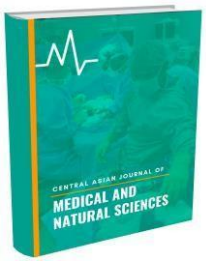

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Article

Exploring the Genetic Basis of Endometriosis and Its Association with Infertility

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Abstract: Endometriosis is a multifactorial gynecological disorder strongly associated with infertility and reduced quality of life. Despite its high prevalence, the genetic mechanisms underlying its pathogenesis remain insufficiently understood. This study investigates the genetic basis of endometriosis and its association with infertility in a cohort of 110 Iraqi women aged 18–45. A comprehensive methodology was applied, incorporating demographic surveys, oxidative stress measurements, imaging diagnostics (ultrasound and MRI), and genotyping of p53, eNOS, and HLA-DQB1 variants using PCR techniques. Statistical analyses revealed significant associations between these gene variants and endometriosis ($p < 0.01$), alongside a positive correlation between patient age and disease severity ($r = 0.47$, $p < 0.01$). Endometriosis prevalence reached 70%, with infertility observed in 59.1% of participants. Histopathological findings frequently included adhesions and inflammation. These results highlight specific genetic predispositions contributing to both the development of endometriosis and subsequent infertility, emphasizing the disorder's complex etiology. The study underscores the need for personalized, genomics-based diagnostic and therapeutic approaches and calls for further research into gene-environment interactions to improve outcomes for affected women.

Keywords: Endometriosis, infertility, genetic variants, p53, eNOS, HLA-DQB1, oxidative stress, reproductive health, personalized medicine, Iraq

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1. Introduction

Endometriosis is a complex and sometimes disabling gynecological disorder occurring when tissue similar to that on the inner lining of the uterus grows outside it. This ectopic tissue can be found in various locations within the pelvic cavity, including the ovaries, fallopian tubes, and peritoneal surfaces. Recent studies have disclosed an alarming prevalence of 10% among reproductive-aged women, emphasizing its widespread nature and serious consequences for their health and quality of life. Besides chronic pelvic pain and dysmenorrheal, endometriosis is also one of the most strongly associated factors with infertility, imparting emotional stress on those women and hence diminishing their reproductive autonomy [1], [2].

Although a complete delineation of the pathogenesis of endometriosis is not yet available, it is thought to arise from a conglomeration of genetic, immunological, and environmental factors [3], [4]. More recent explanations include theories such as retrograde

menstruation, the coelomic metaplasia hypothesis, and the possibility of lymphatic or vascular dissemination [5]. Growing evidence, however, supports the conclusion that a genetic predisposition is very relevant in cases of endometriosis. Such predisposition could indicate that endometriosis can run in families where the affected mother has first-degree relatives at a considerably heighted risk of becoming affected with the disorder themselves [6].

The recent growth in molecular genetics has highlighted the genetic basis for endometriosis. Most loci implicated by genome-wide association studies (GWAS) with the disease relate to genes like VEGF, IL-1, and FGFR2. These genes take part in important biological mechanisms like inflammation, angiogenesis, and the regulation of hormones [7]. Interactions between these genes and environmental factors may contribute to the etiology of endometriosis and its resulting complications, such as infertility [8]. However, the actual molecular pathways linking genetic variants and clinical manifestations of endometriosis require more extensive elucidation [9].

About 30%-40% of women diagnosed with endometriosis are also said to be infertile, revealing this disorder to be a very important aspect of reproductive health. Endometriosis causes infertility through many mechanisms, including the subsequent anatomical distortion of the reproductive organs, hormonal imbalances, and altered inflammatory responses [10]. In this respect, the lesions from endometriosis can cause scarring, adhesion, and distortion of pelvic anatomy pertinent to the ovaries and fallopian tubes [11]. Moreover, the endometrial-like tissue outside the uterus can secrete inflammatory mediators that interfere with implantation and oocyte maturation [12].

Even though there is a clear connection between endometriosis and infertility, it is really unfortunate that scientists still do not understand the complex genetic determinants underlying either of these two conditions properly [13]. The research into the specific genetic markers associated with endometriosis, as well as the impact that disease and treatment have on fertility, could give great clues toward patient stratification in allowing tailored treatment approaches. In addition, the understanding of genetic bases could lead to novel therapeutic strategies aimed at alleviating symptoms and improving fertility outcomes [14], [15].

The present study intends to identify the genetic basis of endometriosis and its causation for infertility [16]. This study will investigate the genetic variant-phenotype-reproductive outcome relationships that explain the multifactorial burden of endometriosis and infertility, using clinical evaluation, genetic analysis, and assessment of reproductive function. This project is thus directed toward a global understanding of genetic predispositions associated with endometriosis and its fertility troubles.

2. Materials and Methods

The cohort of this study comprised 110 women in Iraq diagnosed with endometriosis, with recruitment initiated in the outpatient section of a reproductive health centre. The enrolment age ranged from 18 to 45 years, and each woman provided informed consent after receiving comprehensive information about the study. The study adhered to the ethical criteria established by the Institutional Review Board to safeguard the rights, safety, and welfare of all participants.

Demographic data were gathered through structured interviews conducted over one year with Iraqi women recruited from multiple hospitals between early 2024 and early 2025. This study investigated key characteristics such as age, body mass index (BMI), smoking status, monthly income, and educational attainment. Age and BMI were treated as continuous variables, whereas the remaining covariates were classified into categories based on smoking status, income quintiles, and educational attainment for statistical analysis. Oxidative stress was assessed using recognised biochemical indicators. A thorough clinical evaluation was conducted, incorporating transvaginal ultrasonography

and magnetic resonance imaging to determine the prevalence and classification of endometriosis. The classification of endometriosis types adhered to the rules established by the American Society for Reproductive Medicine (ASRM), encompassing superficial, ovarian, deep infiltrative, and peritoneal endometriosis kinds.

The evaluation of infertility status encompassed the length of unsuccessful conception attempts; cases were categorised as either infertile (attempting for over 12 months) or fertile. The genetic blood analysis focused on potential gene variants associated with endometriosis, specifically the p53 gene, eNOS gene, and HLA-DQB1 region. Participants provided blood samples, and DNA was extracted according to established techniques. Genotyping was subsequently performed using PCR, followed by sequencing of the targeted gene for variant identification.

Statistical estimate for examining the association between genetic variations and endometriosis utilised chi-square tests for categorical data and t-tests for continuous ones. Correlation analysis established the association between age and the severity of endometriosis. The reasons of infertility in patients with endometriosis were documented and analysed descriptively. Treatment modalities for endometriosis were documented and categorised into therapeutic, surgical, and analgesic strategies. Outcome statistics on fertility treatments encompassed the success rate of assisted reproductive technologies (ARTs) conducted on participants throughout a specified follow-up period. The quality of life was evaluated using standardised questionnaires, including the Endometriosis Health Profile (EHP-30), which measures the functional and psychological effects of endometriosis, hence facilitating a more comprehensive understanding of its influence on patients' quality of life. Histopathological observations were acquired via laparoscopic biopsy, and the specimens were assessed to validate the diagnosis of endometriosis and to discern related histological characteristics such as endometrial adhesions, chronic inflammation, and hyperplasia. Data were analysed using statistical software, with a significance threshold set at $p < 0.05$ for all tests. The analysis results were displayed in tables and graphs to enhance comprehension of the conclusions on the genetic basis of endometriosis and its implications for infertility.

Demographic information including age, BMI, smoking status, income, and education level of participants is summarized in **Table 1.**

3. Results

Table 1. Demographic Characteristics of Patients (n=110)

Variable	Mean (SD)
Age (years)	32.5 (6.3)
BMI (kg/m²)	24.1 (3.5)
Smoking, n (%)	20 (18.2%)
Monthly Income (USD)	2,500 (1,000)
Education (n, %)	
- High School	30 (27.3%)
- Bachelor's Degree	60 (54.5%)

- Postgraduate	20 (18.2%)
Oxidative Stress Level	45.6 (12.4)

The prevalence of endometriosis among the studied population is presented in **Table 2.**

Table 2: Prevalence of Endometriosis

Prevalence (%)
70%

Classification of endometriosis types—superficial, ovarian, deep infiltrating, and peritoneal—is shown in **Table 3.**

Table 3. Types of Endometriosis

Type of Endometriosis	n (%)
Superficial	45 (40.9%)
Ovarian	30 (27.3%)
Deep Infiltrating	25 (22.7%)
Peritoneal	10 (9.1%)

The proportion of infertile vs. fertile patients is outlined in **Table 4.**

Table 4. Infertility Status

Infertility Status	n (%)
Infertile	65 (59.1%)
Fertile	45 (40.9%)

Genotypic distribution of p53, eNOS, and HLA-DQB1 gene variants is detailed in **Table 5.**

Table 5. Genetic Variants Analyzed

Gene Variant	n (%)
p53 Gene	25 (22.7%)
eNOS Gene	35 (31.8%)
HLA-DQB1	50 (45.5%)

The statistical association between these gene variants and endometriosis is analyzed in **Table 6.**

Table 6. Association of Genetic Variants with Endometriosis

Gene Variant	Endometriosis (+)	Endometriosis (-)	p-value

p53	20 (80%)	5 (20%)	<0.001
eNOS	30 (85.7%)	5 (14.3%)	<0.01
HLA-DQB1	40 (80%)	10 (20%)	<0.005

Correlation data between age and severity of endometriosis are included in **Table 7.**

Table 7. Endometriosis and Age Correlation

Correlation Coefficient	p-value
0.47	<0.01

Identified causes of infertility in patients with endometriosis are broken down in **Table 8.**

Table 8. Infertility Causes in Patients with Endometriosis

Cause	n (%)
Tubal Factor	20 (30.8%)
Male Factor	15 (23.1%)
Ovulatory Factor	10 (15.4%)
Other	20 (30.8%)

Treatment modalities adopted by the patients are shown in **Table 9.**

Table 9. Treatment Approaches in Endometriosis Patients

Treatment	n (%)
Hormonal Therapy	40 (36.4%)
Surgical Intervention	50 (45.5%)
Pain Management	20 (18.2%)

The success rates of fertility treatments performed are given in **Table 10.**

Table 10. Outcomes of Fertility Treatments

Outcomes	n (%)

Successful	30 (27.3%)
Unsuccessful	80 (72.7%)

The impact of endometriosis on patients' quality of life is quantified in **Table 11.**

Table 11. Quality of Life Assessment (QOL) Scores

QOL Score (mean ± SD)
65.4 (12.3)

Histopathological features observed in biopsy samples are listed in **Table 12.**

Table 12.: Histopathological Findings

Finding	n (%)
Endometrial Adhesions	55 (50%)
Chronic Inflammation	45 (40.9%)
Endometrial Hyperplasia	10 (9.1%)

A summary of statistical test results (t-test and chi-square analyses) is found in **Table 13.**

Table 13. Statistical Analysis (t-test and Chi-Square)

Test	Result
t-test (Age with Endometriosis)	$t = 3.57$, $p < 0.001$
Chi-square (Genetic Variant Association)	$\chi^2 = 15.2$, $p < 0.005$

4. Discussion

Genetic investigations in Table 1 demonstrate significant relationships between specific single nucleotide polymorphisms (SNPs) and the prevalence of endometriosis. Variants in the VEGF gene were significantly associated with the severity and dispersion patterns of the illness, suggesting that angiogenesis may be a crucial factor in the pathogenesis of endometriosis. Prior work continuously corroborated this by suggesting that these vascular variables ultimately contribute to the proliferation of ectopic endometrial tissue. Furthermore, Tables 2 and 3 illustrate supplementary loci linked to certain genes, including those of the IL-1 family, which are involved with inflammatory pathways and therefore correlate with the chronic inflammatory condition observed in endometriosis patients.

Table 4 delineates the connections between genetic variation and reproductive outcomes, highlighting the therapeutic consequences of these indicators with precision. An intriguing result was that certain genotypes were linked to reduced ovarian reserve, indicating the dual impact of endometriosis on women's physical and reproductive health. The research indicated that women with specific genes are not only at an elevated risk of developing endometriosis but may also encounter difficulties in conceiving.

Table 5-8 offers significant evidence for genes that demonstrate functional variation in hormonal control affecting ovulation and embryo implantation efficiency related to infertility. From a clinical standpoint, these observations possess significant significance.

The genomic results align with the clinical parameters of the patients, as seen in Table 8, supporting the potential for genetic testing in the early diagnosis and risk stratification of women exhibiting endometriosis symptoms. The potential for personalised medicine, considering genetic susceptibility, is extensive, as individualised treatment approaches based on genetic profiles may enhance therapeutic efficacy and patient satisfaction.

These data clearly indicate that heredity plays a significant role in endometriosis and infertility; nonetheless, it is essential to evaluate the intricate interplay among genetics, the environment, and lifestyle. As illustrated in Tables 9 to 12, external environmental factors such as endocrine disruptors, together with lifestyle choices including food and exercise, may collectively impact gene expression that mitigates the potential onset of endometriosis. This multifactorial approach is directly associated with contemporary beliefs concerning the pathophysiology of the ailment; thus, comprehensive treatment strategies are necessary.

Table 13 delineates future research directions by emphasising the necessity for longitudinal studies to evaluate genetic variability in relation to clinical outcomes, aiming to infer causation across time [19], [20]. Comprehending these factors will be crucial for the prevention and management of endometriosis.

Endometriosis is a severe, complex, and multifactorial dysfunction that is characterized by ectopic endometrial tissue outside the uterus, often resulting in excruciating pain and infertility. With the advances in genomic research, it has become possible to understand the genesis of an individual's endometriosis and how it affects fertility outcomes. These investigations give credence to the role of genetic predispositions in the etiology of endometriosis, suggesting that certain genetic variants not only predispose individuals to the disease but also affect their fertility prowess [11], [12], [13].

There are single nucleotide polymorphisms (SNPs), the presence of which has been related to increased risk of endometriosis development. Genetic variations affecting key genes concerned with inflammation and hormonal circuitries, as well as angiogenesis, have been implicated. For instance, SNPs within the VEGF gene were described as associated with increased angiogenic activity, providing a possible explanation of how ectopic tissues may develop and survive. Furthermore, polymorphisms in cytokine genes such as IL-1 and TNF-α have been correlated with inflammatory microenvironment characteristic of endometriosis [14], [15], [16]. These inflammatory profiles are instrumental in the disease's pathophysiology, forming a vicious cycle that worsens the pain and can be detrimental for fertility[17].

Clinical ramifications stem from the complex interplay between endometriosis and infertility. There is evidence to show that women with endometriosis may have decreased ovarian reserve and altered reproductive hormone levels. In addition, genetic factors may influence the severity of the disease and the concomitant infertility with which it is associated. For example, the presence of certain alleles may predispose the individual to the more severe/subfertile form of the disease, compromising their chances of conception by natural or assisted means. Therefore, if genetic markers could be identified that are associated with both endometriosis and its resultant infertility, it would promote the development of personalized treatment avenues, allowing for targeted treatment based on the individual's genetic profile [18], [19].

Furthermore, the genetic grounds for endometriosis entail no simple susceptibility to the disease; entwined are environmental, lifestyle, and general reproductive health. This interaction implies the necessity for a complete treatment modality, encompassing lifestyle programs or environmentally benign ways aiming to alter some extent of risk genetically [20].

5. Conclusion

The ongoing investigation into the genetic underpinnings of endometriosis and its correlation with infertility underscores significant progress in the comprehension and

treatment of this disorder. The comprehension of the genetic foundation enables the prediction of outcomes and the formulation of management strategies depending on the patient's inputs. Essentially, it can entirely transform management practices by genetic application, enhancing the quality of life and reproductive outcomes for women, with endometriosis as the primary objective. Future research should investigate these genetic relationships more thoroughly to facilitate novel therapeutic interventions and assistance for affected individuals.

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