

HABITUAL MISCARRIAGE

¹Muradova Emma Vladimirovna, ²Shernazarov Farrukh

¹PhD, Assistant of Microbiology, Immunology and virusology department
of Samarkand State Medical University

²Student of Samarkand State Medical University

<https://doi.org/10.5281/zenodo.10391049>

Abstract. *In January 2023, ESHRE (European Society of Human Reproduction and Embryology — European Society of Specialists in Human Reproduction and Embryology) issued updated recommendations on habitual miscarriage to replace the previous version of 2017. All changes and additions to the recommendations in the guidelines were formulated after evaluating the most qualitative and relevant evidence that appeared in the literature and their discussion by an expert group that took into account the benefit-harm ratio, patient preferences and the experience of clinicians [1].*

Keywords: *3D ultrasound, sonohysteroscopy, hysterosalpingography, epidemiology.*

Despite the fact that there are many studies in the field of habitual miscarriage, in about half of the cases we still cannot answer the question of what reason or combination of reasons led to another pregnancy loss. But even when there is the most probable cause, it is not always possible to offer effective measures to prevent repeated losses that increase the probability of live birth. So far, there are not so many therapeutic options with unambiguously proven effectiveness for patients with habitual miscarriage, but data is accumulating, and some of them are moving from the purely scientific sphere into our daily clinical practice. In the ESHRE protocol, some abstracts are marked with the clause "recommended only during clinical trials", so far they are given only for familiarization with news in this area and should not be used in routine clinical practice. In the near future, some of them may become "recommended" — for use in the practical work of a doctor, while the rest will forever remain only part of the scientific search with the designation "not recommended". When studying and comparing the ESHRE and ROAG protocols, there are many reasons for reflection. Controversial issues arise already at the definition stage. According to the study by E. Van den Boogaard et. al. [2], the frequency of detection of antiphospholipid syndrome (AFS) in patients with habitual miscarriage does not depend on whether pregnancies were lost in a row or not, as well as on whether a woman had a history of 2 or 3 miscarriages. In a large retrospective study, it was shown that the distribution of concomitant risk factors in couples who lost 2 and 3 pregnancies was the same [3]. It is also important to note that of all couples with PV, no more than 10% will have ≥ 2 inconsistent pregnancy losses, the rest of the patients will have consecutive losses. Therefore, the inclusion of such couples in the list of those subject to examination and treatment will not significantly change the picture [4]. Thus, the prevalence of PV among women with two or more pregnancies in the anamnesis ranges from 0.8 to 1.4%. However, all these studies were conducted quite a long time ago, at a time when methods for detecting very early pregnancy loss were far from perfect. If these studies were repeated today, the prevalence of PV would probably be greater.

Examination and risk assessment

Age. The ESHRE protocol prescribes the need to inform patients that the risk of miscarriage is minimal at the age of 20-35 years, and after 40 years it increases significantly. The

age of a woman over 40 is a generally recognized risk factor for female infertility, fetal abnormalities, stillbirth and obstetric complications [8, 9]. Based on computer modeling with the inclusion of data on the probability of pregnancy loss after conception, depending on age, it was shown that in order to build a family with two children with a 90% probability, a couple should start trying to conceive a child until a woman is over 31 years old. If the couple is not considering IVF, then in order to achieve the same probability, it is worth starting at all at the age of no older than 27 years. To create a family with one child, couples should start trying before the age of 35 (up to 32 years old, if they are not considering IVF) [10]. In women with PV, the probability of a live birth decreases with increasing age. After 35 years, the risk of another loss in the presence of PV is 2 times higher than before 35 years [11]. A meta—analysis conducted in 2020 showed that the age of the father also matters: with increasing age, the risk of miscarriage increases - the relative risk for the age groups 30-34 years, 35-39 years, 40-44 and 45+ was 1.04, 1.15, 1.23 and 1.43, respectively [12]. However, the experts did not find any studies that would study the influence of the father's age on the risk of miscarriage in PV. Perhaps, in the future, the definition will be clarified, but at the moment it is useful to pay attention to patients who have lost 2 pregnancies, not only from the point of view of examination (for example, to determine antibodies to phospholipids, although formally 2 losses are not yet a criterion of AFS), but also from the point of view of providing them with psychological assistance [13]. ESHRE experts recommend calculating the prognosis based on the age of the woman and her obstetric history, including the number of previous pregnancy losses, live births and their sequence.

Chronic endometritis. In recent years, very often patients are diagnosed with chronic endometritis, which is very doubtful, given the lack of generally recognized standards for the diagnosis and treatment of this disease. Chronic endometritis is characterized by plasmocellular infiltration of the endometrium associated with a number of pathogenic microorganisms. According to some studies, the prevalence of chronic endometritis in women with PV ranges from 7 to 58% of cases [14-16]. The prevalence depends on the detection method: high rates were obtained during hysteroscopy and/or immunohistochemistry using antibodies to CD138 [17-19]. However, the only study comparing the prevalence of chronic endometritis with fertility control did not reveal any significant differences between healthy women and women with PV [20]. There is evidence that antibiotics reduce the severity of endometritis, followed by an improvement in the live birth rate [14, 15]. However, this concept has not been tested in randomized controlled trials. Based on the results of these studies, ESHRE experts emphasize the need for further studies (including prospective observational and randomized controlled studies) before recommending examination for chronic endometritis to women with PV.

Antiphospholipid syndrome.

Immunological aspects. In the European recommendations on immunological screening regarding the study of HLA, a slight amendment was made compared to the recommendations of 2017. The definition of HLA is still not recommended routinely, but in very specific circumstances and in a narrow ethnic group, this may be important [21]. In a recent large case—control study involving 1,078 Caucasian women with PV and 2,066 control group patients, it was found that the HLA-DRB1*07 allele was associated with an increased risk of PV (relative risk 1.29 in heterozygous patients and 2.27 in homozygous patients). In this study, the frequency of HLA-DRB*07 did not differ significantly between patients with primary and secondary PV, and the

frequency of occurrence of the allele did not change with an increase in the number of miscarriages [22]. At the moment, the clinical significance of these findings is not clear.

ESHRE experts also consider it appropriate to examine patients with PV for antinuclear antibodies (ANA). ANA are a group of autoantibodies against the components of the cell nucleus that bind to proteins, nucleic acids and protein—nucleic acid complexes. The presence of high ANA titers (>1:160) is closely associated with autoimmune diseases, which in turn are associated with adverse pregnancy outcomes. ANA circulation can also occur among healthy individuals, with the prevalence varying from 5.92 to 30.8% depending on the study population. However, it has been shown that the frequency of PV is 3 times higher in patients with ANA at a concentration of more than 1:160 [23, 24].

Diseases of the uterus. The anatomy of the uterus should be evaluated to identify abnormalities of its structure, which occur in 10-15% of patients with PV, which significantly exceeds their prevalence in the general population. The preferred screening method is 3D ultrasound, sonohysteroscopy or hysterosalpingography can also be used, and in some cases, MRI. In all these issues, both leaders are in solidarity. European experts, based on the latest data that adenomyosis is associated with a higher frequency of pregnancy loss, even if it is not PV [25, 26], considered it important to emphasize this and added a recommendation to conduct a 2D ultrasound to exclude adenomyosis. This recommendation relates more to the calculation of the prognosis for PV than to the choice of treatment.

Endocrine disorders. Both guidelines and recommendations regarding endocrine examination are consistent. It is necessary to exclude thyroid diseases, for this you should donate blood for thyroid-stimulating hormone (TSH) and antibodies to thyroperoxidase (TPO). In the absence of symptoms of hyperprolactinemia, the level of prolactin has no clinical significance, it is also impractical to assess the ovarian reserve, androgen levels and luteinizing hormone (this will not improve the prognosis for the next pregnancy). Determination of the level of progesterone in serum and examination to identify the inferiority of the luteal phase are also of no fundamental importance due to the lack of standardized approaches to diagnosis and clear criteria.

Hypercoagulation. It is known that several genetic mutations increase the risk of thrombosis and thromboembolism, these include factor V mutation (Leiden mutation), prothrombin mutation, protein C deficiency, protein S and antithrombin III. Even in the case of venous thromboembolism, the value of the analysis for congenital thrombophilia is controversial [27], although this examination and further anticoagulant therapy are still recommended. But does it make sense to examine patients with PV without a history of thrombosis for congenital thrombophilia, as it often happens in clinical practice? On the one hand, it has indeed been shown that women with the Leiden mutation have an increased risk of miscarriage, but at the same time there is no effective method of prevention: low molecular weight heparins (NMH) do not improve pregnancy outcomes and do not increase the likelihood of live birth. Other types of congenital thrombophilia are not associated with an increased risk of PV at all, and the prevalence of hereditary thrombophilia in women with PV is unclear. It is in connection with the above data that ESHRE experts do not recommend testing for congenital thrombophilia in patients with PV in the absence of other indications. In the Russian KR, examination for the Leiden mutation, prothrombin mutation and evaluation of protein S activity are recommended.

The male factor. ESHRE experts suggest evaluating the fragmentation of sperm DNA, which may help in determining the cause of PV. In the Kyrgyz Republic, the Ministry of Health

of Russia recommended carrying out a spermogram of her husband, and it was clarified that the examination of men is carried out by a urologist, guided by the guidelines developed by the Russian Society of Urologists. But for some reason, the link under this thesis leads to the CD "Male infertility", where there is not a word about PV3. So while the scope of the examination of men in Russia is not regulated. Although the role of a man, his age and state of health is increasingly being traced in the problem of habitual miscarriage.

Conclusion

In conclusion, habitual miscarriage, or recurrent pregnancy loss, is a distressing condition that affects couples worldwide. It is characterized by the occurrence of three or more consecutive pregnancy losses before 20 weeks of gestation. The etiology of habitual miscarriage is often multifactorial and can include genetic abnormalities, anatomical factors, hormonal imbalances, autoimmune disorders, thrombophilic disorders, and environmental factors. The management of habitual miscarriage involves a comprehensive evaluation of both partners, including genetic testing, hormonal assessments, anatomical evaluations, and immunological screening. Treatment approaches may include lifestyle modifications, hormonal supplementation, surgical interventions to correct anatomical abnormalities, and assisted reproductive techniques such as in vitro fertilization (IVF) with preimplantation genetic testing. Psychological support and counseling are also important components of care for couples experiencing habitual miscarriage. With advancements in medical knowledge and individualized treatment strategies, the prognosis for couples affected by habitual miscarriage continues to improve, offering hope for successful pregnancies and healthy births in the future.

REFERENCES

1. Sarkisova V., Xegay R., Numonova A. ENDOCRINE CONTROL OF THE DIGESTION PROCESS. GASTROINTESTINAL ENDOCRINE CELLS //Science and innovation. – 2022. – T. 1. – №. D8. – C. 582-586.
2. Sarkisova, V., R. Xegay, and A. Numonova. "ENDOCRINE CONTROL OF THE DIGESTION PROCESS. GASTROINTESTINAL ENDOCRINE CELLS." *Science and innovation* 1.D8 (2022): 582-586.
3. Sarkisova, V., Xegay, R., & Numonova, A. (2022). ENDOCRINE CONTROL OF THE DIGESTION PROCESS. GASTROINTESTINAL ENDOCRINE CELLS. *Science and innovation*, 1(D8), 582-586.
4. Sarkisova V. ASPECTS OF THE STATE OF THE AUTONOMIC NERVOUS SYSTEM IN HYPOXIA //Science and innovation. – 2022. – T. 1. – №. D8. – C. 977-982.
5. Sarkisova, V. "ASPECTS OF THE STATE OF THE AUTONOMIC NERVOUS SYSTEM IN HYPOXIA." *Science and innovation* 1.D8 (2022): 977-982.
6. Sarkisova, V. (2022). ASPECTS OF THE STATE OF THE AUTONOMIC NERVOUS SYSTEM IN HYPOXIA. *Science and innovation*, 1(D8), 977-982.
7. Sarkisova V. et al. ESSENTIAL ROLE OF BRADIKININ IN THE COURSE OF BASIC LIFE PROCESSES //Science and innovation. – 2022. – T. 1. – №. D8. – C. 576-581.
8. Sarkisova, V., et al. "ESSENTIAL ROLE OF BRADIKININ IN THE COURSE OF BASIC LIFE PROCESSES." *Science and innovation* 1.D8 (2022): 576-581.
9. Sarkisova, V., Mavlyanova, U., Xegay, R., & Numonova, A. (2022). ESSENTIAL ROLE OF BRADIKININ IN THE COURSE OF BASIC LIFE PROCESSES. *Science and innovation*, 1(D8), 576-581.

10. Vladimirovna S. V. About the Causes of Endometrial Hyperplasia and Forms of Endometrial Hyperplasia //Global Scientific Review. – 2023. – Т. 12. – С. 25-32.
11. Vladimirovna, Sarkisova Viktoriya. "About the Causes of Endometrial Hyperplasia and Forms of Endometrial Hyperplasia." *Global Scientific Review* 12 (2023): 25-32.
12. Vladimirovna, S. V. (2023). About the Causes of Endometrial Hyperplasia and Forms of Endometrial Hyperplasia. *Global Scientific Review*, 12, 25-32.
13. Vladimirovna S. V. Epidemiology, Theories Of The Development, Conservative And Operative Treatment Of The Endometriosis //The Peerian Journal. – 2023. – Т. 15. – С. 84-93.
14. Vladimirovna, Sarkisova Viktoriya. "Epidemiology, Theories Of The Development, Conservative And Operative Treatment Of The Endometriosis." *The Peerian Journal* 15 (2023): 84-93.
15. Vladimirovna, S. V. (2023). Epidemiology, Theories Of The Development, Conservative And Operative Treatment Of The Endometriosis. *The Peerian Journal*, 15, 84-93.
16. Саркисова В., Абдурахманова К. Астено-вегетативные нарушения, оценка качества жизни у женщин климактерического возраста с гиперпластическими процессами в матке //Журнал вестник врача. – 2014. – Т. 1. – №. 1. – С. 163-166.
17. Саркисова, В., and К. Абдурахманова. "Астено-вегетативные нарушения, оценка качества жизни у женщин климактерического возраста с гиперпластическими процессами в матке." *Журнал вестник врача* 1.1 (2014): 163-166.
18. Саркисова, В., & Абдурахманова, К. (2014). Астено-вегетативные нарушения, оценка качества жизни у женщин климактерического возраста с гиперпластическими процессами в матке. *Журнал вестник врача*, 1(1), 163-166.
19. Sarkisova V., Xegay R. Causes, Diagnosis, Conservative And Operative Treatment Of Uterine Myoma //Science and innovation. – 2022. – Т. 1. – №. D8. – С. 198-203.
20. Sarkisova, V., and R. Xegay. "Causes, Diagnosis, Conservative And Operative Treatment Of Uterine Myoma." *Science and innovation* 1.D8 (2022): 198-203.
21. Sarkisova, V., & Xegay, R. (2022). Causes, Diagnosis, Conservative And Operative Treatment Of Uterine Myoma. *Science and innovation*, 1(D8), 198-203.
22. Саркисова В. В. Патогенетические отношения артериальной гипертензии и сопротивления инсулина //IQRO. – 2023. – Т. 2. – №. 1. – С. 727-731.
23. Саркисова, Виктория Владимировна. "Патогенетические отношения артериальной гипертензии и сопротивления инсулина." *IQRO* 2.1 (2023): 727-731.
24. Shernazarov Farrukh ORGANIZATION OF DIGITALIZED MEDICINE AND HEALTH ACADEMY AND ITS SIGNIFICANCE IN MEDICINE // SAI. 2023. №Special Issue 8. URL: <https://cyberleninka.ru/article/n/organization-of-digitalized-medicine-and-health-academy-and-its-significance-in-medicine> (дата обращения: 20.11.2023).