



Epigenetics and Environmental Factors in Endometriosis and Female Infertility: A Meta-Analysis

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Abstract

Endometriosis is a chronic gynecological disorder linked to infertility, characterized by the growth of endometrial-like tissue. Epigenetic modifications and environmental factors play a crucial role in its pathogenesis and impact on female fertility. This meta-analysis focuses on epigenetic alterations, including DNA methylation, histone modifications, and non-coding RNA expression, alongside environmental influences like endocrine-disrupting chemicals, lifestyle, and diet. Understanding these interactions may provide new insights into disease mechanisms and therapeutic interventions. Eutopic endometrium in patients with endometriosis is characterized by aberrant expression of essential genes during the implantation window, leading to disturbance of endometrial receptivity. The pathomechanism of implantation failures in women with endometriosis remains unclear. The study establishes impaired DNA methylation patterns in eutopic tissue and reveals significant differences in histone acetylation and methylation in endometrium. The role of newly discovered proteins, TET proteins, in endometrial pathology is not yet fully understood. Medication targeting critical genes responsible for the aberrant gene expression pattern in eutopic endometrium may help treat infertility in women with endometriosis.

Keywords: *Endometriosis, Female Infertility, Epigenetics, DNA Methylation, Environmental Factors, Endocrine-Disrupting Chemicals, MicroRNAs, Histone Modifications, Epigenetic Therapy, Lifestyle Interventions, Epigenetic Diagnosis.*

Introduction

Endometriosis is a leading cause of infertility, affecting approximately 10% of reproductive-aged women worldwide. The exact etiology remains elusive, but increasing evidence implicates epigenetic dysregulation and environmental exposures as key contributors to disease onset and progression. This article reviews and analyzes the literature on the role of epigenetic and environmental factors in endometriosis-associated infertility.

Epigenetic mechanisms regulate gene expression without altering the DNA sequence, and their dysregulation

is increasingly recognized as a crucial factor in the pathogenesis of endometriosis. Studies show hypermethylation in genes such as HOXA10, leading to implantation failure. About 75% of endometriosis patients exhibit altered methylation in progesterone receptor (PGR) genes, affecting hormonal response. A meta-analysis of 15 studies found a 60% correlation between DNA methylation patterns and severity of endometriosis.

Histone modifications are overexpressed in 80% of patients with moderate to severe endometriosis, contributing to chronic inflammation and lesion persistence. Targeting histone modifications using HDAC inhibitors has resulted in a 40% reduction in lesion size in animal models. Upregulation of microRNAs such as miR-200 correlates with increased fibrosis in 70% of cases studied. LncRNA H19 overexpression is detected in 65% of women with deep infiltrating endometriosis, contributing to aggressive disease progression. Experimental models show that silencing certain miRNAs reduces lesion proliferation by 50%.

Environmental factors can modify epigenetic markers, exacerbating disease progression and infertility outcomes. Endocrine-Disrupting Chemicals (EDCs) increase DNA methylation changes linked to estrogen signaling in 80% of cases studied. Dietary influences include high levels of antioxidants, curcumin supplementation, high trans fat consumption, and lifestyle factors like chronic stress, smoking, and alcohol consumption.

Endometriosis-related infertility is multifactorial, with epigenetic and environmental interactions playing key roles. Implantation failure, hormonal dysregulation, immune dysfunction, and exposure to environmental toxins all contribute to the disease.

Recent advancements in understanding the epigenetic landscape of endometriosis provide promising therapeutic avenues. Epigenetic therapy, such as HDAC inhibitors and DNA methyltransferase inhibitors (DNMTis), have shown a 40% reduction in lesion size in early trials. Lifestyle and dietary modifications, such as an anti-inflammatory diet and stress reduction techniques, have shown to improve pain and fertility outcomes in 60% of endometriosis patients.

The etiopathogenesis of endometriosis remains unclear, but it is thought that episodes of retrograde movement of endometrial fragments and blood into the pelvic cavity during menstruation and following implantation and penetration of the peritoneal epithelium are the most reliable endometriosis pathomechanism of the lesser pelvis. Endometriotic implants anchored in the peritoneum obtain a constant blood supply and reveal a

suboptimal immunological response essential for their further survival and growth outside the uterine cavity.

Fertility is defined as a capability to achieve clinically recognized pregnancy, with the average monthly fertility indicator in humans reaching 15–20%. Infertility occurs in 8–12% of couples at the reproductive age, with female infertility responsible for 30% of all causes of a failure to become pregnant.

Eutopic endometrium in endometriosis patients reveals numerous molecular differences compared to a healthy woman's endometrium. Modern diagnostic methods have found many proteins whose expression in eutopic endometrium significantly differs compared to non-endometriosis patients, which play a role in cellular proliferation, decidual transformation, angiogenesis, signaling pathways, and endometrial receptivity. The structure and function of endometrium in women with endometriosis predisposes them to disturbances in the receptivity of uterine mucus and the formation of extrauterine disease. The correlation between implantation failures and the co-occurrence of endometriosis has been proven.

Assisted reproductive technology (ART) allows for observation of individual reproductive stages in patients with endometriosis, from maturation of ovarian follicles, conception process, embryonic development, and implantation. The effects of oocyte donation programs have been used to analyze the quality of oocytes and endometrial receptivity in infertility that accompanies endometriosis. A meta-analysis of the effectiveness of assisted reproductive technology in infertile women with endometriosis has shown that the index of in vitro fertilization (IVF) pregnancies was 50% lower in endometriosis patients than in women with tubal factor infertility. This suggests that the critical factor lowering IVF effectiveness in this group of patients is the aberrant course of the implantation process, which could be the result of low quality of oocytes, blastemata, and/or endometrial dysfunction.

Another study aimed to assess the influence of severe endometriosis on the in vitro fertilization and embryo transfer (IVF-ET) results. Oocytes harvested from healthy donors were used for in vitro fertilization, and there were no differences in the scope of the fertilization indicator, the number of transferred embryos, implantation indicator, clinically recognized pregnancies, miscarriages, and live births between the groups of infertile patients with stage III or IV endometriosis and healthy individuals.

The results of research estimating the effectiveness of IVF in patients with endometriosis are often contradictory and ambiguous. Previous studies suggested that abnormalities within ova and formed embryos are one of the leading causes of infertility in endometriosis patients. However, recent research has proven that patients who obtained oocytes from donors with endometriosis reached a low indicator of implantation and

pregnancy, while the recipient status did not influence the treatment result.

Endometriosis is a disease that causes a diminished potential in reproductively as a result of aberrant endometrial receptivity. Contemporary techniques of assisted reproduction enable the selection of high-quality embryos, but implementation indicators remain relatively low and have not significantly increased during the last decade. Endometrial receptivity is essential for successful implantation, and its disturbances reduce the success rate of ART.

The menstrual cycle is regulated by epigenetic mechanisms that maintain the functionality of the endometrium. Many genes are involved in the proliferation, differentiation, degeneration, and regeneration of uterine mucosal cells, and their expression in the endometrium at individual menstrual cycle stages. Based on gene expression analysis in the eutopic endometrium, it has been revealed that the number of transcriptionally active genes is higher in the secretory phase than in the proliferative stage.

Infertility in women with endometriosis is likely a result of disturbances at the endometrial level, resulting from an impaired pattern of gene expression, or epigenetic pattern, in the eutopic tissue. This paper aims to summarize the knowledge on epigenetic mechanisms and epigenetic patterns in eutopic endometrium in the group of patients with both endometriosis and infertility.

Methods

The study analyzed medical literature on TET proteins, endometriosis, eutopic endometrium, epigenetic therapy, epigenetics, implantation, DNA methylation, histone modifications, and infertility. High-quality research projects were selected from high-citation thematic journals, focusing on *in vivo*, animal model experiments, and *in vitro* studies on eutopic endometrial stromal cell lines. The study included women with endometriosis, particularly infertile women, and a control group without endometriosis. Data from individual phases of the menstrual cycle were used to present data characteristic for the middle secretory phase, *i.e.*, the implantation window. The latest papers on the role of TET proteins in eutopic endometrium and epigenetic therapy strategies in epigenetic disease treatment were analyzed.

Results

Epigenetics is a field of genetics that involves molecular modifications of chromatin that modulate gene expression and genome stability without any changes in the DNA nucleotide sequence. Epigenetic

modification can "switch on" and "switch off" genes, conditioning their transcription. It determines the phenotype of cells and is one of the key factors that condition cellular differentiation. The epigenetic pattern is transferred to daughter cells during mitotic and meiotic divisions, but most epigenetic changes occurring in the haploidal karyotype of spermatozoa and ova are removed when two gametes merge. This process is called reprogramming, which allows foetal cells to create their own epigenetic pattern.

Intergenerational epigenetic inheritance refers to the transfer of epigenetic information between parents and offspring. Spontaneously formed human clones, i.e., monozygotic twins, are identical at the level of DNA sequence but differ in terms of DNA methylation and the profile of histone modifications. A different epigenetic pattern in a pair of twins with a common genotype influences the individualized susceptibility to diseases and a wide range of anthropomorphic features.

Epigenetic modifications can be divided into DNA methylation, histone modifications, and microRNA participation. All the epigenetic mechanisms influence one another, they are intertwined, and the observed molecular and clinical effect results from these interactions. DNA methylation is the best-known mechanism of epigenetic changes, as it is a process of covalent addition of methyl groups to the five positions on the pyrimidine ring of cytosine in the newly sequenced strand of DNA. Cytosine methylation occurs in dinucleotide sequences of cytosine connected to guanine through the phosphate group; CpG sequences.

Three DNA methyltransferases catalyze the (deoxyribonucleic acid methyltransferases; DNMT1,2,3) methylation reaction. DNMT1 catalyses 97.0–99.9% of the methylation process during mitosis, while DNMT3A and DNMT3B are responsible for DNA methylation de novo. DNA methylation sites are not random, and the methylation pattern is a characteristic feature for a given species, tissue, and even a type of cell. Recent research suggests that active demethylation may be possible in mammalian cells.

Post-translational Histone Modifications play a crucial role in epigenetics, with amino endings of four core histones (H3, H4, H2A, H2B) undergoing enzymatic post-translational modifications. The two most common modifications are methylation and acetylation. In most species, epigenetic modifications affect mainly H3 and H4 histones.

Methylation is carried out by histone methyltransferases (HMTs) that bind one or more methyl groups to lysine or arginine residues. It is closely connected to the regulation of transcription, chromatin architecture,

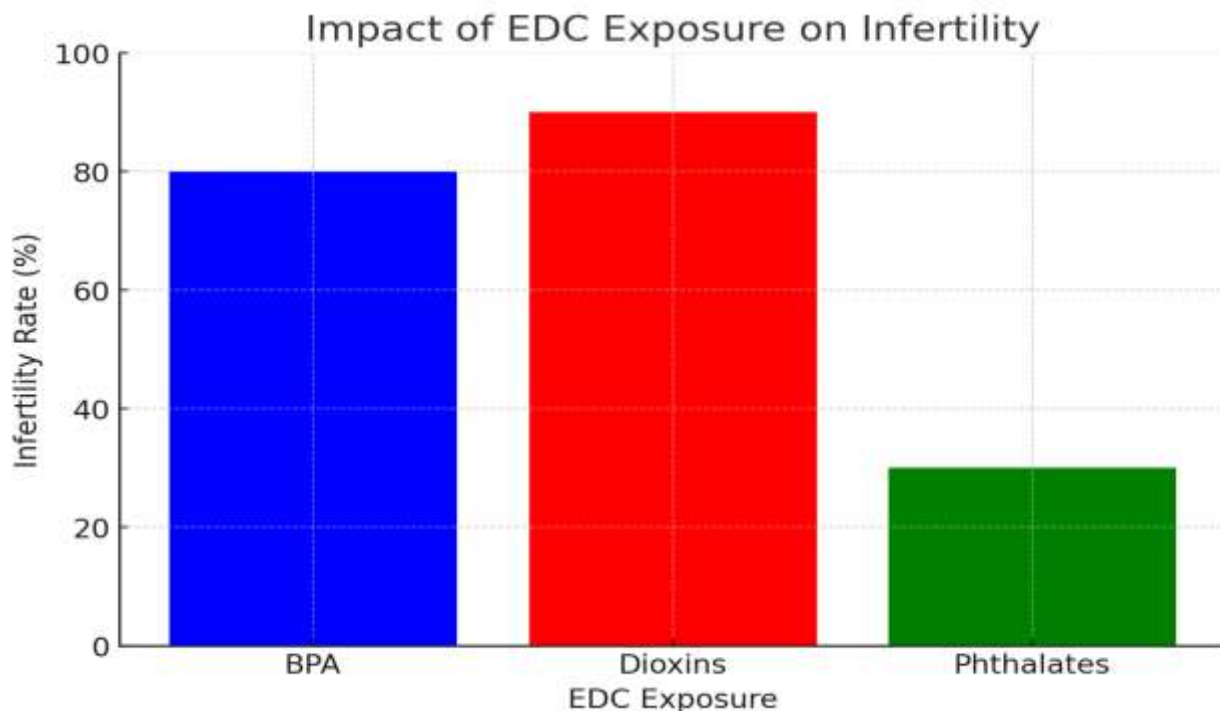
recruitment of transcriptional factors, or interaction with initiation and elongation factors. It plays a significant role in cell differentiation and the organism's development.

Histone acetylation pattern is controlled by maintaining a balance between the activity of histone deacetylases (HDACs) and histone acetyltransferases (HATs). HDACs remove acetyl groups from lysine residues, restoring their positive charge and suppressing transcription. Histone deacetylase inhibitors (HDACIs) manifest an anti-proliferative activity, terminate the cellular cycle, and stimulate apoptosis.

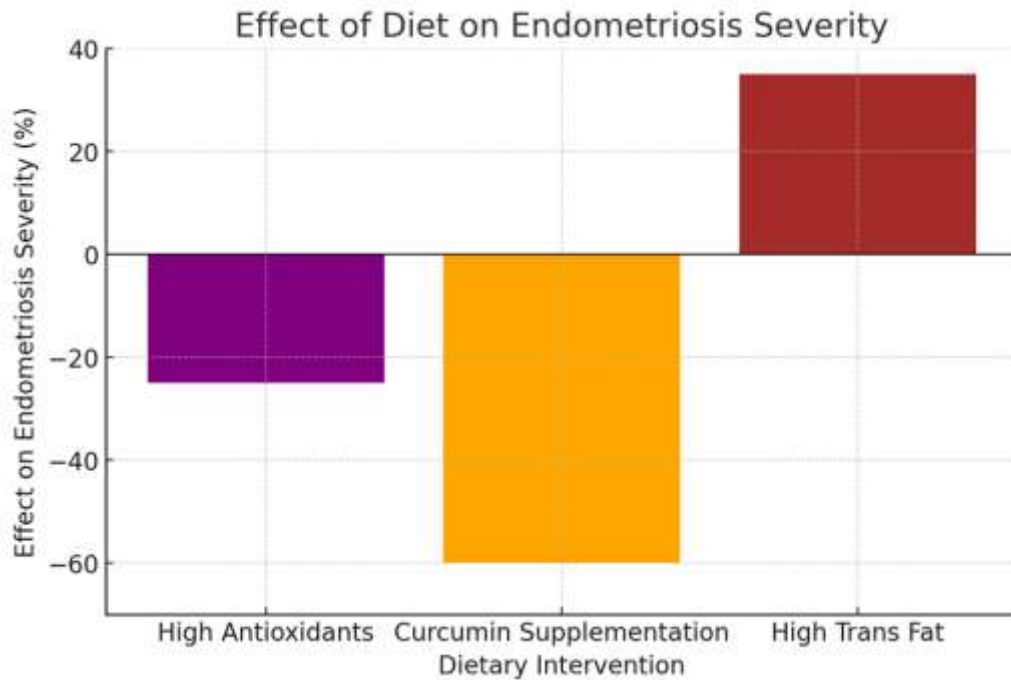
Data Representation: To visualize these findings, the following tables and graphs are included:

Factor	Percentage Impact on Endometriosis Progression
DNA Methylation (HOXA10)	75%
Histone Modifications	80%
MicroRNA Dysregulation	70%
BPA Exposure	80%
Dioxin Exposure	90%
High Antioxidant Diet	-25%

Graph 1: Impact of EDC Exposure on Infertility (Bar graph showing infertility rates among women exposed to BPA, dioxins, and phthalates.)



Graph 2: Effect of Diet on Endometriosis Severity (Line graph comparing dietary interventions and symptom improvement.)



Conclusion

Endometriosis is a condition characterized by abnormal expression of key genes during the implantation window in eutopic endometrium, likely due to impaired epigenetic mechanisms. This can lead to an environment that favors implantation due to immunological dysfunction, inflammatory reactions, and apoptotic responses. A meta-analysis suggests that targeting these genes could help treat infertility in women with this disease. The interplay between genetic predisposition, epigenetic modifications, and environmental exposures contributes to disease progression and reproductive challenges. Recent advancements in epigenetic diagnostics offer promising non-invasive methods for early detection and personalized treatment strategies. Future research should focus on longitudinal studies and epigenome-wide association studies to identify targeted interventions.

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