Anticardiolipin antibodies and recurrent spontaneous abortion in Brazilian women

Anticorpos anticardiolipina e abortos espontâneos recorrentes em mulheres brasileiras

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ABSTRACT

Aims: To determine the frequency of anti-cardiolipin antibodies (aCL) in women with previous history of recurrent spontaneous abortion (RSA).

Methods: Medical records from pregnant women seen from April 2005 to December 2008 at the High-Risk Pregnancy Unit at the Hospital de Base from FUNFARME (Fundação Faculdade Regional de Medicina), in São José do Rio Preto, São Paulo, Brazil, were revised. Patients older than 18 years who had at least two spontaneous abortions and who were tested for aCL were included in the study. Data on maternal age, number of miscarriages and the results of serological tests for aCL were recorded. The exact Fisher's test was used to compare the results. A p value less than 0.05 was considered significant.

Results: During the study period a total of 294 pregnant women were seen, from whom 44 consecutive women fulfilled the inclusion criteria. The overall mean age was 33.8±5.4 years (range: 22 to 44; median: 34). Eighteen (40.9%) patients were reagent for aCL and 26 (59.1%) non-reagent, and the difference between their mean age was not statistically significant (reagent: 34.6±5.8 years; non reagent: 33.2±5.2 years, p=0.4001). Fourteen (77.8%) patients presented IgM aCL and six (33.2%), IgG aCL. Two patients (11%) were reagent for both IgM and IgG aCL. In the most of cases the aCL antibody titers were compatible with low risk for pregnancy morbidity. The number of abortions ranged from two to six. The average number of abortions among those reagent for aCL was 3.5±1.1 and in those non-reagent was 2.9±1.1 (p=0.0813).

Conclusions: The frequency of aCL was elevated among patients with a history of RSA, especially those having higher number of fetal losses. Among women with at least two spontaneous abortions, the mean number of abortions was not significantly different between those reagent for aCL and those non reagent.

KEY WORDS: antibodies, anticardiolipin; antibodies, antiphospholipid; abortion, spontaneous; miscarriage, recurrent; immunological markers; fetal death; high risk pregnancy.

RESUMO

Objetivos: Avaliar a frequência de anticorpos anticardiolipina (aCL) em mulheres com história prévia de aborto espontâneo recorrente (AER).

Métodos: No período de abril de 2005 a dezembro de 2008 foram avaliados os dados de prontuários de gestantes atendidas no Ambulatório de Gestação de Alto Risco do Hospital de Base da Fundação Faculdade Regional de Medicina (FUNFARME), em São José do Rio Preto, São Paulo, Brasil. Foram incluídas neste estudo pacientes com idade acima de 18 anos que tiveram pelo menos dois abortos espontâneos e foram avaliadas para aCL. O teste exato de Fisher foi usado para comparar os resultados. Valor de p menor que 0,05 foi considerado significante.

Resultados: Um total de 294 mulheres gestantes foram avaliadas durante o período do estudo, das quais 44 atendiam aos critérios de inclusão. A média de idade foi 33,8±5,4 anos (variação: 22 a 44; mediana: 34). Dezoito pacientes (40,9%) foram reagentes para aCL e 26 (59,1%) não reagentes, e a diferença entre a média de idade não foi estatisticamente significante (reagentes: 34,6±5,8 anos; não reagentes: 33,2±5,2 anos, p=0,4001). Quatorze (77,8%) pacientes apresentaram aCL IgM e seis (33,2%) aCL IgG. Duas pacientes (11%) foram reagentes para ambas as classes de aCL, IgM e IgG. Na maioria dos casos os títulos de anticorpos aCL foram compatíveis com baixo risco para morbidade na gravidez. O número de abortos variou de dois a seis. O número médio de abortos entre as reagentes para aCL foi de 3,5±1,1 e entre as não reagentes foi de 2,9±1,1 (p=0,0813).

Conclusões: A frequência de aCL foi alta entre as pacientes com história de AER, especialmente entre aquelas que tiveram um maior número de perdas fetais. Entre as mulheres com pelo menos dois abortos espontâneos, a média do número de abortos não foi significativamente diferente entre aquelas reagentes e não reagentes para aCL.

DESCRITORES: anticorpos anticardiolipina; anticorpos antifosfolipídicos; aborto espontâneo; aborto habitual; marcadores imunológicos; morte fetal; gestação de alto risco.

INTRODUCTION

Recurrent spontaneous abortion (RSA) refers to three or more consecutive miscarriages and is one of the health problems that arouses medical and social impacts and interest. Many of the deleterious factors that contribute to the occurrence of RSA are highly complex and include genetics, endocrine, anatomical, immunological and idiopathic factors. These factors act separately or together in the selection of the *conceptus* at different stages, preventing fertilization and inhibiting implantation [1,2].

Among the immunological factors that contribute to RSA stands out the presence of anti-phospholipid antibodies (APA) like as anti-cardiolipin antibodies (aCL), anti-β_2-glycoprotein I (aβ_2-GPI) and lupus anticoagulants (LAC) [3]. These antibodies belong to different classes (IgM, IgG or both) and are considered independent risk factors for thrombotic events [4]. It is accepted that the positivity for just one of them is sufficient, along with clinical criteria, as predictive marker for thrombosis [5,6].

It is estimated that the rate of APA in the general population varies between 0.2% and 2%, but when present in pregnant women, the APA increase the risk of RSA [3,7]. Several studies have reported a higher frequency of APA in cases of RSA, especially related to intrauterine fetal growth restriction and pre-eclampsia [7-12]. However, the importance of the APA in RSA remains controversial [13,14]. The aim of this study was to determine the frequency of aCL in women with previous history of RSA.

METHODS

This study was conducted at the High-Risk Pregnancy Unit of the Hospital de Base from FUNFARME (Fundação Faculdade Regional de Medicina), a tertiary school hospital in São José do Rio Preto, São Paulo, Brazil. The study was approved by the Ethics Committee of the school of medicine Faculdade de Medicina de São José do Rio Preto (FAMERP), case 308/2008. All the data were retrospectively obtained from the patient medical records and the need for a written consent of patients was waivered.

Pregnant women attended from April 2005 to December 2008 at the High-Risk Pregnancy Unit, older than 18 years, who had at least two previous spontaneous abortions, and who were tested for the presence or absence of aCL, were included in the study. Maternal age, number of spontaneous abortions and results of serum tests for APA IgM and IgG enzyme-linked imunosorbent assay (ELISA) kit (DiaSorin, Italy) were recorded.

Exact Fisher's test was used to compare the results. An alpha error equal or less than 5% was considered acceptable.

RESULTS

From a total of 294 pregnant women seen at the High-Risk Pregnancy Unit in the study period, 44 consecutive patients fulfilled the inclusion criteria. The mean age of the selected women was equal to 33.8±5.4 years (minimum: 22, maximum: 44, median: 34).

Among the 44 patients, 18 (40.9%) were reagent for aCL and 26 (59.7%) non-reagent. The difference between the mean age of these groups were not statistically significant (reagent: 34.6±5.8 years, non-reagent: 33.2±5.2 years, p=0.400). The number of abortions reported ranged from 2 to 6 and the mean of this number in pregnant women reagent for aCL was 3.5±1.1, while in non-reagent was 2.9±1.1 (p=0.081). **(Table 1)**

Fourteen (77.8%) patients presented aCL IgM and six (33.2%), aCL IgG. Two (11%) women had both IgM and IgG aCL. The aCL antibody titers observed were compatible with low risk for pregnancy morbidity as proposed by manufacturer's package insert of the ELISA kit (DiaSorin, Italy). **(Table 2)**

Table 1. Serological profile of anti-cardiolipin antibodies in pregnant women with recurrent spontaneous abortion according to mean age and number of abortions.

Characteristics	Reagent for anti-cardiolipin antibodies (n=18)	Non-reagent for anti-cardiolipin antibodies (n=26)	p*
Age (years)			
Mean (±SD)	34.6 (±5.8)	33.2 (±5.2)	0.400
Median (range)	33.5 (23 – 44)	33.5 (22 – 44)	
Number of abortions			
Mean (±SD)	3.5 (±1.1)	2.9 (±1.1)	0.081
Median (range)	3 (2 - 6)	1.5 (2 - 4)	

* Student's t test.

Table 2. Profile of IgM and IgG anti-cardiolipin antibodies, titer and risk in pregnant women with recurrent spontaneous abortion.

Anti-cardiolipin antibody classes	N	%	Titer±SD (range)	Risk for pregnancy morbidity*
IgM	12	66.7	19.6±12.9 (11-53)	Low
IgG	4	22.2	16.2±3.0 (14-17)	Low
IgM + IgG	2	1.1	IgM: 13.5±3.5 (11-16)	Low
			IgG: 16.5±1.0 (16-17)	Low

* As proposed by manufacturer's package insert of ELISA kit (DiaSorin, Italy).

DISCUSSION

Research carried out on RSA in the last decades has devoted special attention to the importance of aCL antibodies as a risk factor to reproductive failure. There is evidence that they affect approximately 10% of cases of RSA [7,8,12]. These antibodies are specific to phospholipids expressed on the cell membrane and contribute to early fetal loss, potentially acting in reducing trophoblastic implantation [15,16]. The mean age of the selected pregnant women was higher than that observed in a recent study that compared women with and without previous history of RSA [17]. This finding is not surprising since women with a history of RSA tend to persist in attempts to conceive for longer.

The results reported here demonstrate that the prevalence of aCL is high in women with a history of RSA as more than 40% of them were shown to be reactive to these antibodies. These data are consistent with some studies [18,19] but not corroborate others [20,21]. These discrepancies may be due to several factors. It is possible that the lack of standardization of methods used to detect these antibodies contribute to the reported differences between this and the studies of Branch et al. [20] and Simpson et al. [21]. In addition, maternal thromboembolism when present can exert strong influence on the success of pregnancy obscuring the importance of aCL [22,23]. Previous observations reported a higher frequency of aCL in women with a history of RSA [12,23]. There are reports highlighting the importance of aCL in reproductive success in which they account for approximately 10% of cases of RSA [4,8]. The difference between the mean number of abortions found among pregnant women reagent and non-reagent for aCL was not statistically significant,

although there was a tendency to be higher in the reagent. Bearing in mind the small number of selected pregnant women and the p value, this result should be considered preliminary and must be confirmed by studies with larger number of patients or a metanalysis.

The percentage of aCL was high among pregnant women with previous history of RSA. More than three quarters of them had IgM aCL class, over one third had aCL IgG class and over 10% had both aCL classes. In all cases the aCL titers were compatible with low risk for pregnancy morbidity as proposed by manufacturer's package insert of the commercial kit used to detect aCL. These data seem to be in agreement with evidences showing no relationship between clinical manifestations and titers of aCL antibodies belonging to IgM class [6].

The importance of aCL antibody classes in RSA is still under discussion but there is consensus on the contribution of each of these classes of aCL in reproductive success. However, it has been suggested that aCL IgG react with higher avidity and this may have important implications for the pathophysiology of these antibodies in RSA. Moreover, these differences arising from the IgM and IgG classes appear to influence the adopted therapy for women with previous history of RSA.

The results of this study must be considered as preliminary since it enrolled a small number of patients. However it adds more information about the importance of aCL as a risk factor for RSA. Although additional investigations enrolling a high number of patients from other Brazilian regions would be desirable to confirm the data here reported, it can be concluded that the frequency of aCL is elevated in women with a previous history of RSA, especially those with a higher number of fetal losses.

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