drug use increase the risk of pregnancy loss[2].

Environmental factors: Exposure to excessive lead, arsenic, air pollution, and radiation are also associated with an increase in pregnancy loss[2].

Subchorionic hemorrhage: In the presence of subchorionic hemorrhage, the risk of pregnancy loss is two times higher[10].

Which etiologies should be considered in pregnant women with bleeding in the first trimester?

- Implantation Bleeding: A small amount of bleeding on the 10^{th}-14^{th} day of fertilization, spotting
- Threatened abortion
- Miscarriages (missed abortus, abortus incipiens)
- Ectopic pregnancy
- Pregnancy + IUD
- Pregnancy + Arteriovenous malformation
- Gestational trophoblastic disease (molar pregnancy)
- Genital infections
- Cervical and vaginal pathologies: Cervical polyp or myoma, cervical ectropion, cervical cancer, lacerations, disseminated vaginal condyloma acuminata[11,12].

How is threatened abortion diagnosed?

Vaginal spotting or bleeding can occur in approximately 25% of pregnancies in the first trimester. First trimester bleeding is often due to damage to the blood vessels in the decidua during implantation, or it can be caused by cervical or vaginal lesions. The diagnosis can be made by excluding other conditions in the differential diagnosis, by looking at the gestational week, bleeding severity and characteristics (spotting, mild or severe, intermittent or continuous, painful or painless). Initial diagnosis may be supported or revised after physical examination, laboratory tests, and imaging methods[3].

What are the symptoms suggestive of threatened abortion?

Symptoms such as bleeding and cramping are the most common in threatened abortion. A decrease in nausea and vomiting may also be seen[4,12,13].

Should pelvic and speculum examinations be performed in the diagnosis of threatened abortion?

A speculum examination is necessary during the physical examination. Bimanual pelvic and speculum examination allows one to distinguish between threatened abortion, inevitable miscarriage (abortus incipiens), and incomplete abortion.

In ectopic pregnancies, cervical and adnexal tenderness or a mass may be detected. Viewing the cervix with a speculum allows for estimating the severity of bleeding and removing any endocervical conception products. Rarely, cervical lesions and masses that may cause bleeding can also be identified[14].

What is the role of ultrasonography (USG) in the diagnosis of threatened abortion?

How often should USG be done?

Symptoms such as vaginal bleeding and uterine cramps can be observed in normal, ectopic and molar pregnancies, as well as early pregnancy loss. Therefore, it is important to distinguish threatened abortion from other early pregnancy complications. A thorough medical history and physical examination, along with a USG and, as the case may be, serum beta-hCG testing, can be helpful in making a diagnosis. If possible, USG should be performed to confirm the presence of a live intrauterine pregnancy. After it is determined that the pregnancy is intrauterine, USG can be considered again in case of findings such as severe bleeding, hemodynamic instability, and abdominal tenderness on physical examination. Otherwise, routine pregnancy follow-up protocols should be applied[15,16].

When can a gestational sac first be seen in USG?

With a transvaginal USG, the gestational sac can be seen between weeks 4.5-5 of gestation at the earliest according to the last menstrual date. These structures may be noticed slightly later in the transabdominal USG examination[17].

What is the minimum beta-hCG level necessary for the gestational sac to be seen with transvaginal and transabdominal USG?

In a retrospective study, the lowest serum beta-hCG level was measured using transvaginal USG as 390 mIU/mL in a live intrauterine pregnancy. The minimum threshold values for imaging the yolk sac and fetus using transvaginal USG were 1,094 mIU/mL and 1,394 mIU/mL, respectively[18]. However, in clinical practice, the widely accepted serum beta-hCG level for which the gestational sac can be visualized with transvaginal USG is 1,500-2,000 mIU/mL[19]. When beta-hCG level reaches 6,500 mIU/mL, the gestational sac can be visualized using transabdominal USG[20]. However, current studies show that as a result of developments in USG technology, values can be reduced to much lower limits[18].

At which gestational weeks are the yolk sac and embryo typically seen?

With transvaginal USG, the yolk sac is typically monitored between the 5th and 6th weeks of pregnancy, and with transvaginal USG, the measurable embryo is monitored between the 6th and 7th weeks according to the last menstrual period[21].

What is the minimum gestation time, embryo size and gestational sac size expected for fetal cardiac activity?

Based on the date of the last menstrual period, embryonic cardiac activity is expected to be monitored with transvaginal USG around the 6th week of pregnancy. Fetal cardiac activity should be observed when the embryo reaches ≥7 mm in size or when the gestational sac size is ≥25 mm[21].

What are the USG criteria for the diagnosis of a nonviable pregnancy?

There are strict criteria for the diagnosis of a nonviable pregnancy:

- No fetal cardiac activity when the embryos head-rump distance is ≥7 mm
- Failure to monitor the embryo when the gestational sac is ≥25 mm in size
- In an early pregnancy in which a gestational sac was observed but no yolk sac was observed, an embryo with a heartbeat could not be monitored in the control performed 2 weeks later.
- Failure to monitor an embryo with a heartbeat after ≥11 days in early pregnancy in which the yolk sac was also observed in the gestational sac[21].

What is the role of laboratory tests in the diagnosis of threatened abortion?

How often is beta-hCG testing recommended for a woman with vaginal bleeding and pain to make a differential diagnosis of threatened abortion and ectopic pregnancy?

In cases where intrauterine and ectopic pregnancies cannot be differentiated with transvaginal USG, beta-hCG follow-up at 48-hour intervals may be beneficial. An increase of more than 50% in beta-hCG levels at this 48-hour interval can be interpreted in favor of an intrauterine pregnancy. The expected rate of increase also differs according to the initial beta-hCG level. The baseline beta-hCG value shows different percentages depending on the concentration: 49% if it is <1,500 mIU/mL, 40% if it is in the range of 1,500-3,000 mIU/mL, and 33% if it is in the range of >3,000-<10.000 mIU/mL[22].

Is serum progesterone level useful in the diagnosis of threatened abortion?

Although it has been used in the past, the use of serum progesterone levels in cases with no observed intrauterine gestational sac is controversial and has not found a routine place in clinical practice. The difference in serum progesterone levels between spontaneous pregnancies and assisted reproductive technology pregnancies also limits their use in the diagnosis of threatened abortion.

In a recent meta-analysis, a one-time serum progesterone measurement of <12 ng/mL in the first trimester was found to be effective in predicting the probability of a miscarriage

in pregnant women with threatened abortion[23]. Therefore, measurement of serum progesterone levels can be considered to predict the prognosis in pregnant women with threatened abortion rather than diagnosing it.

What are the possible obstetric consequences of a pregnancy with threatened abortion?

Bleeding and cramps are common in early pregnancy. Studies have shown that about 25% of pregnant women experience vaginal bleeding before the 20th week of pregnancy, and between 12% and 57% of these pregnant women will eventually experience early pregnancy loss. Subchorionic hematomas are associated with threatened abortion; risk of early pregnancy loss is higher in pregnancies with large subchorionic hematomas, but the presence of a subchorionic hematoma does not increase birth complications in ongoing pregnancies[24]. Heavy bleeding, especially when accompanied by pain or cramping, has a significantly worse prognosis than light bleeding or spotting. In addition, pregnant women with heavy vaginal bleeding should be evaluated for hemorrhagic anemia; this is usually a precursor of early pregnancy loss and is associated with a poor prognosis[25,26].

In pregnancies with threatened abortion, the risk of adverse outcomes such as pregnancy loss, premature rupture of membranes, premature birth, fetal growth restriction, placental abruption, cesarean delivery, postpartum uterine atony, and the need for neonatal intensive care increases in the later stages of pregnancy[27]. In addition, women who experienced an early pregnancy loss had an increased risk of depression, sleep disturbance, feelings of anger and guilt[28,29].

Part 2: Treatment of Threatened Abortion

Is bed rest and/or hospitalization beneficial in the treatment of threatened abortion?

High-quality evidence supporting bed rest to prevent miscarriages in women with confirmed fetal viability and vaginal bleeding in the first half of pregnancy is insufficient[30]. Bed rest does not improve outcomes and may cause psychological harm to pregnant women who later experience early pregnancy loss[31]. Since most cases of early pregnancy losses are due to chromosomal or fetal anomalies, activity restriction is unlikely to affect the final outcome of these pregnancies[32].

The effectiveness of bed rest to prevent early pregnancy loss in pregnant women experiencing threatened abortion has not been proven[25,33-35]. While there are no randomized controlled trials or meta-analyses proving that bed rest improves patient outcomes, there is only one retrospective study suggesting its effectiveness. In this study, women who adhered to bed rest had fewer spontaneous abortions (9.9% *vs.* 23.3%, p=0.006) and a higher rate of term pregnancy (89% *vs.* 70%, p=0.004) than those who did not. However, large, prospective, randomized studies are needed to confirm whether bed rest has a true therapeutic effect (Table 1)[36].

Therapeutic bed rest continues to be widely used, even though it has no benefits and has known harms. The benefit of bed rest was only demonstrated in a single non-controlled non-randomized study[31].

Since differentiating the diagnosis of bleeding in the first trimester is not easy, hospitalization of pregnant women with unconfirmed diagnoses should be considered. However, there is not enough information in the literature to recommend hospitalization of pregnant women diagnosed with a threatened abortion.

Should restriction of sexual intercourse be recommended in threatened abortion?

Although sexual intercourse restriction is recommended in threatened abortion as a general practice in Türkiye, there is no study on this subject in the literature. Therefore, it is rational to recommend avoiding sexual intercourse during the acute bleeding period until randomized controlled trials are conducted, or until solid evidence is available.

Table 1. Bed rest at threatened abortion

Author, year	n	Study design	Treatment group	Control group	Efficacy of bed rest
Diddle et al.[33] 1953	9742	Prospective, observational	Bed rest ± sedation	Normal physical activity	No difference
Hamilton et al.[34] 1991	23	Randomized controlled	Bed rest	Normal physical activity	Three miscarriages were reported, but it was not specified which group they belonged to. The study has been terminated.
Harrison[35] 1993	61	Double-blind randomized controlled	Bed rest	Placebo and hCG injection	In the prevention of miscarriage, hCG treatment was found to be significantly better than bed rest
Ben-Haroush et al.[36] 2003	230	Retrospective analysis	Compliant with bed rest	Non-compliant with bed rest	Fewer spontaneous abortions (p=0.006) and more term pregnancies (p=0.004) were observed in those who were compliant with bed rest

Does natural progesterone therapy have a place in the treatment of threatened abortion?

The use of natural progesterone in threatened abortion has not been shown to be beneficial in increasing live birth rate[37-41]. In a randomized controlled trial, in those with a history of ≥1 miscarriage (from diagnosis to 16th gestation week), use of vaginal 400 mg progesterone, twice daily, has been shown to increase the rate of live birth[39]. In an interim analysis of another recent randomized controlled trial, it was concluded that the use of 400 mg vaginal progesterone did not change the live birth rate, even in those with a history of miscarriage, and the study was therefore terminated before the targeted number of patients was reached[38]. A study which shows that oral use of natural progesterone is more effective than vaginal use has a low level of evidence due to the small number of patients and it was not designed to be a double-blind study[42]. Similarly, there is a randomized controlled trial in the literature showing that the rate of miscarriage decreases with the use of vaginal progesterone, but the level of evidence is low due to the small sample size (30 controls, 30 patients)[43].

Therefore, use of natural progesterone is not recommended after the diagnosis of threatened abortion in pregnant women without a history of miscarriage. However, in pregnant women who have had a previous miscarriage, use of vaginal progesterone 400 mg twice daily, can be considered until the 16th week of gestation.

Does synthetic progesterone therapy have a place in the treatment of threatened abortion?

Two recent (2018 and 2021) meta-analyses on the use of progesterone in the treatment of threatened abortion with different designs have been published in the Cochrane Library[29,40]. In the 2018 analysis, data from 7 studies containing a total of 696 pregnant women were compiled. In threatened abortion, the use of progesterone was evaluated to be more effective in reducing the rate of miscarriage compared to placebo or control groups [relative risk (RR): 0.64, confidence interval (CI): 0.47-0.87]. When pregnant women who used oral progesterone were compared with those who did not receive treatment, the rate of miscarriage was reduced with oral progesterone (RR: 0.57; CI: 0.38-0.85); while there was no difference in those using vaginal progesterone compared to placebo (RR: 0.75; CI: 0.47-1.21). In this meta-analysis, it was reported that progesterone use did not increase the risk of congenital anomalies, although its evidence level was low (RR: 0.7, 95% CI: 0.1-4.82)[29]. In the more recent 2021 meta-analysis, data from 7 studies involving 5,682 pregnancies were examined[40]. Subgroup analysis was also conducted excluding cases with recurrent miscarriage. In these analyses comparing the effectiveness against placebo, data from two studies including 4,090 pregnant women for vaginal micronized progesterone and the data from one study including 406 pregnant women for dydrogesterone were evaluated. Vaginal natural progesterone did not provide a statistically significant reduction in the miscarriage rate compared to placebo (RR: 0.9, CI: 0.8-1.01). Similarly, no significant difference was observed in the data of the only study in which dydrogesterone was compared with placebo (RR: 0.9, CI: 0.55-1.47)[44]. In the only study comparing the effectiveness of oral micronized progesterone and dydrogesterone, no difference was found in the reduction of miscarriage rates (RR: 0.76, CI: 0.25-1.75)[45]. This review stated that there are no data available to evaluate the effectiveness of 17-α hydroxyprogesterone or oral micronized progesterone in threatened abortion[45].

In a recent study, an increased risk of malignancy was reported in individuals exposed to 17-α hydroxyprogesterone in the womb for the treatment of threatened abortion[46]. For this reason, the Türkiye Pharmaceuticals and Medical Devices Agency (*Türkiye İlaç ve Tıbbi Cihaz Kurumu*) suspended the licenses of drugs containing this molecule with a letter they published in 20.09.2024. As PERİDER, Due to this increased risk, we do not recommend the use of 17-α hydroxyprogesterone in the treatment of threatened abortion.

In addition, no increased risk of adverse effects and congenital anomalies has been detected with the use of progesterone (vaginal micronized, dydrogesterone), compared to placebo, but the level of evidence is low[40].

In another recent meta-analysis, data from 4907 pregnant women were examined[47]. In a subgroup analysis of this study (n=4833) in which threatened abortion treatments were evaluated, miscarriage rate was reduced with progesterone treatment, compared to placebo and control groups (RR: 0.7, CI: 0.52-0.95). However, in this meta-analysis, sub-analyses were not conducted in terms of progesterone form, dose, or application methods.

Another meta-analysis showed that the use of progesterone in threatened abortion significantly reduced the miscarriage rate compared to the control group (those receiving placebo and those receiving no treatment) (RR: 0.53, CI: 0.36-0.78). The least risk of miscarriage was detected in the oral dydrogesterone group (RR: 0.43, CI: 0.26-0.71). There was no significant difference in the risk of miscarriage between the use of vaginal micronized progesterone and the control group (RR: 0.72, CI: 0.39-1.34). In the subgroup analysis of two different studies comparing oral dydrogesterone and vaginal micronized progesterone treatments, no difference was found in terms of reducing the risk of miscarriage (RR: 1.06, CI: 0.42-2.66). As a result, progesterone therapy-especially oral dydrogesterone-has been reported to be effective in preventing pregnancy loss in women with threatened abortion[48].

In another meta-analysis that included 10 studies with a total of 5056 pregnancies, progesterone treatments were shown to reduce the risk of miscarriage, (RR: 0.73, CI: 0.59-0.92), but this benefit was detected only for oral progesterone (RR: 0.58, CI: 0.42-0.80) and was not observed for vaginal progesterone (RR: 0.90, CI: 0.80-1.01)[49].

A recent network meta-analysis including data of 10,424 pregnant women from 59 randomized controlled trials, in which threatened abortion was treated with progesterone, showed that oral dydrogesterone treatment was the most effective in preventing miscarriage (SUCRA 100%), followed by vaginal progesterone treatment (SUCRA 67.9%), while oral micronized progesterone treatment was the least effective (SUCRA 15.7%). As a result, it is reported that oral dydrogesterone treatment is the most effective treatment in threatened abortion and these results may help physicians in informing pregnant women and in making treatment choices[50].

In a prospective double-blind randomized controlled study including 50 pregnant women with threatened abortion, synthetic vaginal 8% 90mg, progesterone gel was compared with placebo, and it was reported that uterine contractility, pain, and miscarriage rates decreased significantly in the treatment arm[51].

In another randomized controlled study conducted in 2009, including 191 pregnancies, it was reported that dydrogesterone treatment (40 mg oral loading dose followed by 2x10 mg maintenance dose until the 16th week of gestation) in pregnant women with threatened abortion reduced the risk of miscarriage compared to placebo[52].

In a different randomized controlled study published in the same year, including 146 threatened miscarriages, dydrogesterone treatment (2x10 mg oral maintenance, until the end of one week after bleeding stops) reduced the miscarriage rate compared to placebo ($p \leq 0.05$), and no difference was found between the two groups in terms of congenital anomalies[53].

In another randomized controlled study published in 2005, where 154 pregnant women at risk of miscarriage were evaluated and it was found that the dydrogesterone group (40 mg oral loading dose followed by 2x10 mg maintenance dose until vaginal bleeding stops) resulted in fewer miscarriages compared to the control group without treatment ($p<0.05$)[54].

In a randomized controlled study in which 53 pregnant women with threatened abortion participated, the primary aim was to investigate the effects of progesterone use on utero-placental blood flow. The number of miscarriages was fewer with dydrogesterone (30 mg daily for 6 weeks) compared to micronized vaginal progesterone (300 mg daily for 6 weeks), but statistical analysis was not performed[55].

In a study published in 2021, in which dydrogesterone treatment (40 mg oral loading followed by 3x10 mg oral maintenance, continued until the 12th week of pregnancy or 1 week after bleeding stopped) was compared with placebo in threatened abortion (including 406 pregnant women), no difference was found between the groups in terms of the miscarriage rate ($p=0.772$)[44].

In another study from 2018, in which 118 pregnant women with threatened abortion were randomized to dydrogesterone (2x10 mg oral, 2 weeks) and micronized progesterone (2x200 mg oral, 2 weeks) groups, the effectiveness of these treatments was assessed. No significant difference was observed between the treatment groups, but side effects, such as dizziness and lightheadedness, were more frequently observed in the micronized progesterone group ($p=0.003$)[45].

In a prospective cohort study, 1,285 pregnant women with threatened abortion were examined, and no significant difference was found in miscarriage rates when dydrogesterone (40 mg, oral loading followed by 3x10 mg, oral maintenance for 2 weeks) and progesterone (2x100 mg, oral for 2 weeks) treatments were compared ($p=0.566$)[56].

The effectiveness of oral micronized progesterone is less than that of dydrogesterone has not been shown except for cases with a previous history of miscarriage. Therefore, considering its possible side effects, it is not the first choice in threatened miscarriage.

Vaginal use of micronized progesterone should be considered due to its difficulty of use in bleeding patients and local side effects.

In line with all the evidence above, oral dydrogesterone treatment may be considered as the first choice in threatened abortion, since it has fewer side effects and is found to be more effective in most studies compared to micronized progesterone.

Do other treatments contribute to the treatment of threatened abortion?

No concrete data have been found in the literature regarding the benefits or harms of additional treatments such as magnesium, iodine, folic acid or vitamin D in pregnant women with threatened abortion. Thus, a recommendation on this subject cannot be given.

Can invasive diagnostic tests be performed on pregnant women with threatened abortion?

There is only one study in the literature that was published in 1979, which examines this question. In the study, 1600 pregnant women who underwent amniocentesis for prenatal diagnosis were included. Among these pregnant women, 73 had gone through threatened abortion in their current pregnancy, but none of them had a miscarriage after the following amniocentesis procedure[57].

There weren't any publications reporting negative results regarding an indicated amniocentesis in pregnant women who do not have active bleeding and have had a threatened miscarriage. There are no data regarding chorionic villus biopsy or cordocentesis.

Considering the limited data available; amniocentesis can be performed in pregnant women who have had a threatened abortion.

Should anti-D be administered to pregnant women diagnosed with threatened abortion in the presence of Rh incompatibility?

The information on this subject is contradictory. In addition to publications that do not recommend anti-D in early pregnancy, guidelines that recommend anti-D immunoglobulin for all bleedings also exist (Table 2)[58].

Table 2. A review of recommendations in the guidelines for the use of anti-D immunoglobulin in pregnant women with threatened abortion[58]

	ACOG	SOGC	RCOG	RANZCOG
Threatened abortion <12 weeks	Unspecified	Yes	Unspecified	No
Threatened abortion >12 weeks	Yes	Yes	Yes	Yes

ACOG: American College of Obstetricians and Gynecologists, SOGC: Society of Obstetricians and Gynaecologists of Canada, RCOG: Royal College of Obstetricians and Gynaecologists, RANZCOG: The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Although the cause of bleeding in pregnant women at risk of miscarriage is not always known, it is often due to separation of the placenta, which may cause fetomaternal bleeding. Due to the risk of alloimmunization, anti-D immunoglobulin is recommended, especially in pregnant women with significant bleeding[59]. For bleedings in the first three months, a dose of 50 micrograms is sufficient, since less bleeding may occur, but there is no harm in using the normal dose of 300 micrograms[60]. Most pregnant women presenting to the emergency department with threatened abortion at earlier than the 12th week of pregnancy have heavy or recurrent bleeding or accompanying abdominal pain. The risk of fetomaternal bleeding is high in these pregnant women, and as a result, Rh isoimmunization is possible. The Rh status of these pregnant women should be recorded in the emergency department. Anti-D immunoglobulin should be recommended to all Rh D negative pregnant women who present to the emergency department with threatened abortion before the 12th week of pregnancy[61].

Considering current data, the use of anti-D immunoglobulin should be recommended in pregnant women with threatened abortion and Rh incompatibility.

Recommendations

This guideline was compiled by PERİDER after a detailed screening and review process for all gynecologists and obstetricians. Clear recommendations could be made on certain topics thanks to the availability of robust evidence. All the literature data used in concluding these suggestions has been explained in detail so that clinicians can evaluate them as well. Therefore, when using this guideline, it would be ideal to make your Clinical decisions after examining the presented data in detail.

Studies and literature on some important topics of the guide are insufficient, and for some subjects, no evidence exists at all. The recommendations we give, especially on these issues, are based on general common sense and habits to make safer choices for our patients. Scientific studies are needed to make more accurate and evidence-based recommendations on these issues in the future. Researchers might consider taking on questions such as "What is the incidence and prevalence of threatened abortion in Türkiye?", "Is bed rest and/or hospitalization beneficial in the treatment of threatened abortion?", "Should sexual intercourse restriction be recommended in threatened abortion?". These future studies may shed light on medical practice, improve healthcare for our patients by changing several habits that are not evidence-based.

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Footnotes

Authorship Contributions

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