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PROGINS (T2) VARIANT OF THE *PGR* GENE MAY REDUCE THE *ESR1* GENE-DEPENDENT RISK OF UTERINE LEIOMYOMA DEVELOPMENT

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The purpose of this study was to investigate the effect of *ESR1, PGR* genes variants and hypermethylation of promoter region of the *ESR1* gene on the risk of uterine leiomyoma in women. The risk of disease development was associated with *ESR1* genes variants, and in the presence of 397CC genotype of the *ESR1* gene were observed significantly larger size of the dominant node and early onset of the disease in patients. *PGR* gene variant modified the risk of uterine leiomyoma development. The T1/T2 heterozygous variant of the gene was associated with a reduced risk of uterine leiomyoma development in women. In the presence of the T1/T1 gene variant, the risk of uterine leiomyoma development was significantly 2.5-time increased, and was significantly 4-time increased for patients with this genotype in combination with 351AA genotype of the *ESR1* gene. Hypermethylation of the *ESR1* gene promoter region was an additional risk factor for uterine leiomyoma development and was detected in patients with unsuccess treatments response.

Key words: genetic risk, *ESR1*, *PGR*, methylation, uterine leiomyoma

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PROGINS (T2) ВАРІАНТ ГЕНА *PGR* МОЖЕ ЗНИЖУВАТИ *ESR1* ЗАЛЕЖНИЙ ГЕНЕТИЧНИЙ РИЗИК РОЗВИТКУ ЛЕЙОМІОМИ МАТКИ

Метою роботи було дослідити вплив варіантів генів *ESR1*, *PGR* та гіперметилування промоторної ділянки гена *ESR1* на ризик розвитку лейоміоми матки у жінок. Ризик розвитку захворювання був асоційованим з варіантами гена *ESR1,* а при наявності генотипу 397CC за геном *ESR1* спостерігали значуще більший розмір домінантного вузла та ранній початок захворювання у пацієнток. Варіант гена *PGR* модифікував ризик розвитку лейоміоми матки. Гетерозиготний варіант гена T1/T2 був асоційованим зі зниженням ризику розвитку лейоміоми матки у жінок. За наявності варіанта гена T1/T1 ризик розвитку лейоміоми матки значуще підвищувався у 2,5 рази, і був значуще підвищеним у 4 рази для пацієнток з цим генотипом у поєднанні з генотипом 351AA за геном *ESR1*. Гіперметилування промоторної ділянки гена *ESR1* було додатковим чинником ризику лейоміоми матки та визначалося у пацієнток з відсутністю ефекту при застосуванні стандартних методів лікування.

Ключові слова: генетичний ризик, *ESR1, PGR,* метилування, лейоміома матки

The work is a fragment of the research project "*Investigate the mechanisms of influence of conservative and surgical treatment of uterine leiomyoma on the morphofunctional state of the target organs of the reproductive system in women of childbearing age*"*, state registration No 0117U004535.*

Uterine leiomyoma (UL) is a benign, monoclonal tumor of the female genital tract that originates from the myometrium, leading to excessive uterine bleeding, chronic pelvic pain, infertility, and obstetric pathology. UL is diagnosed in some populations in 80 % of women during life and at least in 70 % women before menopause [3]. The development of UL depends of many factors: age, elevated body mass index, positive family history and genetic predisposition. It is believed that elevated levels of estrogen and progesterone are among the most important factors contributing to the formation and growth of UL [3].

The impact of *ESR1* and *PROGINS* gene variants on UL development and course has been studied for almost two decades. In this regard, some convincing results were obtained. In a study of a group of women who underwent surgery for UL, as compared to healthy individuals, researchers found the association between the 397CC genotype of the *ESR1(-397TC)* gene and an increased risk of developing the disease in the Caucasian race and others. A correlation of the 397CC genotype with the size of leiomyoma, was also found; the weight of myoma in patients with this genotype was significantly higher, sometimes more than 400 grams [11]. Later, a thorough meta-analysis confirmed the association between the *ESR1 PvuII* (rs2234693) gene variant and an increased risk of leiomyoma, and for the *XbaI* (rs9340799) gene variant, it was proposed to continue the study [7]. In some subsequent studies, the association of the

ESR1 gene variants with UL development was not confirmed [4]. In Ukraine, the researchers found an association of the *ESR1* gene variants with the development of benign neoplasms of the female reproductive system in women with a family history burdened with oncological pathology [14]. For *PROGINS* variants of the *PGR* gene, most studies did not reveal an increase in the risk of developing UL, but a study conducted by Gomes M.T. et al. found the opposite – a reduced risk of developing the disease in the presence of a mutant variant of the gene [5]. The combined effect of the *ESR1* and *PGR* gene variants has not yet been evaluated. Hypermethylation in the promoter region of the gene is also associated with dysfunction of the *ESR1* gene. In patients with breast cancer and hypermethylated promoter region of the *ESR1* gene, gene expression is reduced, which correlated with resistance to hormone therapy [15]. Decreased gene expression due to hypermethylation of the promoter site may have a multidirectional effect in patients with UL, as it is known that gene hypermethylation can be persistent, inherited, and affect the risk of disease and determine their course [8].

The purpose of the study was to examine the impact of the *ESR1*, *PGR* gene variants and hypermethylation of the *ESR1* gene promoter region on the risk of UL development.

Materials and methods. The study enrolled 62 female patients with UL. The average age of patients with UL was 38.2±6.9 years. Comparison group 1 consisted of 41 women of the appropriate age (average age – 38.7±11.0 years), who were not diagnosed with the disease during a standard examination. In addition, to evaluate the results obtained in the selected comparison groups, a comparison was made with the data of other Ukrainian researchers, in whose works a detailed clinical description of the comparison groups was provided [13, 14]. Clinically healthy women were selected from these studies and comparison groups 2 and 3 were formed. The structure and topography of myomatous nodes, features of their vascularization were studied. Two classifications were used (ICD 10, 1990 and FIGO, 2011). Biopsy material for the study of methylation of the promoter region of the *ESR1* gene was taken during surgery or by pipelle biopsy.

Informed consent was obtained from each participant included in the study before the collection of blood and tumor samples. The study was approved by the Ethics Committee of the State Institution "Institute of Pediatrics, Obstetrics and Gynecology of NAMS of Ukraine".

The insertional polymorphism *PROGINS* (306-bp Alu insertion in intron G) of the *PGR* gene was determined using the method of allele-specific PCR, and determination of polymorphic variants *A351G* (rs9340799) and *T397C* (rs2234693) of the *ESR1* gene was performed using the PCR-RFLP method according to previously published protocols [1, 2, 14]. The methylation status of the promoter region of the *ESR1* gene was determined using the molecular genetic method [6]. The result of determining the methylation status of the promoter region of the *ESR1* gene was taken into account depending on the number of hypermethylated alleles: in the heterozygous state – Met/UnMet, and in the absence of methylation – UnMet/UnMet.

Statistical data processing was performed using the Microsoft Excel Pro Plus 2016 and SPSS v.27 software. In the analysis of basic clinical characteristics, the mean value±standard deviation was calculated. The studied parameters were checked for the normalcy of distribution using the Kolmogorov-Smirnov test. In the case of a normal distribution, the probability of differences in quantitative results was determined using Student's t-test, and in a distribution that differed from the normal one, the Mann-Whitney U test was used. Differences were considered reliable for all types of analysis at a significance level (p) of less than 0.05.

Results of the study and their discussion. When analyzing the distribution of polymorphic variants of the *ESR1* and *PGR* genes in patients with UL and in the comparison group 1 (table 1), we did not reveal significant differences in the variants of the *ESR1* genes. Patients with UL had a significantly increased distribution frequency of the T1/T1 genotype and a significantly reduced distribution frequency of the T1/T2 genotype of the *PGR* gene in contrast to women in the comparison group 1.

The obtained results indicate that the presence of the T1/T1 genotype of the *PGR* gene is associated with an increased risk of developing UL (χ^2=4.18, p=0.048, OR=2.43 (1.03-5.74)), increasing it by almost 2.5 times, whereas the presence of heterozygous T1/T2 genotype is associated with a reduced risk of the disease (χ^2=4.82, p=0.0281, OR=0.38 (0.15-0.91)). When comparing the frequencies of genotype combinations in the comparison groups, differences were found for the following variants in the studied genes: in patients with UL, the combination of genotypes T1/T1+351AA (30.7 % vs 9.8 %, χ^2=5.06, p=0.024, OR=4.09 (1.28-13.09)) of the *PGR* and *ESR1* gene variants were significantly elevated in contrast to the comparison group 1. Therefore, the *PGR* gene variant modifies the risk of fibromyoma in women with the *ESR1* gene variants.

Table 1

Comparison of the distribution frequency of the *PGR* and *ESR1* gene variants in the comparison groups

Gene (polymorphism)	Genotype, allele	UL group (n=62)	Comparison group 1 (n=41)	Comparison group 2 (n= 55)	Comparison group 3 (n= 25)	Statistic
PGR (PROGINS)	T1/T1	48 (77.4 %)	24 (58.5 %)	-	13 (52.0 %)	$p<0.05^a$ $p>0.05^b$ $p<0.05^c$
	T1/T2	12 (19.4 %)	16 (39.0 %)	-	10 (40.0 %)	$p<0.05^a$ $p>0.05^b$ $p<0.05^c$
	T2/T2	2 (3.2 %)	1 (2.4 %)	-	2 (8.0 %)	$p>0.05^a$ $p>0.05^b$ $p>0.05^c$
	Allele T1	0.87	0.78	-	0.72	$p>0.05^a$ $p>0.05^b$ $p<0.05^c$
	Allele T2	0.13	0.22	-	0.28	
ESR1 (T397C)	397TT	16 (25.8 %)	11 (26.8 %)	34 (61.8 %)	-	$p>0.05^a$ $p<0.05^b$ $p<0.05^c$
	397TC	31 (50.0 %)	24 (58.5 %)	18 (32.7 %)	-	$p>0.05^a$ $p<0.05^b$ $p>0.05^c$
	397CC	15 (24.2 %)	6 (14.6 %)	3 (5.5 %)	-	$p>0.05^a$ $p>0.05^b$ $p<0.05^c$
	Allele 397T	0.51	0.56	0.78	-	$p>0.05^a$ $p<0.05^b$ $p<0.05^c$
	Allele 397C	0.49	0.46	0.22		
ESR1 (A351G)	351AA	28 (45.2 %)	15 (36.6 %)	37 (67.3 %)	-	$p>0.05^a$ $p<0.05^b$ $p<0.05^c$
	351AG	24 (38.7 %)	23 (56.1 %)	18 (32.7)	-	$p>0.05^a$ $p<0.05^b$ $p>0.05^c$
	351GG	10 (16.1 %)	3 (7.3 %)	0 (0.0 %)	-	$p>0.05^a$ $p>0.05^b$ $p<0.05^c$
	Allele 351A	0.65	0.65	0.84	-	$p>0.05^a$ $p<0.05^b$ $p<0.05^c$
	Allele 351G	0.35	0.35	0.16	-	

a – when comparing frequencies "UL group – comparison group 1; b – when comparing frequencies "comparison group 1 – comparison group 2, 3"; c – when comparing frequencies "UL group – comparison group 2, 3"

In Ukraine, few studies have been conducted on the contribution of *ESR1* and *PGR* gene variants to the development of pathology of the female reproductive system, and large-scale population studies have not been conducted at all, therefore, comparisons with population frequencies have not been possible. When comparing the frequency distribution of the genotypes obtained in our study and the frequencies in comparison groups 2 and 3, significant differences were found (Table 1). In particular, comparison group 1 in contrast to comparison group 2, we found a significant increase in the frequency of heterozygotes 397TC and 351AG, and, accordingly, an increase in the frequency of alleles 397C and 351G for polymorphic variants T397C and A351G of the *ESR1* gene. For the group of patients with UL, in contrast to comparison group 2, we revealed a decrease in the distribution frequency and, accordingly, the protective effect of genotypes 397TT (χ^2=15.44, p=0.0001, OR=0.21 (0.10-0.47)) and 351AA (χ^2=5.77, p=0.0163, OR=0.38 (0.19-0.85)), as well as an increased risk in the presence of genotypes 397CC (χ^2=6.49, p=0.0109, OR=5.53 (1.51-20.32)), 351GG (χ^2=9.87, p=0.0017) and alleles 397C (χ^2=18.89, p=0.0001, OR=3.47 (1.96-6.16)) and 351G (χ^2=10.94, p=0.0009, OR=2.81 (1.50-5.25)) of the studied polymorphic variants of the *ESR1* gene. The analysis of the clinical characteristics of comparison group 2 indicated the absence of complications in the obstetric and gynecological history and the absence of the burdened family history by any oncological pathology (morbidity of relatives of the first and second degree of kinship). Due to the detected differences, we analyzed the family history of the examined women. In the examined women of the comparison group 1, 65.9 % had family histories, burdened with oncological pathology, of which 24.4% had relatives with oncological pathology, belonging to the first degree of kinship. In addition, 82.9% of the examined women in the comparison group had a burdened obstetric and gynecological history.

Analyzing the frequencies obtained for our comparison group 1 and comparison group 3, we did not find significant differences. For patients with UL, as opposed to the comparison group 3, we detected a significant increase in the distribution frequency of the T1/T1 genotype (χ^2=5.49, p=0.0191, OR=3.16 (1.18-8.47)) and the T1 allele (χ^2=5.69, p=0.0171, OR=2.63 (1.17-5.90)) and a significant decrease in the distribution frequency of the heterozygous T1/T2 variant of the PGR gene (χ^2=4.02, p=0.045, OR=0.36 (0.13-0.99)). The detected genetic features of the distribution of genotype combinations in the comparison groups revealed that the presence of the *PGR* T1/T2 gene variant reduces the risk of UL development in women.

Another aspect of our study was to examine the possible influence of the examined polymorphic variants of the *PGR* and *ESR1* genes on the course of the disease. To do this, we analyzed the clinical parameters in the group of patients with UL depending on genotypes (table 2).

Table 2

Association of genotypes with patient and disease characteristics

	ESR1 (T397C)			*ESR1* (A351G)			*PGR* (PROGINS)		
	TT	TC	CC	AA	AG	GG	T1/T1	T1/T2	T2/T2
Age (y)	38.0±6.2	40.1±6.5	34.5±7.1	39.7±6.8	37.5±6.2	35.8±8.3	37.9±7.1	39.1±5.6	41.0±9.9
Type of treatment									
Conservative	37.5 %	37.5 %	25.0 %	54.2 %	29.2 %	16.7 %	79.2 %	16.7 %	4.2 %
Surgical	19.4 %	58.3 %	22.2 %	41.7 %	44.4 %	13.9 %	77.8 %	19.4 %	2.8 %
Focality of myomatosis									
Unifocal	20.0 %	40.0 %	40.0 %	40.0 %	40.0 %	20.0 %	75.0 %	20.0 %	5.0 %
Multifocal	30.6 %	52.8 %	16.7 %	47.2 %	38.9 %	13.9 %	80.6 %	16.7 %	2.8 %
Size of the dominant node (mm)	31.7±24.1	40.8±28.8	63.3±48.5	36.5±27.3	52.4±28.7	65.8±56.8	45.8±28.1	57.8±58.7	32.0±31.1
FIGO stage									
0-II	50.0 %	50.0 %	0.0 %	100.0 %	0.0 %	0.0 %	50.0 %	50.0 %	0.0 %
III-V	29.4 %	47.1 %	23.5 %	52.9 %	32.4 %	14.7 %	88.2 %	8.8 %	2.9 %
VI-VII	19.0 %	52.4 %	28.6 %	28.6 %	52.4 %	19.0 %	66.7 %	28.6 %	4.8 %

As a result of the analysis, it was found that carriers of the 397CC genotype had a significantly earlier ($p<0.05$) onset of the disease (34.5±7.1 years) as compared to the 397TC genotype (40.1±6.5 years). Carriers of the 397CC genotype also showed significantly larger dominant nodes (63.3±48.5 mm) as compared to the 397TT genotype (31.7±24.1 mm). Similar but not significantly differences were found for genotypes in the polymorphic A351G variant of the *ESR1* gene. For the rest of the studied characteristics listed in table 2, no significant differences were found.

The methylation status of the promoter region of the *ESR1* gene was studied in 7 patients, among them – in 4 patients in the peripheral blood and in the biopsy material, and in 3 patients – only in the biopsy material (table 3). Heterozygous hypermethylation was detected in 4 patients in the biopsy material, in one of the patients hypermethylation was found only in the biopsy material. Heterozygous Met/UnMet variant was detected in different variants of genotype combinations – 397TT+351AA+T1/T1, 397TC+351AA+T1/T1, 397TC+351AG+T1/T1 as well as the unmethylated variant UnMet/UnMet – 397TT+351AA+T1/T1, 397TC+351AA+T1/T1, 397CC+351GG+T1/T2.

Table 3

Methylation profile in the examined UL patients

Patient	Age (year)	Samples	ESR1 (Met/UnMet)	ESR1 (T397C)	ESR1 (A351G)	PGR (PROGINS)
Patient 1	32	biopsy material from uterine nodes	Met/UnMet	397TC	351AG	T1/T1
		venous blood	Met/UnMet	397TC	351AG	T1/T1
Patient 2	32	biopsy material from uterine nodes	Met/UnMet	397TC	351AG	T1/T1
Patient 3	35	biopsy material from uterine nodes	UnMet/UnMet	397TC	351AA	T1/T1
Patient 4	35	biopsy material from uterine nodes	UnMet/UnMet	397CC	351GG	T1/T2
Patient 5	38	biopsy material from uterine nodes	Met/UnMet	397TT	351AA	T1/T1
		venous blood	UnMet/UnMet	397TT	351AA	T1/T1
Patient 6	36	biopsy material from uterine nodes	Met/UnMet	397TC	351AA	T1/T1
		venous blood	Met/UnMet	397TC	351AA	T1/T1
Patient 7	39	biopsy material from uterine nodes	UnMet/UnMet	397TT	351AA	T1/T1
		venous blood	UnMet/UnMet	397TT	351AA	T1/T1

For women with the heterozygous Met/UnMet variant, the presence of leiomatous nodules of large size (type 4) with a tendency to rapid growth is characteristic, in particular, in patients 1, 2 and 6, regardless of localization. Moreover, patient 1 had a history of uterine artery embolization without effect, whereas patient 5 had a recurrence of leiomyoma after hysteroresectoscopy (node type 2). Patients 2 and 5 had a history of treatment with modulators of progesterone receptors (Gynestril 50 mg per day for 3 months) also without effect. Patients 1 and 4 underwent preoperative preparation with gonadotropin-releasing hormone agonists (Diphereline, Zoladex for 3 months), which allowed for organ-sparing surgery.

For women with unmethylated UnMet/UnMet variant, the presence of small nodes without a tendency to grow is characteristic. Thus, submucosal nodes (type 1) up to 2 cm in size were found in patients 3 and 4, in respect of which hysteroresectoscopy was performed as the method of choice for this localization of leiomatous nodes. Patient 7 had a single intramural node (type 4) of small size, which did not increase in size during the observation period (5 years).

Thus, the presence of hypermethylation of the promoter region of the *ESR1* gene is characterized by large leiomatous nodes with a tendency to rapid growth, recurrence and ineffectiveness of conservative therapy, which requires surgery. Meanwhile, in the unmethylated variant of the *ESR1* gene (UnMet/UnMet), there are small nodes and their rapid growth is not observed, while the treatment tactic is determined by the localization of the nodes.

The methylation status of *ESR1* was determined during treatment, therefore, for these patients, it is impossible to establish its involvement in the risk of developing the disease. However, we found no hypermethylation of the promoter region of the *ESR1* gene in women without UL.

As one can observe from table 3, when examining 2 types of biological material in 4 patients with UL, we found that the study of peripheral blood was less informative. In 25 % of patients with UL, no hypermethylation of the promoter region of the gene was detected in the peripheral blood as opposed to the biopsy sample. In the examined women from the comparison group 1, the study was mostly conducted in the peripheral blood, therefore, it is important for further studies to collect biopsies for methylation in the comparison group. Meanwhile, the assessment of hypermethylation of the promoter region of the *ESR1* gene in patients with UL should be performed before treatment, preferably after the first diagnosis.

As for the role of estrogen and estrogen receptors, estradiol has been traditionally considered a major stimulus for UL growth and development, and numerous studies in cell culture and animal models support this concept [9]. Unlike estrogen, the contribution of progesterone to the development of UL is not fully understood. Studies have shown that progesterone can both stimulate the growth of cultured myoma cells and inhibit it [12]. According to recent data, progesterone due to the activation of progesterone receptors may promote UL growth by increasing proliferation, cellular hypertrophy and degradation of the extracellular matrix [12]. Based on these data, it can be assumed that variants of the progesterone receptor gene, which lead to changes in its functional activity, may indirectly affect the risk of UL development and progression.

The presence of Alu insertion in 306 bp in the G intron of the *PGR* gene reduces the stability of transcript and promotes the appearance of defective forms of progesterone receptors with altered properties, in particular, with reduced sensitivity to progesterone [10]. Meanwhile, progesterone receptors and progesterone, as mentioned above, play a key role in the development and growth of UL. However, in most studies on the impact of the *PROGINS* polymorphic variant of the *PGR* gene on the risk of developing UL, no relationship was found between them [5]. In this context, only a study conducted by Gomes M.T. et al. indicated the protective effect of the *PROGINS* variant of the *PGR* gene (in particular T1/T2+T2/T2 genotypes) on the risk of developing UL [5]. The authors of this study suggested that a possible protective mechanism is associated with a minor action of progesterone on target genes. Our study confirmed the association of the T1/T2 genotype of the *PGR* gene with a reduced risk of developing UL.

Thus, further research and analysis of the *ESR1*, *PGR* gene variants and determining the methylation of the promoter region of the *ESR1* gene in patients with UL are promising and necessary to select the optimal strategy for personalized treatment.

Conclusions

1. The risk of developing uterine leiomyoma in women is associated with variants of the *ESR1* gene, and a significantly larger size of the dominant node and early onset of the disease were observed in patients with the 397CC genotype of the *ESR1* gene.

2. In the presence of the heterozygous T1/T2 gene variant of the *PGR* gene, the risk of developing uterine leiomyoma was significantly reduced, and in the presence of the T1/T1 gene variant, it significantly increased by almost 2.5 times.

3. The *PGR* gene variant modified the risk of developing uterine leiomyoma, and increased by 4 times in women with a combination of 351AA genotypes of the *ESR1* gene and T1/T1 of the *PGR* gene.

4. Hypermethylation of the promoter region of the *ESR1* gene is a risk factor in the development of uterine leiomyoma and is determined in patients with no effect when using standard treatments.

References

1. Albalawi IA, Mir R, Abu-Duhier FM. Utility of amplification-refractory mutation system for the detection clinically significant estrogen and progesterone receptors gene variations in breast cancer patients in Saudi Arabia. IAJPS. 2019; 6(2):4734–47. doi:10.5281/ZENODO.2582886.

2. Anousha N, Hossein-Nezhad A, Biramijamal F, Rahmani A, Maghbooli Z, Aghababaei E, et al. Association study of estrogen receptor alpha gene polymorphisms with spontaneous abortion: Is this a possible reason for unexplained spontaneous abortion? Biomed Res Int. 2013;2013:256470. doi:10.1155/2013/256470.

3. Boclin Kde L, Faerstein E. Prevalence of self-reported medical diagnosis of uterine leiomyomas in a Brazilian population: demographic and socioeconomic patterns in the Pro-Saúde Study. Rev Bras Epidemiol. 2013 Jun;16(2):301–13. English, Portuguese. doi:10.1590/S1415-790X2013000200007.

4. Ciebiera M, Wrzosek M, Wojtyła C, Łoziński T, Nowicka G, Jakiel G, et al. Oestrogen receptor alpha PvuII polymorphism and uterine fibroid incidence in Caucasian women. Prz Menopauzalny. 2018 Dec;17(4):149–154. doi:10.5114/pm.2018.81735.

5. Da Silva F, Pabalan N, Ekaratcharoenchai N, Serpa Neto A, Christofolini DM, de Oliveira R, Bianco B, Barbosa CP. PROGINS polymorphism of the progesterone receptor gene and the susceptibility to uterine leiomyomas: a systematic review and meta-analysis. Genet Test Mol Biomarkers. 2018 May; 22(5):295–301. doi:10.1089/gtmb.2017.0233.

6. Fan XP, Dou CY, Fan YC, Cao CJ, Zhao ZH, Wang K. Methylation status of the estrogen receptor 1 promoter predicts poor prognosis of acute-on-chronic hepatitis B liver failure. Rev Esp Enferm Dig. 2017 Dec;109(12):818–827. doi:10.17235/reed.2017.4426/2016.

7. Feng Y, Lin X, Zhou S, Xu N, Yi T, Zhao X. The associations between the polymorphisms of the ER-α gene and the risk of uterine leiomyoma (ULM). Tumour Biol. 2013 Oct;34(5):3077–82. doi:10.1007/s13277-013-0874-0.

8. Hofmeister BT, Lee K, Rohr NA, Hall DW, Schmitz RJ. Stable inheritance of DNA methylation allows creation of epigenotype maps and the study of epiallele inheritance patterns in the absence of genetic variation. Genome Biol. 2017 Aug 16;18(1):155. doi:10.1186/s13059-017-1288-x.

9. Kim JJ, Sefton EC. The role of progesterone signaling in the pathogenesis of uterine leiomyoma. Mol Cell Endocrinol. 2012 Jul 25;358(2):223–31. doi:10.1016/j.mce.2011.05.044.

10. Li M, Schifanella L, Larsen PA. Alu retrotransposons and COVID-19 susceptibility and morbidity. Hum Genomics. 2021 Jan 4;15(1):2. doi: 10.1186/s40246-020-00299-9.

11. Liu X, Huang J, Lin H, Xiong L, Ma Y, Lao H. *ESR1* PvuII (rs2234693 T>C) polymorphism and cancer susceptibility: Evidence from 80 studies. J Cancer. 2018 Jul 30;9(16):2963–2972. doi: 10.7150/jca.25638.

12. Omar M, Laknaur A, Al-Hendy A, Yang Q. Myometrial progesterone hyper-responsiveness associated with increased risk of human uterine fibroids. BMC Womens Health. 2019 Jul 9;19(1):92. doi:10.1186/s12905-019-0795-1.

13. Pakharenko LV. Evaluation of progesterone and progesterone receptor gene PROGINS polymorphism in the development of some forms of premenstrual syndrome. Reproductive health of woman. 2020;1(41):10–4. doi:10.30841/2708-8731.1.2020.471241.

14. Paliychuk OV, Polishchuk, LZ, Rossokha ZI, Chekhun VF. Molecular-genetic models for prognosis of development of tumors of reproductive system in women with family history of cancer. Exp Oncol. 2018 Mar;40(1):59–67. doi:10.31768/2312-8852.2018.40(1):59-67.

15. Tsuboi K, Nagatomo T, Gohno T, Higuchi T, Sasaki S, Fujiki N, et al. Single CpG site methylation controls estrogen receptor gene transcription and correlates with hormone therapy resistance. J Steroid Biochem Mol Biol. 2017 Jul;171:209–217. doi: 10.1016/j.jsbmb.2017.04.001.

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