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Maternal cardiovascular events in autoimmune rheumatic diseases and antiphospholipid syndrome pregnancies

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Abstract

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OBJECTIVE: Antiphospholipid syndrome (APS) and autoimmune rheumatic diseases (ARDs) are known to increase the risk for cardiovascular events (CVEs) in the general population.[1,2] However, research in pregnancy is limited. We compared the occurrence of acute CVEs in pregnant women with and without ARDs or primary APS using a Californian population-based cohort.

STUDY DESIGN: This was a retrospective cohort study of pregnant individuals who delivered singleton infants in California between 2005 and 2020. Birth certificates were linked by the Study of Outcomes of Mothers and Infants to maternal records. The study was approved by institutional review boards of the State of California and the University of California San Diego.

Pregnancies with ARDs were identified by ≥1 International Classification of Diseases (ICD) code for rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), spondyloarthritis, Sjogren's syndrome, and other ARDs (systemic sclerosis, inflammatory myositis, and vasculitides) in maternal hospital discharge, emergency, or ambulatory surgery records. Lupus nephritis (LN) was defined as SLE plus glomerulonephritis, renal failure, nephritic or nephrotic syndrome, or proteinuria. Primary APS included women with APS without concurrent ARDs. Women without ARDs or APS comprised the reference group. Acute CVEs during pregnancy and up to 6 weeks postpartum were identified by ICD codes and compared between groups. CVEs were classified as myocardial infarction, cardiovascular accident, heart failure and peripartum cardiomyopathy, inflammatory heart diseases, cardiac dysrhythmias, and venous thromboembolism (VTE).

Covariates identified and adjusted for include age, race and ethnicity, insurance, education, prepregnancy body mass index, preexisting hypertension, diabetes, hyperlipidemia, depression, and substance use disorders.

A log linear regression with a Poisson distribution was used to estimate the adjusted relative risks (aRRs) and 95% confidence intervals (CIs) for the associations of ARDs and APS with CVEs. Analyses were performed using Statistical Analysis Software (SAS), version 9.4 (SAS Institute, Cary, NC). Causal mediation analyses were performed for potential mediators, such as gestational diabetes, gestational hypertension, and preeclampsia.[3]

RESULTS: Overall, 19,340 women had ARDs, 7758 had primary APS, and 7,004,334 had neither condition. The ARD and APS groups had more traditional cardiovascular risk factors. Acute CVEs were observed in 2.0% of ARD cases (388/19,340), 7.0% of primary APS cases (540/7,758), and 0.4% of reference group cases (24,402/7,004,334). The aRR for CVEs in the ARD and APS groups in comparison with the reference group was 4.1-fold (95% CI, 3.7–4.5) and 14.7-fold (95% CI, 13.5–16.0), respectively (Table).

Of the 388 CVEs that occurred in women with ARDs, 164 (42%) were VTEs, 96 (25%) were heart failure or peripartum cardiomyopathy, and 92 (24%) were cardiac dysrhythmias. In primary APS cases, 453 of 540 (83%) CVEs were VTE. Acute CVEs occurred in 3.1% (159/8,422) of patients with overall SLE, in 10.7% (55/513) of patients with SLE with APS, and in 8.5% (77/903) of patients with SLE with LN (Table). The aRR for CVEs was 6-fold higher among those with SLE (95% CI, 5.3–6.8) and was notably increased with concurrent APS or LN, with aRRs of 18.1 (95% CI, 13.9–23.6) and 12.7 (95% CI, 10.1–15.9), respectively (Figure). The risks for both VTE and non-VTE CVEs was increased among pregnancies affected by ARD and APS (Figure).

Five of 6 in-hospital deaths in ARD pregnancies (5/388 or 1.3%) occurred among women with acute CVEs (Table).

The risks for CVEs were higher during all perinatal periods. In mediation analyses, 11.2% of the excess risk for CVE in ARD pregnancies was mediated by preeclampsia, whereas <0.5% was mediated by gestational diabetes or hypertension.

CONCLUSION: Pregnancies affected by ARDs and APS had both more traditional cardiovascular risk factors and about a 4-fold and 15-fold higher CVE risk, respectively, than the reference group. Pregnancies affected by SLE with APS (18.1-fold) and LN (12.7-fold) had substantial increased risks for CVEs. VTEs were the most frequently observed CVEs. The in-hospital mortality rate for any acute CVE in ARD pregnancies was 1.3% (Table).

Analyses using the United States National Inpatient Sample database also showed higher rates of CVEs among birth hospitalizations for SLE.[4] Conversely, a study from Taiwan did not show an increased risk for CVEs among pregnant individuals with RA.[5]

Recognizing CVE risks may be challenging because of lower suspicion among young patients and symptom overlap with normal pregnancy. Future studies should explore biomarkers, imaging tests, and practice-based enhancements, such as multidisciplinary clinics and electronic health record alerts for earlier detection and reduction of maternal CVE morbidity. Limitations included reliance on ICD codes and no data on disease history, medications, or test results. Under-recording of covariates may have led to unmeasured confounding.

Strengths of the study included use of a large, population-based sample covering a 15-year period.

This study suggested strong associations of ARDs and APS with CVEs. Although the absolute risks are low, the consequences can be substantial for both the mother and the baby.

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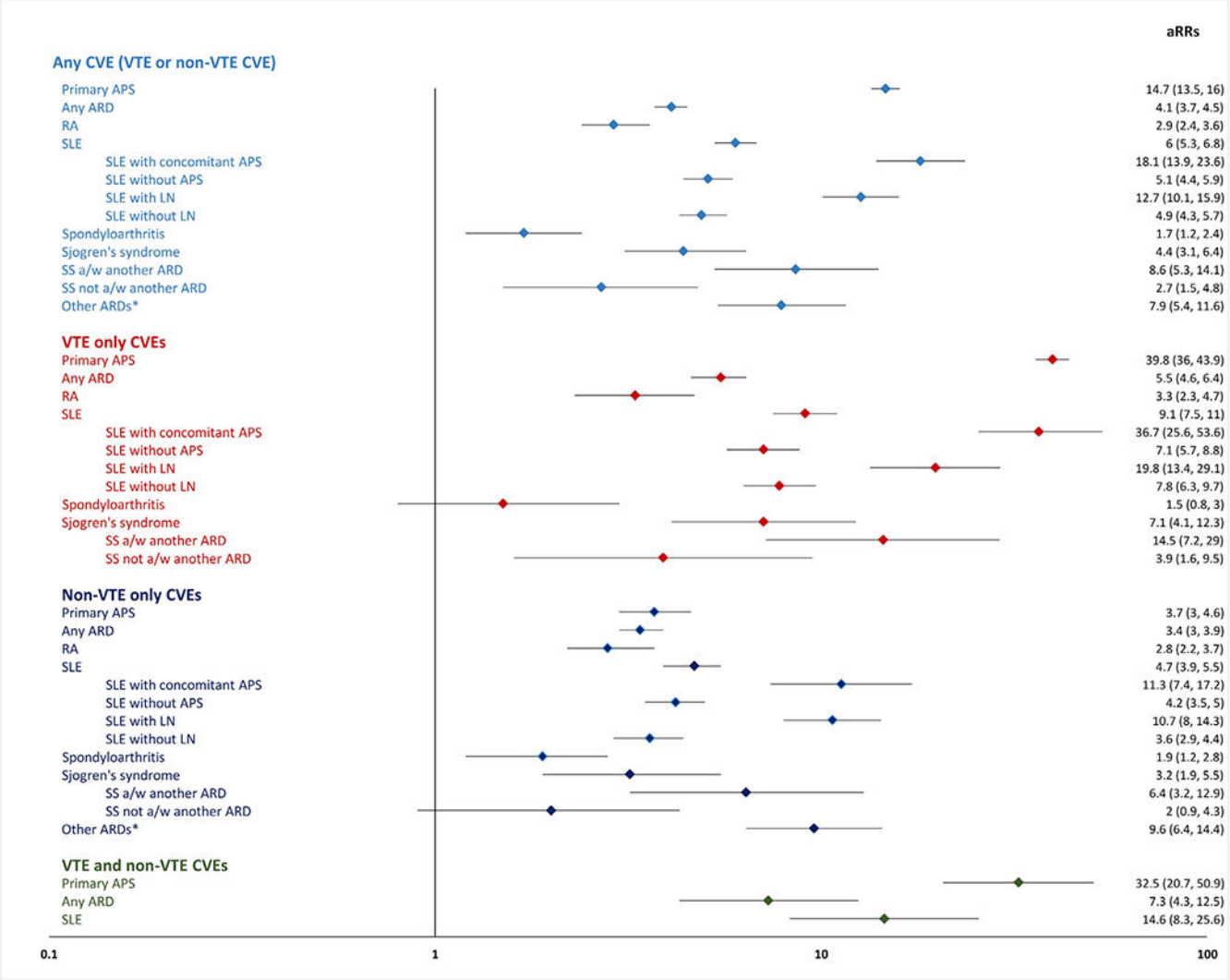

FIGURE. Risks of acute maternal CVEs by ARD categories and CVE types

Asterisk denotes systemic sclerosis, inflammatory myositis, and vasculitides.

APS, antiphospholipid syndrome; *ARD*, autoimmune rheumatic disease; *aRR*, adjusted relative risk; *LN*, lupus nephritis; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SpA*, spondyloarthritis; *ss*, Sjorgen syndrome; *VTE*, venous thromboembolism.

TABLE

Occurrence of various CVEs during pregnancy or within 6 weeks postpartum by ARD category, 2005–2020

CVE	No ARD or APS (Reference) n (%)	Any ARD n (%)	Categories of ARDs					Primary APS n (%)
			RA n (%)	SLE n (%)	SpA n (%)	Sjogren's syndrome n (%)	Other rheumatic diseases n (%)	
Sample	7,004,334	19,340	6478	8422	3415	1472	705	7758
Any CVE	24,402 (0.4)	388 (2.0)	94 (1.5)	259 (3.1)	30 (0.9)	28 (1.9)	27 (3.8)	540 (7.0)
VTE	7903 (0.1)	164 (0.9)	31 (0.5)	122 (1.5)	<11	14 (1.0)	<11	453 (5.8)
PE	910 (0.0)	24 (0.1)	<11	20 (0.2)	<11	<11	<11	57 (0.7)
Other VTE	7507 (0.1)	156 (0.8)	28 (0.4)	117 (1.4)	<11	12 (0.8)	<11	437 (5.6)
Heart failure or PPCM	4342 (0.1)	96 (0.5)	23 (0.4)	64 (0.8)	<11	<11	13 (1.8)	21 (0.3)
Cardiac dysrhythmia	9677 (0.1)	92 (0.5)	27 (0.4)	50 (0.6)	15 (0.4)	<11	<11	26 (0.3)
Atrial fibrillation or flutter	1820 (0.0)	31 (0.2)	<11	19 (0.2)	<11	<11	<11	<11
Ventricular arrhythmia, cardiac arrest	7902 (0.1)	51 (0.3)	17 (0.3)	27 (0.3)	<11	<11	<11	16 (0.2)
Dysrhythmia, unspecified	1119 (0.0)	13 (0.1)	<11	<11	<11	<11	<11	<11
Acute CVA	1068 (0.0)	33 (0.2)	<11	23 (0.3)	<11	<11	<11	54 (0.7)
Hemorrhagic stroke	652 (0.0)	11 (0.1)	<11	<11	<11	<11	<11	14 (0.2)
Ischemic stroke	457 (0.0)	25 (0.1)	<11	18 (0.2)	<11	<11	<11	45 (0.6)
AMI	403 (0.0)	13 (0.1)	<11	<11	<11	<11	<11	<11
Inflammatory heart disease	153 (0.0)	14 (0.1)	<11	12 (0.1)	<11	<11	<11	<11
Myocarditis	55 (0.0)	<11	<11	<11	<11	<11	<11	<11
Pericarditis	107 (0.0)	<11	<11	<11	<11	<11	<11	<11
In-hospital mortality	550 (0.0)	<11	<11	<11	<11	<11	<11	<11
CVE mortality	336 (0.0)	<11	<11	<11	<11	<11	<11	<11
Without the above CVEs	214 (0.0)	<11	<11	<11	<11	<11	<11	<11

Numbers of specific ARDs and CVEs add up to more than the total ARDs or any CVE event because these were not mutually exclusive.

AMI, acute myocardial infarction; *APS*, antiphospholipid syndrome; *ARD*, autoimmune rheumatic disease; *CVA*, cerebrovascular accident; *CVE*, cardiovascular event; *PE*, pulmonary embolism; *PPCM*, peripartum cardiomyopathy; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SpA*, spondyloarthritis; *VTE*, venous thromboembolism.