



AGE-RELATED CHARACTERISTICS OF ENDOMETRIAL PATHOLOGY IN WOMEN UNDERGOING ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAMS

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Abstract.

Background. Endometrial condition is a critical determinant of embryo implantation success in assisted reproductive technology programs. Chronic endometritis is frequently asymptomatic and remains underdiagnosed, particularly in women of advanced reproductive age.

Objective. To assess the frequency and severity of endometrial pathology in women of advanced reproductive age using hysteroscopy, histological, and immunohistochemical evaluation, compared with women younger than 35 years.

Materials and Methods. A retrospective cross-sectional descriptive study was conducted, analyzing 569 office hysteroscopy protocols with endometrial biopsy and CD138 immunohistochemical assessment. Patients were divided into two age groups: <35 years and ≥35 years.

Results. Chronic endometritis was highly prevalent in both age groups; however, severe forms were significantly more common among women aged 35 years and older. No significant differences in CD138 expression intensity were observed between age groups within the same severity categories. Stromal fibrosis was the most frequent associated endometrial abnormality.

Conclusion. Severe chronic endometritis is more frequently observed in women of advanced reproductive age, supporting the need for mandatory hysteroscopic and immunohistochemical endometrial assessment prior to assisted reproductive technology programs.

Key words: chronic endometritis, endometrium, advanced reproductive age, hysteroscopy, assisted reproductive technologies

ВОЗРАСТНЫЕ ОСОБЕННОСТИ ПАТОЛОГИИ ЭНДОМЕТРИЯ У ЖЕНЩИН, ПРОХОДЯЩИХ ПРОГРАММЫ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ

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Аннотация.

Актуальность. Состояние эндометрия является одним из ключевых факторов, определяющих успешность имплантации эмбриона в программах вспомогательных репродуктивных технологий. Хронический эндометрит часто протекает бессимптомно и остается недиагностированным, особенно у женщин старшего репродуктивного возраста.

Цель исследования. Оценить частоту и выраженность патологических изменений эндометрия у женщин старшего репродуктивного возраста по данным гистероскопии, гистологического и иммуногистохимического исследований в сравнении с пациентками младше 35 лет.

Материалы и методы. Проведено ретроспективное описательное поперечное исследование, включившее анализ 569 протоколов офисной гистероскопии с биопсией эндометрия и иммуногистохимической оценкой экспрессии CD138. Пациентки были разделены на две возрастные группы: младше 35 лет и 35 лет и старше.

Результаты. Хронический эндометрит выявлялся в обеих возрастных группах с высокой частотой, однако выраженные формы достоверно чаще встречались у женщин 35 лет и

старше. Различий в уровне экспрессии CD138 между возрастными группами при одинаковой степени выраженности воспаления не выявлено. Наиболее распространенной сопутствующей патологией являлся фиброз стромы эндометрия.

Закключение. У женщин старшего репродуктивного возраста чаще диагностируются тяжелые формы хронического эндометрита, что обосновывает необходимость обязательного проведения гистероскопии с биопсией и иммуногистохимическим исследованием перед программами вспомогательных репродуктивных технологий.

Ключевые слова: хронический эндометрит, эндометрий, старший репродуктивный возраст, гистероскопия, вспомогательные репродуктивные технологии

YORDAMCHI REPRODUKTIV TEXNOLOGIYALAR DASTURLARIDAN O'TAYOTGAN AYOLLARDA ENDOMETRIY PATOLOGIYASINING YOSHGA BOG'LIQ XUSUSIYATLARI

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Annotatsiya.

Dolzarblik. Endometriyning funksional va morfologik holati yordamchi reproduktiv texnologiyalar dasturlarida embrion implantatsiyasi muvaffaqiyatini belgilovchi asosiy omillardan biridir. Surunkali endometrit ko'pincha klinik belgilarisiz kechadi va ayniqsa katta reproduktiv yoshdagi ayollarda kech aniqlanadi.

Tadqiqot maqsadi. 35 yosh va undan katta ayollarda endometriy patologiyasining uchrash chastotasi va og'irlik darajasini gisteroskopiya, gistologik va immunogistokimyoviy tekshiruvlar asosida baholash hamda 35 yoshgacha bo'lgan ayollar bilan solishtirish.

Materiallar va usullar. Retrospektiv kesimli tavsifiy tadqiqot o'tkazilib, 569 ta ofis gisteroskopiyasi protokollari, endometriy biopsiyasi va CD138 ekspressiyasining immunogistokimyoviy bahosi tahlil qilindi. Bemorlar ikki yosh guruhiga bo'lindi: 35 yoshgacha va 35 yosh va undan katta.

Natijalar. Surunkali endometrit har ikkala yosh guruhida yuqori chastotada aniqlangan bo'lsa-da, og'ir shakllari 35 yosh va undan katta ayollarda sezilarli darajada ko'proq uchradi. Bir xil og'irlik darajasida CD138 ekspressiyasida yoshga bog'liq farqlar aniqlanmadi. Eng ko'p uchragan qo'shimcha patologiya endometriy stromasining fibrozidir.

Xulosa. Katta reproduktiv yoshdagi ayollarda surunkali endometritning og'ir shakllari ko'proq aniqlanadi, bu esa yordamchi reproduktiv texnologiyalar dasturlaridan oldin majburiy gisteroskopik va immunogistokimyoviy tekshiruv o'tkazishni asoslaydi.

Kalit so'zlar: surunkali endometrit, endometriy, katta reproduktiv yosh, gisteroskopiya, yordamchi reproduktiv texnologiyalar

Introduction. Successful outcomes of assisted reproductive technology programs depend not only on embryo quality but also on the functional and morphological state of the endometrium at the time of embryo transfer. Endometrial receptivity is a critical determinant of implantation, and even embryos with high developmental potential fail to implant in the presence of an altered uterine environment [1]. One of the most common yet underdiagnosed causes of impaired endometrial receptivity is chronic endometritis, a persistent inflammatory condition of the endometrial lining that is frequently asymptomatic or presents with nonspecific clinical manifestations [2].

The prevalence of chronic endometritis in the general population remains relatively low; however, among women with infertility, recurrent implantation failure, or recurrent pregnancy loss, its incidence rises substantially [3,4]. Several studies have demonstrated that chronic endometritis is

detected in up to 40–60% of women with repeated implantation failure when sensitive diagnostic approaches are applied [5,6]. The pathogenic mechanisms underlying this association include dysregulation of local immune responses, altered cytokine and chemokine signaling, impaired angiogenesis, and structural remodeling of the endometrial stroma, all of which negatively affect embryo–endometrium interaction [7]. Standard histological examination using hematoxylin and eosin staining has limited sensitivity in detecting chronic endometritis due to difficulties in identifying plasma cells within the endometrial stroma, especially during the secretory phase of the menstrual cycle [8]. Immunohistochemical staining for CD138, a specific plasma cell marker, has significantly improved diagnostic accuracy and is now considered a reference method for confirming chronic endometritis [9,10]. In addition, office hysteroscopy allows direct visualization of characteristic inflammatory features such as stromal edema, focal or diffuse hyperemia, and endometrial micropolyps, further increasing diagnostic yield [11].

Advanced reproductive age is independently associated with reduced fertility potential and poorer outcomes of in vitro fertilization. Age-related changes in immune regulation, cumulative inflammatory exposure, and repeated intrauterine interventions may predispose older women to more severe endometrial pathology [12]. Despite this, data directly comparing the frequency and severity of chronic endometritis between younger and older reproductive-age women remain limited. The present study was designed to analyze age-related differences in endometrial pathology, with particular attention to chronic endometritis, using hysteroscopy combined with histological and immunohistochemical assessment.

Materials and Methods. A retrospective descriptive cross-sectional study was conducted at a specialized reproductive medicine center between 2020 and 2022. A total of 569 hysteroscopy protocols with endometrial biopsy and subsequent immunohistochemical evaluation were analyzed. All procedures were performed as part of routine pre-treatment assessment prior to planned in vitro fertilization or intracytoplasmic sperm injection cycles. The study included women of reproductive age from 18 to 49 years who provided informed consent and had complete clinical, histological, and immunohistochemical data available for analysis. Patients with prior uterine surgery, acute pelvic inflammatory disease within six months, incomplete biopsy data, or no planned embryo transfer were excluded. Participants were stratified into two age-based groups: women younger than 35 years and women aged 35 years and older. Office hysteroscopy was performed during the proliferative phase of the menstrual cycle using a rigid hysteroscope with saline distension. Endometrial biopsy specimens were obtained from the uterine fundus under direct visualization. Tissue samples were fixed in neutral formalin, embedded in paraffin, and processed for routine histology and immunohistochemical staining using monoclonal antibodies against CD138. The number of CD138-positive plasma cells per high-power field was assessed visually and used to classify chronic endometritis severity as mild, moderate, or severe. Statistical analysis was performed using standard descriptive and comparative methods. Quantitative variables were expressed as means with standard deviations, while qualitative variables were presented as percentages. Differences between groups were evaluated using Student's t-test and chi-square test, with statistical significance set at $p < 0.05$.

Results. Endometrial pathology was evaluated at the level of individual hysteroscopy protocols rather than unique patients, allowing assessment of repeated examinations prior to different assisted reproduction attempts. Of the 569 protocols analyzed, 256 were performed in women younger than 35 years and 313 in women aged 35 years and older. The younger group was characterized predominantly by primary infertility, whereas secondary infertility was significantly more common in the older group. Normal hysteroscopic and histological findings were observed in a minority of cases in both groups. Chronic endometritis was identified in more than 80% of protocols in women under 35 years and in more than 85% of protocols in women aged 35 years and older. While the overall prevalence of chronic endometritis did not differ significantly between age groups, severe forms of the disease were detected significantly more often in older women. The

proportion of severe chronic endometritis was approximately threefold higher in the ≥ 35 -year group compared with younger women, indicating an age-associated increase in inflammatory burden.

Analysis of CD138 expression demonstrated no statistically significant differences in the mean number of plasma cells between age groups within the same severity categories. This finding suggests that while the frequency of severe disease increases with age, the immunohistochemical intensity of inflammation at each severity level remains comparable across age groups. In addition to chronic endometritis, structural endometrial abnormalities were frequently identified. Stromal fibrosis or sclerosis was the most common pathological finding in both age groups, followed by combined lesions involving fibrosis with lymphocytic infiltration, hypoplasia, or endometrial polyps. The distribution of these pathologies did not differ significantly between younger and older women, indicating that age primarily influenced the severity rather than the type of endometrial pathology.

Discussion. The findings of this study confirm a high prevalence of chronic endometritis among women undergoing evaluation prior to assisted reproductive technology, regardless of age. However, the significantly higher frequency of severe chronic endometritis in women of advanced reproductive age highlights the clinical importance of age-specific diagnostic strategies. These results are consistent with previous reports demonstrating an increased burden of inflammatory endometrial pathology in women with recurrent implantation failure and reproductive aging [4,6]. The discrepancy between the very high prevalence of chronic endometritis observed in this cohort and lower rates reported in earlier studies may be explained by methodological differences. The combined use of office hysteroscopy and CD138 immunohistochemistry substantially increases diagnostic sensitivity compared with conventional histology alone [8,10]. This comprehensive approach likely reveals subclinical or previously undetected inflammatory changes, particularly in women with long-standing infertility or repeated assisted reproduction attempts.

Despite the higher prevalence of severe chronic endometritis in older women, the lack of age-related differences in CD138 expression intensity suggests that the inflammatory response itself is not intrinsically stronger with age, but rather more persistent or cumulative. Repeated intrauterine manipulations, prolonged exposure to infectious or inflammatory stimuli, and age-related immune dysregulation may contribute to this phenomenon [12]. The clinical relevance of these findings is underscored by evidence that successful treatment of chronic endometritis leads to improved implantation, pregnancy, and live birth rates [13–15]. Therefore, failure to identify and treat severe inflammatory endometrial pathology prior to embryo transfer may partly explain reduced assisted reproduction success in older patients. The retrospective design and single-country population represent limitations of the present study, and prospective multicenter investigations are required to validate these observations and assess treatment outcomes. Nevertheless, the results provide strong support for incorporating routine hysteroscopic and immunohistochemical evaluation of the endometrium into pre-IVF assessment, particularly for women aged 35 years and older.

Conclusion. Endometrial pathology is highly prevalent among women preparing for assisted reproductive technology, with chronic endometritis representing the dominant finding. Although the overall frequency of chronic endometritis is similar across age groups, severe forms occur significantly more often in women of advanced reproductive age. These findings emphasize the necessity of comprehensive endometrial evaluation, including office hysteroscopy and CD138 immunohistochemistry, prior to embryo transfer, especially in women aged 35 years and older. Early detection and targeted treatment of chronic endometritis may improve implantation success, reduce repeated IVF failures, and optimize reproductive outcomes.

References.

1. Cicinelli, E., Matteo, M., Tinelli, R., Lepera, A., Alfonso, R., Indraccolo, U., & Marrocchella, S. (2015). Prevalence of chronic endometritis in repeated unexplained implantation failure and the IVF success rate after antibiotic therapy. *Human Reproduction*, 30(2), 323–330. <https://doi.org/10.1093/humrep/deu292>

2. Greenwood, S. M., & Moran, J. J. (1981). Chronic endometritis: Morphologic and clinical observations. *Obstetrics & Gynecology*, 58(2), 176–184.
3. Kasius, J. C., Broekmans, F. J. M., Sie-Go, D. M. D. S., Bourgain, C., Eijkemans, M. J. C., Fauser, B. C. J. M., & Devroey, P. (2012). The reliability of the histological diagnosis of endometritis in asymptomatic IVF cases: A multicenter observer study. *Human Reproduction*, 27(1), 153–158. <https://doi.org/10.1093/humrep/der341>
4. Kitaya, K., Takeuchi, T., Mizuta, S., Matsubayashi, H., & Ishikawa, T. (2018). Endometritis: New time, new concepts. *Fertility and Sterility*, 110(3), 344–350. <https://doi.org/10.1016/j.fertnstert.2018.04.012>
5. Romero, R., Espinoza, J., & Mazor, M. (2004). Can endometrial infection/inflammation explain implantation failure, spontaneous abortion, and preterm birth after in vitro fertilization? *Fertility and Sterility*, 82(4), 799–804. <https://doi.org/10.1016/j.fertnstert.2004.05.076>
6. Vitagliano, A., Saccardi, C., Noventa, M., Di Spiezio Sardo, A., Saccone, G., Gizzo, S., & Nardelli, G. B. (2018). Effects of chronic endometritis therapy on in vitro fertilization outcome in women with repeated implantation failure: A systematic review and meta-analysis. *Fertility and Sterility*, 110(1), 103–112.e1. <https://doi.org/10.1016/j.fertnstert.2018.03.017>
7. Cheng, X., Huang, Z., Xiao, Z., & Bai, Y. (2022). Does antibiotic therapy for chronic endometritis improve clinical outcomes of patients with recurrent implantation failure in subsequent IVF cycles? A systematic review and meta-analysis. *Journal of Assisted Reproduction and Genetics*, 39(8), 1797–1813. <https://doi.org/10.1007/s10815-022-02558-1>