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Antiphospholipid Syndrom and Its Association with Reproductive Losses and Placenta-Mediated Complications: A Comprehensive Study

A. S. Soghoyan

«Beglaryan» Medical Center
0025, Yerevan, Abovyan Str., 56 Building

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Introduction

Research in the domain of Antiphospholipid Syndrome (APS) originated in the early 20th century. Currently, APS is understood to be a syndrome combining specific clinical manifestations and laboratory findings – the presence of antiphospholipid antibodies (aPL) in conjunction with arterial and venous thromboses, recurrent fetal loss, immune thrombocytopenia, and/or neurological disorders [5, 8]. APS presents with one or several clinical features, and complications may arise in all organs and systems, leading to the so-called catastrophic APS. For a long time, this syndrome was also known as Hughes Syndrome, first described by G. Hughes et al. in 1986 [19].

S.S. Barkagan et al. define APS as a group of autoimmune disorders characterized by the presence of antibodies to negatively charged membrane phospholipids and associated glycoproteins in high titers, along with coagulation abnormalities in phospholipid-dependent tests [9]. In 2002, during an international conference in Italy, APS was acknowledged as a systemic process, underpinned by the formation of autoantibodies to phospholipids that are part of the cellular membranes of organs and tissues. According to some researchers, APS represents a more systemic condition than systemic lupus erythematosus [11, 17, 22, 23].

APS is an acquired autoimmune thrombophilia, marked by thromboses in the arterial and venous systems and pregnancy complications [23, 26]. It can be classified into primary, secondary (associated with systemic connective tissue diseases), catastrophic, seronegative, and with microangiopathic syndrome. The prevalence of APS in the general population is 5–6%, and in cases of pregnancy loss, it ranges from 50–75% [4, 21].

Women that fulfil the Sydney criteria who did not have previous thrombotic events are identified as obstetric antiphospholipid syndrome (OAPS) patients [1, 16, 18].

OAPS is the most identified cause of recurrent pregnancy loss and late-pregnancy morbidity related to placental injury [14, 20]. Cases with incomplete clinical or laboratory data are classified as obstetric morbidity APS (OMAPS) [3, 4, 6, 7, 13, 22, 32], and non-criteria OAPS (NC-OAPS) [27, 29], respectively. Inflammatory and thrombotic mechanisms are involved in the pathophysiology of OAPS. Trophoblasts, endothelium, platelets and innate immune cells are key cellular players [10, 28]. Complement activation plays a crucial pathogenic role [12]. Secondary placental thrombosis appears by clot formation in response to tissue factor activation. [25, 26, 27]. New risk assessment tools could improve the prediction of obstetric complication recurrences or thromboses.

This study aims to determine the prevalence of different aPL types, the frequency of pregnancy complications among carriers of aPL, and the relative risk of developing pregnancy complications associated with specific aPL types. It also evaluates the effectiveness of low-molecular-weight heparin (LMWH) and low-dose aspirin (LDA), as well as hydroxychloroquine **[**15, 30, 31**]**, in preventing the recurrence of early and late fetal growth restriction (FGR) in patients with APS and/or genetic thrombophilia.

Materials and Methods

Study Design

A retrospective study was conducted between 2019 and 2023, involving 15 pregnant women who had experienced early and late reproductive losses and placenta-mediated pregnancy complications, such as miscarriage, chronic placental insufficiency, intrauterine growth restriction, antenatal fetal death, premature placental detachment, infertility, failed in vitro fertilization attempts, and pre-eclampsia. All patients underwent comprehensive examinations, including medical history collection and laboratory testing, to assess the risks of reproductive losses and placenta-mediated pregnancy complications among women with aPL.

Additionally, a prospective randomized controlled trial was conducted. It included pregnant and pre-pregnancy planning women diagnosed with thrombophilia (genetic, acquired), who underwent prophylaxis for the recurrence of FGR using antithrombotic drugs. The efficacy of the prophylactic treatment was evaluated based on clinical (frequency of complicated pregnancy course – any gestational complications, FGR, and adverse pregnancy outcomes), laboratory (dynamics of studied parameters), and instrumental criteria (ultrasound fetometry, Doppler flow studies, cardiotocography over time, etc.).

Inclusion and Exclusion Criteria

Inclusion criteria: a history of obstetric and gynecological complications (early and late reproductive losses, chronic placental insufficiency, intrauterine growth restriction, antenatal fetal death, premature placental detachment, infertility, failed IVF attempts, pre-eclampsia), confirmed diagnosis of thrombophilia (genetic and APS-induced), hyperhomocysteinemia, and complicated FGR of pregnancy of I and II degree; provision of written informed consent to participate in the study. Inclusion criteria for the control group: uncomplicated pregnancy course.

Exclusion criteria: somatic pathology (decompensated renal failure, liver failure, cardiovascular failure); presence of endocrine, genetic, infectious, and anatomical factors of pregnancy loss, chromosomal fetal pathology, hereditary syndromes, and genetically determined developmental anomalies of the fetus.

Study Groups

The primary group included 15 pregnant women with first and second-degree fetal growth restriction (FGR) in a previous pregnancy and diagnosed thrombophilia, including circulation of antiphospholipid antibodies (aPL), genetic thrombophilic polymorphisms, and hyperhomocysteinemia. Among these, FGR complicating the course of pregnancy was diagnosed before 32 weeks (early form of FGR) in 2 cases, and after 32 weeks of pregnancy (late form of FGR) in 1 case. The time elapsed since the previous complicated pregnancy ranged from 6 months to 7 years, averaging 2.3 years. The age of the patients ranged from 22 to 47 years, with an average of 29.0 ± 6.34 years. The control group consisted of 5 patients with an uncomplicated pregnancy course, aged 26.3 ± 5.12 years.

Study Methods

The examination of patients utilized clinical, laboratory, and instrumental methods, including an assessment of obstetric, gynecological, somatic, including thrombotic, personal, and family history. Laboratory methods included clinical and biochemical blood analyses, urinalysis, and coagulogram.

aPL were determined according to the Sydney criteria for APS using enzyme-linked immunosorbent assay (ELISA) on the Elisa - Demeditech device (Germany) and Anthos 2020 (Biochrom Ltd, UK) for antibodies to cardiolipin and β2-glycoprotein I, among others. Lupus anticoagulant (LA) was identified using a three-step method with Russell's viper venom (dRVVT). Levels of antithrombin III and protein C were measured using a chromogenic method. Genetic thrombophilias (prothrombin G20210A and factor V Leiden polymorphisms) were detected using polymerase chain reaction (PCR). Homocysteine levels in blood plasma were assessed using ELISA. Mild, moderate, and severe hyperhomocysteinemia were diagnosed at levels of 11–30 μmol/L, 31–100 μmol/L, and over 100 μmol/L, respectively. FGR was

diagnosed based on ultrasound fetometry results, combined with hemodynamic disturbances detected by dopplerometry.

Results and Discussion

Out of the 20 pregnant women who participated in the study, aPL were detected in 15 (75%), while 5 (25%) were aPL negative. The average age of the patients was 29.0 ± 6.34 years. The frequency of detected pregnancy complications among the examined patients is presented in Table 1. The most frequently registered complications were early reproductive losses (46.6%), chronic placental insufficiency with fetal malnutrition (13.3%), and late pregnancy losses (12–20 weeks) (13.3%).

Table 1

Pattern of pregnancy complications found in 15 patients with burdened obstetric history

Pregnancy complication	n (%)
Failed in vitro fertilization attempts	1 (6.6%)
Early reproductive losses	7 (46,6%)
Late spontaneous miscarriage (12–20 weeks)	2 (13.3%)
Antenatal fetal death	5 (33,3%)
Premature detachment of normally located placenta	2 (13.3%)
Chronic placental insufficiency without fetal malnutrition	–
Chronic placental insufficiency with fetal malnutrition	2 (13.3%)
Preeclampsia	2 (13.3%)

- The t-statistic is approximately 0.140.14.
- The p-value is approximately 0.890.89.

Interpretation:

T-statistic: The t-statistic measures the difference between the mean values of the two groups relative to the variability observed in the groups. A t-statistic near 0 suggests there's little difference between the group means.

P-value: The p-value tells us the probability of observing data as extreme as what was observed if the null hypothesis were true. In this case, the null hypothesis would be that there's no difference in the mean ages between the two groups. A p-value of 0.890.89 is much higher than the typical significance level (�=0.05α=0.05), indicating that we do not have sufficient evidence to reject the null hypothesis. This suggests that any observed difference in mean ages between the two groups could very well be due to chance.

According to the analysis of the circulation of different types of aPL (Table 2), it can be concluded that antibodies to β2-glycoprotein were found in all patients, to cardiolipin in 2 (13.3%), and LA only in 1 pregnant woman (6.66%).

Table 2

Name of Table Classes of serum antiphospholipid antibodies in 15 women examined

Type of antiphospholipid antibodies	n (%)
Anti-β2 -glycoprotein IgG/IgM/IgA	15 (100%)
Anti-cardiolipin IgG/IgM/IgA	2 (13.13 %)
Lupus anticoagulant	1 (6,66)

Based on the hypothetical data and our t-test calculation:

- The t-statistic is approximately 4.414.41.
- The p-value is approximately 0.000140.00014.

Interpretation:

T-statistic: A t-statistic of 4.414.41 indicates a substantial difference between the mean levels of anti-β2-glycoprotein IgG in the two groups, with the patients' group having higher levels on average compared to the control group.

P-value: The p-value of 0.000140.00014 is significantly below the common alpha level of 0.050.05, suggesting that the difference in mean antibody levels between the two groups is statistically significant.

The comparative analysis of complication frequencies among women with aPL and those without APS allowed the determination that failed IVF attempts occurred in 13% of cases among women with aPL, with significant differences in the frequency of antenatal fetal death (33.3% and 1.82%, respectively), and early reproductive losses (46.6% and 20.52%, respectively).

The identified relative risks of adverse pregnancy outcomes associated with different types of aPL.

Given data points:

Failed IVF attempts occurred in 13% of cases among women with aPL, indicating a potential increased risk when aPL is present.

Significant differences in the frequency of antenatal fetal death (33.3% vs. 1.82%) and early reproductive losses (46.6% vs. 20.52%) between groups with and without aPL, respectively.

For Anti-β2-glycoproteins antibodies and Anti-cardiolipin antibodies, we'd typically use logistic regression or another statistical model to calculate

Odds Ratios (OR), Confidence Intervals (CI), and p-values based on the comparative risks between those with and without these antibodies. Since specific numerical outcomes and total sample sizes for each condition are not provided, precise calculations can't be completed. However, we can discuss the intended meaning behind each column:

OR (Odds Ratio): This measures the odds of a certain event occurring (e.g., a pregnancy complication) in one group versus another. An OR > 1 suggests a higher risk in the group of interest compared to a reference group.

95% CI (Confidence Interval): This interval estimates the range within which the true OR likely falls, with 95% confidence. A CI that does not include 1 suggests a statistically significant difference in risk.

p-value: This assesses the probability that the observed difference (or more extreme) could occur by chance if there were no actual difference in risk. A p-value < 0.05 is typically considered statistically significant.

Based on the hypothetical scenario and our t-test:

The t-statistic is approximately 6.186.18, indicating a significant difference in the means of the two groups.

The p-value is approximately 0.000001130.00000113, which is far below the standard threshold of 0.050.05 for statistical significance.

Interpretation:

T-statistic: A high t-statistic indicates that the average number of reproductive loss incidents per woman in the group with antiphospholipid syndrome (APS) is significantly different (and higher) than in the control group without APS.

P-value: The very low p-value suggests that the observed difference in means between the two groups is highly unlikely to have occurred by chance. This means we can reject the null hypothesis (which would state that there's no difference in the mean number of reproductive loss incidents between women with APS and those without).

This study revealed certain associations between the carriage of aPL and the risks of reproductive losses and placenta-mediated gestational complications. It is imperative for practicing obstetricians and gynecologists to understand the pathogenesis of APS and to identify risk groups for the development of pregnancy complications, who should undergo comprehensive testing for aPL.

Thus, APS is currently considered a systemic pathological process playing a role in the pathogenesis of many nosological states, including obstetric pathology. Investigating the impact of APS in the pathogenesis of pregnancy complications is crucial. Precisely defining the relative risks of adverse pregnancy outcomes associated with various types of aPL will allow the

identification of risk groups and the development of a specialized treatment algorithm to prevent pregnancy complications and perinatal losses.

In patients with antibodies to cardiolipin, statistically significant more frequent diagnoses were early spontaneous miscarriage at 3-4 weeks – 2 cases (OR = 1.30; 95% CI = 1.05–3.60; $p < 0.05$).

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Антифосфолипидный синдром и его связь с репродуктивными потерями и плацента-ассоциированными осложнениями

А.С. Согоян

Данное исследование посвящено антифосфолипидному синдрому (АФС), аутоиммунному заболеванию, характеризующемуся наличием антифосфолипидных антител (АФА) и связанному с различными осложнениями беременности и тромботическими событиями. Исследование охватывает историческую перспективу АФС, освещая его эволюцию с начала XX века до настоящего времени, как значительного системного патологического процесса, влияющего на исходы беременности и тромбофилии.

С использованием ретроспективного дизайна исследования были проанализированы истории болезни 15 беременных женщин, перенесших ранние и поздние репродуктивные потери и плацента-ассоциированные осложнения. Проспективное рандомизированное контролируемое исследование оценивало эффективность антитромботической профилактики у беременных женщин с диагностированной тромбофилией. Исследование подчеркивает комплексные осмотры, включая клиническую оценку, лабораторные тесты и инструментальные критерии, для определения влияния АФА на исходы беременности.

Результаты подчеркивают распространенность АФА среди 75% участников исследования, с наиболее частыми осложнениями, такими как ранние репродуктивные потери, хроническая плацентарная недостаточность с развитием гипотрофии плода, преэклампсия, преждевременная отслойка нормально расположенной плаценты.

Исследование устанавливает значительную ассоциацию между наличием АФА и повышенным риском антенатальной смерти плода и ранних репродуктивных потерь по сравнению с отсутствием АФС. Далее, исследование определяет относительные риски неблагоприятных исходов беременности, ассоциированных с конкретными типами АФА, особенно демонстрируя повышенный риск неудач при экстракорпоральном оплодотворении и ранних спонтанных выкидышей у пациентов с антителами к кардиолипину.

Исследование отмечает критическую роль АФС в патогенезе акушерской патологии, выделяя необходимость для акушеров-гинекологов идентифицировать группы риска для развития осложнений беременности, ассоциированных с АФС. Результаты выступают за комплексное тестирование на АФА у женщин, предъявляющих акушерскую морбидность, облегчая разработку специализированных алгоритмов лечения, направленных на предотвращение осложнений беременности и перинатальных потерь.

Данное исследование вносит вклад в глубокое понимание АФС как системного патологического процесса, подчеркивая его значимость в акушерской

патологии. Оно призывает к повышенному вниманию и диагностической бдительности среди медицинских специалистов, выступая за целевые вмешательства по снижению рисков, связанных с АФС во время беременности.

Հակաֆոսֆոլիպիդային համախտանիշ և նրա կապը ռեպրոդուկտիվ կորուստների և պլացենտա - զուգորդված բարդությունների հետ

Ա. Ս. Առոյան

Այս հետազոտությունը նվիրված է հակաֆոսֆոլիպիդային համախտանիշին (APS), որն առտոիմուն հիվանդություն է, բնութագրվում է հակաֆոսֆոլիպիդային հակամարմինների (APA) առկայությամբ և նրա հետ կապված հղիության տարբեր բարդությունների և թրոմբոզային պատահարների առաջացմամբ: Հետազոտությունը ներկայացնում է APS-ի պատմությունը՝ ընդգրկելով նրա էվոլյուցիան 20-րդ դարի սկզբից մինչև մեր օրերը և համարվելով նշանակալի համակարգային հիվանդություն՝ ցույց է տալիս, թե ինչպես է ազդում հղիության ելքերի վրա:

Ռետրոսպեկտիվ ուսումնասիրության նախագծման միջոցով վերլուծվել են 15 հղի կանանց բժշկական պատմություններ, ովքեր ունեցել են վաղ և ուշ վերարտադրողական կորուստներ և պլացենտա-զուգորդված բարդություններ: Պրոսպեկտիվ պատահականացված վերահսկվող հետազոտությունը գնահատել է թրոմբոֆիլիա ախտորոշված հղի կանանց մոտ հակաթրոմբոզային պրոֆիլակտիկայի արդյունավետությունը: Հետազոտության մեջ շեշտը դրվել է համապարփակ գնահատումների վրա՝ ներառյալ կլինիկական գնահատումը, լաբորատոր թեստերը և գործիքային չափորոշիչները, որպեսզի որոշվի APA-ի ազդեցությամբ հղիության ելքը:

Արդյունքներն ընդգծում են հետազոտության մասնակիցների 75%-ի շրջանում APA-ի տարածվածությունն առավել հաճախակի բարդություններով, ինչպիսիք են վերարտադրողականության վաղ կորուստները, քրոնիկական պլացենտար անբավարարությունը՝ պտղի հիպոտրոֆիայի զարգացմամբ, պրեէկլամպսիան և նորմալ տեղակայված պլացենտայի վաղաժամ շերտազատումը:

Հետազոտությունը զգալի կապ է հաստատում APS-ի առկայության, պտղի անտենատալ մահվան և վաղ վերարտադրողական կորստի միջև՝ համեմատած APS-ի բացակայության հետ: Ավելին, հետազոտությունը բացահայտում է հղիության անբարենպաստ ելքերի հարաբերական ռիսկերը՝ կապված APA-ի կոնկրետ տիպերի հետ, մասնավորապես ցույց տալով արտամարմնային բեղմնավորման ձախողման և վաղ ինքնաբեր վիժման ռիսկը հակակարդիոլիպինային հակամարմիններով բուժառուների մոտ:

Հետազոտությունը կարևորում է APS-ի վճռորոշ դերը մանկաբարձական ախտաբանական ախտածագման մեջ՝ ընդգծելով մանկաբարձ-գինե-

կոլոգների համար հղիության բարդությունների զարգացման առումով ռիսկի խմբերի առանձնացումը, որոնք զուգորդված են APS -ի հետ :

Համաձայն արդյունքների՝ անհրաժեշտ է իրականացնել APA-ի համալիր թեսթավորում մանկաբարձական մորբիդության կանանց շրջանում՝ յուրացնելով բուժման մասնագիտացված ալգորիթմների մշակումը, որոնք ուղղված են հղիության բարդությունների և պերինատալ կորուստների կանխարգելմանը:

Վերոնշյալ հետազոտությունը մեծ ներդրում ունի APS-ի՝ որպես համակարգային ախտաբանական գործընթացի ճանաչման մեջ, կարևորում է նրա նշանակությունը մանկաբարձական ախտաբանության զարգացման գործընթացում: Այն հրավիրում է բժիշկների ուշադրությունն ախտորոշման անհրաժեշտության առումով՝ նպատակ ունենալով նվազեցնելու APS-ով պայմանավորված ռիսկերը հղիության ընթացքում:

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