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Prevalence of antiphospholipid antibodies and risk of subsequent adverse obstetric outcomes in women with prior pregnancy loss☆

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ABSTRACT

The reported prevalence of antiphospholipid antibodies in women with a chief complaint of pregnancy loss varies, as does the risk of adverse outcomes in subsequent pregnancies. Our objectives were to assess the prevalence of antiphospholipid antibodies meeting revised Sapporo thresholds among women presenting with a chief complaint of pregnancy loss and risks in subsequent pregnancies for these women. We examined a retrospective cohort of patients presenting with a chief complaint of pregnancy loss between 2003 and 2012. Antiphospholipid antibodies were assessed at the providers' discretion, and patients were considered positive if they met the revised Sapporo criteria. Patient data were obtained by review of the medical records. 338/390 women (86.7%) presented with a chief complaint of pregnancy loss and had testing for antiphospholipid antibodies. 19/338 women (5.6%) persistently tested positive for at least one antiphospholipid antibody. Seven women who tested positive had isolated recurrent early pregnancy loss ≤10 weeks, and 12 women who tested positive had venous thromboembolism (VTE), systemic lupus erythematosus (SLE), delivery <34 weeks for pre-eclampsia, and/or placental insufficiency, or fetal demise >10 weeks. Subsequent pregnancy outcomes were available for 13 patients. Compared with women with recurrent early pregnancy loss alone, subsequent obstetric morbidity was significantly more likely in those patients with a history of SLE and/or VTE ($p = 0.048$). We conclude that the prevalence of positive antiphospholipid antibodies in women with a chief complaint of pregnancy loss and without autoimmune disease or prior thrombosis is low and that among these women, subsequent pregnancy outcomes are largely favorable.

1. Introduction

Early pregnancy loss is a common problem that occurs in approximately 12–14% of clinically recognized pregnancies and up to 30% of conceptions (Branch et al., 2010). Approximately 2% of women attempting pregnancy experience two consecutive pregnancy losses, and 0.4–1% experience three consecutive losses (Branch et al., 2010, Salat-Baroux, 1988). While most remain unexplained, recurrent early miscarriages (REM) are usually pre-embryonic or embryonic

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(<10 weeks' gestation) and may be due to etiologies such as parental balanced chromosomal translocations (2–4%) (Reindollar, 2000, Franssen et al., 2005) or non-genetic causes that include uterine malformations, poorly controlled diabetes, or the presence of antiphospholipid antibodies (5–15%) (Reindollar, 2000).

Antiphospholipid syndrome (APS) is an autoimmune disorder defined by specific clinical and laboratory criteria and is associated with significant obstetric morbidity. Consensus classification criteria for APS were first proposed in 1998 during a post-conference workshop following the Eighth International Symposium on Antiphospholipid Antibodies in Sapporo, Japan, and came to be known as the "Sapporo criteria" (Wilson et al., 1999). The clinical criteria included vascular thrombosis or obstetric morbidity defined as one or more unexplained deaths of a morphologically normal fetus ≥10 weeks' gestational age, one or more premature births of a morphologically normal neonate ≤34 weeks' gestational age for severe pre-eclampsia or severe placental insufficiency, or three or more *unexplained, consecutive* spontaneous abortions <10 weeks' gestation (i.e., REM). Initial laboratory criteria included testing positive for either lupus anticoagulant or anticardiolipin (aCL) IgG or IgM in medium to high titers on two occasions at least six weeks apart. Additional research and clinical experience provided more insight into the syndrome and resulted in a revision to the diagnostic laboratory criteria in 2006 in Sydney, Australia, referred to as the "revised Sapporo criteria." Specifically, these revisions included the addition of anti-β_2 glycoprotein-I ($a\beta_2GP1$) IgG or IgM to the diagnostic criteria, extension of the minimum confirmation period from 6 to 12 weeks, and assignment of minimum values for aCL and $a\beta_2GP1$ antibodies (Miyakis et al., 2006). The initial obstetric criteria remained unchanged and have since been largely adopted by medical specialty organizations including the American College of Obstetricians and Gynecologists (Committee on Practice Bulletins–Obstetrics and Gynecologists, 2012) and the Royal College of Obstetricians and Gynaecologists (2011).

Studies examining the association of antiphospholipid antibodies (aPL) with recurrent miscarriage have yielded variable results. The frequency of aPL associated with REM has ranged from 5 to 20% (Branch et al., 2010), attributable in part to the various definitions of pregnancy used (pregnancy test versus clinical), number of pregnancy losses required for study inclusion (at least two versus at least three), variable exclusions of other causes of REM (e.g., uterine malformations), types of aPL included in testing, and thresholds for aPL laboratory testing cutoffs (Branch et al., 2010). Importantly, studies that have examined subsequent pregnancies for women diagnosed with APS by REM have been limited by small sample size and questionable quality. Due to the prevalence of pregnancy loss in general and the heterogeneity of studies, the association of aPL with REM has been questioned (Branch et al., 2010).

Our objectives were to assess the prevalence of aPL meeting the revised Sapporo criteria among women who present to an obstetric clinic with a chief complaint of pregnancy loss and to assess subsequent pregnancy outcomes for women who persistently test positive.

2. Materials and methods

This was a retrospective cohort study of women who presented with a chief complaint of pregnancy loss at one of two clinical settings in Salt Lake City, Utah, from 2003 to 2012. Patient data, including past medical history and subsequent pregnancy outcomes, were obtained from a review of the medical record.

Patients were included for analysis if they tested positive for aPL and met at least one of the following clinical criteria: a history of REM (defined as ≥2 recurrent miscarriages at less than 10 weeks' gestation), a history of fetal demise (defined as occurring at greater than or equal to 10 weeks' gestation), a history of systemic lupus erythematosus (SLE), history of venous thromboembolism (VTE), or a history of preterm delivery at less than 34 weeks' gestation for severe pre-eclampsia and/or placental insufficiency. aPL testing was performed at the providers' discretion, and patients were considered to be aPL positive if they met the following revised Sapporo classification criteria (Miyakis et al., 2006): positive lupus anticoagulant detected according to the guidelines of the International Society on Thrombosis and Haemostasis, aCL IgG or IgM present in medium or high titer (i.e., >40 GPL or MPL), and/or $a\beta_2GP1$ IgG or IgM present in titer >99th percentile or >40 SU. Patients were excluded from the final analyses if they failed to meet clinical criteria for the study and/or if they either did not have aPL tested or were tested and found to be aPL negative. If patients were initially aPL positive but retested and found to be aPL negative, they were considered to be aPL negative and thus excluded from further analyses. Patients with known APS prior to presentation or those referred for indications other than pregnancy loss (such as thrombosis) were also excluded.

Subsequent pregnancy outcomes were examined when available and were considered to be adverse if they included any of the following: early pregnancy loss (<10 weeks' gestation), fetal demise (>10 weeks' gestation), delivery <34 weeks for severe pre-eclampsia or placental insufficiency, or venous thromboembolism during the subsequent pregnancy or post-partum period. Treatment for APS during subsequent pregnancies was at the discretion of the primary provider.

Categorical variables were compared using Fisher's exact test, and a p value of less than 0.05 was considered significant. The Institutional Review Boards of the University of Utah and Intermountain Healthcare approved this study.

3. Results

Three hundred and ninety women presented with a chief complaint of pregnancy loss, of whom 338 (86.7%) underwent aPL testing (Fig. 1). Initial testing was negative for 316 (93.5%) and positive for 22 (6.5%). Fifteen of the 22 women who initially tested positive underwent repeat testing, 3 of whom subsequently tested negative based on revised Sapporo thresholds.

Thus, 19 women were included in further analyses, 12 who had retested positive and 7 who had initially tested positive but had not been retested. Seven of the women