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## Original Article

### The effect of anti-phospholipid syndrome on pregnancy outcomes in patients with habitual abortus

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#### ABSTRACT

**Objective:** The aim of this study was to research the pregnancy outcomes of women with anti-beta2 glycoprotein 1 and anti-cardiolipin antibody positivity and to determine the association with pregnancy morbidity.

**Materials and methods:** This retrospective study contained pregnant women with anti-beta2 glycoprotein 1 and anti-cardiolipin antibody positivity and a control group without these antibodies. Totally 190 sera sent from Obstetrics and Gynecology clinics between January 2019 and January 2023 were analyzed in the medical microbiology laboratory of xx.

**Results:** In a patient population separated into antibody-positive and antibody-negative groups, the gravida was found to be  $3.8 \pm 0.1$  and  $3.5 \pm 0.3$  respectively ( $p=0.333$ ). Parity was  $1.1 \pm 0.1$  and  $0.8 \pm 0.1$  ( $p=0.071$ ), abortion rates were  $2.3 \pm 0.1$  and  $2.5 \pm 0.2$  ( $p=0.659$ ), and gestational age was  $35.7 \pm 0.8$  and  $34 \pm 1.5$  ( $p=0.047$ ). Intrauterine fetal death was found to be higher in the antibody-positive group compared to the antibody-negative group ( $p=0.03$ ). There was no statistically significant difference between the two groups regarding additional pregnancy complications such as intrauterine growth restriction, oligohydramnios, gestational diabetes, and gestational hypertension (respectively  $p=0.623$ ,  $0.074$ ,  $0.312$ ,  $0.626$ ). However, smoking was significantly higher in the antibody-positive group ( $p=0.049$ ).

**Conclusion:** Antiphospholipid syndrome adversely affects pregnancy outcomes. During the initial visit, a thorough patient history should be obtained, and in pregnant women with a history of poor obstetric outcomes or habitual abortions, this syndrome should be considered.

**Keywords:** antiphospholipid syndrome; pregnancy complication; pregnancy outcome

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## Introduction

Among various antiphospholipid antibodies, especially anticardiolipin (aCA) and anti-B2-glycoprotein 1 (aβ2GP1) antibodies have been associated with poor pregnancy outcomes [1]. These antibodies identify many phospholipids and phospholipid-binding proteins during pregnancy and cause antiphospholipid syndrome characterized by hypercoagulopathy during pregnancy [2]. Antiphospholipid syndrome (APS) stands as an autoimmune disorder defined by non-inflammatory mechanisms, which can clinically present as both venous and arterial thrombosis, thrombocytopenia, and adverse outcomes during pregnancy, including fetal loss [3]. The occurrence of APS is approximated to be 5 instances per 100,000 individuals annually for incidence and 40-50 cases per 100,000 population annually for prevalence [4]. While the complete understanding of APS's pathogenesis remains elusive, the defining features of this condition involve the existence of antiphospholipid antibodies like lupus anticoagulant (LA), aCA antibodies, and aβ2GP1 antibodies [5]. These autoantibodies are thought to affect haemostasis and complement activation to promote thrombosis, although the underlying mechanisms are not yet clear [6].

Obstetrical issues associated with APS encompass repetitive early miscarriages, fetal demise, and later pregnancy complications like pre-eclampsia and fetal growth restriction (FGR) [7]. There's a proposition that these obstetrical issues arise from inadequate placental function triggered by the hindrance of trophoblast growth in the initial trimester, alongside compromised invasion/proliferation of extravillous trophoblasts and the occurrence of placental thrombosis [8].

Diligent obstetric surveillance and preventive measures involving low-dose aspirin (LDA) and low molecular weight heparin (LMWH) can yield favorable obstetric results in the majority of APS cases; however, complications still manifest in approximately 20-30% of pregnancies [9].

Several studies in the literature have described obstetric complications of APS [10,11]. Moreover, numerous investigations have recognized potential factors that could contribute to adverse obstetric results among women with AFS. These encompass a past record of thrombosis and pregnancy-related complications, the existence of other autoimmune disorders, positive testing for multiple antiphospholipid antibodies, reduced levels of complement proteins C3 and C4, and atypical readings from umbilical artery Doppler velocimetry during the 23-26 weeks of gestation [12,13]. Nevertheless, information regarding risk elements associated with pregnancy-related complications in APS-afflicted women is currently restricted.

The aim of this study was to evaluate the potential impact of positive Anti-Beta-2 Glycoprotein (aβ2GP1) and Anti-Cardiolipin antibodies on obstetric complications and pregnancy outcomes.

## Material and methods

### Study Centre and Participants

The study was conducted in the Medical Microbiology and Gynaecology Clinic of Tepecik Education and Research Hospital, between January 2019 and January 2023. Blood samples of patients with habitual abortus were collected for

measurement of antiphospholipid antibodies. Patients with antibody positivity were assigned to study group and patients with antibody negativity were assigned to control group. During pregnancy follow-up, blood sera were obtained from 190 patients, including 133 patients who exceeded the 20th gestational week and developed complications during pregnancy and 57 control group. Patients with uterine anomalies and genetic disorders were excluded. aCA and aβ2GP1 antibody levels were analyzed. The study was approved by the Ethics Committee of Tepecik Education and Research Hospital (ethics approval number: 2023/03-05, date: 05.04.2023). The diagnosis of intrauterine growth retardation was made when the ultrasound estimated fetal weight was <10 per cent or the birth weight was <5% or the birth weight was < -2SD units.

**Immunological Analysis**

aCA and aβ2GP1 were analysed according to the manufacturer's instructions by enzyme-linked immunosorbent assay (ELISA) (Alegria®; ORGENTEC Diagnostika, Mainz, Germany). aCA IgG and aβ2GPI IgG were measured by using a random-access analyser (Alegria®; ORGENTEC Diagnostika). The cut-off value was performed for aCA IgG and aβ2GPI IgG was >10 GPL and >8 GPL, respectively.

**Statistical Analysis**

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used to evaluate normal distribution. When comparing two groups with positive or negative marker results, T-Test was used for normally distributed parameters and Mann-Whitney U test was used for non-normally distributed parameters. Quantitative data analysis results were presented as mean±standard deviation and median, and categorical data were presented as frequency (percentage). p value below 0.05 was considered statistically significant in all tests.

**Results**

A total of 190 patients participated in the study. Maternal age in the study population was 34.2±6.05 years. Table 1 shows the evaluation of continuous variables according to antibody status. There was no statistically significant difference between gravida, parity, number of living children and number of abortions (p=0.333, 0.071, 0.059 and 0.659, respectively). When antibody-positive pregnant women were compared with antibody-negative pregnant women, the level of intrauterine excitus was found to be higher in the antibody-positive group (p=0.03). Gestational age was higher in antibody-positive pregnant women (p=0.047). The number of neonatal excitus, birth weight and APGAR (activity - pulse - grimace - appearance - respiration) score were similar in both groups (p=0.258, 0.246 and 0.348, respectively).

Table 1. Examination of continuous variables

	Antibody Positive	Antibody Negative	p
Gravida	3.8±0.1	3.5±0.3	0.333
Parity	1.1±0.1	0.8±0.1	0.071
Alive	1±0.09	0.7±0.1	0.059
Abort	2.3±0.1	2.5±0.2	0.659
Neo ex	0.06±0.03	0.1±0.04	0.258
Intrauterine fetal death	0.1±0.06	0.01±0.01	0.030*
Gestational age (weeks)	35.7±0.8	34±1.5	0.047*
Birth weight (g)	2649.5±193.5	2227.5±389.3	0.246
APGAR	7±0.3	5.1±1.3	0.348

Values are expressed as mean±standard deviation. Abbreviations: Neo ex; Neonatal excitus, APGAR; activity - pulse - grimace - appearance - respiration. Significant values (p<0.05) are indicated with \*

In Table 2, among the categorical variables, intrauterine growth retardation (IUGR) was present in 16% of the patients. There was no statistically significant difference between antibody positive and negative groups in terms of IUGR (p=0.623). Antibody positivity was found in 33% of patients with oligohydramnios and there was no statistically significant difference between the two groups (p=0.074). Antibody positivity was found in 71% of pregnant women with gestational diabetes and 85% of pregnant women without gestational diabetes. There was no significant difference in antibody status in the gestational diabetes group (p=0.312). In the gestational hypertension group, antibody positivity was present in 78%. There was no statistically significant difference between both groups in this patient population (p=0.626). In the patient population using acetylsalicylic acid, previous operation, and low molecular weight heparin, both groups were found to be statistically similar (p=0.11, 0.264, 0.743, respectively). However, antibody positivity was present in 100% of pregnant smokers.

Table 2. The comparison of patients' characteristics in APS and Control groups

	APS n=133	Control n=57	p
IUGR (n=50)			
Positive	6 (%12)	2 (%4)	0.623
Negative	35 (%70)	7 (%14)	
Oligohydramnios (n=52)			
Positive	1 (%2)	2 (%4)	0.074
Negative	42 (%81)	7 (%13)	
Gest DM (n=56)			
Positive	5 (%9)	2 (%4)	0.312
Negative	42 (%75)	7 (%13)	
Gest HT (n=56)			
Positive	7 (%13)	2 (%4)	0.626
Negative	40 (%71)	7 (%13)	
ASA (n=56)			
Positive	14 (%26)	0 (%0)	0.110
Negative	49 (%88)	13 (%23)	
Previous op (n=86)			
Positive	18 (%21)	1 (%1)	0.264
Negative	56 (%65)	11 (%13)	
Smoking (n=54)			
Positive	12 (%22)	0 (%0)	0.049*
Negative	30 (%56)	12 (%22)	
LMWH (n=103)			
Positive	20 (%19)	30 (%29)	0.743
Negative	43 (%42)	10 (%10)	

IUGR; intrauterine growth retardation, GestDM; Gestational Diabetes Mellitus, GestHT; Gestational Hypertension, Asa; Acetylsalicylic acid, Previous op; previous operation, LMWH; Low molecular weight heparin. Significant values (p<0.05) are indicated with \*

Anti-cardiolipin antibody or aβ2GP1 antibody was positive in 71% of non-smokers. There was a statistical difference between both groups (p=0.049). Table 3 show clinical characteristics of patients with and without adverse pregnancy outcomes in the APS group.

Table 3. Results according to adwers and non-adwers outcome

	Adwers (n=24)	Non-Adwers (n=32)	p
Maternal age	31.2±5.9	31.1±5.7	0.832
Primiparous	5 (21%)	11 (34%)	0.025*
Multiparous	19 (79%)	21 (66%)	0.042*
Abort	2 (0; 8)	2 (0; 5)	0.169
Gestasional Age	35.8±5.1	36.2±5.3	0.258
ACA	1 (4%)	1 (3%)	0.093
aβ2GP1	7 (29%)	14 (44%)	0.037*

Data are presented as the mean ± standard deviation, n (%) or median (min-max). aβ2GP1; anti-β2- glycoprotein-1, aCA anticardiolipin antibody; \*Statistically significant value

## Discussion

APS is an autoimmune disease characterized by the occurrence of arterial or venous thrombotic events and/or pregnancy morbidity in the presence of at least one of three circulating antiphospholipid antibodies; aCA, a $\beta$ 2GP1 antibody and lupus anticoagulant [14]. APS is considered a rare disease although it has an estimated prevalence in the general population, which is 0.05% [15]. However, it is 3.5 times more common in women than in men. Women with APS are at risk of adverse pregnancy outcomes including preeclampsia, pregnancy loss, thromboembolism, premature delivery, and perinatal death [16]. In this study, no difference was found in terms of obstetric complications including abortion, neonatal death, IUGR, oligohydramnios, gestational diabetes, gestational hypertension in pregnant women with aCA or a $\beta$ 2GP1 positivity, but in terms of intrauterine fetal death, antibody-positive patients were found to be significantly higher than antibody-negative patients.

The mechanism behind the presence of aCA in the sera of pregnant women who experience miscarriage is currently largely believed to be undergoing structural changes in phospholipids in the cell membrane; these changes stimulate overproduction of aCA [17-19]. As a result, the miscarriage rate is increased in patients who test positive for aCA. Some pregnant women may experience a normal pregnancy despite positivity for aCA, but the likelihood of miscarriage in pregnant women who test positive for both antibodies may be 2 to 4 times higher than in those with the presence of only one of both antibodies [20,21]. In this study, abortion rates were found to be similar in antibody-positive and antibody-negative pregnant women. The reason for this may be that the development time of microthrombosis in antibody-positive patients varies up to 10 years. In some patients who were positive for antibodies but were not affected by placental microcirculation thrombosis formation during pregnancy, half of these patients were found to develop thrombosis within 3 to 10 years after delivery, especially during follow-up visits planned for patients positive for aCA, and approximately 10% of these patients developed lupus erythematosus [22,23].

Fetal morbidity stands out as a distinctive clinical presentation of APS, encompassing occurrences like early and late pregnancy miscarriages, intrauterine growth restriction, and premature births. In addition, maternal morbidity (pre-eclampsia, eclampsia and placental abruption) is also relatively common in pregnant patients with APS [24]. In this study, in parallel with the literature, intrauterine fetal death was found to be significantly higher in the group with antibody positivity. Bagger et al. [25] found that aCA was positively correlated with intrauterine fetal death in 158 pregnant women with fetal loss. Lee et al. [26] found that a $\beta$ 2GP1 levels were not associated with fetal death or abortion in 414 pregnant women who were negative for aCA but positive for anti a $\beta$ 2GP1. In the meta-analysis conducted by Xu et al. [27], a statistically significant association between a $\beta$ 2GP1 and late fetal loss was observed in four of the eight selected studies. Two investigations established a favorable yet statistically insignificant correlation. However, the results showed a nonsignificant association between a $\beta$ 2GP1 and late fetal loss (OR 3.13, 95% CI .75-5.50) [28,29]. According to the subgroup analysis by study type, no statistical association of a $\beta$ 2GP1 with late fetal loss was found in the cohort studies group (OR 3.53, 95% CI-2.74 to 9.79) or the case-control studies group (OR 3.07, 95% CI .51-5.63). Furthermore, one case-control study showed a nonsignificant association between a $\beta$ 2GP1 and late fetal loss (OR .83, 95% CI .26-

2.65) [30]. Moderate heterogeneity was observed in many of these analyses [31].

a $\beta$ 2GP1 and aCA, which cause antiphospholipid antibody syndrome and which we examined in this study, may cause IUGR by affecting placental circulation because they cause arterial and/or venous thrombosis [10]. In this study, no significant difference was found between the patient group with antibody positivity and the group with negative antibody positivity in terms of IUGR. While IUGR was found in 12 (18.5%) of 65 pregnant women with systemic lupus in Madazlı et al. [32] study, 16% IUGR was found in parallel with this in our study. In the meta-analysis conducted by Xu et al, a correlation was found between IUGR and aCA levels in 4976 pregnant women with aCA positivity [33]. In the same study, a strong correlation was found between a $\beta$ 2GP1 and IUGR. a $\beta$ 2GP1 is rare among antibodies identified alone in patients with clinical characteristic of antiphospholipid antibody syndrome. However, it is the main target of antiphospholipid antibodies and plays an important role in the pathogenesis of unfavorable obstetric outcomes [34]. Saccone et al. [35] suggested that a $\beta$ 2GP1 was associated with the lowest live birth rate and the highest incidences of IUGR, very early IUGR and stillbirth compared to aCA.

In this study, smoking was found to be significantly higher in the antibody positive group compared to the antibody negative group. Many studies have been conducted to determine whether antiphospholipid antibodies are an independent risk factor for thrombotic events such as myocardial infarction and stroke. Most of these studies have used matched controls to eliminate the effect of smoking because tobacco use is an established risk factor for thrombosis. The strategy of matching smoking rates in anti-phospholipid antibody (aPL)-positive and aPL-negative patient groups was first used to describe the antibody profiles of myocardial infarction survivors [36]. In this study, aCA-positive patients were found to be active smokers; these patients were matched with 49 aCA-negative patients, of whom 43 were active smokers and 3 were ex-smokers. Certainly, it is noteworthy that 92% of patients with myocardial infarction were smokers, but the authors did not comment on this finding. As a result of the widespread use of this approach to define control groups, the association between smoking and the presence of aPL could not be determined in many studies [37].

In the study conducted by Yang et al. [38], out of a group of pregnant women, adverse effects were observed in 64 of them, while 256 of them were taken as a control group of healthy pregnancies. When both groups were compared, no difference was observed between the group with adverse effects and the group without adverse effects in terms of ACA, consistent with our study. Contrary to ACA, sera a $\beta$ 2GP1 levels were found to be higher in the non-adverse group compared to the group with adverse effects [38].

### Limitations of the Study

The fact that it was a retrospective and single-center study is the main limitation of the present study. Another limitation was that aCA and a $\beta$ 2GP1 antibodies, which are among the antibodies harboring APS, were examined in our study, while lupus anticoagulant was not. The small patient population is another limitation of our study.

### Conclusion

In our study, the number of intrauterine fetal deaths was significantly higher in pregnant women with positive aCA and a $\beta$ 2GP1 antibodies. In other pregnancy complications such as IUGR, oligohydramnios, gestational diabetes mellitus and gestational hypertension, there was no significant result between antibody positivity and negativity. Even if we have contributed to the literature on this subject,

prospective, multicenter studies are needed.

#### Ethics committee approval

This study was approved by Non-Interventional Clinical Research Ethics Committee of xx (Date: 5.04.2023 and Decision no: 2023/03-5).

#### Disclosure

Authors have no potential conflicts of interest to disclose.

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