Combined Effect of the PGR +331C > T, CYP17A1 -34A > G and CYP19A1 1531G > A Polymorphisms on the Risk of Developing Endometriosis

Efeito combinado dos polimorfismos PGR +331C > T, CYP17A1 -34A > G e CYP19A1 1531G > A no risco de desenvolvimento da endometriose

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Abstract

Purpose   To evaluate the magnitude of the association of the polymorphisms of the genes *PGR, CYP17A1* and *CYP19A1* in the development of endometriosis.

Methods   This is a retrospective case-control study involving 161 women with endometriosis (cases) and 179 controls. The polymorphisms were genotyped by real-time polymerase chain reaction using the TaqMan system. The association of the polymorphisms with endometriosis was evaluated using the multivariate logistic regression.

Results   The endometriosis patients were significantly younger than the controls (36.0 ± 7.3 versus 38.0 ± 8.5 respectively, $p = 0.023$), and they had a lower body mass index (26.3 ± 4.8 versus 27.9 ± 5.7 respectively, $p = 0.006$), higher average duration of the menstrual flow (7.4 ± 4.9 versus 6.1 ± 4.4 days respectively, $p = 0.03$), and lower average time intervals between menstrual periods (25.2 ± 9.6 versus 27.5 ± 11.1 days respectively, $p = 0.05$). A higher prevalence of symptoms of dysmenorrhea, dyspareunia, chronic pelvic pain, infertility and intestinal or urinary changes was observed in the case group when compared with the control group. The

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interval between the onset of symptoms and the definitive diagnosis of endometriosis was 5.2 ± 6.9 years. When comparing both groups, significant differences were not observed in the allelic and genotypic frequencies of the polymorphisms *PGR +331C > T, CYP17A1 -34A > G* and *CYP19A1 1531G > A*, even when considering the symptoms, classification and stage of the endometriosis. The combined genotype *PGR +331TT/CYP17A1 -34AA/CYP19A11531AA* is positively associated with endometriosis (odds ratio [OR] = 1.72; 95% confidence interval [95%CI] = 1.09–2.72).

Conclusions   The combined analysis of the polymorphisms *PGR-CYP17A1-CYP19A1* suggests a gene-gene interaction in the susceptibility to endometriosis. These results may contribute to the identification of biomarkers for the diagnosis and/or prognosis of the disease and of possible molecular targets for individualized treatments.

Resumo

Objetivo   Avaliar a magnitude de associação de polimorfismos nos genes *PGR, CYP17A1* e *CYP19A1* no desenvolvimento da endometriose.

Métodos   Este é um estudo retrospectivo do tipo caso-controle, envolvendo 161 mulheres com endometriose (casos) e 179 controles. Os polimorfismos foram genotipados pela reação em cadeia da polimerase em tempo real utilizando o sistema TaqMan. A associação dos polimorfismos estudados com a endometriose foi avaliada pela regressão logística multivariada.

Resultados   As pacientes com endometriose eram significativamente mais jovens do que os controles (36,0 ± 7,3 versus 38,0 ± 8,5, respectivamente, *p* = 0,023), apresentaram um índice de massa corporal menor (26,3 ± 4,8 versus 27,9 ± 5,7, respectivamente, *p* = 0,006), maior tempo médio de duração do fluxo menstrual (7,4 ± 4,9 versus 6,1 ± 4,4 dias, respectivamente, *p* = 0,03) e menor tempo médio do intervalo entre as menstruações (25,2 ± 9,6 versus 27,5 ± 11,1 dias, respectivamente, *p* = 0,05). Uma maior prevalência dos sintomas de dismenorreia, dispareunia, dor pélvica crônica, infertilidade, alterações intestinais e urinárias foi observada no grupo casos comparado ao grupo controle. O tempo médio entre o início dos sintomas e o diagnóstico definitivo de endometriose foi de 5,2 ± 6,9 anos. Comparando os dois grupos, não foram observadas diferenças significativas nas frequências alélicas e genotípicas dos polimorfismos *PGR +331C > T, CYP17A1 -34A > G* e *CYP19A1 1531G > A*, e nem considerando os sintomas, a classificação e o estadiamento da endometriose. O genótipo combinado *PGR +331TT/CYP17A1 -34AA/CYP19A11531AA* está associado positivamente com a endometriose (razão de possibilidades [RP] = 1,72; intervalo de confiança de 95% [IC95%] = 1,09–2,72).

Conclusões   A análise combinada dos polimorfismos *PGR-CYP17A1-CYP19A1* sugere uma interação gene-gene na susceptibilidade à endometriose. Estes resultados podem contribuir para a identificação de biomarcadores para o diagnóstico e/ou prognóstico da doença, assim como de possíveis alvos moleculares para um tratamento individualizado.

Introduction

Endometriosis is a benign gynecological estrogen-dependent disease characterized by the presence of endometrial tissue out of the uterine cavity, affecting nearly 10% of women of reproductive age. Symptoms may include dysmenorrhea, dyspareunia, chronic pelvic pain and infertility.[1] The pathogenesis and the molecular mechanisms that are involved in the development of endometriosis are not yet clear, and hereditary susceptibility is an area of growing investigation for the identification of genetic polymorphisms that may lead to an increased risk of developing the disease.[2,3]

Estrogen performs a fundamental role in endometriosis, which predominantly occurs in women of reproductive age who have high estrogen production.[4,5] An increase in enzyme expression is responsible for the estrogen synthesis and reduction of progesterone receptor (PGR) expression

observed in samples of endometrial injuries, but these phenomena are not found in controls.[6,7] As endometriosis is an estrogen-dependent disease, genetic polymorphisms involved in the biosynthesis and regulation of estrogens could be considered possible biomarkers for its diagnosis and/or prognosis. Cytochrome P450 17A1 (CYP17A1) is involved in the initial stages of estrogen synthesis, converting pregnenolone into 17α-hydroxypregnenolone and, subsequently, into dehydroepiandrosterone. Furthermore, cytochrome P450 19A1 (CYP19A1) acts in the final stage by converting androstenedione into estrone, and testosterone into estradiol.[4,8] The enzyme CYP17A1, also known as 17 α-hydroxylase, is encoded by the gene with the same name, located in chromosome 10q24.3.[8] The single nucleotide polymorphism (SNP) *CYP17A1 -34A > G* is located in the 5′ untranslated region (UTR) of the *CYP17A1* gene, and it causes a significant increase in the expression of 17 α-hydroxylase.[8] A different gene product, the aromatase enzyme, is encoded by the gene *CYP19A1*, which is located in chromosome 15q21. The SNP *CYP19A1 1531G > A* is found in the 3′UTR of this gene, and it causes a significant change in the levels of circulating estradiol.[8] Progesterone is also involved in the pathogenesis of endometriosis, as it is a strong antagonist of estrogen, and thus plays an essential role in the regulation of endometrial cell proliferation.[6] The *PGR* gene, located in chromosome 11q22–q23, is responsible for encoding both progesterone receptor isoforms (PR-A and PR-B) by transcribing from alternative promoters.[9] The SNP *PGR +331C/T*, located in the gene promoter region, creates an additional TATA box, and causes higher transcription of PR-B.[9]

As the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* are located near potential elements that regulate their respective genes, interfering with the levels of expression of the corresponding proteins, it becomes relevant to evaluate the influence of these SNPs in the development of endometriosis. To date, 12 studies have evaluated the association of the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* in the development of endometriosis in different populations. However, the results of the analyses are controversial.[10–21] In this context, the objective of this study was to evaluate the magnitude of the association of the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* with the development of endometriosis in women treated in two public reference hospitals in Brazil.

Methods

Study Design

This was a retrospective, case-control study approved by the Human Research Ethics Committees of two of our institutions (under protocols number 414/11 and 1.244.29 respectively), both located in the city of Rio de Janeiro, Brazil. All participating patients ($n = 340$) provided written informed consent, and visited one of the two institutions between March 2011 and October 2015. The research was conducted in accordance with the Declaration of Helsinki, which was revised in 2008. Patients with a surgical diagnosis (after

laparoscopy or laparotomy) of endometriosis with histological confirmation of the disease, as well as those diagnosed by magnetic resonance imaging (MRI), were considered the case group ($n = 161$). The control group ($n = 179$) consisted of women with a negative diagnosis of endometriosis, after laparoscopy or laparotomy for tubal ligation ($n = 48$) or for the treatment of benign diseases, such as myoma ($n = 52$), ovarian cysts ($n = 30$), hydrosalpinx ($n = 5$), or for other reasons ($n = 44$). Women with any history or diagnosis of cancer or adenomyosis were excluded.[2]

The stage of the endometriosis was determined according to the revised American Fertility Society classification, which divides the disease into four stages: I (minimum), II (mild), III (moderate) and IV (severe).[22] Regarding the classification of the endometriosis, we considered the proposal of Nisolle and Donnez:[23] superficial endometriosis (SUP), ovarian endometrioma (OMA), and deep infiltrative endometriosis (DIE). Superficial endometriosis and ovarian endometrioma may be found in association with deep endometriosis,[24] and the cases in which this association was observed were considered DIE.

The body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Only severe and incapacitating symptoms of pain were included. Women who failed to conceive after one year of regular, contraceptive-free intercourse were considered infertile. Cyclical intestinal or urinary symptoms were defined as bowel and/or urinary pain and/or bleeding coinciding with menstrual periods.

Genotyping

Genomic DNA was extracted from the peripheral blood sample using a genomic DNA extraction kit (Genomic DNA Extraction, Real Biotech Corporation, Banqiao City, Taiwan), according to the manufacturer's instructions.

Genotyping of *PGR +331C > T* (rs10895068), *CYP17A1 -34A > G* (rs743572) and *CYP19A1 1531G > A* (rs10046) SNPs was performed by real-time polymerase chain reaction (PCR) using the TaqMan system. Oligonucleotides and probes specific to each SNP were obtained from Applied Biosystems: rs10895068 (C_27858738_10), rs743572 (C_2852784_30) and rs10046 (C_8234731_30). For all SNPs, PCRs were performed with 30 ng of template DNA, 1× TaqMan Universal Master Mix (Applied Biosystems, Foster City, CA, US), and with each primer and probe assay at 1× dilution, and H2O to 8µL. The PCR conditions were: 95°C for 10 minutes, followed by 40 cycles of denaturation at 92°C for 15 seconds, and annealing at 60°C for 1 minute. Allele-detection was performed on a 7500 Real-Time System (Applied Biosystems, Foster City, CA, US), and the genotypes were then determined directly.

Statistical Analyses

The continuous variables were expressed as the mean $\pm$ standard deviation (SD), and the differences between means were evaluated using the Student's t-test. The categorical data were expressed as percentages, and evaluated by the Chi-square (χ2) test or Fisher's exact test, when applicable. For each SNP, the Hardy-Weinberg equilibrium (HWE) was calculated, and the allelic and genotypic

Table 1 Demographic and clinical characteristics of the study population ($N = 340$)

Variable	Controls (N = 179)	Cases (N = 161)	p^*
Age (years)	n (%)		
18–29	30 (16.8)	29 (18.0)	0.011
30–39	60 (33.5)	79 (49.1)	
$\geq$ 40	86 (48.0)	48 (29.8)	
No information	3 (1.7)	5 (3.1)	
Marital status			
Married/partner	96 (53.6)	111 (68.9)	0.046
Single	53 (29.6)	38 (23.7)	
Divorced/Widow	5 (2.8)	1 (0.6)	
No information	25 (14.0)	11 (6.8)	
Level of Schooling			
Elementary education	38 (21.3)	24 (14.9)	< 0.001
High school	89 (49.7)	60 (37.3)	
Higher education	26 (14.5)	67 (41.6)	
No information	26 (14.5)	10 (6.2)	
BMI			
< 18.5	3 (1.7)	7 (4.4)	0.013
18.5–24.9	48 (26.8)	48 (29.8)	
25–29.9	50 (27.9)	63 (39.1)	
30–40	65 (36.3)	35 (21.7)	
> 40	13 (7.3)	8 (5.0)	
Infertility			
Primary	19 (10.6)	53 (32.9)	< 0.001
Secondary	3 (1.7)	16 (9.9)	
None**	133 (74.3)	58 (36.1)	
No attempt	20 (11.2)	32 (19.9)	
No information	4 (2.2)	2 (1.2)	
Parity			
0	19 (10.6)	53 (32.8)	< 0.001
1	23 (12.8)	37 (23.0)	
2	58 (32.5)	27 (16.8)	
3 or more	55 (30.7)	10 (6.2)	
No attempt	20 (11.2)	32 (20.0)	
No information	4 (2.2)	2 (1.2)	
Symptoms***			
Dysmenorrhea	29 (16.1)	77 (47.5)	< 0.001
Chronic pelvic pain	70 (38.9)	124 (76.5)	
Dyspareunia	50 (27.8)	102 (63.0)	
Cyclical urinary complaints****	9 (6.4)	41 (27.5)	
Cyclical intestinal complaints****	8 (6.0)	74 (49.7)	

Abbreviation: BMI, body mass index.
Notes:*p-value obtained by Pearson's Chi-squared (χ2) test. **Number of fertile women. ***The same woman can have more than one symptom.
****Pain or bleeding during the menstrual period.

distributions were compared between cases and controls by the χ2 test or Fisher's exact test. To evaluate the association between the SNPs and the development of endometriosis, as well as the presence of symptoms, the classification and staging of the disease were used to estimate the odds ratios (ORs) and their respective 95% confidence intervals (95% CIs), with adjustment for possible confounding factors, using a multivariate logistic regression. Values of $p < 0.05$ were considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 20.0.

Results

The endometriosis cases were diagnosed through laparoscopy ($n = 90$, 55.9%), laparotomy ($n = 27$, 16.8%) or MRI ($n = 44$, 27.3%), and 87 (54%) were classified as DIE. Of the 117 surgery cases, 37 (31.6%) presented stages I-II diseases, and 80 (68.4%) presented stages III-IV. The most common locations of the endometriotic lesions were in the ovary (31%), followed by the intestine (19%), and the uterosacral ligaments (15%). The average age of the endometriosis patients at the time of diagnosis was 31.5 ± 7.5, and the average time for disease diagnosis, which was the time since the beginning of the symptoms until the definitive diagnosis, was 5.2 ± 6.9 years.

In ►Table 1, the demographic and clinical data from the study population are described. The patients with endometriosis were significantly younger than the controls (36.0 ± 7.3 versus 38.0 ± 8.5 respectively, $p = 0.023$), and presented a higher education level (41.6% versus 14.5%), as well as a lower BMI (26.3 ± 4.8 versus 27.9 ± 5.7 respectively, $p = 0.006$). The number of infertile women (primary or secondary) was significantly higher in the case group (42.9%) than in the control group (12.3%), and nearly 63% of the women from the control group had 2 or more children. The patients with endometriosis presented a higher prevalence ($p < 0.001$) of symptoms, including dysmenorrhea, dyspareunia, chronic pelvic pain, and urinary and intestinal changes. Considering the characteristics of the menstrual cycle, a significant difference was detected between cases and controls in relation to the average duration of the menstrual flow (7.4 ± 4.9 versus 6.1 ± 4.4 days respectively, $p = 0.03$) and the average interval between menstrual periods (25.2 ± 9.6 versus 27.5 ± 11.1 days respectively, $p = 0.05$).

When comparing the allelic and genotypic frequencies of the SNPs PGR +331C > T, CYP17A1 -34A > G and CYP19A1 G > A between the cases and controls (►Fig. 1), no significant differences were detected, even when considering the staging and endometriosis classification (data not shown). The allelic distribution of the SNPs PGR +331C > T, CYP17A1 -34A > G and CYP19A1 G > A in relation to the absence or presence of symptoms (dysmenorrhea, pelvic pain, dyspareunia, infertility, and urinary and intestinal problems, for example) in the endometriosis patients is summarized in ►Fig. 2. Considering the symptoms of the disease, no significant differences were found.
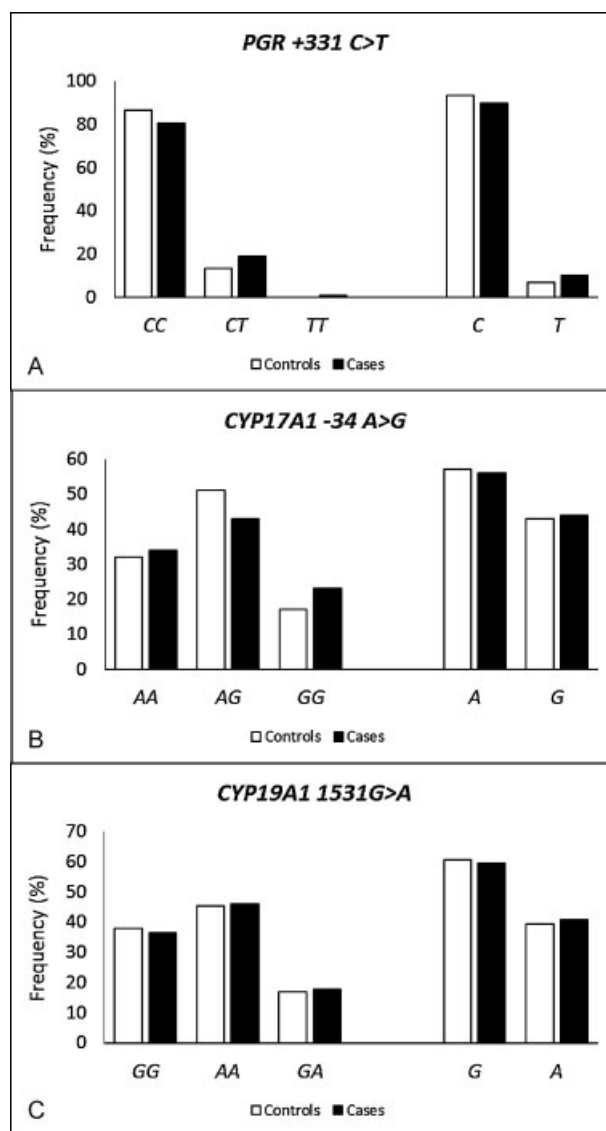

Fig. 1 Allelic and genotypic frequencies of the polymorphisms PGR +331C > T, CYP17A1 -34A > G and CYP19A1 G > A in the study population.

A combined analysis of the three studied SNPs (PGR +331C > T, CYP17A1 -34A > G and CYP19A1 G > A), compared between the endometriosis cases and controls, was performed to investigate whether the presence of more than 1 SNP would increase the risk of developing the disease (►Table 2). It has been observed that relative to the combined wild-type genotype (PGR +331CC/CYP17A1 -34AA/CYP19A11531GG), the combined genotype PGR +331TT/CYP17A1 -34AA/CYP19A11531AA is associated with an increased risk of developing endometriosis. A combined analysis of the PGR +331C > T, CYP17A1 -34A > G and CYP19A1 G > A genotypes was also performed in relation to the absence or presence of symptoms (dysmenorrhea, pelvic pain, dyspareunia, infertility, and urinary and intestinal problems, for example) in the endometriosis patients. However, no significant differences were found (data not shown).

In ►Table 3, we describe the variant allele frequencies of the SNPs PGR +331 T, CYP17A1 -34 G and CYP19A1A in
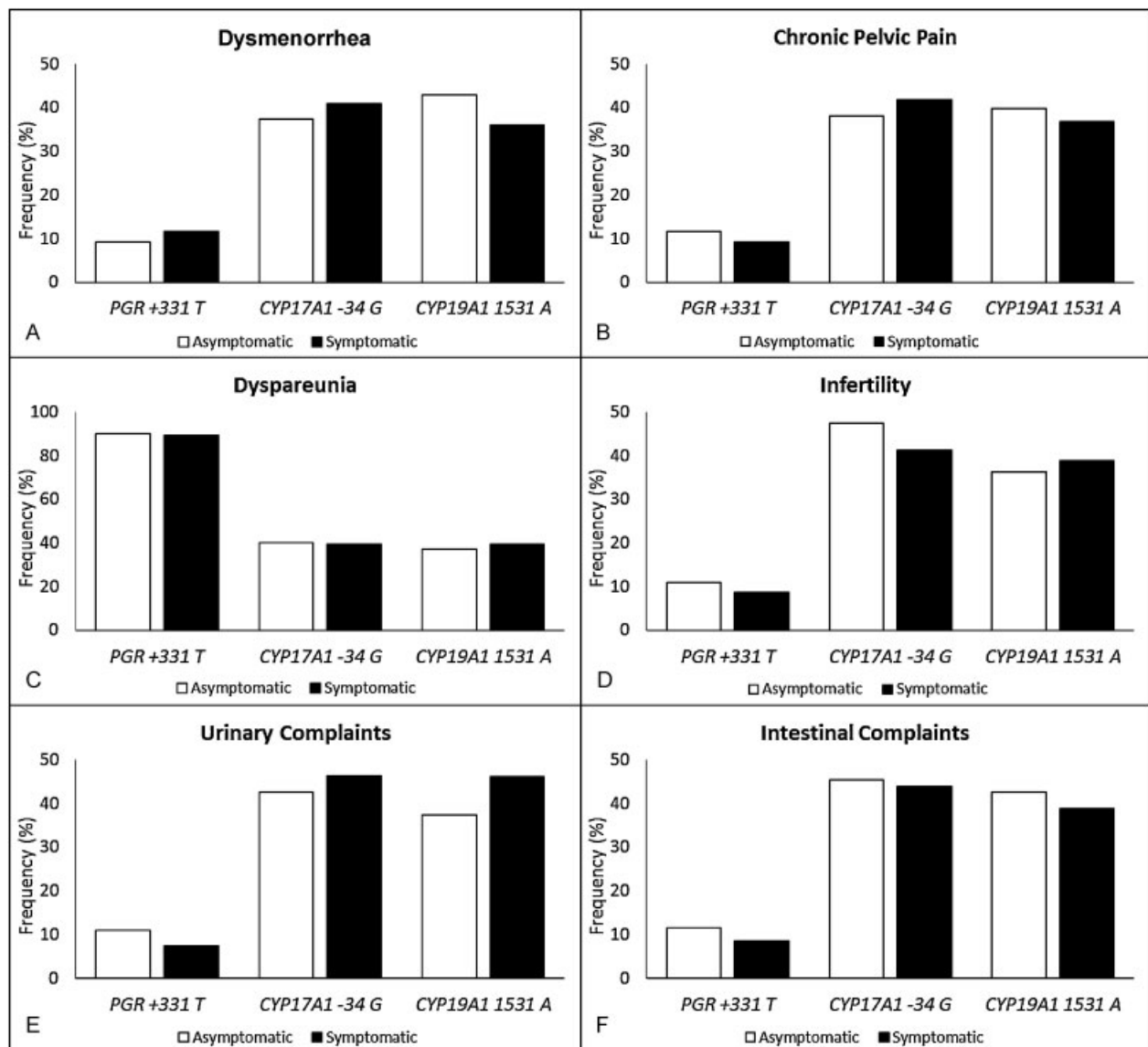
Fig. 2 Minor allelic frequencies of the polymorphisms studied among symptomatic and asymptomatic endometriosis patients.

different populations. The allele frequency *PGR +331 T* varied between 2% and 10% and 5% and 10% in the cases and controls respectively, based on 3 studies that have evaluated this SNP, including the present one. The SNP rs743572 has been evaluated in 7 studies, in addition to the present study, and the frequency of the *CYP17A1 -34 G* allele varied between 35% and 58% in the cases and between 31% and 63% in the controls. In addition to our study, 4 other studies also evaluated the SNP rs10046, and the allele frequency of *CYP19A1 1531A* varied between 35% and 58% and between 41% and 60% in the cases and controls respectively.

Discussion

Endometriosis is a complex multifactorial gynecological disease caused by the combination of hormonal, genetic and environmental factors, as well as immunological processes. Estrogen and progesterone are essential in the regu-

lation of endometrial tissue growth, and, as such, they may play a central role in the pathogenesis of endometriosis.[5,6] In this study, a positive association between the combined genotype *PGR +331TT/CYP17A1 -34AA/CYP19A1 1531AA* and the development of endometriosis was observed.

Supporting our results, neither Lamp et al,[18] in Estonia, nor Trabert et al,[19] in the United States, could find an association with only the *PGR +331T* allele. However, van Kaam et al,[15] in the Netherlands, observed a protective effect (OR = 0.22; 95%CI = 0.06–0.77) for the development of endometriosis. In agreement with our findings, 5 studies from China,[13] Japan,[10] Turkey,[17] Italy[16] and the United States[19] failed to observe an association between the SNP *CYP17A1 -34G* and endometriosis. However, 2 studies in the Chinese population[11,12] found a positive association between endometriosis and the *CYP17A1 -34A* allele ($p = 0.046$ and $p = 0.009$). With relation to the SNP *CYP19A1 1531G > A*, none of the studies found an association with endometriosis,

Table 2 Combined genotype frequencies of the polymorphisms *PGR +331C > T, CYP17 -34A > G* and *CYP19 1531G > A* between controls and cases, and their association with the risk of endometriosis

Genotypes	Controls N (%)	Cases N (%)	p *	OR (95%CI)**
PGR +331C > T, CYP17 -34A > G and *CYP19 1531G > A*				
WT / WT / WT	23 (13.5)	11 (7.3)		1***
WT / WT / VAR	29 (17.1)	28 (18.6)	0.20	1.82 (0.73–4.57)
WT / VAR / VAR	70 (41.2)	60 (40.0)	0.17	1.35 (0.88–2.05)
VAR / WT / WT	2 (1.2)	4 (2.7)	0.18	1.57 (0.82–3.00)
VAR / VAR / WT	7 (4.1)	10 (6.7)	0.20	1.23 (0.90–1.67)
VAR / WT / VAR	1 (0.6)	7 (4.7)	0.02	1.72 (1.09–2.72)
WT / VAR / WT	25 (14.7)	22 (14.7)	0.15	1.13 (0.96–1.34)
VAR / VAR / VAR	13 (7.6)	8 (5.3)	0.87	1.02 (0.85–1.21)

Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.
Notes: WT/WT/WT, *CC/AA/GG*; WT/WT/VAR, *CC/AA/GA* or *CC/AA/AA*; WT/VAR/VAR, *CC/GG/AA* or *CC/AG/GA* or *CC/AG/AA* or *CC/GG/GA*; VAR/WT/WT, *CT/AA/GG* or *TT/AA/GG*; VAR/VAR/WT, *CT/AG/GG* or *CT/GG/GG* or *TT/AG/GG* or *TT/GG/GG*; VAR/WT/VAR, *CT/AA/GA* or *CT/AA/AA* or *TT/AA/GA* or *TT/AA/AA*; WT/VAR/WT, *CC/GG/GG* or *CC/AG/GG*; VAR/VAR/VAR, *TT/GG/AA*; *p-value obtained through the Chi-squared test (Pearson *P*-value) or Fisher's exact test. **Adjusted by age and BMI. ***Reference group.

Table 3 Frequency of the studied polymorphisms among different populations (endometriosis patients and controls)

Polymorphism	Population	N*	Frequency among the controls (%)	Frequency among the cases (%)	Association with endometriosis	Reference
PGR +331 C > T (rs10895068)			*PGR +331 T*			
	Estonia	349	8.8	6.7	No association	Lamp et al[18]
	United States	823	4.8	5.1	No association	Trabert et al[19]
	Netherlands	165	9.7	2.3	Protective (T allele)	van Kaam et al[15]
	Brazil	179	6.6	10.1	No association	Present study
CYP17A1 -34 A > G (rs743572)			*CYP17A1 -34 G*			
	Turkey	93	30.8	57.6	No association	Bozdag et al[17]
	China	247	60.2	50.8	Risk (A allele)	Hsieh et al[11]
	China	227	62.9	50.8	Risk (A allele)	Hsieh et al[12]
	China	510	54.3	58.2	No association	Juo et al[13]
	Japan	317	39.8	42.9	No association	Kado et al[10]
	United States	823	39.3	34.8	No association	Trabert et al[19]
	Italy	190	37.2	42.3	No association	Vietri et al[16]
	Brazil	180	42.7	44.4	No association	Present study
CYP19A1 1531 G > A (rs10046)			*CYP19A1 1531 A*			
	Korea	412	55.9	55.8	No association	Hur et al[14]
	Estonia	349	59.8	55.0	No association	Lamp et al[18]
	China	371	56.4	57.5	No association	Wang et al[20]
	China	202	41.0	35.3	No association	Yang et al[21]
	Brazil	180	39.4	40.6	No association	Present study

Abbreviations: CYP17A1, cytochrome P450 17A1; CYP19A1, cytochrome P450 19A1; PGR, progesterone receptor.
Note: *N total number of individuals included in the study (cases + controls).

which is similar to our results.[14,18,20,21] To date, no study has investigated the combined effect of the SNPs *PGR +331TT/ CYP17A1 -34AA/CYP19A1 1531AA* on the development of endometriosis.

The strength of the present study is that it is the first study performed in the Brazilian population that evaluated the SNPs *PGR +331C > T*, *CYP17A1 -34A > G* and *CYP19A1 1531G > A* in terms of endometriosis development, while considering the symptoms of the disease. All control patients were surgically evaluated to confirm a negative diagnosis of endometriosis; 27% of them had previously undergone sterilization, and 63% had already had 2 or more children. A limitation of this study was that the controls also included women with other gynecological diseases, providing lower risk estimations. Furthermore, considering the endometriosis patients, 27% were diagnosed by MRI. However, this has been a specific and accurate method for the detection of deep endometriosis.[25–28]

In conclusion, the combined analysis of the polymorphisms *PGR-CYP17A1-CYP19A1* suggests a gene-gene interaction in the susceptibility to endometriosis. The results may contribute to the identification of genetic biomarkers that are able to help in disease diagnosis and/or prognosis, as well as in the identification of possible molecular targets for individualized treatments.

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