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# Role of *WNT4*, *HOXA10* and *TWIST1* genes in the pathogenesis of external genital endometriosis and uterine leiomyoma

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***BACKGROUND:*** Uterine leiomyoma and endometriosis are the most common gynecological diseases in women of reproductive age. A number of data indicate that there are common elements in the pathogenesis of these hyperproliferative conditions. This article is devoted to comparative analysis of the role of the *WNT4*, *HOXA10* and *TWIST1* genes in the development of uterine leiomyoma and external genital endometriosis.

***AIM:*** The aim of this study was to evaluate the frequency of polymorphic variants rs7521902 (*WNT4*) and rs4721745 (*TWIST1*) in patients with uterine leiomyoma, external genital endometriosis and in the comparison group; to determine the frequency of rare allelic variants of the *HOXA10* gene in patients with external genital endometriosis; and to study the expression of these genes in the endometrium in patients with uterine leiomyoma, EGE and in the comparison group.

***MATERIALS AND METHODS:*** The polymorphic variants of the WNT4 and TWIST1 genes were studied by real-time PCR in patients with external genital endometriosis, uterine leiomyoma and in the comparison group. In patients with EGE and women in the comparison group, the second exon of the *HOXA10* gene was sequenced. Real-time PCR with reverse transcription analysis of the expression of the *WNT4*, *TWIST1* and *HOXA10* genes in endometrial samples from the patients of the study groups was performed.

***RESULTS:*** The frequencies of polymorphic variants rs7521902 (*WNT4*) and rs4721745 (*TWIST1*) in patients with uterine leiomyoma, external genital endometriosis and in the comparison group did not differ significantly. Minor alleles of the *HOXA10* gene were not identified in patients with external genital endometriosis. Expression of the *WNT4* gene in the endometrium of patients with external genital endometriosis was independent of menstrual cycle phase and was reduced by 1.9 times compared to the endometrium of women with uterine leiomyoma. Expression of the *HOXA10* gene in the endometrium of endometriosis patients on days 20-23 of the menstrual cycle was significantly reduced compared to the women in the comparison group. Expression of the *TWIST1* gene was not altered in the endometrium of patients with uterine leiomyoma and external genital endometriosis.

***CONCLUSIONS:*** We did not identify associations of the studied polymorphic variants of the *WNT4* and *TWIST* genes and minor variants of the *HOXA10* gene with uterine leiomyoma and external genital endometriosis. The expression of the *WNT4* and *HOXA10* genes is reduced in the endometrium in patients with external genital endometriosis, but not in women with uterine leiomyoma. Changes in expression patterns of the studied genes in the endometrium differ significantly in these two diseases.

**Keywords:** endometriosis; uterine leiomyoma; *WNT4*; *HOXA10*; *TWIST1*; gene polymorphism; expression.

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# Анализ роли генов *WNT4*, *HOXA10* и *TWIST1* в патогенезе наружного генитального эндометриоза и миомы матки

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***Обоснование.*** Миома матки и эндометриоз — наиболее распространенные гинекологические заболевания у женщин репродуктивного возраста. Ряд данных свидетельствует о наличии общих элементов в патогенезе этих гиперпролиферативных состояний. Работа посвящена сравнительному анализу роли генов *WNT4*, *HOXA10* и *TWIST1* в развитии миомы матки и наружного генитального эндометриоза.

***Цель*** — оценить частоту полиморфных вариантов rs7521902 (ген *WNT4*) и rs4721745 (ген *TWIST1*) у пациенток с миомой матки, наружным генитальным эндометриозом и в группе сравнения; определить частоту редких аллельных вариантов гена *HOXA10* у пациенток с наружным генитальным эндометриозом; изучить особенности экспрессии данных генов в эндометрии у пациенток с миомой матки, наружным генитальным эндометриозом и в группе сравнения.

***Материалы и методы.*** У пациенток с наружным генитальным эндометриозом, миомой матки и в группе сравнения методом полимеразной цепной реакции в реальном времени были исследованы полиморфные варианты генов *WNT4* и *TWIST1*. У пациенток с наружным генитальным эндометриозом и женщин группы сравнения было проведено секвенирование экзона 2 гена *HOXA10*. Методом полимеразной цепной реакции в реальном времени с обратной транскрипцией проанализирована экспрессия генов *WNT4*, *TWIST1* и *HOXA10* в образцах эндометрия пациенток исследуемых групп.

***Результаты.*** Частота полиморфных вариантов rs7521902 (ген *WNT4*) и rs4721745 (ген *TWIST1*) у пациенток с миомой матки, наружным генитальным эндометриозом и в группе сравнения достоверно не отличалась. Минорные аллели *HOXA10* не были выявлены у больных наружным генитальным эндометриозом. Экспрессия гена *WNT4* в эндометрии пациенток с наружным генитальным эндометриозом не зависит от фазы менструального цикла и снижена в 1,9 раза по сравнению с эндометрием женщин с миомой матки. Экспрессия гена *HOXA10* в эндометрии пациенток с наружным генитальным эндометриозом на 20–23-й день менструального цикла достоверно снижена по сравнению с женщинами группы сравнения. Экспрессия гена *TWIST1* не изменена в эндометрии пациенток с миомой матки и наружным генитальным эндометриозом.

***Заключение.*** Мы не выявили ассоциации исследованных полиморфных вариантов генов *WNT4* и *TWIST* и минорных вариантов гена *HOXA10* с миомой матки и наружным генитальным эндометриозом. Экспрессия генов *WNT4* и *HOXA10* снижена в эндометрии у пациенток с наружным генитальным эндометриозом, но не у женщин с миомой матки. Изменения в характере экспрессии в эндометрии изученных генов достоверно отличаются при этих двух заболеваниях.

**Ключевые слова:** эндометриоз; миома матки; *WNT4*; *HOXA10*; *TWIST1*; полиморфизм генов; экспрессия.

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# BACKGROUND

External genital endometriosis (EGE) and uterine leiomyoma (UL) are considered the most common proliferative diseases in women of reproductive age. EGE and UL are the major causes of pelvic pain, infertility is a typical complication of endometriosis, and fertility is often reduced in patients with UL. These processes are characterized by a high relapse rate and a familial predisposition to the disease development. Several researchers suggest that some aspects of etiology and pathogenesis may be common in the development of both leiomyoma and EGE [1–3].

Studies performed by the Genome-wide association study (GWAS) method, including meta-analysis, have revealed an association of polymorphic variants of the *WNT4* and *HOXA10* genes and some other genes with the development of these hyperproliferative processes [4, 5].

The most popular hypotheses for the occurrence of endometriotic foci are the theories of retrograde menstruation, celomic metaplasia, and embryonic remnants [6]. None of them have been proven, and the exact causes of the ectopic growth of the endometrial tissue remain unknown. According to modern concepts, gene mutations play the most significant role in the development of UL, primarily somatic mutations of the *MED12* gene, detected in 50%–70% of UL nodules [7]. However, causes of leiomyomas without mutations, as well as of multiple and recurrent leiomyomas, are still unknown.

Recently, most researchers recognize the leading role of stem cells in the formation of endometriotic foci [8, 9]. The major discussions are held about the origin of these stem cells (eutopic endometrium, bone marrow, and tissue stem cells) and about the direct causes of ectopic growth and differentiation. Several researchers also indicate the existence of stem cells in UL nodules [10]. Thus, theoretically, both UL and EGE can be considered results of the abnormal differentiation of stem cells, leading to the formation of ectopic foci of endometrioid tissue (with inclusions of muscle, nervous, and connective tissue elements) in endometriosis and UL nodules consisting (in leiomyoma) mainly of myocytes and fibroblasts with the inclusion of cartilage cells and the possible presence of the nervous tissue elements.

**This work aimed** to analyze the frequency of specific polymorphic and minor variants and comparatively analyze the expression in the endometrium of the *WNT4, HOXA10,* and *TWIST1* genes involved in the formation of the female reproductive system and the normal functioning of the endometrium as well as in maintaining stem cell properties in patients in the EGE group, UL group, and comparison group.

# MATERIALS AND METHODS

## Study sample

The EGE group consisted of 61 women aged 25–40 (mean age 32.5 ± 7.5) years with grade I–IV EGE according to classification of the American Fertility Society in 1996. The exclusion criterion was the presence of UL or polycystic ovary syndrome. In all patients, the diagnosis was established during diagnostic laparoscopy at the D.O. Ott Research Institute of Obstetrics, Gynecology, and Reproductology and confirmed by the histological examination results. Additional criteria for inclusion in the group of generalized/recurrent/familial forms of EGE for the study of polymorphic variants of the *WNT4, HOXA10*, and *TWIST1* genes were an early onset of the disease (up to age 25 years), presence of endometriosis in first-degree relatives, recurrent course, and/or a generalized form of the disease.

The UL group consisted of 99 women who underwent treatment (myomectomy or hysterectomy) at the same institute, and their mean age was 38.2 ± 6.8 years. In all patients, the diagnosis was confirmed by histological examination. The exclusion criterion was the presence of endometriosis and/or polycystic ovary syndrome. To assess the population frequencies of alleles, information from the 1000 Genomes Project database (https://www.internationalgenome.org) was used. The characteristics of the two control groups were examined. Control group 1 consisted of 24 healthy women who underwent examination within the framework of pregravid preparation (mean age, 26.8 ± 3 years). All patients from control group 1 underwent ultrasound examination of the pelvic organs and biochemical blood test (including glucose tolerance test and lipid profile). In phase 1 of the menstrual cycle, the levels of follicle-stimulating and luteinizing hormones, prolactin, and estradiol were determined, and in phase 2, progesterone level was determined. Control group 2 consisted of 19 patients without endometriosis and UL (mean age, 31.4 ± 4.2 years), and they underwent diagnostic laparoscopy for complaints of pelvic pain and/or idiopathic infertility and were prescribed with a diagnostic laparoscopy after a standard examination, but the diagnosis of endometriosis was ruled out during the revision of the pelvic organs.

To analyze the polymorphic variants of the *WNT4*, *HOXA10,* and *TWIST1* genes, DNA samples from peripheral blood lymphocytes were examined, which were obtained from patients with generalized/recurrent/familial forms of endometriosis (43 patients in total), patients with single and multiple ULs [96 women in total, including 55 patients with single and 41 with multiple (≥3) UL nodules], and participants of the control group (42 women), with a total of 182 samples.

The expressions of the *WNT4, HOXA10*, and *TWIST1* genes were analyzed by real-time reverse transcription-polymerase

**Table 1.** Endometrial samples studied and distribution by days of the menstrual cycle

| Group | 7–12 dmc | 14–17 dmc | 18–23 dmc |
|---|---|---|---|
| Patients with uterine leiomyoma | 15 | – | – |
| Control group 2 | – | – | 6 |
| Patients with external genital endometriosis | 5 | 7 | 5 |

*Note*: dmc, day of the menstrual cycle.

chain reaction (RT-PCR) in endometrial samples obtained during surgery (diagnostic laparoscopy or myomectomy) at the aforementioned institute. All patients underwent laparoscopy and hysteroscopy. A total of 15 endometrium samples from the UL group, 17 samples from the EGE group, and 6 samples from control group 2 were examined. The distribution of patients by days of the menstrual cycle (dmc) is presented in Table 1.

The study was approved by the ethical committee of the D.O. Ott Research Institute of Obstetrics, Gynecology, and Reproductology (Minutes No. 104 dated 10/23/2020). All patients signed an informed consent for tissue examination and processing of personal data, including data from medical records.

## Materials and methods

DNA from peripheral blood leukocytes were isolated by the standard phenol–chloroform method. Polymorphic variants rs7521902 (*WNT4* gene) and rs4721745 (*TWIST1* gene) were tested by real-time PCR. The corresponding sets of probes and primers TaqMan® single-nucleotide polymorphisms (SNP) Genotyping Assays and the TaqMan Universal MasterMix II reaction mixture (Thermo Fisher Scientific, USA) were used. Each sample was analyzed in duplicate. For the *HOXA10* gene, the sequencing of gene exon 2 was performed, since mutations and minor variants in patients with endometriosis are located in this exon [11]. A PCR product containing the sequence of exon 2 of the *HOXA10* gene was obtained using the oligonucleotides described earlier [11]. Sanger sequencing was performed using the BigDye Terminator Cycle Sequencing Kitv 3.1 on an ABI 3130 Genetic Analyzer (Applied Biosystems, MA, USA).

The expressions of the *WNT4, HOXA10*, and *TWIST1* genes in endometrial samples were studied by real-time RT-PCR. The endometrial material obtained during laparoscopy and hysteroscopy was immediately placed in the conserving agent RNA-later (Thermo Fisher Scientific). RNA was isolated using PureLink RNA Mini Kit columns (Thermo Fisher Scientific) according to the manufacturer's protocol.

Reverse transcription of RNA was performed using the High-Capacity Reverse Transcription Kit (Thermo Fisher Scientific) in accordance with the manufacturer's instructions. Real-time PCR was performed on a Real-Time PCR System 7500 device (Applied Biosystems) using consumables manufactured by Thermo Fisher Scientific's TaqMan Gene Expression Assays, namely, Hs01573505_m1 for the *WNT4* gene, Hs00361186_m1 for the *TWIST1* gene, and Hs00172012_m1 for the *HOXA10* gene. For control, a previously validated kit was used for the *MRPL19* gene (Hs00608519_m1).

Threshold cycles and relative expression levels were calculated with the Expression Suite Software version 1.1 (Thermo Fisher Scientific) using the $2^{-\Delta\Delta Ct}$ method (Livak method). Statistical processing of the results was performed using the GraphPad Prism 6.0 package (GraphPad Software Inc., La Jolla, CA). The significance of differences between quantitative criteria was assessed using the Mann–Whitney *U*-test. Differences between indicators were considered significant at $p \le 0.05$. Statistical processing of data on the analysis of genotype frequencies was performed using standard approaches applied in population genetic studies using the GraphPad Prism 6 software package. Arbitrary contingency tables were analyzed using Pearson's $\chi^2$ test. Differences were considered significant at $p < 0.05$.

# RESULTS

Two polymorphic variants were genotyped by real-time PCR, namely, rs7521902 [*WNT4* gene, chr1:22164231 (GRCh38.p12), A>C substitution in the distal promoter] and rs4721745 [*TWIST1* gene, chr7:19113889 (GRCh38.p12), C>G substitution in the 3'-non-coding region] in the group with presumably hereditary forms of EGE, groups with single and multiple ULs, and control groups. The results are presented in Tables 2 and 3.

We did not found minor variants in exon 2 of the *HOXA10* gene in our patients with generalized/recurrent/familial forms of EGE. The frequency of the identified polymorphic variants rs34957925 and rs560654095 did not differ in the EGE group, UL group, and control groups (Table 4).

We compared the expressions of the studied genes in the endometrium. The expression of the *TWIST1* gene did not differ significantly in any of the study groups and did not change in patients with endometriosis depending on the phase of the menstrual cycle. Significant differences were found in the level of *WNT4* gene expression in the endometrium between the UL and EGE groups in both the general group and taking into account the dmc (Figure).

**Table 2.** Frequencies of alleles and genotypes for polymorphic variants rs7521902 and rs4721745 in the examined groups

| Gene, polymorphic site | Group | Minor allele frequency | Genotype frequency |
|---|---|---|---|
| *WNT4* (rs7521902) | | | CC/CA/AA |
| | Endometriosis | A = 0.24 | 25/12/4 |
| | Uterine leiomyoma (single) | A = 0.31 | 22/25/3 |
| | Uterine leiomyoma (multiple) | A = 0.3 | 21/14/5 |
| | Control group 1 | A = 0.25 | 14/8/2 |
| | Control group 2 | A = 0.53 | 4/10/5 |
| | 1000 Genomes, Europeans | A = 0.21 | – |
| *TWIST1* (rs4721745) | | | CC/CG/GG |
| | Endometriosis | G = 0.15 | 30/10/1 |
| | Uterine leiomyoma (single) | G = 0.11 | 21/6/0 |
| | Uterine leiomyoma (multiple) | G = 0.19 | 23/9/2 |
| | Control group 1 | G = 0.14 | 17/6/1 |
| | Control group 2 | G = 0.26 | 13/6/0 |
| | 1000 Genomes, Europeans | G = 0.126 | – |

**Table 3.** *P* values when comparing genotypes for the rs7521902 polymorphic variant of the *WNT4* gene among the studied groups

| rs7521902 | EGE | Single UL | Multiple ULs | Control group 1 | Control group 2 |
|---|---|---|---|---|---|
| EGE | 1 | $p = 0.132$ | $p = 0.741$ | $p = 0.937$ | **$p = 0.014$*** |
| Single uterine leiomyoma | – | 1 | $p = 0.280$ | $p = 0.402$ | **$p = 0.033$*** |
| Multiple uterine leiomyomas | – | – | 1 | $p = 0.843$ | $p = 0.066$ |
| Comparisons with group 1 | – | – | – | 1 | **$p = 0.038$*** |
| Comparisons with group 2 | – | – | – | – | 1 |

*Note*. EGE, external genital endometriosis; UL, uterine leiomyoma.

**Table 4.** Frequency of polymorphic variants rs34957925 and rs560654095 of the *HOXA10* gene in the external genital endometriosis group and control group

| Polymorphism | Endometriosis ($n = 41$) | | Control group 1 ($n = 24$) | | Control group 2 ($n = 19$) | | $p$ |
|---|---|---|---|---|---|---|---|
| rs34957925 | 3 | 7.3% | 2 | 8% | 1 | 5.3% | >0.05 |
| rs560654095 | 5 | 12% | 2 | 8% | 3 | 15% | >0.05 |

The expression of the *WNT4* gene was on average 1.9 times higher in the UL group than in the EGE group ($p = 0.0155$). When comparing samples obtained at 7–12 dmc, these differences were also significant ($p = 0.0456$). The *WNT4* expression in the endometriosis group did not differ at the 7–12 and 14–17 dmc, and a tendency to an approximately two-fold decrease was noted in the expression of this gene by 20–23 dmc, but these differences were not significant. No differences were noted in the level of *WNT4* expression in the endometrium of the control group and EGE group at 20–23 dmc.

Moreover, no significant differences were found in the level of *HOXA10* gene expression in the endometrium between the UL group and EGE group. In the endometrium of the endometriosis group, the expression of this gene gradually decreased during the transition from dmc 7–12 to 14–17 and 20–23; in the secretory phase of the menstrual cycle, at dmc 20–23, the expression of this gene in patients in the endometriosis group was significantly lower than in the control group 2 ($p = 0.0317$).

## DISCUSSION

The frequency of polymorphic variants and their expression in the eutopic endometrium were investigated for three genes, namely, *WNT4*, *TWIST1*, and *HOXA10*. Proteins

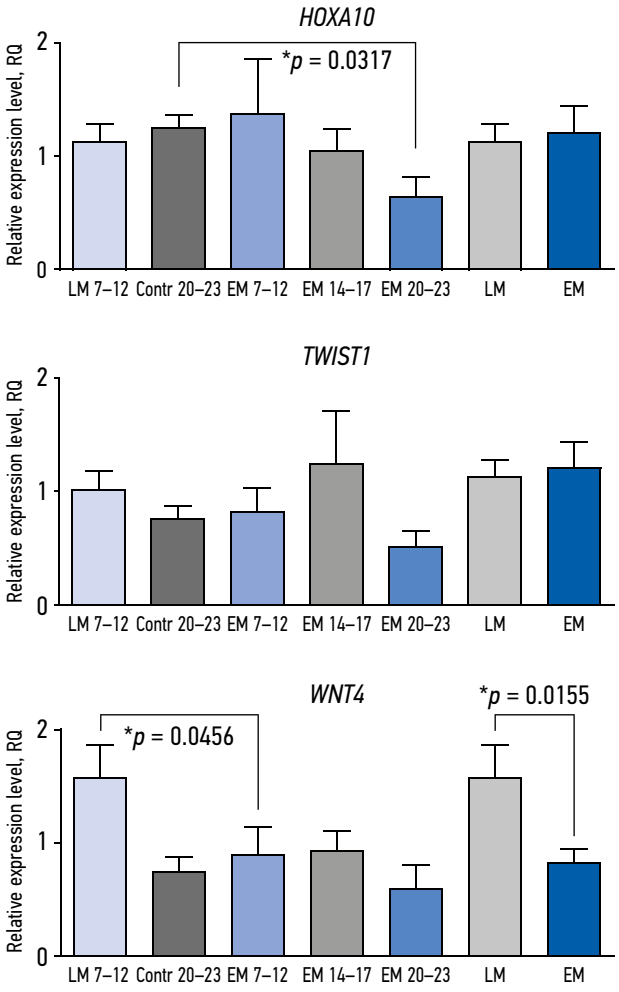


**Figure.** Expression of the *HOXA10*, *TWIST1*, and *WNT4* genes in the endometrium in the external genital endometriosis group, uterine leiomyoma group, and control group 2 by days of the menstrual cycle: LM, uterine leiomyoma; EM, external genital endometriosis; contr, control group 2. The figures correspond to the days of the menstrual cycle

WNT4 (one of the ligands of the Wnt signaling cascade) and homeobox protein A10 (HOX10A, transcription factor) represent key factors required for the normal development of the female reproductive system in embryogenesis [12, 13] and postnatal period; they are also required for the normal decidualization of the endometrium and implantation of embryo [14, 15]. Several studies conducted in various ethnic groups, as well as a meta-analysis of GWAS data, have demonstrated that the 1p36 locus, and more specifically the rs7521902 polymorphic variant of the *WNT4* gene, is one of the most significant SNPs associated with the risk of EGE and UL [5, 16–18]. Another locus associated with the development of endometriosis according to the GWAS data is 7p13–p15, which contains the *HOXA10* gene [19]. The genes of the HOX family are highly conserved, and the *HOXA10* gene does not contain frequent SNPs. However, in some cases, in patients with endometriosis, rare allelic variants of this gene that are not represented in the control group can be identified. Most of these variants are localized in exon 2 of the *HOXA10* gene [11, 19]. In this study, we performed sequencing of exon 2 of the *HOXA10* gene in female patients with endometriosis and in patients of the control group to search for rare variants of this gene.

Several researchers have identified increased expression of the *TWIST1* gene in endometriosis of an ectopic endometrium. This protein serves as a marker of epithelial–mesenchymal transition and increased migration activity of cells [20]. Cells undergoing an epithelial–mesenchymal transition can acquire stem properties, and the mesenchymal status is apparently a condition for the restoration of pluripotency [21]. Thus, the expression of the *TWIST1* gene serves as a potential marker of the stemness of some cells present in the eutopic human endometrium [22], which, according to the modern concepts of the role of stem cells in the pathogenesis of endometriosis, may be significant in the disease development. The epithelial–mesenchymal transition was also considered to affect the implantation and invasiveness of endometrioid heterotopies [20]. In target organs (e.g., peritoneum), some of the cells may lose their epithelial properties; as a result, without an epithelial–mesothelial barrier, adhesion and invasion of endometrial cells (or stem cells) that have entered the abdominal cavity to the underlying peritoneal stroma and the formation of endometrioid foci are facilitated [23]. The expression of the *TWIST1* gene is also significantly increased in leiomyoma nodules compared with that in the myometrium [24]. In this study, the polymorphic site rs4721745 of the *TWIST1* gene was selected for the analysis because numerous studies have revealed that it is associated with the risk of endometrial cancer, which indicates the functional significance of this polymorphic variant [25].

We did not found any significant differences between the majority of the compared groups in terms of the frequencies of alleles and genotypes of the polymorphic loci investigated. However, the frequency of minor variants of the polymorphic locus rs7521902 (*WNT4* gene) did not differ significantly in the EGE group, UL group, and control group 1, while in control group 2, the frequency of the minor allele was two times higher and the genotypes A/A and A/C prevailed in this group. These differences were significant (Table 3). This polymorphic variant of the *WNT4* gene (A at position chr1:22164231 (GRCh38.p12) is apparently not associated with the risk of endometriosis, but may be associated with infertility and/or pelvic pain syndrome, although whether differences represent the study cannot be excluded in this sample.

In patients with generalized/recurrent/familial forms of EGE, we did not identify previously described minor variants in exon 2 of the *HOXA10* gene, and the frequency of polymorphic variants rs34957925 and rs560654095 did not differ from that in the comparison groups. Thus, according

to the results of our study, the rs7521902 (*WNT4* gene) and rs4721745 (*TWIST1* gene) variants in the sample analyzed are not associated with the development of EGE and UL, and minor allelic variants in exon 2 of the *HOXA10* gene in our sample are not associated with the development of severe, early, and hereditary forms of endometriosis.

Despite numerous GWAS confirmations of information on the supposed association of the 1p36 and 7p13p15 loci and the *WNT4* and *HOXA10* genes with the development of EGE and UL, many studies have not confirmed this association. For example, Italian authors did not reveal a relationship between EGE and allelic variants of the *WNT4* gene [26], and studies confirming the association of SNPs in the *HOXA10* gene with the development of this pathology were performed in Asia [11]. Possibly, the probability of the development of EGE and UL demonstrated weak association with the studied SNP, which can be identified only when analyzing very large samples.

In the comparison of the expression of the studied genes in the endometrium, the expression of the *WNT4* gene, at least in patients with endometriosis, did not depend on the phase of the menstrual cycle and was not different between the EGE group and control group. Its expression was on average 1.9 times higher in the UL group than in the EGE group ($p = 0.0155$); these differences were also significant when comparing samples taken at the same phase of the menstrual cycle. Data obtained in the present study corresponded mainly to the findings in other studies. Thus, Bui et al. [27] and Tulak et al. [28] revealed no change in the expression level in the endometrium of healthy women between the proliferative and secretory phases of the menstrual cycle. A study by Chinese authors reported an approximately two-fold decrease in the level of expression of this gene in the endometrium of patients with endometriosis [29]. Unfortunately, our sample did not allow making an unambiguous conclusion about whether the expression of the *WNT4* gene in the endometrium of the UL group changes in comparison with the control group, depending on the menstrual cycle phase, and this issue remains open.

The *HOXA10* gene encodes a conservative transcription factor that plays an important role in the formation of derivatives of the Müllerian ducts, including the uterus, and is also one of the generally accepted markers of endometrial receptivity [13]. Taylor et al. showed that in healthy women, the *HOXA10* gene is expressed in the endometrium in both the stroma and epithelial cells, while the level of its expression increases mainly in cells of the endometrial glands by the middle of the secretory phase (which approximately corresponds to the implantation window). Such an increase in expression does not occur in the endometrium of patients with endometriosis [30, 31]. This result was confirmed by other researchers [32]. According to our data, in endometriosis in the endometrium, there is a pronounced tendency to a decrease in the expression of the *HOX10A* group during the transition from 7–12 to 14–17 and then to 20–23 dmc, although these differences are not significant. In the comparison of the control group and EGE group at 20–23 dmc, a significant (approximately two-fold) decrease was found in the expression of this gene ($p = 0.0317$).

In some with patients UL, the expression of the *HOXA10* gene may be reduced. Thus, according to Rakov et al. [33], the *HOXA10* gene expression is reduced in patients with submucous leiomyomas in comparison with healthy women, even in the proliferative phase of the menstrual cycle. We did not reveal significant differences in the level of *HOXA10* gene expression in the endometrium on 7–12 dmc between patients with UL and EGE. Unfortunately, our sample did not allow us to study the expression level of this gene and its dynamics depending on the phase of the menstrual cycle in the control group; therefore, the issue of changing the expression of the *HOXA10* gene in patients with UL and EGE remains open.

Finally, the expression of the *TWIST1* gene, which was supposed to play a role in the pathogenesis of EGE and UL, did not differ significantly in any of the studied groups and did not change in patients with EGE when analyzed according to the phase of the menstrual cycle. The expression of this gene in the endometrium has been barely studied; several studies have shown that the *TWIST1* gene is expressed in the ectopic endometrium at a higher level than in the eutopic endometrium [22, 34, 35]. Lee et al. also report that the expression of *TWIST1* in the eutopic endometrium of some patients with EGE is slightly increased when compared with patients without this pathology, which leads to significant differences between the two groups [35]. In our sample, specimens with increased *TWIST1* gene expression in the endometrium were identified, but this aspect is characteristic only for a small proportion of EGE women and cannot be a universal marker of this pathology.

Thus, we did not found an association of the studied polymorphic variants of the *WNT4* and *TWIST* genes and minor variants of the *HOXA10* gene with UL and EGE. The expression of the *WNT4* and *HOXA10* genes is reduced in the endometrium of patients with EGE, but not in patients with UL, while in patients with EGE, the regulation of the *HOXA10* gene expression in the endometrium during the menstrual cycle may be disrupted, which leads to the absence in its increase during the implantation window. Changes in the natural expression of the studied genes in the endometrium differ significantly in UL and EGE, at least in patients who do not have these comorbidities. Further analysis of the expression aspects of the *WNT4* and *HOXA10* genes in healthy women and in patients with EGE and UL may be useful to understand the mechanisms of infertility, which often accompanies this pathology.

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