



Review article

Antiphospholipid syndrome and recurrent miscarriage: A systematic review and meta-analysis



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ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune condition that is associated with thrombosis and morbidity in pregnancy. The exact mechanisms by which these associations occur appear to be heterogeneous and are not yet well understood. The aim of this study was to identify and analyze publications in recent years to better understand the diagnosis and its contribution to monitoring APS among women with recurrent miscarriage (RM). This systematic review and meta-analysis was conducted using the PubMed and Web of Knowledge databases, with articles published between 2010 and 2014, according to the PRISMA statement. Of the 85 identified studies, nine were selected. Most of the studies reported an association between recurrent miscarriage and specific antiphospholipid antibodies, as anticardiolipin antibodies (aCL), lupus anticoagulant (LA), anti- β 2-glycoprotein I antibodies (a β 2GPI) and antiphosphatidylserine (aPS), which showed a relationship with RM. The main result of the meta-analysis revealed association between antiphospholipid antibodies (aPLs) and/or APS compared to the patients with RM (OR: 0.279; 95% CI: 0.212-0.366) and APS cases compared to the patients with RM (OR: 0.083; 95% CI: 0.036-0.189). High heterogeneity among these studies ($I^2 = 100.0\%$, $p < 0.001$) was observed. In addition, there was no significant publication bias across studies according to Begg's test ($p = 0.230$), although Egger's test ($p = 0.037$) suggests significant publication bias. The funnel plot was slightly asymmetrical. Systematic review and meta-analysis demonstrated a positive association between antiphospholipid antibodies and/or antiphospholipid syndrome in patients with recurrent miscarriage.

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune condition that is characterized by the production of antiphospholipid antibodies (aPLs) and associated with thrombosis and morbidity in pregnancy (Kutteh and Hinote, 2014). The major aPLs that is found in APS are anticardiolipin antibodies (aCLs), lupus anticoagulant (LA) and anti- β 2-glycoprotein I antibodies (a β 2GPI) (Kutteh and Hinote, 2014; Miyakis et al., 2006). The international Sapporo criteria (1999), revised in 2006, emphasizes the diagnosis of APS when at least one of the major aPLs is detected on two or more occasions in a 12-week interval between measurements and associated with a clinical condition, such as

thrombosis or morbidity in pregnancy. Morbidity in pregnancy includes unexplained stillbirths at ≥ 10 weeks of gestation, preterm delivery due to eclampsia, preeclampsia, or placental insufficiency, and three or more consecutive miscarriages (Miyakis et al., 2006).

The APS is associated with recurrent miscarriage (RM) (Kutteh and Hinote, 2014), defined by the American Society for Reproductive Medicine as two or more spontaneous pregnancy losses (Practice Committee of the American Society for Reproductive Medicine, 2013). The incidence of aPLs in RM patients is between 15% and 20% (Kutteh and Hinote, 2014). Given the complexity and heterogeneity of RM, the etiology remains unknown in about 50% of couples (American Society for Reproductive Medicine, 2016). Research on APS has decreased in

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such indeterminate cases (Cecatti et al., 2000). There is a discussion in the literature about the definition of RM. The commonly accepted and widely adopted definition of recurrent miscarriage is three or more consecutive miscarriages (Diejomaoh, 2015; Stirrat, 1990). However, in practice, many researchers and clinicians have now revised the definition to two or more consecutive miscarriages, a less rigorous definition (American Society for Reproductive Medicine, 2016; Diejomaoh, 2015; Stirrat, 1990; Sugiura-Ogasawara et al., 2014). Without treatment, APS can contribute to 90% of recurrent miscarriage (Rai et al., 1995). The clinical treatment of choice among patients with APS is the use of heparin and low-dose aspirin (Kwak-Kim et al., 2013). However, therapy should be tailored to the needs of the patient. The identification of additional risk factors should be considered, as well as the dissemination of information to patients about morbidity during and after pregnancy and the positive outcome after appropriate treatment (Ruiz-Irastorza and Khamashta, 2007).

Despite the complexity of APS and its being responsible for a high rate of obstetric complications some advances have been made in our understanding of the pathogenesis of the disease. However, many gaps in our knowledge remain, especially regarding diagnosis and treatment (Branch et al., 2010). Given the large production of research that has related aPLs to RM, we performed a systematic review and meta-analysis to identify and analyze recent publications on the syndrome to better understand the diagnosis and its contribution to monitoring APS among women with history of obstetric complications.

2. Materials and methods

2.1. Search strategy

The research was conducted in accordance with the PRISMA statement (Shamseer et al., 2015) to search for articles that were published from January 2010 to December 2014. The first stage of the research included a definition of search descriptors by three researchers (ALI, HCC, TSS) and an expert (JJVT). The next step was a summary of research in the PubMed and Web of Knowledge databases. We used PubMed MeSH terms and Web of Knowledge topics (TS). The descriptors remained the same for both databases and were divided into two blocks: Block 1: “Antiphospholipid Syndrome” OR “Antibodies, Antiphospholipid”; Block 2: “Abortion, Habitual”- major term (to ensure greater search accuracy). Afterward, both blocks were combined to retrieve the greatest number of abstracts (Supplementary file 1).

2.2. Study selection

According to previously defined strategies, the research was performed using our own filters of the databases: summary available, human, English, and publication period (January 1, 2010, to December 31, 2014). All of the abstracts that approached the topic of interest were selected by three researchers (ALI, HCC, TSS) by consensus. For the selection of articles, we included studies that used different definitions for RM (2 or more abortions; 3 or more abortions) (American Society for Reproductive Medicine, 2016; Stirrat, 1990). Due to literature description that other aPLs and clinical manifestations are strongly associated with APS, and the international consensus recognizes these associations (Miyakis et al., 2006), we excluded other probable causes for abortion, such as cytogenetic, anatomical, hormonal, and metabolic abnormalities and infections. The articles were retrieved in full-text PDF format and reanalyzed by the same three researchers to ensure higher accuracy of selection. The articles were organized and structured into three blocks of items and randomly assigned to the other judges (AMS, IGD, MVCL and QALN) for independent review. After reading and analyzing the articles in the block, each judge exchanged his block with another judge for validation. Doubts encountered in the sample selection were resolved by consensus among the judges. The exclusion criteria were reviews, letters, editorials, news, commentaries,

guidelines, and duplicate publications. Studies that included populations with other diseases related to RM or that did not study the relationship between RM and aPLs were also excluded (Supplementary file 1).

2.3. Quality assessment

Steps which involved selection of items and researchers were performed randomly. To improve and increase the sensitivity of the systematic review, the researchers also conducted additional searches of the original articles' reference lists. The goal was to identify additional references that were not found in the initial stages of the search.

2.4. Data extraction

The data was organized in tables containing the most important variables, including the prevalence of aPLs in patients with RM, the type and number of patients with aPLs for each study, and the positive cutoff values. These features were analyzed according to the following topics: type of study, study period, population, age (mean \pm standard deviation), inclusion and exclusion criteria, author biases, study limitations, and outcomes. Three researchers (ALI, HCC, TSS) extracted the data, and then four reviewers (AMS, IGD, MVCL and QALN) independently validated the data that was extracted. Various consensus meetings were convened to agree with the final structure of the tables and define the most relevant results of the search.

2.5. Statistical analysis

The forest plan was structured with odds ratio (OR) values with 95% confidence interval between grouped variables (Table 1). Various frequency measurements were analyzed, such as aPLs and/or APS and RM cases, aPLs and/or APS cases about the definition used for RM, and APS among RM cases. The evaluation of the heterogeneity among studies was done by using χ^2 test, according to the Higgins and Thompson I^2 statistic classification: low (25%), moderate (50%), and high (75%) (Higgins et al., 2003), the estimate was analyzed in random-effects. For potential publication bias, Begg's (Begg and Mazumdar, 1994) and Egger's tests (Egger et al., 1997) with significance $p < 0.05$ were used, as well as the funnel plots for symmetry analysis. All statistical analyzes for meta-analysis were carried out using the STATA 9.0[®] software package (Stata Corporation, College Station, TX, USA) with significance for $p < 0.05$.

3. Results

3.1. Selection and characteristics of the studies

The search strategy yielded a total of 85 articles identified with the use of filters. Of these, 76 were excluded because they did not meet the objectives of the study, so the final sample contained nine articles (Fig. 1). The main features of the included studies in the review show that the majority of studies on APS are developed in Europe and are case-control designs (Table 1).

The age ranged from 20 to 45 years, the most prevalent age range, corresponding to the fertile age of the women included in studies. All of the authors used inclusion criteria to select their samples, with the common intention to include only patients without a definite cause of RM. For sample selection, three authors used 3 or more consecutive miscarriages as definition for RM (Chen et al., 2012; Motak-pochrzest and Malinowski, 2013; Sater et al., 2012) and six articles used 2 or more consecutive miscarriages (Cohn et al., 2010; Lončar, 2010; Obayashi et al., 2010; Roye-Green et al., 2011; Subrt et al., 2013; Van Den Boogaard et al., 2013) (Table 1). Seven studies of nine included in the meta-analysis showed an association between RM and aPLs (Chen et al., 2012; Cohn et al., 2010; Lončar, 2010; Motak-pochrzest and

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