GENETIC ASPECTS OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY

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Introduction

In the modern literature contradictory information is presented on the causes and pathogenesis of mechanisms for reducing ovarian reserve and endometrioma associated female infertility [1,2]. In the genome-wide association study (GWAS) the connection has been proven a relationship between the carriage of polymorphisms of the genes GREB1, WNT4, FN1, VEZT, HDAC1 and an increased risk of endometriosis [3,4].The presence of such in patients with endometrioid ovarian cysts (EOCs) and infertility has not been previously investigated.

Objective

To expand the understanding of the genetic aspects of infertility formation in patients with EOCs.

Materials & methods

- A prospective cohort study between 2019 and 2021
- ***Patients***

100 women aged 24-40 years old (median 34 y.o.) with a morphologically verified diagnosis of EOC

- ➢ the main group - 60 patients with infertility
- ➢ the comparison group - 40 women who had no history of infertility and realized their reproductive function no more than three years ago

- Real-time polymerase chain reaction (PCR-RT) to analyze of the gene's expression of ***ESR1, ESR2, PGR, VDR, GREB1, WNT4, FN1, VEZT, TGFB1*** in the fragments of the EOC walls
- ***Statistics***

- ➢ Kolmogorov-Smirnov test to assess for normality
- ➢ Student's t-test if the variances were equal and Welch's t-test in the case of unequal variances to comparison of the two groups for a quantitative variable following a normal distribution
- ➢ Pearson's correlation coefficient (in case of the normal distribution of variables) to estimate the direction and strength of the association between two quantitative variables

Results

- During PCR-RT in the ectopic endometrium, the aberrant expression of genes involved in the direct hormonal regulation of the functional and proliferative activity of ovarian tissue was revealed, more pronounced ($p<0.05$) in patients of the main group compared with the control: overexpression of ***ESR2*** (3.75 ± 0.25 cu versus 2.12 ± 0.11 cu) and the estrogen receptor-associated activating transcription factor ***GREB1*** (3.59 ± 0.17 cu . vs. 2.70 ± 0.17 c.u.), decreased expression of ***PGR*** (2.05 ± 0.21 cu. vs. 3.12 ± 0.37 c.u.) and ***VDR*** (1.13 ± 0.15 c.u).
- At the same time, in infertile women, in comparison with patients with preserved fertility, there was a higher ($p<0.05$) expression of genes involved in the implementation of the mechanisms of epithelial-mesenchymal transition in the EOC wall: by 2.8 times, ***TGFB1*** by 1.2 times, ***FN1*** by 1.7 times, ***VEZT*** by 1.3 times (Fig.1)

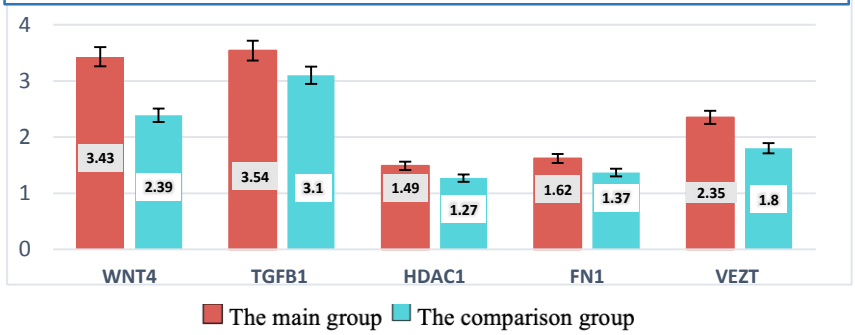

Figure 1 — Comparison of the relative mRNA expression of structural and functional genes responsible for the processes of EMT and intercellular interaction in the EOC wall in patients of the studied groups; c.u.

Table 1 – Results of the correlation analysis of the association between studied genes and steroid receptors in patients with EOCs

Variables		Correlation characteristics	
		ρ / r_{xy}	p
VDR	ESR2	-0,481	0,024*
	WNT4	-0,482	0,023*
	TGFB1	-0,488	0,021*
	GREB1	-0,487	0,021*
ESR2	GREB1	0,869	< 0,001*
	WNT4	0,525	0,012*
	TGFB1	0,826	< 0,001*
WNT4	VEZT	0,531	0,011*
TGFB1	FN1	0,679	< 0,001*
	HDAC1	0,683	< 0,001*
	VEZT	0,809	< 0,001*

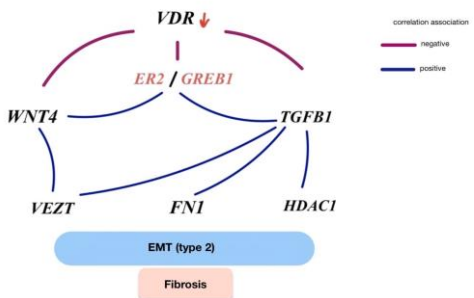

Figure 2 — Schematic representation of genetic changes in the EOCs wall

Conclusions

- Endometrioid cysts wall in infertile patients is characterized by local hyperproduction of estrogens, progesterone resistance and a higher proliferative potential
- Local hormonal disorders with proinflammatory environment probably contribute to aberrant genes expression and the direct activation of epithelial-mesenchymal transition signaling pathways, one of the most powerful inducers of fibrogenesis [5], which subsequently determines the risk of a decrease in the ovarian reserve and fertility potential of patients
- The study of the genetic aspects of the risk of morphological changes in the EOMA wall and their relationship with the state of ovarian tissue and follicular apparatus is a promising area of research on the way to understanding the mechanisms of endometriosis-associated infertility, its prediction and the development of personalized coping tactics in the cohort of patients under study.

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