An Acad Bras Cienc (2022) 94(Suppl. 3): e20211572 DOI 10.1590/0001-3765202220211572
Anais da Academia Brasileira de Ciências | *Annals of the Brazilian Academy of Sciences*
Printed ISSN 0001-3765 I Online ISSN 1678-2690
www.scielo.br/aabc | www.fb.com/aabcjournal

HEALTH SCIENCES

Investigation of biomarkers in Endometriosis-associated infertility: Systematic Review

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Abstract: The relationship between endometriosis and infertility is still unknown, but it is possible that genetic polymorphisms influence these two variables. This study aims to identify, in the literature, which polymorphisms are related to infertility in women with endometriosis. A search was performed in databases using the descriptors: polymorphisms genetics and infertility and endometriosis. 386 articles were identified, and after applying the inclusion and exclusion criteria, 33 case-control studies were included. Genes and their respective polymorphisms, which exhibited statistically significant values, were classified into three categories: related to metabolic/cellular processes, steroidogenesis and sex hormone receptors, inflammation and immune response. In summary, the results of these studies suggest that the polymorphisms rs882605 of *MUC4* gene, rs16826658 of *WNT4* gene, rs10953316 of *MUC17* gene, rs10928050 of *KAZN* gene, rs1799889 of *PAI-1* gene, (TA)n repeats of *ESR1* gene, (CA)n repeats of *ESR2* gene, rs605059 of *HSD17B1* gene, rs743572 of *CYP17A1* gene, insLQ of *LHR* gene, p.Ile49Ser of *AMH* gene, rs12700667 of *NPVF/NFE2L3* gene, G1502A of *LHβ* gene, G + 1730A of *ERβ* gene, rs7528684 of *FCRL3* gene, rs3761549 of *FOXP3* gene and rs28362491 of *NFKβ1* gene are implicated in the etiology of infertility in women with endometriosis.

Key words: endometriosis, genetic polymorphism, infertility, Systematic Review.

INTRODUCTION

Infertility is the disability attributed to a person or couple who, after a year of unprotected sexual intercourse, does not result in pregnancy. It affects about 15% of the world population, with equal contribution of male and female factors (Bala et al. 2021).

A recent review shows the contribution of environmental and lifestyle factors, such as radiation, pollution, stress, smoking, alcohol consumption, caffeine, obesity, exposure to pesticides, fertilizers, socioeconomic and demographic factors, among others, in physiology and its effect on female fertility (Bala et al. 2021). Other causes include genetic alterations (Yatsenko & Rajkovic 2019), ovulatory dysfunctions, tubal factors, idiopathic infertility and endometriosis (Bala et al. 2021).

Endometriosis is a gynecological condition characterized by abnormal growth of the endometrial stroma and glands outside the uterus. The gold-standard method for its diagnosis is the performance of a surgical procedure called laparoscopy, in which inspection of the abdominal cavity and biopsy are performed for histological confirmation of suspicious lesions. Thus, the prevalence of endometriosis remains unknown due to the lack of non-invasive diagnostic tests for its detection. It is estimated to affect 0.8% to 6% of women in the general population and up to 50% of those infertile (Marian & Hermanowick-Szamatowicz 2020).

Patients with endometriosis may present, mainly, alterations in menstrual cycles, chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria and infertility. A systematic review analyzed the prevalence of endometriosis symptoms and found values ranging from 34% to 56% for dyspareunia, 32% and 53% for pelvic pain, 56% to 71% for dysmenorrhea, 72% and 87% for abnormal menstrual flow and 17% to 35% for infertility (Sousa et al. 2015). A Brazilian survey on clinical aspects and quality of life showed that clinical manifestations such as dyspareunia and pain significantly interfere in the quality of life of women with endometriosis and infertility (Pessoa et al. 2020).

A recent study highlights the importance of a multidisciplinary approach to the treatment of endometriosis and associated infertility, including the need for accurate counseling by psychologists and sexologists (La Rosa et al. 2020a). Thus, there is a consensus in the literature that endometriosis is a multidimensional disease that adversely influences the lives of affected women in different ways (La Rosa et al. 2020b).

The exact cause and effect mechanism of the association between endometriosis and infertility is unknown. Two recent studies (Broi et al. 2019, Khan 2020) discuss in detail the proposed mechanisms by which endometriosis causes infertility, which include distorted pelvic anatomy (affects oocyte and sperm transport), altered peritoneal function (increased inflammatory cytokines induce reduced ovarian response and alter sperm motility), ovulatory dysfunction (greater probability of unruptured luteinized follicles promoting a dysregulation in folliculogenesis and a reduction in oocyte quality), effects on gametes and embryos (endometromas lead to accelerated depletion of follicles and inferior embryos are produced for reasons not well understood), impaired implantation (several mechanisms have been proposed such as dysregulation in gene expression and high levels of cytokines) and abnormal uterotubal transport (which makes fertilization difficult and reduces the chances of pregnancy). Another possible mechanism involved in endometriosis-related infertility is reduced endometrial receptivity, which deserves further investigation (Broi et al. 2019).

Due to the complexity of this association, the treatment of infertility associated with endometriosis must be individualized, taking into account some important aspects, such as the patient's age, her ovarian reserve, the stage of the disease, the presence of pelvic pain, endometrioma and previous surgical intervention, the presence or absence of tubal anomaly and the partner's seminal quality (Navarro 2019).

Despite numerous published works, endometriosis currently remains an enigmatic condition, since its etiology is not fully understood (Szamatowicz & Hermanowicz-Szamatowicz 2020).

Immunological, hormonal, environmental and genetic factors may play a role in the pathogenesis of this chronic disease, and in relation to the latter, the investigation of the possible contribution of genetic polymorphisms to the development of endometriosis is increasing (Deiana et al. 2019, Vassilopoulou et al. 2019, Méar et al. 2020).

To our knowledge, there are no systematic review articles in the literature addressing the issue of genetic polymorphisms, infertility and endometriosis. Thus, this study aimed to identify, in the literature, which polymorphisms are related to infertility in women with endometriosis.

MATERIALS AND METHODS

Protocol and Registration

This systematic review was structured according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Liberati et al. 2009) and the protocol was submitted and registered under ID CRD42020210154 in the international database PROSPERO (International Prospective Register of Systematic Reviews).

Eligibility criteria

As inclusion criteria, works considered were those fully available; those specifically addressing genetic polymorphisms and infertility in women with endometriosis; in Portuguese, English or Spanish; published up to the date of the electronic search, also being case-control studies. Those who did not meet the previously established inclusion criteria were excluded.

Study search and selection strategy

The search for scientific articles was carried out on December 9, 2020, independently, by two researchers (E.M.E. and S.C.S.V.T.), in the following databases: SciELO, Scopus, Web of Science, Pubmed and CINAHL, using the descriptors polymorphisms genetics AND infertility AND endometriosis. The strategies were slightly modified considering the specificities of the consulted databases. After excluding duplicate works, the titles and abstracts of the articles were read for selection and, later, those selected were read in full, following the eligibility criteria to be considered valid in this systematic review.

Data analysis

The full reading of the articles was carried out, followed by selection and synthesis of the main data through the construction of tables and figures. The data analyzed were: country, sample size, genotyping method, gene, polymorphisms, polymorphic allele frequency, HWE (Hardy-Weinberg Equilibrium), p value (genotypic frequency) and quality.

To confirm the identity of the genetic polymorphism, classification of function and chromosomal location of each gene, the dbSNPs databases were used (https://www.ncbi.nlm.nih.gov/snp), Gene (https://www.ncbi.nlm.nih.gov/gene) and GeneCards (https://www.genecards.org/), respectively in the Homo sapiens organism.

Quality assessment of selected articles was performed using the Joanna Briggs Institute (JBI) questionnaire for case-control studies (Moola et al. 2020). Three researchers (E.M.E.; M.T.R.C. and S.C.S.V.T.) carried out this analysis, with one point being attributed to each item included in the study. The cases of disagreement between the assigned grades were resolved through a consensus among the researchers.

RESULTS

The result of the search in the databases for articles that dealt with genetic polymorphisms and infertility in women with endometriosis is shown in Figure 1.

The thirty-three articles analyzed were case-control studies, with diagnostic confirmation by videolaparoscopy, with 21 (63.6%) including patients with endometriosis and control (Table I) and 12 studies (36.4%) additionally investigating a group of patients with idiopathic infertility (Table II).

The published studies covered mostly the last decade and populations from different countries were analyzed, with a predominance of studies conducted in Brazil (57.6%). As for the number of samples analyzed, the largest was 650 fertile women as a control group and 394 infertile women with endometriosis. The smallest sample number analyzed was 18 fertile

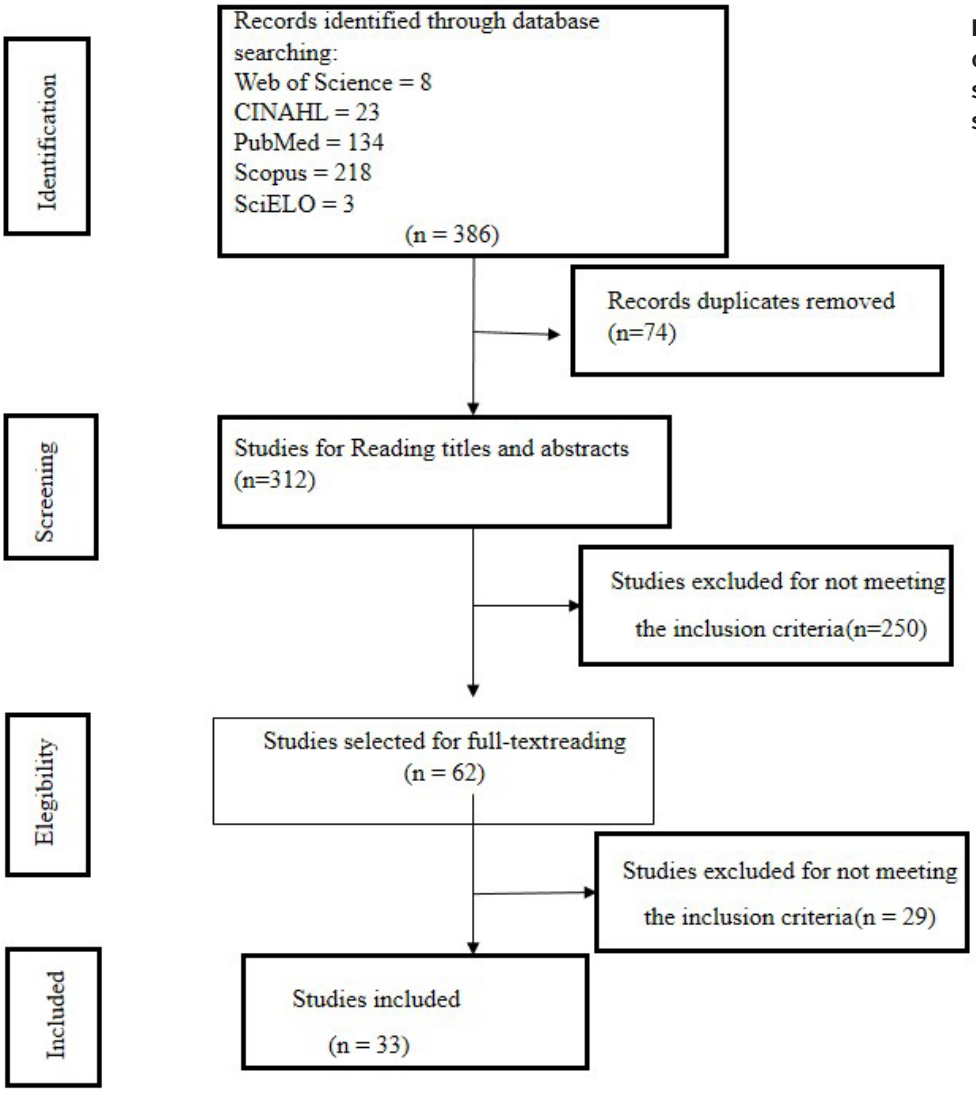

Figure 1. **Flowchart of the search and selection of studies for systematic review.**

and 17 infertile women as control and case groups, respectively. The most used genotyping methods were allelic discrimination (42.4%) and PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) (39.4%). Regarding genes, four studies analyzed *FCRL3*, three the *CYP19A1*, two the *WNT4*, two the *TP53*, two the *ERβ* and two the *LHβ*. The other genes were investigated only once.

Of the thirty-three studies, ten (30.3%) did not perform the HWE calculation. As for the analysis of the quality of the works, regardless of the composition of the study groups, there was a predominance of grades eight and nine in 23 studies (70.00%), which demonstrates good quality. The minimum score achieved by the studies presented in Table I was four and six for Table II. It was observed that studies in Table I with a sample of less than 50 had low quality scores (ranging from 4 to 6). Figure 2 shows the genes and their respective polymorphisms with statistically significant results and was elaborated from data presented in Tables I and II.

Table I. Characteristics of studies that analyzed patients with endometriosis (ED) and controls (C).

Reference	Country	Sample sizeC/ED	Genotypingmethod	Gene	Polymorphism (s)	Polymorphicallele frequency C/ED	HWEC/ED	p value (genotypic frequency)	Quality
Ribeiro Júnior et al. 2009	Brazil	19/19	PCR	TP53	rs1042522	Pro 0.42/0.23	Unrealized	p= 1.0	05
Chang et al. 2011	Taiwan	150/140	Allelic discrimination	MUC4	rs882605	T 0.22/0.28	0.07/0.62	p= 0.04	06
					rs1104760	T 0.80/0.76	0.09/0.94	p= 0.30	
					s2246901	T 0.78/0.75	0.15/0.96	p= 0.56	
					rs2258447	G 0.79/0.77	0.07/0.37	p= 0.70	
					rs2291652	C 0.26/0.30	0.26/0.92	p= 0.52	
					rs2688513	T 0.78/0.77	0.09/0.62	p= 0.66	
Lamp et al. 2011	Estonia	199/150	PCR PCR–RFLP	ESR1	rs2234693	C 0.45/0.51	>0.05/>0.05	p= 0.21	08
					(TA)n	L 0.39/0.48	>0.05/>0.05	p<0.05	
				ESR2	(CA)n	L 0.49/0.36	>0.05/>0.05	p<0.05	
				HSD17B1	rs605059	A 0.50/0.57	>0.05/>0.05	p<0.05	
				PGR	rs10895068	A 0.09/0.07	>0.05/>0.05	p= 0.35	
					Ins/Del Alu	Del 0.87/0.84	>0.05/>0.05	p= 0.10	
				CYP19A1	rs10046	T 0.60/0.55	>0.05/>0.05	p= 0.1	
					(TTTA)n	L 0.41/0.40	>0.05/>0.05	p= 0.75	
					Ins/Del	Del 0.41/0.26	>0.05/>0.05	p= 0.34	
Szczepańska etal. 2011	Poland	150/163	PCR–RFLP	CBS	844ins68	ins 0.10/0.06	>0.05/>0.05	p= 0.05	09
				MTHFD1	rs2236225	T 0.42/0.40	>0.05/>0.05	p= 0.67	
				MTHFR	rs1801133	T 0.27/0.32	>0.05/>0.05	p= 0.11	
				MTR	rs1805087	G 0.17/0.23	>0.05/>0.05	p= 0.07	
				MTRR	rs1801394	G 0.38/0.42	>0.05/>0.05	p= 0.20	
				TCN2	rs1801198	C 0.45/0.46	>0.05/>0.05	p= 0.72	
				BHMT	rs7356530	A 0.41/0.40	>0.05/>0.05	p= 0.63	
					rs3733890	A 0.31/0.30	>0.05/>0.05	p= 0.65	
				CYP19A1	rs10046	T 0.60/0.55	>0.05/>0.05	p= 0.1	
					(TTTA)n	L 0.41/0.40	>0.05/>0.05	p= 0.75	
					Ins/Del	Del 0.41/0.26	>0.05/>0.05	p= 0.34	
Szczepańska etal. 2011	Poland	150/163	PCR–RFLP	CBS	844ins68	ins 0.10/0.06	>0.05/>0.05	p= 0.05	09
				MTHFD1	rs2236225	T 0.42/0.40	>0.05/>0.05	p= 0.67	
				MTHFR	rs1801133	T 0.27/0.32	>0.05/>0.05	p= 0.11	
				MTR	rs1805087	G 0.17/0.23	>0.05/>0.05	p= 0.07	
				MTRR	rs1801394	G 0.38/0.42	>0.05/>0.05	p= 0.20	
				TCN2	rs1801198	C 0.45/0.46	>0.05/>0.05	p= 0.72	

Table I. Continuation.

Reference	Country	Sample sizeC/ED	Genotypingmethod	Gene	Polymorphism (s)	Polymorphicallele frequency C/ED	HWEC/ED	p value (genotypic frequency)	Quality
				BHMT	rs7356530	A 0.41/0.40	>0.05/>0.05	p= 0.63	
					rs3733890	A 0.31/0.30	>0.05/>0.05	p= 0.65	
				CYP19A1	rs10046	T 0.60/0.55	>0.05/>0.05	p= 0.1	
				BHMT2	rs625879	T 0,41/0,38	>0,05/>0,05	p= 0,54	
				CHDH	rs893363	C 0,35/0,36	>0,05/>0,05	p= 0,95	
					rs2289205	A 0,24/0,30	>0,05/>0,05	p= 0,26	
				CHKA	rs7928739	A 0,58/0,58	>0,05/>0,05	p= 0,77	
				PCYT1A	rs712012	T 0.36/0.38	>0.05/>0.05	p= 0.62	
					rs7639752	A 0.49/0.46	>0.05/>0.05	p= 0.47	
				PEMT	rs4244593	A 0.43/0.46	>0.05/>0.05	p= 0.46	
					rs4646406	A 0.43/0.46	>0.05/>0.05	p= 0.47	
Chang et al. 2012	Taiwan	196/195	Allelic discrimination	MUC2	rs2856111	T 0.53/0.56	Unrealized	p= 0.29	05
					rs11245936	A 0.09/0.06	Unrealized	p= 0.34	
					rs10794288	T 0.52/0.60	Unrealized	p= 0.09	
					rs10902088	C 0.53/0.62	Unrealized	p= 0.05	
					rs7103978	G 0.10/0.06	Unrealized	p= 0.05	
							Unrealized		
				BHMT2	rs625879	T 0,41/0,38	>0,05/>0,05	p= 0,54	
				CHDH	rs893363	C 0,35/0,36	>0,05/>0,05	p= 0,95	
					rs2289205	A 0,24/0,30	>0,05/>0,05	p= 0,26	
				CHKA	rs7928739	A 0,58/0,58	>0,05/>0,05	p= 0,77	
				PCYT1A	rs712012	T 0.36/0.38	>0.05/>0.05	p= 0.62	
					rs7639752	A 0.49/0.46	>0.05/>0.05	p= 0.47	
				PEMT	rs4244593	A 0.43/0.46	>0.05/>0.05	p= 0.46	
					rs4646406	A 0.43/0.46	>0.05/>0.05	p= 0.47	
Chang et al. 2012	Taiwan	196/195	Allelic discrimination	MUC2	rs2856111	T 0.53/0.56	Unrealized	p= 0.29	05
					rs11245936	A 0.09/0.06	Unrealized	p= 0.34	
					rs11245954	G 0.07/0.05	Unrealized	Not included	
Zhang et al. 2012	China	244/425	Fluorescence Resonance Energy Transfer	BDNF	Val66Met	Met 0.46/0.51	>0.05/>0.05	p= 0.17	09
Szczepańska etal. 2013a	Poland	519/141	PCR–RFLP	FCRL3	rs7528684	C 0.48/0.59	>0.05/>0.05	p<0.05	09
Szczepańska etal. 2013b	Poland	197/115	High-Resolution Melting	CYP17A1	rs743572	A 0.41/ Notincluded	Unrealized	p<0.05	08
				CYP19A1	rs10046	T 0.39/ Notincluded	Unrealized	p= 0.79	
Mafra et al. 2015	Brazil	400/400	Allelic discrimination	WNT4	rs2235529	A 0.12/0.15	0.65/0.18	p= 0.09	09

Table I. Continuation.

Reference	Country	Sample sizeC/ED	Genotypingmethod	Gene	Polymorphism (s)	Polymorphicallele frequency C/ED	HWEC/ED	p value (genotypic frequency)	Quality
					rs3820282	A 0.12/0.15	0.48/0.12	p= 0.05	
					rs16826658	G 0.35/0.35	0.70/0.74	p<0.05	
					rs7521902	A 0.16/0.19	0.72/0.20	p= 0.18	
Schmitz et al.2015	Brazil	65/67	SequencingPCR–RFLP	LH	Trp8Arg	0.12/0.16	>0.05/>0.05	p= 0.51	07
					Ile15Thr	0.12/0.16	>0.05/>0.05	p= 0.51	
				LHR	insLQ	0.10/0.25	>0.05/>0.05	p= 0.01	
					rs11245954	G 0.07/0.05	Unrealized	Not included	
Zhang et al. 2012	China	244/425	Fluorescence Resonance Energy Transfer	BDNF	Val66Met	Met 0.46/0.51	>0.05/>0.05	p= 0.17	09
Szczepańska etal. 2013a	Poland	519/141	PCR–RFLP	FCRL3	rs7528684	C 0.48/0.59	>0.05/>0.05	p<0.05	09
Szczepańska etal. 2013b	Poland	197/115	High-Resolution Melting	CYP17A1	rs743572	A 0.41/ Notincluded	Unrealized	p<0.05	08
				CYP19A1	rs10046	T 0.39/ Notincluded	Unrealized	p= 0.79	
Mafra et al. 2015	Brazil	400/400	Allelic discrimination	WNT4	rs2235529	A 0.12/0.15	0.65/0.18	p= 0.09	09
					rs3820282	A 0.12/0.15	0.48/0.12	p= 0.05	
					rs16826658	G 0.35/0.35	0.70/0.74	p<0.05	
				FSHR	Asn680Ser	Not included	>0.05/>0.05	p= 0.78	
Szczepańska etal. 2015	Poland	347/154	High Resolution Melting PCR–RFLP	GC	rs7041	T 0.40/0.44	>0.05/>0.05	p= 0.16	09
					rs1155563	C 0.28/0.32	>0.05/>0.05	p= 0.31	
					rs2298849	C 0.20/0.21	>0.05/>0.05	p= 0.48	
				RXRA	rs10881578	G 0.30/0.28	>0.05/>0.05	p= 0.52	
					rs10776909	C 0.20/0.18	>0.05/>0.05	p= 0.27	
					rs749759	G 0.25/0.20	>0.05/>0.05	p= 0.13	
				VDR	rs1544410	A 0.35/0.39	>0.05/>0.05	p= 0.44	
					rs2228570	Não consta	>0.05/>0.05	p= 0.12	
Yang et al. 2015	Taiwan	191/189	Allelic discrimination	MUC17	rs4729645	T 0.21/0.17	Unrealized	p= 0.12	06
					rs10953316	G 0.80/0.88	Unrealized	p<0.05	
					rs74974199	C 0.13/0.11	Unrealized	p= 0.42	
				FSHR	Asn680Ser	Not included	>0.05/>0.05	p= 0.78	
Szczepańska etal. 2015	Poland	347/154	High Resolution Melting PCR–RFLP	GC	rs7041	T 0.40/0.44	>0.05/>0.05	p= 0.16	09
					rs1155563	C 0.28/0.32	>0.05/>0.05	p= 0.31	
					rs2298849	C 0.20/0.21	>0.05/>0.05	p= 0.48	
				RXRA	rs10881578	G 0.30/0.28	>0.05/>0.05	p= 0.52	
					rs10776909	C 0.20/0.18	>0.05/>0.05	p= 0.27	

Table I. Continuation.

Reference	Country	Sample sizeC/ED	Genotypingmethod	Gene	Polymorphism (s)	Polymorphicallele frequency C/ED	HWEC/ED	p value (genotypic frequency)	Quality
					rs749759	G 0.25/0.20	>0.05/>0.05	p= 0.13	
				VDR	rs1544410	A 0.35/0.39	>0.05/>0.05	p= 0.44	
					rs2228570	Não consta	>0.05/>0.05	p= 0.12	
Yang et al. 2015	Taiwan	191/189	Allelic discrimination	MUC17	rs4729645	T 0.21/0.17	Unrealized	p= 0.12	06
					rs10953316	G 0.80/0.88	Unrealized	p<0.05	
					rs74974199	C 0.13/0.11	Unrealized	p= 0.42	
				FSHR	Asn680Ser	Not included	>0.05/>0.05	p= 0.78	
Szczepańska etal. 2015	Poland	347/154	High Resolution Melting PCR–RFLP	GC	rs7041	T 0.40/0.44	>0.05/>0.05	p= 0.16	09
					rs1155563	C 0.28/0.32	>0.05/>0.05	p= 0.31	
					rs2298849	C 0.20/0.21	>0.05/>0.05	p= 0.48	
				RXRA	rs10881578	G 0.30/0.28	>0.05/>0.05	p= 0.52	
					rs4729655	C 0.61/0.59	Unrealized	p= 0.55	
					rs4729656	A 0.68/0.66	Unrealized	p= 0.66	
Zhang et al. 2015	China	220/217	PCR–RFLP	FCRL3	rs7528684	C 0.41/0.50	0.35/0.83	p= 0.01	09
					rs11264799	A 0.28/0.30	0.37/0.48	p= 0.57	
					rs945635	G 0.42/0.45	0.64/0.73	p= 0.30	
					rs3761959	A 0.47/0.49	0.74/0.83	p= 0.65	
Barbosa et al.2016	Brazil	42/52	PCR–RFLP	CYP1A1	***CYP1A1m1***	m1 0.14/0.32	Unrealized	p= 0.08	04
De Conto et al. 2017	Brazil	70/74	Allelic discrimination	GDF-9	c.398-39C > G	G 0.15/0.11	>0.05/>0.05	p= 0.51	09
					c.447C > T	T 0.49/0.53	>0.05/>0.05	p= 0.19	
					c.546G > A	A 0.13/0.18	>0.05/>0.05	p= 0.44	
				AMH	p.Ile49Ser	Ser 0.28/0.16	>0.05/>0.05	p= 0.03	
				AMHR2	-482A > G	G 0.20/0.16	>0.05/>0.05	p= 0.68	
					rs4729655	C 0.61/0.59	Unrealized	p= 0.55	
					rs4729656	A 0.68/0.66	Unrealized	p= 0.66	
Zhang et al. 2015	China	220/217	PCR–RFLP	FCRL3	rs7528684	C 0.41/0.50	0.35/0.83	p= 0.01	09
					rs11264799	A 0.28/0.30	0.37/0.48	p= 0.57	
					rs945635	G 0.42/0.45	0.64/0.73	p= 0.30	
					rs3761959	A 0.47/0.49	0.74/0.83	p= 0.65	
Barbosa et al. 2016	Brazil	42/52	PCR–RFLP	CYP1A1	***CYP1A1m1***	m1 0.14/0.32	Unrealized	p= 0.08	04
De Conto et al. 2017	Brazil	70/74	Allelic discrimination	GDF-9	c.398-39C > G	G 0.15/0.11	>0.05/>0.05	p= 0.51	09
					c.447C > T	T 0.49/0.53	>0.05/>0.05	p= 0.19	
Osiński et al. 2017	Poland	410/290	High Resolution MeltingPCR	HSD17B1	rs605059	A 0.48/0.52	>0.05/>0.05	p= 0.19	06
Osiński et al. 2018a	Poland	406/315	High Resolution Melting	NPVF/ NFE2L3	rs12700667	A 0.76/0.81	0.56/0.82	p= 0.04	09
				WNT4	rs12037376	A 0.16/0.18	0.73/0.91	p= 0.30	

Table I. Continuation.

Reference	Country	Sample sizeC/ED	Genotypingmethod	Gene	Polymorphism (s)	Polymorphicallele frequency C/ED	HWEC/ED	p value (genotypic frequency)	Quality
				WNT4/ ZBTB40	rs7521902	A 0.26/0.27	0.87/0.35	p= 0.46	
				GREB1	rs13394619	A 0.45/0.44	0.37/0.98	p= 0.62	
				VEZT/ METAP2	rs10859871	C 0.31/0.31	0.72/0.11	p= 0.83	
				CDKN2B/ DMRTA1	rs1537377	C 0.39/0.41	0.74/0.23	p= 0.49	
				ETAA1/C1D	rs4141819	C 0.31/0.35	0.99/0.31	p= 0.08	
				RNF144B/ ID4	rs7739264	C 0.46/0.46	0.63/0.80	p= 0.77	
				RND3/ RBM43	rs1519761	G 0.42/0.40	0.35/0.31	p= 0.39	
				CKAP2L/ IL1A	rs6542095	C 0.28/0.27	0.21/0.92	p= 0.50	
Osiński et al. 2017	Poland	410/290	High Resolution MeltingPCR	HSD17B1	rs605059	A 0.48/0.52	>0.05/>0.05	p= 0.19	06
Osiński et al. 2018a	Poland	406/315	High Resolution Melting	NPVF/ NFE2L3	rs12700667	A 0.76/0.81	0.56/0.82	p= 0.04	09
				WNT4	rs12037376	A 0.16/0.18	0.73/0.91	p= 0.30	
				WNT4/ ZBTB40	rs7521902	A 0.26/0.27	0.87/0.35	p= 0.46	
				GREB1	rs13394619	A 0.45/0.44	0.37/0.98	p= 0.62	
				VEZT/ METAP2	rs10859871	C 0.31/0.31	0.72/0.11	p= 0.83	
				CDKN2B/ DMRTA1	rs1537377	C 0.39/0.41	0.74/0.23	p= 0.49	
				ETAA1/C1D	rs4141819	C 0.31/0.35	0.99/0.31	p= 0.08	
				RNF144B/ ID4	rs7739264	C 0.46/0.46	0.63/0.80	p= 0.77	
				RND3/ RBM43	rs1519761	G 0.42/0.40	0.35/0.31	p= 0.39	
				CKAP2L/ IL1A	rs6542095	C 0.28/0.27	0.21/0.92	p= 0.50	
Osiński et al. 2017	Poland	410/290	High Resolution MeltingPCR	HSD17B1	rs605059	A 0.48/0.52	>0.05/>0.05	p= 0.19	06
Osiński et al. 2018a	Poland	406/315	High Resolution Melting	NPVF/ NFE2L3	rs12700667	A 0.76/0.81	0.56/0.82	p= 0.04	09
				WNT4	rs12037376	A 0.16/0.18	0.73/0.91	p= 0.30	
				WNT4/ ZBTB40	rs7521902	A 0.26/0.27	0.87/0.35	p= 0.46	
				GREB1	rs13394619	A 0.45/0.44	0.37/0.98	p= 0.62	

Table I. Continuation.

Reference	Country	Sample sizeC/ED	Genotypingmethod	Gene	Polymorphism (s)	Polymorphicallele frequency C/ED	HWEC/ED	p value (genotypic frequency)	Quality
				VEZT/ METAP2	rs10859871	C 0.31/0.31	0.72/0.11	p= 0.83	
				CDKN2B/ DMRTA1	rs1537377	C 0.39/0.41	0.74/0.23	p= 0.49	
				ETAA1/C1D	rs4141819	C 0.31/0.35	0.99/0.31	p= 0.08	
				RNF144B/ ID4	rs7739264	C 0.46/0.46	0.63/0.80	p= 0.77	
Santos et al. 2018	Brazil	18/17	Amplification Refractory Mutation System-Polymerase ChainReactionPCR	TP53	rs1042522	Pro Notincluded	Unrealized	Not included	06
				eNOS	rs1799983	Asp Notincluded	Unrealized	Not included	
Cardoso et al. 2019	Brazil	217/283		MMP3	rs679620	A 0.34/0.40	>0.05/>0.05	p= 0.09	09
Christofolini et al. 2019	Brazil	650/394	Allelic discrimination	TAC3	rs733629	C 0.09/0.08	0.73/1	p= 0.57	09
				KAZN	rs10928050	G 0.16/0.20	0.14/1	p<0.05	
			Allelic discrimination	LAMA5	rs2427284	A 0.07/0.05	<0.05/<0.05	p= 0.1	
Tanase et al. 2020	Romania	34/44		FSHR	rs1394205	A 0.23/0.22	Unrealized	p= 0.87	05
				*FSH*β	rs10835638	T 0.09/0.07	Unrealized	p= 0.63	
Santos et al. 2018	Brazil	18/17	Amplification Refractory Mutation System-Polymerase ChainReactionPCR	TP53	rs1042522	Pro Notincluded	Unrealized	Not included	06
				eNOS	rs1799983	Asp Notincluded	Unrealized	Not included	
Cardoso et al. 2019	Brazil	217/283		MMP3	rs679620	A 0.34/0.40	>0.05/>0.05	p= 0.09	09
Christofolini et al. 2019	Brazil	650/394	Allelic discrimination	TAC3	rs733629	C 0.09/0.08	0.73/1	p= 0.57	09
				KAZN	rs10928050	G 0.16/0.20	0.14/1	p<0.05	
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				*FSH*β	rs10835638	T 0.09/0.07	Unrealized	p= 0.63	
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				eNOS	rs1799983	Asp Notincluded	Unrealized	Not included	

Table I. Continuation.

Reference	Country	Sample sizeC/ED	Genotypingmethod	Gene	Polymorphism (s)	Polymorphicallele frequency C/ED	HWEC/ED	p value (genotypic frequency)	Quality
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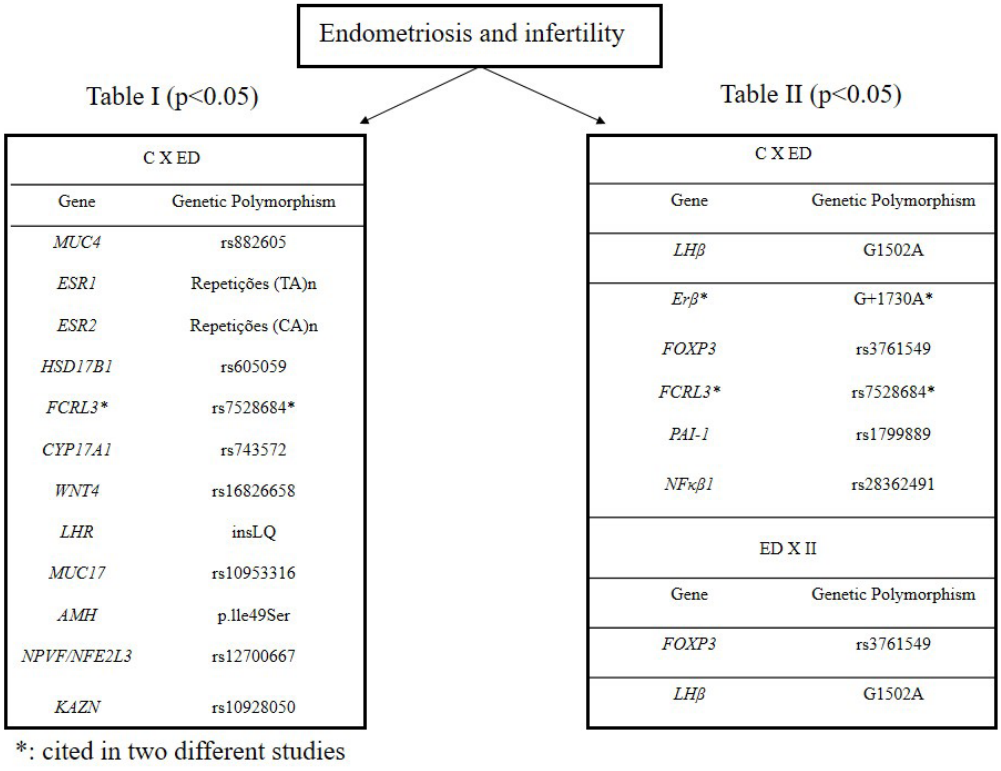
Christofolini et al. 2019	Brazil	650/394	Allelic discrimination	TAC3	rs733629	C 0.09/0.08	0.73/1	p= 0.57	09
				KAZN	rs10928050	G 0.16/0.20	0.14/1	p<0.05	
			Allelic discrimination	LAMA5	rs2427284	A 0.07/0.05	<0.05/<0.05	p= 0.1	
Tanase et al. 2020	Romania	34/44		FSHR	rs1394205	A 0.23/0.22	Unrealized	p= 0.87	05
				*FSH*β	rs10835638	T 0.09/0.07	Unrealized	p= 0.63	
Santos et al. 2018	Brazil	18/17	Amplification Refractory Mutation System-Polymerase ChainReactionPCR	TP53	rs1042522	Pro Notincluded	Unrealized	Not included	06
				eNOS	rs1799983	Asp Notincluded	Unrealized	Not included	
Cardoso et al. 2019	Brazil	217/283		MMP3	rs679620	A 0.34/0.40	>0.05/>0.05	p= 0.09	09
Christofolini et al. 2019	Brazil	650/394	Allelic discrimination	TAC3	rs733629	C 0.09/0.08	0.73/1	p= 0.57	09
				KAZN	rs10928050	G 0.16/0.20	0.14/1	p<0.05	

Notes: TP53: Tumor Protein p53. MUC4: Mucin-4. ESR1: Estrogen Receptor 1. ESR2: Estrogen Receptor 2. HSD17B1: Hydroxysteroid 17 – Beta Dehydrogenase Type 1. PGR:Progesterone Receptor. *CYP19A1:* **Cytochrome P450 Family 19 Subfamily A Member 1.** *CBS:* **Cystathionine Beta-Synthase.** *MTHFD1:* **Methylenetetrahydrofolate Dehydrogenase.Cyclohydrolase And Formyltetrahydrofolate Synthetase 1.** *MTHFR:* **Methylenetetrahydrofolate Reductase.** *MTR:* **Methionine Synthase.** *MTRR:* **Methionine Synthase Reductase.** *TCN2:***Transcobalamin 2.** *BHMT:* **Betaine-Homocysteine Methyltransferase.** *BHMT2:* **Betaine-Homocysteine S-Methyltransferase 2.** *CHDH:* **Choline Dehydrogenase.** *CHKA:* **Choline Kinase Alpha.** *PCYT1A:* **Phosphate Cytidylyltransferase 1. Choline. Alpha.** *PEMT:* **Phosphatidylethanolamine N-Methyltransferase.** *MUC2:* **Mucin-2.** *BDNF:* **Brain-Derived Neurotrophic**
Factor. FCRL3: Fc Receptor–Like 3. CYP17A1: Cytochrome P450 Family 17 Subfamily A Member 1. WNT4: Wnt Family Member 4. LH: Luteinizing Hormone. LHR: Luteinizing Hormone Receptor. FSHR: Follicle Stimulating Hormone Receptor. GC: Vitamin D Binding Protein. RXRA: Retinoid X Receptor Alpha. VDR: Vitamin D Receptor. MUC17: Mucin-17. *CYP1A1:* **Cytochrome P450 1A1.** *GDF-9:* **Growth Differentiation Factor 9.** *AMH:* **Anti-Mullerian Hormone.** *AMHR2:* **Anti-Mullerian Hormone Receptor Type 2.** *NPVF/NFE2L3***: Neuropeptide VF Precursor/ Nuclear Factor. Erythroid 2 Like 3.** *WNT4/ZBTB40:* **Wnt Family Member 4/ Zinc Finger And BTB Domain Containing 40.** *GREB1:* **Growth Regulating Estrogen Receptor Binding 1.** *VEZT/METAP2:* **Vezatin. Adherens Junctions Transmembrane Protein/ Methionyl Aminopeptidase 2.** *CDKN2B/DMRTA1:* **Cyclin Dependent Kinase Inhibitor 2B/ DMRT Like Family A1.** *ETAA1/C1D:* **Ewing'S Tumor-Associated Antigen 1/ Nuclear Receptor Corepressor.** *RNF144B/ID4:* **Ring Finger Protein 144B/ Inhibitor Of Differentiation 4.** *RND3/RBM43:* **Rho Family GTPase 3/ RNA Binding Motif Protein 43.** *CKAP2L/IL1A:* **Cytoskeleton Associated Protein 2 Like/ Interleukin 1 Alpha.** *eNOS:* **Endothelial Nitric Oxide Synthase.** *MMP3:* **Matrix Metallopeptidase 3.** *TAC3:* **Tachykinin Precursor 3.** *KAZN:* **Kazrin. Periplakin Interacting Protein.** *LAMA5:* **Laminin Subunit Alpha 5.** *FSHβ:* **Follicle Stimulating Hormone Beta.**



C X ED	
Gene	Genetic Polymorphism
MUC4	rs882605
ESR1	Repetições (TA)n
ESR2	Repetições (CA)n
HSD17B1	rs605059
*FCRL3**	rs7528684*
CYP17A1	rs743572
WNT4	rs16826658
LHR	insLQ
MUC17	rs10953316
AMH	p.Ile49Ser
NPVF/NFE2L3	rs12700667
KAZN	rs10928050

C X ED	
Gene	Genetic Polymorphism
LHβ	G1502A
*Erβ**	G+1730A*
FOXP3	rs3761549
*FCRL3**	rs7528684*
PAI-1	rs1799889
NFκβ1	rs28362491
ED X II	
Gene	Genetic Polymorphism
FOXP3	rs3761549
LHβ	G1502A

*: cited in two different studies

Figure 2. Genes and their respective polymorphisms that exhibited statistically significant values with endometriosis-related infertility (C: control; ED: endometriosis and II: idiopathic infertility).

Regarding the functions, the classification of these genes is presented in Figure 3. In the present study, the genes belonging to the metabolic/cellular processes classes, steroidogenesis and sex hormone receptors, inflammation and immune response have been linked to infertility in women with endometriosis. The genes shown in Figure 3 are located on the following human chromosomes: 1 (*WNT4*, *KAZN*, *FCRL3*), 2 (*LHR*), 3 (*MUC4*), 4 (*NFKβ1*), 6 (*ESR1*), 7 (*MUC17, PAI-1, NPVF/NFE2L3*), 10 (*CYP17A1*) 14 (*ESR2, ERβ*), 17 (*HSD17B1*), 19 (*AMH, LHβ*) and X (*FOXP3*).

DISCUSSION

Endometriosis is an important cause of female infertility and affects women of childbearing age. However, the etiopathogenesis of endometriosis associated with infertility remains unknown (Lete 2019). Thus, studies investigating the relationship among genetic polymorphisms, infertility and endometriosis can help to understand the molecular mechanisms involved in the pathophysiology of these conditions.

It was found that most of the studies included in this systematic review were carried out in Brazil, by groups of related researchers, evidencing the concern of the Brazilian scientific community about endometriosis and female infertility, highlighting the country's position in the production of scientific knowledge.

Studies that evaluate genetic polymorphisms need a sufficient sample size so that the analyses performed have robust statistical power to determine whether the associations, if observed, are true (Cardoso et al. 2020). Variability was observed in the sample number of studies included in this study, which can be attributed to the fact that the only currently reliable method for diagnosing endometriosis is videolaparoscopy, a surgical and invasive procedure (Kiesel & Sourouni 2019,

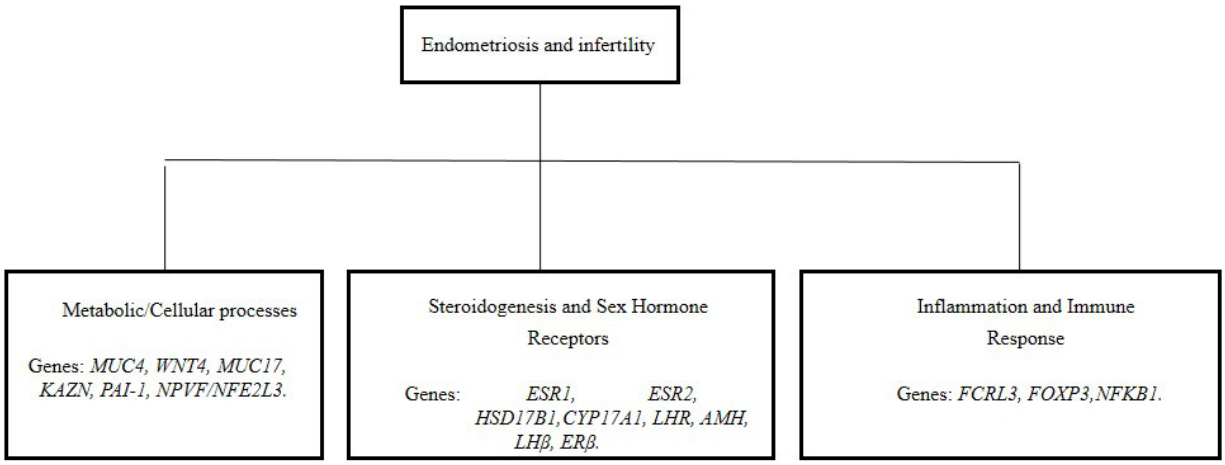


Figure 3. Classification of gene functions with statistically significant polymorphisms.

Lete 2019). Thus, it is essential to search for non-invasive diagnostic methods such as imaging tests, genetic tests and/or biomarkers (Kiesel & Sourouni 2019).

The most used genotyping techniques were allelic discrimination and PCR-RFLP, which were predominant because they are more common, with low cost and high specificity (Zaha et al. 2014).

In analyses with genetic polymorphisms, the HWE calculation is used to explain whether evolutionary factors (natural selection, mutation effects, genetic drift and gene flow) influenced the genotypic and allelic frequencies of the genes studied (Hartl & Clark 2010). However, it was not verified in all studies.

This study observed that some polymorphisms in genes related to metabolic/cellular processes, steroidogenesis and sex hormone receptors, and inflammation and immune response were associated with the development of infertility and endometriosis in different populations.

In relation to the first class of genes, mucins are high molecular weight glycoproteins with a significant role in the progression of several types of cancers (Marimuthu et al. 2021). Considering that endometriosis has several similarities with cancer, changes in mucins, both in the level of gene expression and polymorphic variations, may contribute to the development of this gynecological condition (Yang et al. 2015). Although two studies associate isolated polymorphisms of genes *MUC4* - rs882605 (Chang et al. 2011) and *MUC17* - rs10953316 (Yang et al. 2015) with endometriosis and infertility, a recent study described that the *MUC4* haplotypes referring to rs2291653/rs2291654/rs375068067 may contribute to the increased risk of endometriosis (Kim et al. 2020).

The *WNT4* gene is exclusively involved in the development of the female phenotype in the fetus and in the maintenance of Müllerian and reproductive tissues, thus highlighting its fundamental role in gender determination and differentiation of the female reproductive system. Furthermore, polymorphisms in this gene appear to be involved in the pathogenesis of some gynecological conditions that include various types of cancers, uterine fibroids, endometriosis and infertility (Pitzer et al. 2021). Corroborating the data presented here, the rs16826658 polymorphism of the *WNT4* gene was associated with endometriosis in a recent systematic review, together with the rs2235529 (Méar et al. 2020).

Table II. Characteristics of studies that analyzed patients with endometriosis (ED), patients with idiopathic infertility (II) and controls (C).

Reference	Country	Sample sizeC/ ED/II	Genotypingmethod	Gene	Polymorphism(s)	Polymorphic allele frequencyC/ED/II	HWE C/ED/II	p value (genotypic frequency) (CxED/ EDxII)	Quality
Mafra et al. 2010	Brazil	209/110/84	PCR–RFLP	LHβ	G1502A	A 0.20/0.30/0.29	Unrealized	<0.05/Not included	08
Zulli et al. 2010	Brazil	209/136/69	PCR-RFLPAllelic discrimination	ERβ	G + 1730A	A 0.12/0.21/0.21	>0.05/<0.05/>0.05	<0.05/0.15	08
André et al. 2011	Brazil	171/177/71	Allelic discrimination	FOXP3	rs3761548	C 0.70/0.66/0.62	-/0.97/<0.05	0.28/0.42	09
					rs3761549	T 0.07/0.14/0.03	-/0.52/0.87	<0.05/<0.05	
					rs2232366	T 0.97/0.97/0.99	-/1.0/1.0	0.86/0.37	
					rs2232368	A 0.28/0.31/0.38	-/0.53/<0.05	0.38/0.17	
					rs2280883	G 0.27/0.31/0.38	-/0.60/<0.05	0.30/0.17	
Bianco et al. 2011	Brazil	166/170/91	Allelic discrimination	FCRL3	rs7528684	C 0.38/0.49/0.46	>0.05/>0.05/>0.05	<0.05/Not included	09
					rs11264799	A 0.34/0.30/0.29	>0.05/>0.05/>0.05	0.63/Not included	
					rs945635	G 0.60/0.54/0.54	>0.05/>0.05/>0.05	0.24/Not included	
					rs3761959	G 0.52/0.49/0.50	>0.05/>0.05/>0.05	0.80/Not included	
Christofolini et al. 2011a	Brazil	145/165/83	Allelic discrimination	BLyS	rs9514828	T 0.30/0.34/0.39	0.99/0.66/0.99	0.33/Not included	09
Christofoliniet al. 2011b	Brazil	206/201/80	PCR-RFLP	PROGINS	PR	C 0.07/0.05/0.08	Unrealized	0.56/Not included	08
				*ER*β	G + 1730A	A 0.15/0.20/0.22	Unrealized	<0.05/0.85	
				*LH*β	G1502A	A 0.20/0.35/0.16	Unrealized	<0.05/<0.05	
Gonçalves-Filho et al. 2011	Brazil	148/140/64	PCR–RFLP	PAI-1	rs1799889	5G0.58/0.48/0.53	Unrealized	<0.05/0.20	08
Teles et al. 2011	Brazil	167/167/60	Allelic discrimination	FCRL3	rs7528684	T 0.63/0.50/0.50	>0.05/>0.05/>0.05	<0.05/Not included	09
Bianco et al. 2012	Brazil	189/172/77	PCR–RFLP	*NFKβ1*	rs28362491	Del 0.47/0.38/0.31	0.65/0.50/ 0.97	<0.05/Not included	09
Peluso et al. 2013	Brazil	307/275/92	Allelic discrimination	TYK2	rs34536443	C 0.06/0.02/0.03	0.51/0.05/ <0.05	<0.05/Not included	06

Table II. Continuation.

Reference	Country	Sample sizeC/ ED/II	Genotypingmethod	Gene	Polymorphism(s)	Polymorphic allele frequencyC/ED/II	HWE C/ED/II	p value (genotypic frequency) (CxED/ EDxII)	Quality
					rs2304256	A 0.23/0.24/0.17	0.83/0.92/ 0.76	0.71/Not included	
					rs280523	A 0.89/0.91/0.89	0.92/0.35/ 0.07	0.25/Not included	
					rs12720270	T 0.17/0.19/0.13	0.30/0.78/ 0.96	0.42/Not included	
					rs12720356	G 0.93/0.93/0.95	0.28/0.99/ 0.90	1.0/Not included	
Wang et al.2014	China	225/146/65	Allele-specificPCR PCR–RFLP PCR	CYP19A1	rs2236722	C 0.05/0.03/0.01	>0.05/>0.05/>0.05	0.36/Not included	08
					rs700518	G 0.46/0.43/0.33	>0.05/>0.05/>0.05	0.11/Not included	
					rs10046	T 0.56/0.57/0.53	>0.05/>0.05/>0.05	0.64/Not included	
					[TTTA]n	L 0.57/0.58/0.56	>0.05/>0.05/>0.05	0.8/Not included	
Cavalcanti et al. 2016	Brazil	522/114/251	High-Resolution Melting	COX-2	rs20417	G 0.75/0.79/0.79	<0.05/0.30/0.08	Not included	09

Notes: *LHβ*: **Luteinizing Hormone Subunit Beta.** *ERβ*: **Estrogen Receptor Beta.** *FOXP3*: **Forkhead Box P3.** *BLyS*: **B-Lymphocyte Stimulator.** *PROGINS*: **Progesterone Receptor.** *ERβ*:**Estrogen Receptor Beta.** *PAI-1*: **Plasminogen Activator Inhibitor 1**. *NFKβ1:* **Nuclear Factor Kappa B Subunit 1**. *TYK2*: **Tyrosine Kinase 2.** *COX-2*: **Cyclooxygenase 2.**

Variations in the *KAZN* gene may contribute to endometrial cell adhesion outside the uterine cavity and would justify the role of the rs10928050 polymorphism in endometriosis associated with infertility (Christofolini et al. 2019, Vassilopoulou et al. 2019).

Just as the *WNT-4* gene, *PAI-1*, which belongs to the fibrinolytic system, is related to reproductive diseases such as polycystic ovary syndrome, gestational diabetes mellitus, pre-eclampsia and endometriosis. With a similar function in tumor cells, *PAI-1* promotes invasion of endometriotic cells during endometriosis. In general, an increased expression of *PAI-1* in the blood is associated with an increased risk of infertility and a worse pregnancy outcome (Ye et al. 2017). A recent study showed high expression of *PAI-1* in endometriosis and an association between *PAI-1* and worsening of dysmenorrhea, a common clinical sign in patients with this gynecological disease (Alotaibi et al. 2019). The rs1799889 polymorphism has been associated with an increased risk of developing endometriosis and infertility (Gonçalves-Filho et al. 2011). It has also been linked to gestational diabetes mellitus and polycystic ovary syndrome (Ye et al. 2017). A systematic review carried out to assess the role of genetic polymorphisms in endometriosis did not find any association of the *PAI-1* gene rs1799889 polymorphism, whose official symbol is *SERPINE1*, with endometriosis (Méar et al. 2020).

Finally, the *NFE2L3* gene encodes a transcription factor that participates in the regulation of cell differentiation, inflammation and carcinogenesis (Cardoso et al. 2020). A meta-analysis showed that four Genome-Wide Association Study (GWAS) found a strong association of SNP loci in endometriosis, including the rs12700667 polymorphism located between the *NPVF* and *NFE2L3* genes at 7p15.2 (Sapkota et al 2015). This polymorphism is located

upstream of the gene family cluster, which includes *HOXA 10* (Homeobox A10) and *HOXA 11* (Homeobox A11), transcription factors that may play important roles in uterine development. The *HOXA 10* gene may also be involved in the regulation of embryo implantation and other aspects of endometriosis, which may partially explain the infertility in these patients (Fung et al. 2015).

Endometriosis is a complex disease characterized by a chronic estrogen-dependent inflammatory process that primarily affects pelvic tissues, including the ovaries (Bulun et al. 2019). When endometrial tissue grows outside the uterine cavity, progesterone and estrogen signaling are disrupted, often resulting in progesterone resistance and estrogen dominance. This hormonal imbalance leads to increased inflammation and can also increase pelvic pain from the disease and decrease endometrial receptivity to embryo implantation. A review of the literature focuses on the molecular mechanisms that govern progesterone and estrogen signaling that support endometrial function and how they become deregulated in endometriosis. This approach is important to understand how these mechanisms contribute to the pelvic pain and infertility associated with endometriosis, as it may open new avenues for medical therapies aimed at providing relief to millions of women suffering from their effects (Marquardt et al. 2019). For this reason, polymorphisms in the *ESR1* and *ESR2* genes, the latter also known as *ER-β*, may be related to endometriosis. A meta-analysis including 17,045 cases of endometriosis and 191,596 controls identified five new gene loci involved in sex steroid hormone pathways significantly associated with the risk of endometriosis, including *ESR1* (Sapkota et al. 2017). Another meta-analysis published in 2016 was conducted to analyze associations between the three *ESR1* gene polymorphisms and endometriosis. Only the (TA)n polymorphism could contribute to susceptibility to, or the protection against, the pathogenesis of endometriosis (Zhao et al. 2016).

The 17β-hydroxysteroid dehydrogenase 1 protein, with several isoforms expressed in the endometrium, participates in estrogen metabolism pathways by catalyzing the conversion of estrone to a biologically active form of estradiol in the final phase of estrogen synthesis (Mu et al. 2015, Gibson et al. 2020). The rs605059 polymorphism of the *HSD17B1* gene has been investigated in some studies and has shown an association with risk of endometrial cancer, endometriosis, uterine myoma and stage I and II infertility (Osiński et al. 2018a, Mu et al. 2015). However, a study that evaluated the expression of this gene did not show differences in the levels of transcripts in the eutopic endometrium of fertile women compared to infertile women with endometriosis (Osiński et al. 2018b).

Cytochrome P450 enzymes participate in androgen synthesis through cholesterol metabolism. The P450c17α enzyme, encoded by the *CYP17A1* gene, participates in the conversion of androgens (androsteredione and testosterone) into estrogens (estrone and estradiol). Androgens have an impact on processes related to the establishment of endometriotic lesions (such as proliferation, tissue remodeling and repair), which are characterized by high concentrations of testosterone (Simitsidellis et al. 2018). The rs743572 polymorphism of this gene may be associated with increased estradiol production. The study by Cong et al. in 2018 showed that the T allele of this polymorphism could act as a risk factor for endometriosis, although it has no effect on disease stages and its characteristics. In addition, according to Méar et al. 2020 this

gene and its polymorphism was associated with endometriosis; confirmation is required, though.

Endometriosis can also lead to ovulatory dysfunction, compromised folliculogenesis, defective implant, ectopic endometrial changes, abnormal peritoneal immune environment, and luteal phase problems leading to infertility (Caldeira et al. 2017). The effect of hormones involved in folliculogenesis, such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), have a direct effect on endometriosis that remains unclear (Zondervan et al. 2018). The *LHR* gene is expressed in theca cells in the ovary, also in granulosa and cumulus cells. The rs4539842 (insLQ) polymorphism is characterized by the insertion of the CTCCAG sequence that results in the insertion of two amino acids (Leu-Gln/LQ) and is involved in the production of estradiol (Borgbo et al. 2018), while the change in position 1502 of the *LHB* gene may have a potential effect on LH function and may be related to endometriosis and infertility.

AMH (Anti-Mülerian Hormone) is an important hormone, especially in reproductive organs of women, and a promising biomarker in reproductive medicine (Bedenk et al. 2020). A previous study showed a possible involvement of AMH in endometriosis through the high expression of protein and mRNA in the endometrium and endometriotic lesions (Carrarelli et al. 2014). Other recent research reported a decrease in AMH, suggesting a reduction in ovarian reserve in patients with endometriosis, especially in those with advanced stage ovarian endometrioma (Tian et al. 2021).

Inflammation is known to be the central process of endometriosis. It can lead to pain, remodeling of neighboring tissues, fibrosis, adhesion formation and infertility (Bulun et al. 2019). The influence of immune cells on the onset and progression of endometriosis is discussed in detail in a recent narrative review of the literature (Crispim et al. 2021). In this sense, polymorphisms in genes related to inflammation and immune response may contribute to endometriosis and infertility.

The *FCRL3* gene rs7528684 polymorphism has been investigated in several autoimmune diseases, such as systemic lupus erythematosus (Song et al. 2013), multiple sclerosis (Yuan et al. 2016), rheumatoid arthritis (Lin et al. 2016), among others. A systematic review and meta-analysis was conducted to investigate an association between endometriosis and autoimmune diseases considering that abnormalities in the immune system have been suggested to explain the origin of ectopic endometrial tissues. The results showed that genetic analyzes are needed to clarify whether endometriosis is a risk factor for, or a consequence of, autoimmune diseases, and whether these two types of disorders share pathophysiological mechanisms, even if they arise independently (Shigesi et al. 2019).

Like the *FCRL3* gene, *FOXP3* is also related to the development of autoimmune diseases, with the rs3761549 polymorphism being significantly associated with susceptibility to Graves' disease in two independent meta-analyses (Li et al. 2020, Tan et al. 2021). However, this polymorphism exhibited no association with cancer susceptibility (Cheng et al. 2018, Chen et al. 2019), despite endometriosis evidencing common features with carcinogenesis. However, two new pathogenic variants of the *FOXP3* gene cause male infertility, suggesting a possible role for this gene in human fertility (Qiu et al. 2019).

Inflammation plays a vital role in the onset and progression of endometriosis. The *NFκB* gene is an important inflammatory regulator in this disease, as it induces cell proliferation, inflammation and inhibits the apoptotic process (Samimi et al. 2019). It participates in the regulation of cytokines and is active in peritoneal endometriotic lesions, possibly due to the

increased level of pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and Interleukin-8 (IL-8), which are associated with infertility in the microenvironment of the lesions (Zondervan et al. 2018, Samimi et al. 2019). The rs2836249 polymorphism, characterized by the deletion of four nucleotides in the gene's promoter region, leads to lower levels of transcripts that modify mRNA stability (Fu et al. 2017). However, the only study that analyzed this polymorphism in endometriosis showed that the deletion was associated with infertility in these conditions (Bianco et al. 2012). A study published in 2016 analyzed 209 patients with recurrent implantation failures and showed statistically significant differences observed in allelic and genotypic frequencies of the rs28362491 promoter in the *NF-κB* gene, important in embryonic implantation (Luo et al. 2016). This previous finding could explain the contribution of this polymorphism to the etiology of infertility associated with endometriosis.

Regarding the chromosomal location of genes with polymorphisms that exhibited statistical results, our findings corroborate previous studies, which also identified polymorphisms with risk of endometriosis on chromosomes 1, 6 and 7 (Kiesel & Sourouni 2019, Cardoso et al. 2019).

Furthermore, the *ESR1*, *CYP17A1*, *MUC4*, *KAZN*, *WNT4* and *NFE2L3* genes identified in this review are considered candidate genes associated with the development of endometriosis (Vassilopoulou et al. 2019, Cardoso et al. 2020, Smolarz et al. 2020). A recent review showed that the following genes might be responsible for potential risk factors for endometriosis-associated infertility: *ESR1*, *ESR2*, *LHB*, *FOXP3*, *FCRL3*, *CYP171A1*, *MUC17*, *WNT4*, and *NFKB1* (Smolarz et al. 2020).

One of the limitations of the present study was the fact that the meta-analysis was not performed, which constitutes an important statistical support to evidence, in a more robust way, possible biomarkers in infertility in patients with endometriosis. Although the ethnicity factor has not been considered, one must emphasizes that in studies with genetic polymorphisms it is possible that specific risk alleles act differently, in different populations, in the pathogenesis of these conditions. However, this systematic review represents an advance in the search for biomarkers related to infertility and endometriosis, as there is a consensus in the literature on the need for non-invasive diagnostic tests to identify women with a high predisposition to endometriosis.

The results of these studies suggest that polymorphisms rs882605 of the *MUC4* gene, rs16826658 of the *WNT4* gene, rs10953316 of the *MUC17* gene, rs10928050 of the *KAZN* gene, rs1799889 of the *PAI-1* gene, (TA)n repeats of the *ESR1* gene, (CA)n repeats of the *ESR2* gene, rs605059 of the *HSD17B1* gene, rs743572 of the *CYP17A* gene insLQ from the *LHR* gene, p.Ile49Ser from the *AMH* gene, rs12700667 from the *NPVF/NFE2L3* gene, G1502A from the *LHβ* gene, G + 1730A from the *ERβ* gene, rs7528684 from the *FCRL3* gene, rs3761549 from the *FOXP3* gene and the rs28362491 of the *NFK1* gene are implicated in the etiology of infertility in women with endometriosis.

Acknowledgments

The authors would like to thank FAPEMIG (Fundação de Amparo à Pesquisa do Estado de Minas Gerais) and the Vice-Rectory of Research and Post Graduation (Pró-Reitoria de Pesquisa e Pós-Graduação) at UFTM for their financial support.

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How to cite

EGASHIRA EM, TROVÓ-MARQUI AB, TANAKA SCSV & CINTRA MTR. 2022. Investigation of biomarkers in Endometriosis-associated infertility: Systematic Review. An Acad Bras Cienc 94: e20211572. DOI 10.1590/0001-3765202220211572.

Manuscript received on December 16, 2021;
accepted for publication on January 1, 2022

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EME: contributed with data acquisition, interpretation and wrote the manuscript; ABTM: contributed with conception, data acquisition, interpretation and wrote the manuscript; SCSVT: contributed with data acquisition, interpretation and wrote the manuscript; MTRC: contributed with conception, data acquisition, interpretation and wrote the manuscript. All authors read and approved the final version of the manuscript.