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Joint Interaction of Polymorphisms of The Nos3, Sod2, Edn1, Il1b, And Il6 Genes in Endometriosis in Women with Infertility

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Abstract: Endometriosis is one of the leading causes of female infertility and is characterized by a complex polygenic and systemic pathogenesis, including impaired endothelial function, oxidative homeostasis, and chronic inflammation. It was established that the studied polymorphisms form a unified pathogenetic network with a synergistic effect on microcirculation, inflammation, and angiogenesis. The highest risk of developing endometriosis and infertility is associated with the triad combinations NOS3C–SOD2Val–IL6C and EDN1Asn–IL1BC–IL6C. In primary infertility, the endothelial-oxidative phenotype predominates, while in secondary infertility, the inflammatory-fibrous phenotype predominates. The obtained data confirm the significance of gene-gene interactions in the pathogenesis of endometriosis and substantiate the prospects for personalized prognosis and therapy.

Keywords: Endometriosis; infertility; gene-gene interactions; oxidative stress; endothelial dysfunction; inflammation; angiogenesis; personalized medicine.

Introduction: Endometriosis is a chronic estrogen-dependent disease of a systemic immuno-inflammatory nature, in which pathological implantation and persistence of endometrial tissue outside the uterine cavity are accompanied by disturbances in angiogenesis, endothelial function, oxidative stress, and cytokine regulation [8, 18]. According to large epidemiological studies, endometriosis is diagnosed in 6–10% of women of reproductive age and in up to 30–50% of patients with infertility, highlighting its significant role in the structure of reproductive losses [1, 2]. Modern concepts of endometriosis pathogenesis consider the disease as the result of a complex interaction of genetic, epigenetic, and environmental factors, manifested through systemic disorders of immune response and microcirculation [6, 7]. Particular importance is attributed to endothelial dysfunction, which contributes to pathological angiogenesis and the survival of endometriotic heterotopias. In this context, the endothelial nitric oxide synthase gene (NOS3) is regarded as a key regulator of vascular tone and angiogenesis, and its functional polymorphisms are associated with impaired nitric oxide production, increased hypoxia, and progression of endometriosis-associated inflammation [9, 12]. Oxidative stress plays a significant role in the pathogenesis of endometriosis, developing against the background of an imbalance between pro-oxidant and antioxidant systems. The mitochondrial enzyme superoxide dismutase type 2 (SOD2) ensures neutralization of reactive oxygen species, while the Val16Ala polymorphism is associated with altered antioxidant activity and increased tissue vulnerability to inflammatory damage [11, 15]. Enhanced oxidative stress, in turn, potentiates the expression of pro-inflammatory cytokines and growth

factors, forming a vicious circle of inflammation and angiogenesis. The endothelin-1 gene (EDN1), a potent vasoconstrictor and mediator of fibrosis, is also involved in the pathogenesis of endometriosis. Increased EDN1 expression promotes vascular spasm, tissue hypoxia, and activation of fibrotic processes in the endometrium and myometrium, which is of particular importance in the development of secondary infertility [13, 14]. Key mediators of chronic inflammation in endometriosis are the cytokines interleukin-1β (IL1B) and interleukin-6 (IL6). Elevated levels of IL1B and IL6 in the peritoneal fluid and blood serum of patients with endometriosis are associated with macrophage activation, impaired endometrial receptivity, and reduced implantation potential [10, 16]. Polymorphic variants of the IL1B and IL6 genes affect cytokine expression levels and the intensity of the inflammatory response, determining individual susceptibility to disease development and progression. In recent years, increasing attention has been paid not to the isolated effects of individual genetic markers, but to their combined interaction. Gene–gene (epistatic) effects are capable of amplifying pathological cascades, forming various clinical and reproductive phenotypes of endometriosis [17]. However, data on the joint interaction of polymorphisms in the NOS3, SOD2, EDN1, IL1B, and IL6 genes in endometriosis in women with infertility remain fragmented and insufficiently systematized [1–5, 6–18]. Thus, the study of complex gene–gene interactions among vascular, oxidative, and inflammatory regulators appears to be a promising direction for deepening the understanding of endometriosis pathogenesis and for developing personalized approaches to predicting disease course and treatment efficacy.

Aim of the study

To assess the contribution of the joint interaction of polymorphisms in the NOS3, SOD2, EDN1, IL1B, and IL6 genes to the development of endometriosis in women with infertility and their association with clinical phenotypes of the disease.

METHODS

To achieve a more comprehensive understanding of the mechanisms determining infertility in 93 women with endometriosis (main group), special interest was directed toward clarifying the role of molecular-genetic disturbances in the pathogenesis of this disease, specifically the C786T polymorphism in the NOS3 gene, Lys198Asn polymorphism in the EDN1 gene, Ala16Val polymorphism in the SOD2 gene, T31C polymorphism in the IL1B gene, and C-174G polymorphism in the IL6 gene, since these genes ensure the maintenance of tissue homeostasis and are expected to respond to heterotopically displaced endometrial tissue. An analysis of the frequency of molecular-genetic abnormalities was performed in women with endometriosis and primary infertility (n = 52) and secondary infertility (n = 41). The molecular-genetic part of the study was carried out at the Republican Specialized Scientific and Practical Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan, Department of Molecular Medicine and Cellular Technologies (Head: Prof. Karimov Kh.Ya.). The following polymorphisms were investigated: C786T in the NOS3 gene, Lys198Asn in the EDN1 gene, Ala16Val in the SOD2 gene, T31C in the IL1B gene, and C-174G in the IL6 gene. These loci were analyzed using quantitative PCR with the use of “Gene Expression Assessment Kits for NOS3, SOD2, EDN1, IL1B, and IL6” (Inogene, Saint Petersburg, Russia). DNA extraction from blood plasma and polymerase chain reaction analysis were performed using specific reagents and test systems from “Ampli Prime Ribo-prep” (Next Bio LLC, Russia). The concentration of the obtained nucleic acid preparations was determined spectrophotometrically using a NanoDrop-2000 device (NanoDrop Technologies, USA). Mutation identification and characterization were carried out using a Corbett Research system PCR amplifier (Australia) with test systems from Syntol LLC (Russia), based on the basic model provided by the manufacturer. Statistical processing of the obtained results, as well as assessment of significance and specificity levels, was performed using the statistical programs EpiCalc 2010 and Epicourse 2020 Version 1.02. The obtained data were recorded in tables according to the Hardy–Weinberg equilibrium.

RESULTS

The studied polymorphisms represent components of a unified pathogenetic network, in which each modulates the activity of key signaling cascades—NO-dependent, oxidative, and inflammatory. Gene–gene

interactions manifest as additive, synergistic, or compensatory effects on microcirculation, immune-inflammatory response, angiogenesis, and apoptosis, determining the severity of the inflammatory-hypoxic phenotype and, consequently, the clinical type of infertility.

As shown in the presented data (Table 1), the T allele remains the major allele in all groups; however, its proportion differs markedly between the control group and patients. In the main group of patients, a pronounced "enrichment" of the C variant is observed: C = 33.33%, T = 66.67%; the proportion of the T/T genotype decreases to 53.8%, while the frequency of C/T and C/C increases to 25.8% and 20.4%, respectively. This shifted structure indicates a possible association of C carriage (especially the C/C genotype) with the presence of endometriosis and reproductive dysfunction. In the subgroup of primary infertility associated with endometriosis, the proportion of C is maximal (39.4% versus 60.6% for T), and the C/C genotype reaches 25.0% with T/T at 46.2%. In contrast, in secondary infertility, the profile is closer to the control group: C = 25.6%, T = 74.4%; T/T = 63.4%, C/T = 22.0%, C/C = 14.6%. Risk and odds ratios indicate a pronounced association (RR = 3, OR = 4), which remains significant when conservative confidence intervals are applied.

Table 1

Distribution frequency of alleles and genotypes of the C786T polymorphism in the NOS3 gene in patient and control groups

Group	Allele frequency				Genotype distribution frequency					
	C		T		C/C		C/T		T/T	
	n	%	n	%	n	%	n	%	n	%
Main group (n = 93)	62	33,33	124	66,67	19	20,4	24	25,8	50	53,8
Primary infertility of endometriosis (n = 52)	41	39,4	63	60,6	13	25,0	15	28,8	24	46,2
Secondary infertility of endometriosis (n = 41)	21	25,6	61	74,4	6	14,6	9	22,0	26	63,4
Control group (n = 90)	20	11,1	160	88,9	5	5,6	10	11,1	75	83,3

A comparative analysis of the second subgroup and the control group demonstrated an association of the C allele and the homozygous C/C genotype of the C786T polymorphism in the NOS3 gene with the development of primary infertility ($\chi^2 = 2.40$; p = 0.01; OR = 2.6; 95% CI: 0.57–4.46). These findings indicate that the presence of the homozygous C/C genotype increases the risk of primary infertility in women with endometriosis by 1.7 times compared with secondary infertility (Table 2).

According to the obtained results, the frequencies of the Ala and Val alleles of the SOD2 gene polymorphism in the main group of patients were 55.0% and 45.0%, respectively; in the first subgroup, 54.8% and 45.2%; in the second subgroup, 54.9% and 45.1%; compared with 64.0% and 36.0% in the control group, respectively. The Ala/Ala genotype was identified in 34.4% of patients, the Ala/Val genotype in 40.6% of cases, and the Val/Val genotype in 25.0% of cases. In the control group, the Ala/Ala genotype was detected in 44.7% of individuals, the Ala/Val genotype in 38.8% of cases, and the Val/Val genotype in 16.5% of cases. Among women with endometriosis and primary infertility, the Ala/Ala genotype was observed in 34.5%, the Ala/Val genotype in 40.0%, and the Val/Val genotype in 25.5% of cases. In the group with secondary infertility, the Ala/Ala genotype was identified in 34.1% of women with endometriosis, the Ala/Val genotype in 41.5%, and the

Val/Val genotype in 24.4% of cases.

Table 2

Differences in the frequency of allelic and genotypic variants of the C786T polymorphism in the NOS3 gene depending on primary and secondary infertility among women with endometriosis

allele and genotype	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Primary infertility in endometriosis(n = 52)		Secondary infertility in endometriosis (n = 41)							
	n	%	n	%						
C	41	39,4	21	25,6	1,1	0,30	1,2	0,67 - 2,29	1,4	0,75 - 2,55
T	63	60,6	61	74,4	1,1	0,30	0,8	0,45 - 1,45	0,7	0,39 - 1,33
C/C	13	25,0	6	14,6	2,8	2,40	1,5	0,56 - 3,77	2,6	0,57 - 4,46
C/T	15	28,8	9	22,0	0,5	0,99	1,2	0,38 - 2,6	1,3	0,4 - 2,47
T/T	24	46,2	26	63,4	1,5	1,50	1,9	0,37 - 3,06	1,8	0,33 - 3,7

Genetic analysis revealed that in the main group of women with minimal forms of endometriosis (n = 93), the Lys allele of the Lys198Asn polymorphism in the EDN1 gene was detected with a frequency of 76.9%, while the Asn allele was observed in 23.1% of cases. The most prevalent genotype was Lys/Lys (62.4%), whereas the heterozygous Lys/Asn variant was identified in 29.0% of patients, and the homozygous Asn/Asn variant in 8.6%. In the control group (n = 90), the distribution differed slightly: the Lys allele predominated (84.4%), while Asn was less frequent (15.6%). The Lys/Lys genotype was observed in 71.1% of women, Lys/Asn in 26.7%, and Asn/Asn in only 2.2% of cases. Among women with primary infertility associated with endometriosis (n = 52), the Lys allele occurred significantly more frequently (84.6%) than in patients with secondary infertility (67.1%; p = 0.01). In the latter group, a statistically significant increase in the frequency of the Asn allele was observed (32.9% vs. 15.4%; χ^2 = 7.9; p = 0.01), suggesting a possible association of this variant with recurrent reproductive dysfunction (Table 3). Similar patterns were identified in genotype distribution. The frequency of the Lys/Lys genotype among women with primary infertility was 75.0%, whereas in secondary infertility it was only 46.3% (χ^2 = 8.0; p = 0.01). At the same time, the Lys/Asn genotype was more common in secondary infertility (41.5% vs. 19.2%; p = 0.03), and the proportion of the Asn/Asn genotype was slightly higher (12.2% vs. 5.8%), although this difference did not reach statistical significance (p = 0.30). Analysis of allele and genotype distributions among women with minimal forms of endometriosis also demonstrated that the frequency of the homozygous C/C variant was higher in patients (14.5% vs. 8.9% in controls), whereas the T/T genotype was more frequently detected in healthy individuals (58.9% vs. 40.6%).

Table 3

Differences in the frequency of allelic and genotypic variants of the Lys198Asn polymorphism in the EDN1 gene among the studied groups

allele and genotype	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
Lys	143	76,9	152	84,4	3,3	0,10	0,9	0,59-1,41	0,6	0,36 - 1,04
Asn	43	23,1	28	15,6	3,3	0,10	1,1	0,6-2,01	1,6	0,97 - 2,76
Lys/Lys	58	62,4	64	71,1	1,6	0,30	0,9	0,5-1,53	0,7	0,36 - 1,25
Lys/Asn	27	29,0	24	26,7	0,1	0,80	1,1	0,59-2	1,1	0,59 - 2,15
Asn/Asn	8	8,6	2	2,2	3,6	0,10	3,9	1,97-7,61	4,1	0,95 - 17,96

The heterozygous T/C variant, which was the most frequent among patients (44.9%), likely determines an intermediate level of IL-1β expression, providing a moderate but chronic inflammatory activity characteristic of minimal forms of endometriosis (Table 4). Comparison of subgroups of women with primary and secondary infertility revealed no significant differences in the distribution of alleles and genotypes of the T31C polymorphism in the IL1B gene ($p > 0.05$).

Table 4

Differences in the frequency of allelic and genotypic variants of the T31C polymorphism in the IL1B gene in patient groups

Allele and phenotype	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
T	87	63,0	135	75,0	5,3	0,03	0,8	0,52 - 1,37	0,6	0,35 - 0,92
C	51	37,0	45	25,0	5,3	0,03	1,2	0,75 - 1,9	1,8	1,09 - 2,84
T/T	28	40,6	53	58,9	5,2	0,03	0,7	0,34 - 1,41	0,5	0,25 - 0,9
T/C	31	44,9	29	32,2	2,7	0,20	1,4	0,7 - 2,77	1,7	0,9 - 3,27
C/C	10	14,5	8	8,9	1,2	0,30	1,6	0,67 - 3,99	1,7	0,65 - 4,63

The C allele frequency was virtually identical (36.9% and 37.0%, respectively). However, there was a trend toward a higher proportion of T/C heterozygotes in secondary infertility (51.9% versus 40.5%), which may indicate a role for this genotype in the persistence of the inflammatory process and reduced reproductive potential in recurrent infertility (Table 5).

Frequency distribution analysis showed (Table 6) that the C allele of the C-174G polymorphism in the IL6 gene was significantly more common in women with mild forms of endometriosis (31.9% versus 17.2% in the control group; $\chi^2 = 9.3$; $p = 0.01$). Moreover, the risk of developing the disease in carriers of this variant more than doubles (OR = 2.2; 95% CI 1.34–3.79).

At the same time, the G allele exhibited a protective effect (OR = 0.4; 95% CI 0.26–0.75). Significant differences were also observed in genotype frequencies: the homozygous C/C variant was found in 13.0% of patients and only 4.4% of healthy women ($p = 0.05$), heterozygous C/G in 37.7% versus 25.6%, and homozygous G/G in 49.3% versus 70.0% ($p = 0.01$). The C/G genotype was also more common in primary infertility (41.0% versus 33.3%).

Table 5

Differences in the frequency of allelic and genotypic variants of the T31C polymorphism in the IL1B gene depending on primary and secondary infertility among women with endometriosis.

Allele and genotype	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Primary infertility of endometriosis (n = 42)		Secondary infertility of endometriosis (n = 27)							
	n	%	n	%						
T	53	63,1	34	63,0	0,0	0,99	1,0	0,58 - 1,73	1,0	0,5 - 2,04
C	31	36,9	20	37,0	0,0	0,99	1,0	0,43 - 2,32	1,0	0,49 - 2,02
T/T	18	42,9	10	37,0	0,2	0,70	1,2	0,55 - 2,43	1,3	0,47 - 3,43
T/C	17	40,5	14	51,9	0,9	0,40	0,8	0,36 - 1,69	0,6	0,24 - 1,67
C/C	7	16,7	3	11,1	0,4	0,60	1,5	0,61 - 3,68	1,6	0,38 - 6,75

Table 6

Differences in the frequency of allelic and genotypic variants of the C-174G polymorphism in the IL6 gene across patient groups

Allele and genotype	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						

C	44	31,9	31	17,2	9,3	0,01	1,9	1,14-3,01	2,2	1,34-3,79
G	94	68,1	149	82,8	9,3	0,01	0,5	0,31-0,95	0,4	0,26-0,75
C/C	9	13,0	4	4,4	3,8	0,05	2,9	1,31-6,57	3,2	1-10,39
C/G	26	37,7	23	25,6	2,7	0,20	1,5	0,74-2,94	1,8	0,9-3,46
G/G	34	49,3	63	70,0	7,1	0,01	0,7	0,36-1,39	0,4	0,22-0,79

The obtained data on gene-gene interactions allow us to systematically demonstrate how combinations of polymorphisms influence the risk of "minor forms" of endometriosis and infertility (Table 7).

Table 7

Quantitative distribution and integrated assessment of gene-gene interactions in women with "minor forms" of endometriosis and infertility.

№	Combination of polymorphisms (genotype/allele)	Interaction type	ОГ, %	КГ, %	χ^2	p	RR	95 % CI (RR)	OR	95 % CI (OR)
1	NOS3*C* + *SOD2*Val	Oxidative-endothelial synergism	41,3	18,9	7,8	0,01	2,2	1,25–3,85	2,9	1,31–6,26
2	NOS3*C* + *IL6*C	Inflammatory-angiogenic axis	38,4	17,8	6,9	0,01	2,1	1,14–3,76	2,6	1,18–5,72
3	EDN1*Asn* + *IL1B*C	Endothelial-cytokine synergism	35,0	14,4	8,3	0,004	2,3	1,28–4,14	3,0	1,34–6,55
4	EDN1*Asn* + *IL6*C	Vasoconstriction + cytokine overexpression	33,8	13,3	8,0	0,005	2,2	1,23–3,99	2,9	1,31–6,24
5	IL1B*C* + *IL6*C	Proinflammatory cytokine cascade	40,6	19,0	7,6	0,01	2,1	1,19–3,68	2,8	1,28–6,07

6	NOS3*C* + *SOD2*Val + IL6*C	Complex vascular-inflammatory triad	28,9	9,0	9,7	0,002	2,6	1,34–5,04	3,8	1,46–9,81
7	EDN1*Asn* + *IL1B*C + IL6*C	Inflammatory fibrotic cluster	25,5	7,8	10,2	0,001	2,8	1,45–5,39	4,1	1,52–11,04
8	NOS3*C* + *EDN1*Asn	NO/ET-1 imbalance (vasospastic type)	32,0	14,4	6,2	0,013	2,0	1,12–3,67	2,5	1,12–5,56
9	SOD2*Val + IL6*C	Oxidative-cytokine cascade	36,2	18,8	5,9	0,02	1,9	1,08–3,36	2,3	1,05–5,09
10	NOS3*T + IL1B*T + IL6*G	Protective combination	12,5	27,8	6,7	0,01	0,45	0,22–0,90	0,4	0,18–0,82

As can be seen from the presented data, the most significant interactions were triadic combinations (NOS3C + SOD2Val + IL6*C and EDN1Asn + IL1BC + IL6*C), which have the highest relative risk (RR > 2.5) and a reliable significance level ($p \leq 0.01$). These combinations form two molecular patterns: the angiogenic-oxidative type (characteristic of primary infertility) and the inflammatory-fibrotic type (characteristic of secondary infertility).

These dual interactions (dyads) reflect local pathogenetic axes: NOS3 × SOD2 - endothelial-redox imbalance; EDN1 × IL1B / IL6 - inflammatory-angiogenic synergism; IL1B × IL6 - a key cytokine cascade of chronic inflammation.

The protective combination (NOS3T + IL1BT + IL6*G) indicates preservation of normal vascular and cytokine regulation and is associated with a low disease risk (OR = 0.4).

The -786T>C promoter variant of the NOS3 gene and the Lys198Asn codon substitution of the EDN1 gene act in the same vascular-endothelial pathway, but in opposite directions. The C allele of NOS3 reduces endothelial NO synthase expression and decreases NO production, which weakens vasodilation. The minor Asn variant of the EDN1 gene, conversely, increases the synthesis of endothelin-1 (ET-1), a potent vasoconstrictor.

Combined carriage of NOS3C + EDN1Asn creates an NO/ET-1 imbalance, leading to persistent vasospasm, endometrial hypoxia, and impaired angiogenesis. These processes create conditions for chronic ischemia, fibrosis, and implantation failure. This genotype combination is particularly common in women with secondary infertility, where the vascular-fibrosis mechanism of the disease is most pronounced.

The SOD2 and NOS3 genes are functionally linked through the regulation of redox homeostasis. The Val allele in the SOD2 gene reduces the efficiency of mitochondrial superoxide dismutase, increasing superoxide radical levels. In the presence of the C allele in NOS3, reactive oxygen species interact with residual NO, forming peroxynitrite, which has a cytotoxic effect. The SOD2Val + NOS3C combination is associated with increased oxidative stress and endothelial damage, leading to structural changes in microvessels and increasing endometrial sensitivity to inflammation.

This constellation of polymorphisms is more often observed in primary infertility, where microcirculation disorders manifest themselves in the early stages of implantation.

Type of interaction: synergistic enhancement of free-radical damage (oxidative-endothelial stress).

The endothelin system is closely linked to the cytokine cascade, as demonstrated by the interaction of EDN1*Asn polymorphisms with IL6*C and IL1B*C variants. Increased expression of ET-1 (in Asn carriers) stimulates the production of IL-6 and IL-1β in endothelial and stromal cells of the endometrium.

In turn, the C-174G (IL6) and T31C (IL1B) alleles, which increase cytokine synthesis, enhance EDN1 expression, creating a vicious cycle of endothelin-cytokine inflammation. This interaction enhances angiogenesis, edema, and proliferation of the ectopic endometrium, creating conditions for disease progression and the transition of mild forms to more advanced clinical stages. The combination of EDN1Asn + IL6C or IL1B*C is most often associated with secondary infertility, accompanied by recurrent inflammation and fibrosis of the uterine endometrium.

The IL1B and IL6 genes encode cytokines that act in a single inflammatory cascade. The C allele of the T31C IL1B polymorphism increases IL-1β production, initiating activation of the transcription factor NF-κB, which induces IL6 expression. The C allele of the IL6 promoter (C–174G) is also associated with enhanced transcription, causing a secondary increase in IL-6.

The IL1BC + IL6C combination produces a hyperproductive inflammatory phenotype characterized by increased levels of proinflammatory mediators (IL-1β, IL-6, TNF-α), decreased apoptosis, and activated angiogenesis and tissue fibrosis. This genotypic background is more often observed in secondary infertility, where inflammatory and destructive processes become dominant.

In patients with endometriosis, the formation of genetic risk clusters, including three or more interconnected polymorphisms, has been observed.

The most unfavorable combination is NOS3C / SOD2Val / IL6*C, which leads to decreased endothelial NO synthesis, accumulation of reactive oxygen species, and increased cytokine-induced inflammation. This triad of genetic alterations shapes the pathogenetic profile of primary infertility, associated with impaired angiogenesis and implantation.

In turn, the EDN1Asn / IL1BC / IL6*C combination is characteristic of secondary infertility and reflects a chronic inflammatory-fibrous phenotype of the endometrium with activation of endothelin-dependent angiogenesis and an excessive cytokine response (Table 8).

Table 8

Summary diagram of gene-gene interactions in mild forms of endometriosis.

Interaction	Biological effects	Clinical association
NOS3 × SOD2	Decreased NO + oxidative stress → endothelial damage	Primary infertility
NOS3 × EDN1	NO/ET-1 imbalance → vasospasm, hypoxia	Secondary infertility
EDN1 × IL6/IL1B	Endothelin-induced inflammation and fibrosis	Secondary infertility
IL1B × IL6	Hyperproduction of cytokines → chronic inflammation	Secondary infertility
NOS3 × IL6	Impaired angiogenesis + inflammation →	Primary infertility

	implantation defect	

Thus, gene-gene interactions in mild forms of endometriosis are realized through the synergism of vascular-inflammatory and oxidative disturbances. In primary infertility, the NOS3-SOD2-IL6 complex is the dominant one, causing endothelial-angiogenic and redox dysfunction. In secondary infertility, the EDN1-IL1B-IL6 axis, associated with persistent inflammation and endometrial fibrosis, predominates.

CONCLUSIONS

Women with mild forms of endometriosis and infertility exhibit a complex of genetic features reflecting common pathogenetic links in the disease: decreased nitric oxide synthesis (NOS3) indicates the development of endothelial dysfunction; increased oxidative stress (SOD2) indicates tissue damage; increased vasoconstriction and hypoxia (EDN1) indicate the development of fibrosis and inflammation; Overexpression of IL-1β and IL-6 (IL1B, IL6) leads to chronic inflammation and impaired implantation. The combination of these changes forms the molecular genetic profile of endometriosis, characterized by dysregulation of the vascular-immune and antioxidant balance. A combination of unfavorable genetic variants (NOS3 -786C, SOD2 Val, EDN1 Asn, IL1B C, and IL6 C) determines a high risk of developing endometriosis and associated infertility. In primary infertility, the NOS3-SOD2-IL6 complex is the dominant one, causing endothelial-angiogenic and redox dysfunction. In secondary infertility, the EDN1-IL1B-IL6 axis predominates, associated with persistent inflammation and endometrial fibrosis.

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