FACTORS DETERMINING ENDOMETRIAL RECOVERY AND RECEPTIVITY AFTER HYSTEROSCOPIC INTERVENTIONS: CURRENT STATE OF THE PROBLEM

Gulnoza M. Farmonova - Ph.D., trainee researcher
Republican Specialized Scientific and Practical Medical Center for Maternal and Child Health (Tashkent, Uzbekistan)
tatsisstephen@gmail.com

Abstract. Introduction. *Despite the widespread implementation of organ-preserving hysteroscopic procedures, a subset of patients develops impaired endometrial repair, manifested by reduced endometrial thickness, altered structure, and decreased receptivity. These changes are associated with infertility, implantation failure, and recurrent pregnancy loss, underscoring the high clinical relevance of this issue.*

Methods. *A review of scientific publications indexed in PubMed, Scopus, and Web of Science over recent years was conducted. Original studies, systematic reviews, and meta-analyses addressing the pathophysiology of endometrial injury, intrauterine interventions, and factors determining structural and functional recovery of the endometrium were included.*

Results. *Endometrial repair was found to be a multifactorial process influenced by clinical, anamnestic, intraoperative, and molecular factors. Preservation of the basal layer, the extent of surgical trauma, and the type of energy used during the procedure play a critical role. Chronic inflammation and impaired angiogenesis, including imbalance between pro- and anti-angiogenic factors such as PlGF and sFlt-1, are also of major importance. Structural restoration of the endometrium does not necessarily correspond to the recovery of its functional receptivity, highlighting the need for a comprehensive assessment. Emerging therapeutic approaches include regenerative strategies such as platelet-rich plasma (PRP), although current evidence remains limited.*

Conclusion. *Endometrial repair and receptivity following hysteroscopic interventions are determined by a combination of clinical, surgical, and molecular factors. The most significant contributors include damage to the basal layer, inflammatory status, and angiogenic balance. Future research should focus on the development of predictive models and personalized approaches to optimize endometrial recovery.*

Keywords: *endometrium; endometrial repair; endometrial receptivity; hysteroscopy; intrauterine interventions; thin endometrium; angiogenesis; chronic endometritis; implantation; infertility.*

Introduction.

Endometrial injury during intrauterine surgical procedures remains one of the key challenges in modern gynecology. Despite the widespread use of hysteroscopic interventions, a proportion of patients develop impaired endometrial recovery, manifested by reduced endometrial thickness, altered ultrasound structure, and decreased functional receptivity. These changes are associated with adverse reproductive outcomes, including infertility, repeated implantation failure, and recurrent pregnancy loss.

Physiologically, the endometrium possesses a unique capacity for cyclical regeneration, which is maintained by the integrity of the basal layer, the presence of endometrial stem/progenitor cells, adequate angiogenesis, and a balanced immune microenvironment. However, surgical injury—particularly when involving the basal layer—may disrupt these mechanisms, leading to fibrotic remodeling and the formation of intrauterine adhesions, which underlie conditions such as thin endometrium and Asherman syndrome.

In recent years, increasing attention has been focused on identifying factors that determine the regenerative capacity of the endometrium following surgical injury. These factors include patients' clinical and anamnestic characteristics, intraoperative parameters, and molecular mechanisms regulating inflammation, angiogenesis, and tissue repair. It has been demonstrated that chronic endometrial inflammation, imbalance of angiogenic factors, and impaired microcirculation significantly reduce the regenerative potential of the endometrium and its receptivity.

Recent studies indicate that even when morphological parameters of the endometrium, such as its thickness, are restored, functional receptivity may remain compromised. This highlights the need to distinguish between structural repair and functional recovery of the endometrium, as well as the importance of comprehensive assessment using clinical, ultrasonographic, and molecular markers.

Despite the growing body of evidence regarding the pathogenesis of impaired endometrial regeneration, current data remain fragmented, and a unified concept for predicting endometrial recovery is still lacking. Most studies are characterized by heterogeneity in design, variability in outcome definitions, and limited levels of evidence, which complicates the development of clinical recommendations and management algorithms.

In this context, a systematic analysis of contemporary data on clinical, anamnestic, and intraoperative factors affecting endometrial recovery after hysteroscopic interventions is of particular relevance, with the aim of identifying key predictors of regeneration and optimizing management strategies for women of reproductive age.

Objective.

To analyze current evidence on factors influencing endometrial repair and receptivity following hysteroscopic interventions.

Materials and methods.

A review of scientific publications indexed in PubMed, Scopus, and Web of Science was conducted. The analysis included original studies, systematic reviews, and meta-analyses addressing the pathophysiology of endometrial injury, characteristics of intrauterine interventions, and factors determining structural and functional recovery of the endometrium.

Relevant studies were identified using keywords related to endometrial repair, receptivity, and intrauterine adhesion formation. The analysis considered data on patients' clinical and anamnestic characteristics, surgical parameters, and molecular mechanisms, including inflammatory responses and angiogenesis. Particular attention was given to studies evaluating the relationship between morphological restoration of the endometrium and its functional activity, as well as reproductive outcomes.

Results.

In current understanding, damage to the basal layer of the endometrium is considered a central mechanism in the pathogenesis of impaired endometrial repair following intrauterine interventions. This is due to the fact that the basal layer contains cellular populations responsible for cyclical regeneration of the functional layer, including epithelial progenitor cells and the stromal microenvironment that supports tissue repair.

In a large molecular and morphological study, Marečková M. et al. (2024) demonstrated that the endometrial epithelium has a complex architecture, in which basalis glands serve as a reservoir of progenitor cells required for the regeneration of the functionalis layer after physiological shedding. These findings support the concept that surgical trauma involving the basal layer disrupts not only the structural integrity of the endometrium but also its regenerative capacity.

Classical concepts described by Deans R., Abbott J. (2010) and March C.M. (2011) have been confirmed by more recent studies. In particular, the review by Wang P.-H. et al. (2024) highlights that intrauterine adhesions primarily result from injury to the basal layer, leading to replacement of normal repair processes with fibrosis. Similarly, the systematic review by Munro M.G. et al. (2025) identifies intrauterine adhesions as a consequence of surgically induced damage to the basalis layer with

subsequent fibrotic remodeling. Importantly, even after successful adhesiolysis, underlying damage to the basal layer may persist and continue to adversely affect reproductive outcomes.

More recent molecular studies have expanded this concept. In the review by Pardo-Figuerez M. et al. (2025), Asherman syndrome is described not merely as mechanical adhesion formation but as a condition of profound cellular disorganization of the endometrium associated with fibrotic remodeling. Similarly, Zhang X. et al. (2025) emphasize that thin endometrium should be considered a manifestation of impaired regeneration, involving alterations in cellular populations, signaling pathways, and intercellular interactions. This indicates that after hysteroscopic interventions, clinically significant outcomes may include not only adhesion formation but also the development of a functionally inadequate endometrium without overt distortion of the uterine cavity.

The depth of injury appears to be a critical determinant of reproductive outcomes. Contemporary studies indicate that damage to the basalis layer, rather than superficial injury to the functionalis, is associated with a higher risk of persistent fibrosis, reduced endometrial thickness, impaired vascularization, and decreased receptivity. The review by Hu X. et al. (2023) emphasizes that injury to the basal layer disrupts physiological mechanisms of endometrial regeneration. Likewise, Awano-Kim S. et al. (2025) report that partial or complete loss of functional endometrium due to basal layer damage is a key event in the development of Asherman syndrome. Furthermore, progenitor cells have been shown to be localized within the basal layer, explaining the marked reduction in regenerative capacity following its injury.

The clinical significance of these mechanisms is supported by reproductive outcome studies. According to Qiao X. et al. (2025), pregnancy was achieved in 59.38% of patients after hysteroscopic adhesiolysis, while the live birth rate was 42.19%, indicating incomplete restoration of endometrial function in a substantial proportion of women. Additionally, Mortimer R.M. et al. (2024) demonstrated an increased risk of adverse obstetric outcomes, including placenta accreta spectrum, in patients with a history of intrauterine adhesions, reflecting persistent impairment of the endometrial–myometrial interface.

Clinical and anamnestic characteristics of patients also play a significant role in endometrial repair. In the study by Cicinelli E. et al. (2015), chronic endometritis was associated with decreased endometrial receptivity due to altered expression of key implantation factors. Subsequent studies (2022–2024) confirmed that chronic inflammation is accompanied by activation of pro-inflammatory cytokines, particularly IL-6, and the development of subclinical fibrosis, leading to reduced proliferative activity and impaired regeneration.

The study by Kasius J.C. et al. (2014) demonstrated that an endometrial thickness of less than 7 mm is significantly associated with reduced pregnancy rates, indirectly reflecting impaired functional capacity. Recent meta-analyses confirm this association but emphasize that endometrial thickness alone cannot be considered a definitive marker of functional competence.

Additional factors negatively affecting endometrial repair include advanced maternal age, repeated intrauterine interventions (including curettage), and infertility, which reflect baseline impairment of endometrial function. Reduced ovarian reserve and hormonal imbalances may also contribute by altering proliferative activity and estrogen sensitivity.

The nature and extent of hysteroscopic intervention are critical determinants of endometrial regeneration. In the study by Yang J.H. et al. (2021), bipolar energy was associated with less thermal damage compared to monopolar systems. These findings are supported by a meta-analysis by Chen Y. et al. (2023), demonstrating that cold instruments (scissors) result in less tissue trauma, greater postoperative endometrial thickness, and lower recurrence rates of adhesions.

It has also been established that increased resection volume, longer operative time, and aggressive mechanical or electrosurgical manipulation contribute to ischemic and thermal injury and increase the risk of fibrosis. Importantly, recent studies emphasize that the depth of injury, rather than the volume of intervention alone, is the key determinant of impaired repair.

Outcomes are also influenced by surgical technique and operator experience. The review by Loddo A. et al. (2024) highlights that complication rates, including adhesion formation, depend on technical aspects of the procedure, energy modality, and surgical complexity.

Chronic inflammation represents another major determinant of impaired repair. In the study by Li B. et al. (2025), elevated levels of pro-inflammatory cytokines, including IL-6, were associated with fibroblast activation and excessive extracellular matrix deposition, leading to fibrosis and disruption of normal endometrial architecture. In the experimental study by Kumar S. et al. (2025), suppression of fibrotic processes improved vascularization and endometrial thickness.

Recent studies (2023–2024) further indicate that chronic inflammation alters the expression of key receptivity markers (HOXA10, LIF) and disrupts immune balance, contributing to functional impairment even in the absence of overt structural abnormalities.

Importantly, morphological restoration does not necessarily imply functional recovery. Even with normalized endometrial thickness and structure, receptivity may remain impaired due to complex molecular and immunological mechanisms.

This is supported by Chang Y. et al. (2015) and confirmed in more recent studies. Darawshe B. et al. (2025) demonstrated decreased expression of implantation-related genes (HOXA10, IGF-1) and altered immune microenvironment in chronic endometritis. Similarly, Lucan M. et al. (2025) showed that chronic inflammation disrupts the window of implantation through downregulation of key genes.

Molecular studies by Cao Z. et al. (2024) and Wu C. et al. (2025) confirm that endometrial receptivity depends on coordinated regulation of multiple genes and signaling pathways.

Modern diagnostic approaches, including RNA-seq–based receptivity testing (He A. et al., 2023) and personalized embryo transfer (Xu S. et al., 2025), further demonstrate that molecular assessment is essential for predicting implantation success.

Therefore, comprehensive evaluation of the endometrium should include morphological, molecular, immunological, and clinical parameters.

Conclusion.

Endometrial repair following hysteroscopic interventions is a complex multifactorial process determined by clinical characteristics, surgical factors, and molecular mechanisms of regeneration. Preservation of the basal layer is of critical importance, as its damage leads to fibrosis, impaired angiogenesis, and reduced regenerative capacity. Surgical technique and the extent of tissue injury, as well as chronic inflammation, play a decisive role in the development of functional endometrial insufficiency.

Importantly, morphological restoration does not necessarily reflect functional competence, as endometrial receptivity is governed by intricate molecular, immunological, and vascular interactions. Therefore, assessment of endometrial status should be comprehensive, incorporating both structural and functional parameters.

Future research should focus on the development of predictive models and personalized approaches to patient management, as well as on the implementation of novel therapeutic strategies aimed at restoring endometrial function and improving reproductive outcomes.

REFERENCES

1. Abdullaev RH, et al. Chronic endometritis and infertility. Tashkent; 2021.
2. Adamyan LV, Kulakov VI, et al. Intrauterine pathology and hysteroscopy. Moscow: GEOTAR-Media; 2019.
3. Akhmedov AA, et al. Modern aspects of treatment of intrauterine pathology. 2022.
4. Baranov VS, et al. Molecular mechanisms of endometrial receptivity. 2021.
5. Chen Y, et al. Clinical efficacy of hysteroscopic adhesiolysis techniques. Front Endocrinol. 2023.

6. Cicinelli E, et al. Chronic endometritis: a frequent cause of infertility. Fertil Steril. 2015;104(2):427–435.
7. Deans R, Abbott J. Intrauterine adhesions: a review of current management. Fertil Steril. 2010;93(3):775–789.
8. Dobrokhotova YE, et al. Intrauterine adhesions: diagnosis and treatment. Vestnik RSMU. 2021.
9. Gao Y, et al. Risk factors of chronic endometritis. Sci Rep. 2024.
10. Hooker AB, et al. Long-term complications and reproductive outcome after intrauterine adhesions. Hum Reprod Update. 2014;20(2):262–278.
11. Hu X, et al. Cyclical endometrial repair and regeneration. Nat Rev Endocrinol. 2023.
12. Ismailov SI, et al. Reproductive outcomes in intrauterine pathology. 2022.
13. Kasius JC, et al. Endometrial thickness and pregnancy rates in IVF. Hum Reprod Update. 2014;20(4):530–541.
14. Kulakov VI, Adamyan LV. Endoscopy in gynecology. Moscow; 2018.
15. Kuznetsova IV, et al. The role of inflammation in endometrial pathology. 2022.
16. Li B, et al. Inflammatory mechanisms of endometrial injury. Front Bioeng Biotechnol. 2025.
17. Loddo A, et al. Prevention and management of hysteroscopic complications. Gynecol Pelvic Med. 2024.
18. Lucan M, et al. Chronic endometritis and reproductive outcomes. J Clin Med. 2025.
19. Marečková M, et al. An integrated single-cell reference atlas of the human endometrium. Nat Genet. 2024.
20. March CM. Management of Asherman's syndrome. Reprod Biomed Online. 2011;23(1):63–76.
21. Marzooq AA, et al. Effectiveness of hysteroscopic surgery in infertility. 2025.
22. Munro MG, et al. Epidemiology and prevention of intrauterine adhesions. Am J Obstet Gynecol. 2025.
23. Nazarov KM, et al. The impact of surgical interventions on the endometrium. 2023.
24. National Medical Research Center for Obstetrics, Gynecology and Perinatology named after V.I. Kulakov. Chronic endometritis: modern approaches to diagnosis and treatment. Obstet Gynecol. 2021.
25. Orazov MR, et al. Thin endometrium: pathogenesis and treatment. Obstet Gynecol Reprod. 2022.
26. Radzinsky VE, Orazov MR. Chronic endometritis in gynecological practice. Obstet Gynecol. 2020.
27. Riemma G, et al. Diagnostic accuracy of hysteroscopy. Am J Obstet Gynecol. 2025.
28. Savelieva GM, Sukhikh GT. Gynecology: National guideline. Moscow; 2022.
29. Serov VN, Prilepskaya VN. Women's reproductive health. Moscow; 2020.
30. Tsonis O, et al. Hysteroscopic features of chronic endometritis. 2023.
31. Wang PH, et al. Intrauterine adhesion: pathogenesis and management. Taiwan J Obstet Gynecol. 2024.
32. Wang Y, et al. Advances in treatment of thin endometrium. Front Endocrinol. 2024.
33. Yusupov BB, et al. Hysteroscopy in diagnosis and treatment of endometrial pathology. 2020.
34. Yang JH, et al. Effects of electrosurgical systems on endometrial damage. 2021.
35. Zhang X, et al. Thin endometrium at single-cell resolution. Am J Obstet Gynecol. 2025.