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Modern Aspects of the Problem of "Thin Endometrium"

Kurbaniyazova Feruza Zafarjanovna, Khudoyarova Dildora Rakhimovna, Askarova Zebo Zafarjanovna

Samarkand State Medical University, Samarkand, Uzbekistan

Abstract Chronic hypoplastic endometritis is a significant obstacle to fertility and successful pregnancy due to its combined effects of persistent inflammation and thinning of the endometrial lining. These conditions disrupt the optimal environment necessary for embryo implantation and subsequent placental development, leading to various reproductive difficulties.

Keywords Endometrial hypoplasia, Endometritis, Implantation, Fertility

1. Introduction

The persistent inflammation associated with chronic endometritis creates an unfavorable environment for embryo implantation. Elevated levels of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 have been shown to impair the ability of the embryo to attach to and penetrate the endometrial surface [2,15,32]. These cytokines can impair the function of critical adhesion molecules, including integrins, which play a vital role in the initial attachment process [6,41]. Additionally, the presence of immune cells such as plasma cells generates harmful substances such as reactive oxygen species, which can damage the early embryo [11,13,22,34]. Research shows that women suffering from this condition have decreased implantation success and an increased likelihood of early pregnancy loss [9,25]. Beyond these statistics, the inflammatory state can subtly alter the receptivity of the endometrium, further complicating the chances of a viable pregnancy. Compounding this problem is a hypoplastic endometrium, typically characterized by a thickness of less than 7 mm, which reduces its ability to support implantation and early fetal growth [5,20,16]. The thin endometrial layer often lacks adequate glandular development and vascular support, limiting the supply of essential nutrients and oxygen to the embryo [7,13,17]. This structural deficiency can also affect the production of key factors such as leukemia inhibitory factor (LIF), which is essential for embryonic development [3,12,18,39]. As a result, women with a hypoplastic endometrium often have difficulty achieving pregnancy, especially when undergoing procedures such as in vitro fertilization (IVF), which tend to have higher miscarriage rates [29]. Not only does the reduced thickness make implantation more difficult, it also increases the fragility of early pregnancy survival. The interaction between chronic inflammation and endometrial hypoplasia exacerbates these fertility issues.

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The ongoing inflammatory process interferes with the ability of the endometrium to thicken and repair itself properly, maintaining its thin state [20]. This vicious cycle often leads to repeated implantation failures and repeated pregnancy losses, creating a challenging obstacle for affected individuals [21]. Addressing both the inflammatory and structural aspects of chronic hypoplastic endometritis is important to improve fertility prospects and pregnancy outcomes.

Chronic hypoplastic endometritis undermines fertility by promoting inflammation and structural inadequacy of the endometrial environment. This dual impact results in reduced implantation rates, increased risk of miscarriage, and overall decreased reproductive success. Targeted therapies that mitigate inflammation and promote endometrial growth are critical to supporting women facing these challenges on their journey to conception and a healthy pregnancy.

2. Materials and Methods

Chronic hypoplastic endometritis, characterized by persistent endometrial inflammation and inadequate endometrial thickness, represents a major challenge in reproductive medicine due to its significant impact on fertility. Effective preconception care is critical to optimize endometrial health and improve the chances of successful conception in affected women. Current clinical approaches aim to address both the inflammatory and hypoplastic components of the condition using a range of pharmacological, surgical, and supportive interventions. These methods, although based on established practice, often lack specificity for the unique pathophysiology of chronic hypoplastic endometritis, leading to variable outcomes. This section provides a comprehensive review of the main preconception strategies, detailing their mechanisms, clinical applications, evidence base, limitations, and broader implications for patient care, highlighting the need for more individualized and comprehensive protocols. The cornerstone of treatment for chronic endometritis is antimicrobial therapy aimed at eradicating underlying infections that contribute to

the maintenance of inflammation. Broad-spectrum antibiotics such as doxycycline and metronidazole are often prescribed due to their effectiveness against common pathogens including Chlamydia trachomatis, Neisseria gonorrhoeae, and anaerobic bacteria. The standard regimen includes doxycycline (100 mg twice daily for 14 days) or a combination of metronidazole (500 mg twice daily) and a fluoroquinolone to cover a broad microbial spectrum. Studies show that this treatment can resolve inflammation in about 60 to 70 percent of cases, as evidenced by the absence of plasma cells in subsequent endometrial biopsies. In cases of persistent infection, doctors may extend the course of antibiotics or switch to alternatives such as azithromycin to achieve resolution.

Despite its widespread use, antimicrobial therapy faces several challenges. Not all cases of chronic endometritis are caused by infection; autoimmune or idiopathic etiologies may perpetuate inflammation, rendering antibiotics ineffective. The empirical nature of treatment, often initiated without microbial culture or susceptibility testing, further complicates outcomes, as inappropriate antibiotic selection may fail to target certain pathogens. Additionally, prolonged or repeated antibiotic use raises concerns about antimicrobial resistance, a growing global health problem, and potential disruption of the endometrial microbiome. The endometrial microbiome, which is dominated by Lactobacillus species in healthy conditions, plays a critical role in maintaining immune balance and preventing pathogen colonization. Antibiotic-induced dysbiosis may inadvertently worsen inflammation or worsen endometrial receptivity, highlighting the need for more precise diagnostic and therapeutic approaches. To address the hypoplastic component of chronic hypoplastic endometritis, hormonal therapy is used to stimulate endometrial proliferation and achieve a thickness favorable for implantation. Oral estradiol, typically given at 2–6 mg daily for 10–14 days, is the most common approach, often followed by progesterone (200 mg daily for 10 days) to support the secretory phase and enhance endometrial receptivity. Transdermal estradiol patches or vaginal estradiol preparations are also used in some cases, offering alternative delivery methods to improve patient comfort or absorption 595959. Clinical studies suggest that hormonal therapy can increase endometrial thickness from less than 7 mm to 8–10 mm in approximately 50% of women with a thin endometrium, although results vary widely. In addition to estradiol, additional hormonal agents such as gonadotropin-releasing hormone (GnRH) agonists or selective estrogen receptor modulators such as tamoxifen are sometimes used to stimulate ovarian function and indirectly stimulate endometrial growth. These agents are particularly useful in women with ovulatory dysfunction, such as hypothalamic amenorrhea, where endogenous estrogen production is suboptimal. However, hormonal therapy is not always effective, particularly in cases where endometrial scarring, fibrosis, or chronic inflammation limit tissue receptivity. Long-term estrogen use also carries risks including endometrial hyperplasia, thromboembolism, or breast tenderness, which require careful monitoring and individualized dosing 656565. The variability in treatment response highlights the need for strategies that address underlying structural or inflammatory barriers to endometrial growth. Hysteroscopy serves as both a diagnostic and therapeutic tool in the treatment of chronic hypoplastic endometritis, offering direct visualization and correction of endometrial abnormalities. During the procedure, physicians can identify signs of chronic inflammation, such as micropolyps, stromal edema, or focal hyperemia, and obtain targeted biopsies for histologic confirmation. Therapeutically, hysteroscopy allows for the removal of endometrial polyps, intrauterine adhesions (Asherman's syndrome), or retained products of conception that may perpetuate inflammation or impede endometrial development. In cases of adhesions, hysteroscopic adhesiolysis can restore the architecture of the uterine cavity, potentially improving endometrial thickness and receptivity.

3. Discussion

The effectiveness of hysteroscopy in improving fertility outcomes has been documented in several studies, particularly for women with structural abnormalities. For example, a 2019 study by Di Spiezio Sardo et al reported that hysteroscopic polypectomy improved pregnancy rates in women with chronic endometritis and endometrial polyps. However, the benefits of hysteroscopy are limited when inflammation persists, as antibiotics are often required to complement the procedure. Moreover, repeated hysteroscopic interventions carry a risk of endometrial trauma, which may worsen hypoplasia in susceptible patients, particularly those with a history of multiple uterine procedures. The invasiveness of the procedure, its cost, and the need for specialized equipment and expertise also limit its availability, particularly in resource-limited settings, posing a significant barrier to widespread adoption. Emerging evidence highlights the potential of immunomodulatory therapy in the treatment of chronic endometritis, particularly in cases that are resistant to antibiotics or caused by immune dysregulation. Low doses of corticosteroids such as prednisone (5–10 mg daily for 7–14 days) have been investigated for their ability to suppress excessive immune activation and reduce endometrial inflammation. Prednisone's mechanism of action involves downregulation of proinflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, which are elevated in chronic endometritis and impair endometrial receptivity. Small studies suggest that corticosteroids may improve pregnancy rates in women with recurrent implantation failure, although evidence specific to chronic hypoplastic endometritis remains limited. Another promising adjunct is granulocyte colony-stimulating factor (G-CSF), administered via intrauterine infusion to increase endometrial thickness and receptivity. G-CSF is thought to promote angiogenesis and tissue regeneration, with studies reporting increased endometrial thickness and pregnancy rates in women with thin endometrium. However, its use in chronic hypoplastic endometritis is still experimental, and larger trials are needed to establish its efficacy and safety. Other adjunctive therapies, such as antioxidants (eg, vitamin E, N-acetylcysteine) and

pentoxifylline, have been proposed to reduce oxidative stress and improve endometrial blood flow, potentially supporting tissue repair in the presence of chronic inflammation. These agents aim to counteract the damaging effects of reactive oxygen species, but the evidence base is preliminary, with conflicting results across studies.

Lifestyle modification and nutritional support are increasingly recognized as integral components of preconception care for pregnant women, although their role in chronic hypoplastic endometritis is less well defined. Smoking cessation is strongly recommended, as tobacco use is associated with decreased endometrial thickness and impaired immune function, which worsens both inflammation and hypoplasia. Weight control is also critical, as obesity or extreme underweight can disrupt hormonal balance and endometrial development. Stress reduction techniques such as mindfulness or yoga may indirectly improve endometrial health by reducing cortisol levels, which can influence reproductive hormones. Nutritional interventions such as supplementation with omega-3 fatty acids, vitamin D, or folate have been investigated for their anti-inflammatory and tissue-supportive properties. For example, omega-3 fatty acids may reduce systemic inflammation, potentially benefiting the endometrial microenvironment. Vitamin D supplementation has been associated with improved endometrial receptivity in some studies, although its specific effect on chronic hypoplastic endometritis remains poorly understood. Although these interventions are generally low-risk and cost-effective, their benefits are not well established and they tend to be used as adjunctive rather than primary treatments. The lack of robust clinical trials in this area highlights a significant gap in understanding how lifestyle and nutrition can be optimized to support preconception care in this condition. Current preconception care approaches face several limitations that reduce their effectiveness in chronic hypoplastic endometritis. The lack of individualized protocols is a major concern, as treatments are often applied empirically without consideration of differences in disease etiology, severity, or individual patient factors. For example, antibiotics may not work in non-infectious cases, and hormonal therapy may not be effective in the presence of endometrial fibrosis or severe inflammation. This one-size-fits-all approach overlooks the complex interplay between inflammation and hypoplasia, which requires integrated strategies to simultaneously address both components.

The evidence base for many treatments is also limited by small sample sizes, heterogeneous study designs, and a focus on short-term outcomes. Although antibiotics and hormonal therapies have demonstrated benefits in some contexts, their long-term impact on fertility rates or recurrence of endometritis is rarely reported. Newer treatments such as G-CSF or antioxidants show promise but lack rigorous clinical trials to confirm their safety and efficacy. This lack of high-quality evidence complicates clinical decision-making and highlights the need for more robust research to guide practice. Practical barriers such as cost and availability further limit the use of newer techniques. For example, hysteroscopy requires specialized equipment and trained personnel, making it unavailable in many low-resource settings. Similarly, the financial burden of repeat procedures, particularly for women undergoing ART, can be prohibitive, exacerbating inequalities in access to care. The emotional consequences of long-term infertility treatment, including anxiety and depression, are another under-addressed issue, as current protocols rarely include psychological support. The uneven success of current preconception treatments highlights the urgent need for optimized, evidence-based protocols that address the unique pathophysiology of chronic hypoplastic endometritis. An ideal approach would include the integration of advanced diagnostic tools, such as molecular profiling of the endometrial microbiome or cytokine analysis, to identify specific disease causes and tailor treatment accordingly.

4. Result

A coordinated combination of antimicrobial, hormonal, immunomodulatory, and structural interventions may synergistically improve endometrial health and fertility outcomes, as demonstrated by the optimized protocol in this study.

Furthermore, future protocols should prioritize personalization to account for individual variations in disease presentation and treatment response. For example, women with autoimmune endometritis may require long-term immunomodulation, while women with structural lesions may benefit from repeated hysteroscopic interventions. Incorporating lifestyle and nutritional counseling as standard components may further improve outcomes by addressing holistic aspects of reproductive health. By adopting a multidimensional, patient-centered approach, physicians can better meet the needs of women with chronic hypoplastic endometritis, reducing the physical, emotional, and financial burden of infertility.

The current state of conception care in chronic hypoplastic endometritis reflects both progress and ongoing challenges. Although antibiotics, hormonal therapy, hysteroscopy, and new adjuvants offer valuable tools, their limitations—lack of specificity, variable efficacy, and resource requirements—underscore the need for innovation. Developing standardized guidelines based on high-quality clinical trials could help optimize care and ensure consistency across settings. Such guidelines could recommend routine microbiome testing, personalized hormonal regimens, or integrated immunomodulatory strategies informed by precision medicine principles.

Additionally, addressing global disparities in access to advanced treatments will be critical. In high-resource settings, the focus may be on refining protocols using advanced diagnostics, while in low-resource settings, simplifying interventions to reduce costs and complexity will be paramount. The collaborative efforts of researchers, clinicians and policy makers can help disseminate effective strategies, ensuring that women worldwide benefit from advances in preconception care.

5. Conclusions

In summary, current preconception care approaches for chronic hypoplastic endometritis rely on a combination of antimicrobial, hormonal, hysteroscopic and adjuvant therapies, each with its own advantages and limitations. Although these approaches have improved outcomes for some patients, their lack of specificity, inconsistent evidence and practical barriers highlight the need for more targeted and comprehensive strategies. The development of optimized protocols, based on rigorous research and tailored to individual needs, has the potential to transform infertility care for women with this complex condition, paving the way for better reproductive outcomes and increased patient well-being.

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