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Systematic Review

The Association between Antiphospholipid Syndrome after Conventional Treatment and Preeclampsia

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Abstract

Background: Despite conventional treatment, the prognosis of antiphospholipid syndrome (APS) pregnancy remains poor, and some pregnancies are still complicated by preeclampsia (PE). This study aimed to identify the relationship between conventionally-treated APS and the onset of PE. **Methods**: Relevant studies published up to April 2021 were searched on the PubMed, Cochrane Library, and Embase databases. Related data were extracted from the included studies, and we performed a meta-analysis. Review Manager 5.4 were used to calculate the pooled odds ratio (OR) and 95% confidence intervals (CIs). **Results**: This study screened 6 studies, including 1 cohort study and 5 case-control studies. Even after conventional treatment, the rate of PE in APS pregnancy is still significantly higher than in the control group. There was a higher pooled OR in the cohort study (OR: 8.37, 95% CI: 3.42–20.48) than the case-control studies (OR: 2.30, 95% CI: 1.12–4.74) in the subgroup analysis. **Conclusions**: APS pregnancy increases the risk of PE even after conventional treatment. Routine monitoring and standardized and better treatment methods should be developed to prevent the occurrence of PE.

Keywords: antiphospholipid syndrome; preeclampsia; meta-analysis

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune, hypercoagulable condition characterized by venous and/or arterial thrombosis and/or pregnancy morbidity with persistent laboratory evidence of antiphospholipid antibody (APLA) [1]. The APLA mainly include anticardiolipin antibodies (ACA), lupus anticoagulant (LA) and anti-beta2 glycoprotein-1 antibodies (β2GP1) in APS [2]. APS occurs as a single disease (termed primary APS) or as a secondary disease followed with other autoimmune diseases, particularly systemic lupus erythematosus (SLE) [2,3]. Moreover, APS can be classified into two types based on its clinical manifestation: thrombotic APS (TAPS) and obstetric APS (OAPS). The annual incidence of APS is reported to be 2–5 per 100,000 persons, with an estimated prevalence of 40–50 per 100,000 persons [4–6].

Pregnancy is a natural hypercoagulable condition, and adverse obstetric events are increased in APS patients, including pregnancy loss, fetal death, preeclampsia (PE), eclampsia, intrauterine growth restriction (IUGR) and so on [2,7–9]. However, these adverse outcomes have only been reported individually and have not been systematically evaluated.

Thrombotic mechanisms, apoptosis, immune-modulatory molecule impairment in trophoblasts and inflammation are believed to be involved in the development of APS [9,10]. Furthermore, placental insufficiency might result in adverse obstetrics outcomes partly because of the detrimental effects of APLA, resulting in trophoblastic injury or dysfunction and/or placental dysvascularization [11,12]. Moreover, some studies have shown that complement pathways play an essential role in poor pregnancy outcomes in APS [13]. Nevertheless, the pathogenesis of APS in pregnancy remains unclear.

Over the past decades, low-dose acetylsalicylic acid (LDA) alone or in combination with low molecular weight heparin (LMWH) have been therapies in APS pregnancy. Alternative treatments are initiated in case of treatment failure with LDA and LMWH, including the addition of low-dose prednisolone or hydroxychloroquine (HCQ) [14]. Despite conventional treatment, the prognosis of APS pregnancy remains poor, and some pregnancies are still complicated by PE [15]. The relationship between conventionally-treated APS and the onset of PE is still controversial.

This study aimed to deepen our understanding of the association between APS and PE through a meta-analysis following the PICO (patients, intervention, comparison and outcomes) model to select our study population.

2. Materials and Methods

This study protocol was previously followed PRISMA guidelines.

2.1 Sources of Information and Strategy for Search

We searched the relevant studies published up to April 2021 from the PubMed, Cochrane Library, and Embase

Table 1. Characteristics of included studies.

Authors	Year	Country	Design*	Case	Control	NOS score	Diagnosis of APS	Types of APS	Treatments of APS
Högdén *et al*. [17]	2019	Sweden	2	30	327,584	7	the Sydney criteria	TAPS + OAPS	LDA + LMWH
Mekinian *et al*. [18]	2012	France	1	25	21	5	Sapporo criteria	OAPS	LDA + LMWH
Yang *et al*. [19]	2021	China	1	59	256	6	2006 Sydney guidelines	TAPS + OAPS	LDA + LMWH, HCQ, prednisone, intravenous immunoglobulin
Jeremic *et al*. [20]	2015	Serbia	1	55	55	6	Sydney classification	TAPS + OAPS	LDA + LMWH, corticosteroids, intravenous immunoglobulin
Soh *et al*. [21]	2013	UK	1	73	292	6	2006 Sydney criteria	OAPS	LDA + LMWH
Bouvier *et al*. [22]	2014	France	1	517	796	5	the Sydney criteria	OAPS	LDA + LMWH

Abbreviations: NOS, Newcastle-Ottawa scale; APS, antiphospholipid syndrome; TAPS, thrombotic APS; OAPS, obstetric APS; LDA, low-dose acetylsalicylic acid; LMWH, low molecular weight heparin; HCQ, hydroxychloroquine.

*, case-control study = 1; cohort study = 2.

databases. The Medical Subject Headings (MESH) and keywords used were as followed: "antiphospholipid syndrome", "antiphospholipid antibody", "anticardiolipin antibodies", "anti-β2 glycoprotein", "lupus anticoagulant", "preeclampsia" and "pre-eclampsia".

2.2 Study Selection

The inclusion criteria were: (1) studies were case-control, prospective or retrospective cohort, or cross-sectional; (2) the research object was humans; (3) cases were pregnant women with APS; (4) outcomes included preeclampsia. The exclusion criteria were: (1) repeated studies and results; (2) non-English literature; (3) case reports; (4) theoretical research; (5) secondary analysis; (6) literature reviews; (7) congress abstracts; (8) original dataset inaccessible studies. Two independent authors (TY and HP) screened and selected the titles and abstracts of the studies. Disagreements were solved by discussion among the authors or a third investigator.

2.3 Data Extraction

We extracted the following information from each included study: first author's name, year of publication, country, study design, sample size (including the case and control groups), quality score, the definition of APS, the APS treatment, the types of APS, the rate of PE, odds ratio (OR) or relative risk and 95% confidence interval (CI), statistical methods. Similar to the study selection, two authors (TY and HP) conducted the data abstraction.

2.4 Statistical Analyses

RevMan software (version 5.4, Cochrane, London, UK) from the Cochrane Collaboration were used for the all statistical analyses. In this study, $p < 0.05$ was considered statistically significant.

The Mantel-Haenszel method was used to combined the categorical data with a pooled OR. Heterogeneity among the studies was assessed by the χ^2 and I^2 tests. The random-effects model was used in case of significant heterogeneity among studies ($p \leq 0.05$ and an $I^2 > 50\%$). Otherwise, the fixed-effects model was used. We performed the subgroup analysis based on the type of APS, study design, year of publication, and economic level (the study country) to assess the potential sources of heterogeneity. We used forest plots for the graphical representation of the statistical data.

We used the Newcastle-Ottawa scale (NOS) score to evaluate the included studies, basing on the selection of the study group, comparability between the groups and the factors determining exposure/non-exposure [16].

3. Results

3.1 Literature Search Results

The literature search retrieved a total of 2311 articles. Six articles were finally included based on the inclusion and exclusion criteria, as displayed in Table 1 (Ref. [17–22]), which including 1 cohort study and 5 case-control studies with a total of 759 APS patients. The diagnosis of APS was in accordance with the Sapporo criteria or the 2006 Sydney criteria [2] in the included studies. Moreover, each pregnant woman with APS has been treated, mostly with LDA and LMWH. All the NOS scores were greater than or equal to 5 points, which demonstrates high quality.

3.2 The Relationship between APS and Preeclampsia

Fig. 1 shows the OR and 95% CI of each study. Three studies revealed that APS significantly increases the incidence of PE despite regular treatment [17,19,22]. Nevertheless, the association between APS and PE was not statistically significant in 3 studies [18,20,21]. Finally, we used the random-effects model to analysis due to the heterogeneity, resulting in a pooled OR of 2.97 (95% CI: 1.44–6.15). The results indicate that conventionally-treated APS is a risk factor for PE occurrence. In other words, the incidence of PE in APS patients after treatment was 2.97 times that of the control group.

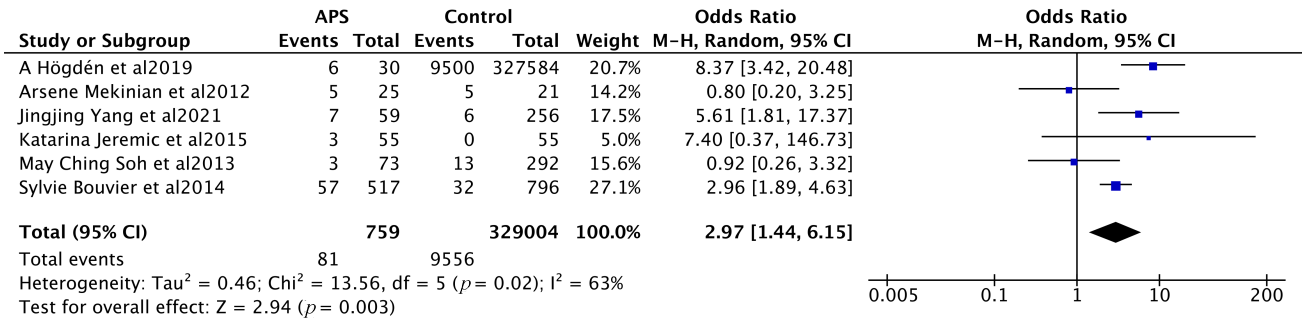

Fig. 1. Meta-analysis of all study participants with APS. APS, antiphospholipid syndrome; OR, odds ratio; 95% CI, 95% confidence interval.

Table 2. The relationship between antiphospholipid syndrome and preeclampsia in subgroup analysis.

Subgroup		Number of studies	p (I^2)	Pooled odds ratio (95% CI)
Types of APS	TAPS + OAPS	3	0.85 (0.0%)	7.19 (3.63–14.23)
	OAPS	3	0.07 (63.0%)	1.55 (0.59–4.06)
Study design	Cohort study	1	/	8.37 (3.42–20.48)
	Case-control study	5	0.10 (49.0%)	2.30 (1.12–4.74)
Year of publication	Before 2016	4	0.12 (49.0%)	1.78 (0.76–4.20)
	After 2016	2	0.57 (0.0%)	7.17 (3.56–14.47)
Economic level	Developed	4	0.007 (75.0%)	5.81 (2.02–16.72)
	Developing	2	0.86 (0.0%)	2.36 (0.93–6.00)

Abbreviations: APS, antiphospholipid syndrome; TAPS, thrombotic APS; OAPS, obstetric APS; CI, confidence interval.

Table 3. The meta-analysis sensitivity analysis.

Exclusion	p (I^2)	Pooled odds ratio (95% CI)
Högdén *et al*. [17]	0.02 (49.0%)	2.30 (1.12–4.74)
Mekinian *et al*. [18]	0.0004 (58.0%)	3.69 (1.80–7.58)
Yang *et al*. [19]	0.03 (68.0%)	2.57 (1.08–6.09)
Jeremic *et al*. [20]	0.009 (70.0%)	2.81 (1.30–6.11)
Soh *et al*. [21]	0.0005 (59.0%)	3.70 (1.77–7.71)
Bouvier *et al*. [22]	0.06 (71.0%)	2.89 (0.94–8.89)

Abbreviations: CI, confidence interval.

3.3 Subgroup and Sensitivity Analysis

Subgroup analysis was performed based on the type of APS (TAPS + OAPS *vs* OAPS), study design (cohort study *vs* case-control study), year of publication (before 2016 *vs* after 2016), and economic level (developing country *vs* developed country) to determine the sources of heterogeneity. Table 2 shows the detailed results. In addition, we performed sensitivity analysis to investigate the association between APS and PE, as shown in Table 3 (Ref. [17–22]), which showing that influence on the pooled OR (95% CI) was little when on exclusion of any individual study. Högdén's study [17] was the only cohort study in the meta-analysis and might be the main source of heterogeneity.

4. Discussion

This study involved a meta-analysis including 6 studies and mainly revealed that the incidence of PE in conventionally-treated APS patients was still significantly higher than that of the control group (p = 0.003, OR: 2.97, 95% CI: 1.44–6.15) [17–22].

At present, the central focus of treatment and prevention of APS thrombosis remains anticoagulation therapy, including treatments such as heparin, warfarin, etc. [23–25]. For patients with obstetric APS, LDA and LMWH are recommended throughout pregnancy, and heparin should be continued until 6 to 12 weeks postpartum [26]. Furthermore, some potential targeted APS treatments are being researched following recent discoveries in APS pathogenic mechanisms, including hydroxychloroquine, statins, belimumab, eculizumab, defibrotide, sirolimus, rituximab, and peptide therapy [14,26]. A growing number of studies have reported significantly improved pregnancy outcomes in APS patients with these treatments, resulting in a 70 to 80% increase in live birth rate compared with untreated pregnancies [27,28]. Nevertheless, the optimal treatment of women with APS remains obscure. Saccone *et al*. [29] found that APS women with triple positive aPL antibodies had only a 30% live birth rate despite treatment in a retrospective, multicenter study included 750 women. A research by Zhou *et al*. [30] revealed that OAPS patients developed pregnancy complications despite treatment. However, the incidence has not been compared with the control group, so we cannot know whether these complications are attributed to the disease or simply the incidence rate in the healthy control population. Högdén *et al*. [17] reported a

higher rate of adverse outcomes in the APS group compared to the control group, even with antithrombotic treatment. Nevertheless, the study of Soh *et al*. [21] reported a lower incidence of PE in APS women after LDA and/or LMWH treatment than the low-risk pregnancies (4.1% *vs* 4.5%). In summary, only a few studies reported the incidence of adverse obstetric outcomes in pregnancies following conventional APS treatment and whether these complications improved when compared with the control group (low-risk pregnancies). Therefore, we performed a meta-analysis and considered that the rate of PE was significantly higher in APS patients compared to the control group, which emphasize the occurrence of PE even after APS treatment.

Preeclampsia is a hypertensive disorder of pregnancy characterized by new-onset hypertension after 20 weeks of gestation with evidence of organ injury. The condition has an average prevalence of 2% to 8% in all pregnancies [31] and is the leading cause of maternal and neonatal morbidity and mortality. Currently, it is acknowledged that aspirin is effective for the prevention of PE, especially preterm PE [32]. However, preventative therapies for PE are limited and the most effective pharmacological therapy is no agreement. Several studies have suggested that LMWH may further reduce the rate or severity of severe preeclampsia and improve fetal outcomes [33]. The mechanism of LMWH for prevention of PE and other pregnancy complications includes anticoagulation-independent mechanisms, improving endothelium-dependent vascular function, antitrophoblastic apoptosis, promoting extravillous trophoblast invasion and cytotrophoblast proliferation, improving angiogenesis and so on [34–36]. However, these findings were obtained from experimental studies, and their relevance in clinical practice remains unknown. We have to emphasize that the worldwide incidence of PE is high, and routine preventive treatments are not performed in low-risk pregnancies. Our study revealed a rate of PE in APS pregnancies of 10.7% across all studies, which is significantly higher than that of the control group (2.9%). When excluding the study of Bouvier *et al*. [22] the rate decreased to 9.9%, which is still higher than the control group, indicating that more effective and better treatment should be developed.

We found the study design might be the main source of heterogeneity based on the subgroup analysis. Furthermore, APS pregnancies in the cohort study were at an increased risk of PE (OR: 8.37, 95% CI: 3.42–20.48) than their counterparts in case-control studies (OR: 2.30, 95% CI: 1.12–4.74). This discrepancy might result from the higher quality of the cohort study and smaller selection bias. In addition, the subgroup analysis revealed that the type of APS (TAPS or OAPS) and economic level did not significantly affect the incidence of PE in conventionally-treated APS patients.

To our knowledge, our study is the first comprehensive systematic review and meta-analysis of the correlation between conventionally-treated APS patients and PE, which provides a theoretical basis for clinical diagnosis and treatment with great clinical significance. Nevertheless, we should be aware of the shortcomings of the study. Firstly, the types of APS were not classified, and primary and secondary APS were both included in the analysis. Moreover, TAPS and OAPS were not clearly identified. Secondly, the stage of PE was not distinguished (mild or severe, early onset or late onset). Thirdly, the included studies of the meta-analysis was small, which limits the quality of our study. At last, only a small number of APS pregnancies were analyzed due to the rarity of the disease. In the future, a prospective, multi-center randomized study should be carried out to identify the incidence of APS in the population and compare the incidence of APS-related complications after treatment to the control group.

5. Conclusions

Pregnant women with APS were treated with conventional therapies because they are prone to PE. However, the rate of PE in conventionally-treated APS patients was still higher than that of the control group. Routine monitoring and standardized and more effective treatment methods should be developed to prevent the occurrence of PE.

Author Contributions

TY and HP designed the research study and performed the research. TY analyzed the data and wrote the manuscript. HP revised the manuscript. All authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5004070.

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