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Cardiovascular Events During Pregnancy: Implications for Adverse Pregnancy Outcomes in Individuals With Autoimmune and Rheumatic Diseases

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Abstract:

Objective: This study examined maternal cardiovascular events relative to adverse pregnancy outcomes among individuals with autoimmune rheumatic diseases (ARDs), primary antiphospholipid syndrome (APS), and those with neither.

Methods: Utilizing a California population-based birth cohort (2005-2020), we identified cardiovascular events, ARDs, and APS through ICD codes in maternal discharge records. Selected adverse pregnancy outcomes identified from birth certificates were preterm birth (PTB: <37 weeks' gestation), small-for-gestational-age infants (SGA, birth weight <10th centile for age and sex), and a composite of either outcome. Adjusted risk ratios (aRRs) for adverse outcomes and their 95% confidence intervals (CIs) were calculated.

Results: Cardiovascular events occurred more frequently in individuals with ARDs (265/19,340, 1.4%) and primary APS (428/7,758, 5.5%) than those without (17,130/7,004,334, 0.3%). The presence versus absence of cardiovascular events was associated with a greater incidence of adverse outcomes in ARD (53.2% versus 26.6%), APS (30.6% versus 20.7%), and non-ARD/APS pregnancies (28.2% versus 15.2%). Cardiovascular events were associated with increased risks of SGA in all groups (aRRs 1.2-1.5), and with PTB in ARD (aRR 1.6, 95% CI 1.3-2.0) and non-ARD/APS (aRR 1.7, 95% CI 1.7-1.8) pregnancies.

Conclusion: Cardiovascular events were associated with modestly increased risks (20-70%) for PTB, SGA, or both across groups. Notably, >50% of ARD pregnancies with cardiovascular events experienced adverse pregnancy outcomes. Given that ARD and APS pregnancies have higher (although still low) rates of cardiovascular events and have higher baseline risks of adverse pregnancy outcomes than the general population, the additional burden conferred by cardiovascular events is clinically important.

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Introduction:

Pregnancies in individuals with autoimmune rheumatic diseases (ARDs) are considered high risk due to an increased risk of adverse pregnancy outcomes, including about a 2 to 3-fold increase in the risk for preterm birth (PTB) and a 2-fold increase in the risk of small for gestational age (SGA) infants, which correlate with underlying disease activity and severity.(1–4) Similarly, antiphospholipid syndrome (APS) is another multisystem autoimmune condition with a well-recognized increased risk of early pregnancy loss, but is also linked to 1.4 and 1.9-fold higher risks of SGA and PTB.(5)

Numerous studies have also established higher risks (1.5 to 4-fold) of cardiovascular events in individuals with ARDs, particularly among those with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).(6–9) Likewise, individuals with APS are known to be at risk of recurrent venous thromboembolism (VTE) and have other cardiovascular risks.(10) Only a few studies have assessed the risks of such cardiovascular events during pregnancy and after delivery for women with ARDs, and found higher risks.(11–14) In our recent analysis of a large population-based California birth cohort, we found significantly higher risks for cardiovascular events during pregnancy and early postpartum among women with ARDs (4.1-fold) and primary APS (14.7-fold) when compared to individuals without such conditions.(13)

There is an extensive literature indicating that adverse pregnancy outcomes exacerbate cardiometabolic risk factors and increase the future risk for cardiovascular diseases and disease-related mortality for the mother.(15–19) However, data are limited on the impact of

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maternal cardiovascular events on the risks of adverse pregnancy outcomes, particularly among pregnant individuals with ARDs and primary APS, even though these conditions are independently associated with higher risks of cardiovascular events as well as adverse pregnancy outcomes.

The primary aim of this study was to investigate the relationship between cardiovascular events occurring in pregnancy and the risks of adverse pregnancy outcomes, specifically PTB and SGA infants, among individuals with ARDs. To contextualize the study findings, we also conducted similar comparisons of adverse pregnancy outcomes associated with cardiovascular events among pregnant individuals with APS, and those without an ARD or APS.

Methods:

Data source:

This study was a retrospective cohort study of pregnant individuals who delivered singleton liveborn infants in California between 2005 to 2020. Birth certificates, maintained by California Vital Statistics, were linked by the UC San Diego Study of Outcomes of Mothers and Infants (SOMI) to maternal and infant hospital discharge, emergency department, and ambulatory surgery records maintained by the California Department of Health Care Access and Information. Diagnoses were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9, 2005 through September 2015) and International Classification

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of Diseases, 10th Revision, Clinical Modification (ICD-10, October 2015 through 2020) codes. The study was approved by the Committee for the Protection of Human Subjects within the Health and Human Services Agency of the State of California and by the Institutional Review Board (IRB) at the University of California San Diego.

Study Population:

Pregnant women with ARDs were identified using ICD-9-CM and ICD-10-CM codes documented on discharge records during pregnancy and categorized as: i) RA; ii) SLE; iii) spondyloarthritis (SpA) [psoriatic arthritis (PsA), and ankylosing spondylitis (AS)]; iv) Sjogren's syndrome (SS); and v) other rheumatic diseases [including systemic sclerosis (Ssc), idiopathic inflammatory myositis (IIM) and vasculitides]. To create the primary APS group, pregnant women with APS were identified using ICD codes for APS and those women with a concurrent ARD diagnosis were excluded (**Supplementary Table 1**). A third group consisted of those individuals without any of the specified ICD codes associated with ARDs or primary APS.

Exposure and Outcomes:

The primary exposure of interest was the presence of one or more maternal cardiovascular events. Acute cardiovascular events during pregnancy were identified using ICD-9 and ICD-10 codes for i) acute myocardial infarction; ii) acute cardiovascular accident (ischemic and hemorrhagic); iii) heart failure and peripartum cardiomyopathy; iv) inflammatory heart disease (myocarditis and

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pericarditis); v) cardiac dysrhythmia (atrial fibrillation/flutter, ventricular arrhythmias and cardiac arrest, arrhythmia unspecified); and vi) VTE (pulmonary embolism, deep vein thrombosis) **(Supplementary Table 2)**.

The primary endpoint was adverse pregnancy outcomes defined as PTB, SGA, or a composite of either. Gestational age was obtained from the best obstetric estimate on the birth certificate record. PTB was defined as delivery occurring prior to 37 weeks of gestation (WOG) and further classified as spontaneous or provider-initiated PTB, and early (<32 weeks of gestation), moderate (32- < 34 weeks of gestation), or late (34 - < 37 weeks of gestation) PTB. Indicators of spontaneous PTB were preterm premature rupture of the membranes (PPROM), premature labor, or tocolytic administration. Pregnancies resulting in provider-initiated PTB were those without PPROM, premature labor, or tocolytic administration who had a code for "medical induction" or "artificial rupture of membranes" or cesarean delivery on birth certificate or hospital discharge records. SGA was obtained from birth certificates, and defined as birthweight <10th centile for gestational age and sex.(20)

We examined the risks of adverse pregnancy outcomes in ARD, APS and non-ARD/APS pregnancies with cardiovascular events compared to those without. Additionally, within each group, we compared the risks of the individual components of adverse pregnancy outcomes between pregnant individuals with and without cardiovascular events. Among ARD pregnancies, we assessed the risks of adverse pregnancy outcomes for different ARD subcategories. In a sensitivity analysis, we further examined the risk of

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adverse pregnancy outcomes by distinguishing between cardiovascular events exclusively related to a VTE or involving a non-VTE cardiovascular event.

Covariates:

Covariates were obtained from birth certificates and hospital discharge records and were categorized as follows: maternal age (<18, 18-34, 35-44, or ≥45 years), maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian and other), expected primary payer (private, public, self-pay or other), maternal education (completion of <12th, 12th, or >12th grades), and maternal pre-pregnancy body mass index (BMI) (calculated from pre-pregnancy weight and height; <18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2). Maternal comorbidities (hypertension, diabetes mellitus, hyperlipidemia, depression), and substance use disorders (smoking, alcohol, and other recreational drugs) were classified from ICD codes obtained from discharge records (**Supplemental Table 2**).

Statistical analyses:

Baseline demographic and clinical characteristics of pregnant individuals with and without cardiovascular events during pregnancy were compared using chi-square statistics. We described the occurrence of composite adverse pregnancy outcomes and individual components of the selected adverse pregnancy outcomes by the presence or absence of cardiovascular events in three groups of pregnant individuals: those with ARDs, those with primary APS and those who had neither ARD nor APS. Log-linear regression with a Poisson distribution was used to calculate unadjusted and adjusted risk ratios (RRs, aRRs) and 95% confidence intervals (CI) for the

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associations between cardiovascular events and adverse pregnancy outcomes for the three distinct groups of pregnant individuals. Furthermore, adverse pregnancy outcome risk in relation to cardiovascular events was assessed for each category of ARDs.

To provide perspective on absolute risk differences for adverse outcomes associated with cardiovascular events in ARD pregnancies, we used linear regression with a binary distribution to calculate unadjusted and adjusted risk differences (RDs, aRDs) and their 95% CIs for adverse pregnancy outcomes, expressed as excess number per 100 births. We compared risk differences in ARD pregnancies, separately for those with and without a cardiovascular event to a reference group without ARD/APS without cardiovascular events.

In sensitivity analyses, aRRs for adverse outcomes were calculated for cardiovascular events grouped as VTE only cardiovascular events [deep vein thrombosis (DVT) and pulmonary embolism (PE)], non-VTE only cardiovascular events (cardiovascular accidents, heart failure, inflammatory heart diseases, cardiac dysrhythmia) and pregnancies complicated by both VTE and non-VTE cardiovascular events . For cells with fewer than 11 events, actual percentages were not reported to comply with IRB confidentiality requirements.

Risks were adjusted for select maternal sociodemographic variables (age, race/ethnicity, primary payer, maternal education, pre-pregnancy BMI) and clinical comorbidities (pre-existing and pregnancy-induced hypertension and diabetes mellitus, hyperlipidemia,

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depression, and substance use disorders) that have been previously identified in the literature as being linked to adverse pregnancy outcomes.(21)All analyses were performed using Statistical Analysis Software (SAS) version 9.4 (Cary, NC).

Results:

The sample included 7,031,432 pregnancies ending in live born singletons, of which 19,340 were births to individuals with ARDs, 7,758 to those with primary APS and 7,004,334 to those with neither condition. Cardiovascular events were observed more frequently in pregnant individuals with ARD and primary APS: 265 (1.4%) and 428 (5.5%), respectively, compared to 17,130 (0.3%) in the group without an ARD or APS (**Table 1**). The majority of pregnant individuals within this cohort belonged to the age group of 18 to 34 years. About 40% of pregnant individuals with ARDs were of Hispanic ethnicity, while primary APS predominantly consisted of non-Hispanic White individuals (53.8%). The pregnant individuals who experienced cardiovascular events during pregnancy differed significantly in baseline demographic and clinical characteristics on nearly all measured covariates compared to those without cardiovascular events (**Table 1**).

Adverse pregnancy outcomes occurred in more pregnant individuals with ARDs (5,206/19,340; 26.9%) and primary APS (1,648/7,758; 21.2%) compared to those without either condition (1,067,961/7,031,432;15.2%). Cardiovascular events were associated with increased risks of composite adverse pregnancy outcomes (aRRs 1.2 to 1.4) across all studied groups, including those with ARDs, those with APS, and those without an ARD or APS. Among the adverse outcomes examined, the highest risks were noted for

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early and moderate PTB for individuals with an ARD (aRR 2.4, 95% CI 1.7-3.6; and aRR 2.5, 95% CI 1.4-4.3, respectively) and for those without an ARD or APS (aRR 3.2, 95% CI 3.0-3.5, and aRR 2.6, 95% CI 2.4-2.9, respectively). Individuals with primary APS who experienced a cardiovascular event during pregnancy had an increased risk of SGA (aRR 1.4, 95% CI 1.1-1.8) but not PTB, compared to those with primary APS without cardiovascular events (**Figure 1**).

Notably, over half (53.2%) of ARD pregnancies complicated by cardiovascular events experienced an adverse pregnancy outcome, higher than ARD pregnancies without cardiovascular events (26.6%), and APS and non-ARD/APS pregnancies with cardiovascular events (30.6% and 28.2%, respectively). Compared to those with no cardiovascular event or ARD/APS, the adjusted risk difference estimates per 100 births were 7.8 (95% CI 7.1-8.6) for no ARD/APS with a cardiovascular event, 8.7 (95% CI 8.0-9.4) for ARD without cardiovascular events, and 27.8 (95% CI 19.3-36.3) for those with ARD and cardiovascular events (**Table 2**).

Further analysis by subcategories of ARDs showed that SLE and SpA pregnancies complicated by cardiovascular events had significantly increased risks of composite adverse pregnancy outcomes (SLE: aRR 1.3, 95% CI 1.1-1.6, and SpA: aRR 2.6, 95% CI 1.4-4.8), PTB (SLE: aRR 1.5, 95% CI 1.2-1.8, and SpA: 3.2, 95% CI 1.5-6.9), as well as SGA infants (SLE: aRR 1.4-95% CI 1.0, 2.0, and SpA: aRR 2.7, 95% CI 1.1-6.8). For RA, cardiovascular events during pregnancy were associated with an increase in risk of PTB by 1.7-fold (95% CI 1.1-2.8), but not of SGA infants **(Supplementary Table 3**).

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In sensitivity analysis, we observed that both VTE and non-VTE cardiovascular events were linked with increased risk of adverse pregnancy outcomes in non-ARD/APS pregnancies as well as in ARD pregnancies, but not in APS. The highest adjusted risk ratios were observed for early and moderate PTB with non-VTE cardiovascular events in ARD pregnancies (aRR 5.2, 95% CI 3.3-8.3; aRR 3.0, 95% CI 1.6-5.6, respectively) **(Supplementary Table 4**).

Discussion:

Utilizing the UC San Diego SOMI database from 2005-2020 with 19,340, 7,758 and 7,004,334 pregnancies ending in live born singletons from individuals with ARDs, primary APS, and those without either condition, we noted higher occurrence of cardiovascular events for pregnant individuals with ARDs (1.4%) and primary APS (5.5%), compared to those without either condition (0.3%). In non-ARD/APS pregnancies, cardiovascular events were associated with a higher incidence of adverse pregnancy outcomes compared to those without an event (28.8%, versus 15.2%), Similarly, cardiovascular events were associated with a higher incidence of adverse outcomes in APS pregnancies (30.6% versus 20.7%). In those with ARDs, cardiovascular events were associated with the largest differential incidence of adverse pregnancy outcomes (53.2% versus 26.6%).

Irrespective of the presence of ARD or APS, the adjusted risk ratios for adverse pregnancy outcomes were higher among those who experienced cardiovascular events during pregnancy relative to those who did not. Maternal cardiovascular events were associated with an increased risk of SGA in all groups of 1.2 to 1.5-fold, and of PTB in the non-ARD/APS (aRR 1.7, 95% CI 1.7-1.8) and the

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ARD groups (aRR 1.6, 95% CI 1.3-2.0). We are unaware of any previously published data that compared the incidence of adverse pregnancy outcomes in those with and without cardiovascular events among ARD and primary APS pregnancies.

Among the outcomes studied, the most pronounced risks were observed for early and moderate PTB, for instance, a 2.4 and 2.5-fold increase, respectively, in ARD pregnancies with cardiovascular events compared to those without. The risks for early and moderate PTB were even higher (5.2-fold and 3-fold) with non-VTE cardiovascular events in ARD pregnancies compared to those not complicated by cardiovascular events. Our findings are consistent with previous studies demonstrating increased risks of cardiovascular events as well as adverse pregnancy outcomes for pregnant individuals with ARDs and APS, including a 2-3 fold increase in PTB and a 2-fold increase in SGA risk in ARDs(1–4) and 1.4 and 1.9-fold higher risks of SGA and PTB in APS.(5,22)

Adverse pregnancy outcomes can significantly impact infant health, wellbeing and mortality. PTB and SGA infants are also more likely to suffer long-term issues such as short stature, puberty disorders, metabolic syndrome, and neurocognitive dysfunction.(23,24) In addition, there is also an extensive literature indicating that adverse pregnancy outcomes contribute to an elevated future risk of cardiovascular diseases and disease-related mortality for the mother.(15–19) Studies have also established higher risks (1.5 to 4-fold) of cardiovascular events in the general population of ARDs(6–9) as well as among the pregnant and postpartum ARD population.(11–14) It is possible that the higher incidence of adverse pregnancy outcomes in ARDs is partly mediated through their relationship with

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cardiovascular events. However, while the incidence of cardiovascular events in ARD and APS pregnancies was elevated (1.4% and 5.5%, respectively) compared to the general population (0.3%), the incidence was still low.

This retrospective cohort study, similar to other administrative database studies, was subject to inherent limitations which included reliance on ICD codes used for billing, misclassification of diagnoses, in particular, low sensitivities for ARDs, and under-recording of covariates, including cardiovascular risk factors, based on hospitalization data. The sensitivity and specificity estimates for ICD-9 codes in administrative data exceeded 90% for most ARDs, with a lower specificity of 72.5% for SLE.(25) However, when restricted to hospitalization data, notably lower sensitivities have been observed, with sensitivity for SLE ranging from 41% to 68%, for example.(26–28) The lower sensitivities could result in misclassification of individuals with these diseases, potentially biasing the results towards null. Administrative codes from inpatient settings generally have moderate to high sensitivity and specificity estimates (>80%) for acute/incident cardiovascular events such as acute myocardial infarction, ischemic stroke, heart failure, dysrhythmias, and pulmonary embolism, but are less reliable for isolated deep vein thrombosis.(29–32) Although risks were adjusted for multiple traditional risk factors, a lack of information on the disease activity, prior adverse pregnancy outcomes, and medications, all of which could influence both cardiovascular diseases and adverse pregnancy outcomes, could restrict clinical interpretation. Medications used in the management of pregnant population with ARDs may have variable impacts on cardiovascular risks and pregnancy outcomes, and studies designed to specifically assess the effects of medications should be a focus of future studies. Relatively fewer occurrences of some studied outcomes for certain groups may have led to imprecise risk estimates. Additionally, due to the nature of

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administrative data from hospital records, most exposures were noted in the delivery record, which raises challenges in determining temporality, as it is not possible to know whether the etiologic underpinnings of SGA precede or follow the cardiovascular events. Although reverse causation, whereby having an SGA infant would cause a cardiovascular event, is improbable, there is a possibility that both conditions could share a common underlying cause, potentially leading to a spurious association. Future prospective studies should aim to precisely time the cardiovascular events in relation to pregnancy stages and the outcomes of interest, such as incorporating ultrasound assessments to detect intrauterine growth restriction (IUGR) in infants. Further, due to not accounting for multiple comparisons, there is a potential for Type 1 error in the interpretations. Given that approximately half of the pregnant individuals in the SOMI database are of Hispanic ethnicity, and non-Hispanic Black population constitutes < 10 % of the sample, these demographics should be considered when generalizing the study results. Finally, the sample is created from infant birth records, and lacks adequate information to link repeat pregnancies to the same mother, thus, includes non-independent observations, and may result in overly precise confidence intervals. Future studies utilizing alternative data sources could complement the findings of the current study. Strengths of this study include the large size and complete population-based sample which was achieved through the linkage of vital statistics records in the state of California to maternal discharge records for all births in California spanning a 15-year period. Furthermore, we were able to examine a broad range of specific ARDs and APS as well as evaluate specific adverse pregnancy outcomes that occurred in relation to different types of cardiovascular events .

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In conclusion, individuals who experience a cardiovascular event in pregnancy have a 1.2 to 1.7-fold increased risk of either PTB or SGA or both compared to those whose pregnancies are not complicated by cardiovascular events, irrespective of ARD or APS diagnosis. There was no evidence that the magnitude of the relative risks associated with cardiovascular events in ARD pregnancies for composite adverse pregnancy outcomes differed from the risk of such events in the general population. However, given that individuals with ARDs already experience higher frequencies of cardiovascular events in pregnancy and have higher baseline risks of adverse pregnancy outcomes compared to the general population, the absolute contribution of cardiovascular events is clinically relevant. Notably, over half (53.2%) of pregnant individuals with ARDs who had cardiovascular events experienced adverse pregnancy outcomes, markedly higher compared to 28.8% in non-ARD/APS pregnancies with cardiovascular events and 26.6% of ARD pregnancies without cardiovascular events. While the overall incidence of cardiovascular events in ARD and APS pregnancies in this study was low (1.4% and 5.5%, respectively), an understanding of the excess risks conferred by these events will help with pregnancy counseling, early risk stratification, and tailored management approaches. Future research endeavors should explore alternative data sources to complement the findings of this study and prioritize prospective studies incorporating comprehensive clinical data on disease characteristics and treatment, alongside precise documentation of cardiovascular events in relation to timing during pregnancy. Such an approach will enable a more thorough investigation into the mechanisms driving the observed adverse outcomes and facilitate the exploration of potential interventions aimed at mitigating these risks.

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References:

1. Hellgren K, Secher AE, Glintborg B, Rom AL, Gudbjornsson B, Michelsen B, et al. Pregnancy outcomes in relation to disease activity and anti-rheumatic treatment strategies in women with rheumatoid arthritis: a matched cohort study from Sweden and Denmark. Rheumatology 2022;61:3711-22.

2. Jakobsen I, Helmig R, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990–2010. Scand J Rheumatol Taylor & Francis; 2015;44:377-84.

3. Palmsten K, Bandoli G, Vazquez-Benitez G, Xi M, Johnson DL, Xu R, et al. Oral corticosteroid use during pregnancy and risk of preterm birth. Rheumatology 2020;59:1262-71.

4. Bandoli G, Singh N, Strouse J, Baer RJ, Donovan BM, Feuer SK, et al. Mediation of Adverse Pregnancy Outcomes in Autoimmune Conditions by Pregnancy Complications: A Mediation Analysis of Autoimmune Conditions and Adverse Pregnancy Outcomes. Arthritis Care Res 2020;72:256-64.

5. Liu L, Sun D. Pregnancy outcomes in patients with primary antiphospholipid syndrome. Medicine (Baltimore) 2019;98:e15733.

6. Del Rincón I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001;44:2737-45.

7. Restivo V, Candiloro S, Daidone M, Norrito R, Cataldi M, Minutolo G, et al. Systematic review and meta-analysis of cardiovascular risk in rheumatological disease: Symptomatic and non-symptomatic events in rheumatoid arthritis and systemic lupus erythematosus. Autoimmun Rev [Internet] 2022 [cited 2022 Jul 13];21:102925. Available from: https://www.sciencedirect.com/science/article/pii/S1568997221002007

8. Hermansen M-L, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. The risk of cardiovascular morbidity and cardiovascular mortality in systemic lupus erythematosus and lupus nephritis: a Danish nationwide population-based cohort study. Rheumatology 2017;56:709-15.

This accepted article is protected by copyright. All rights reserved.

Accepted Article

9. Manzi S, Meilahn EN, Rairie JE, Conte CG, Medsger TA Jr, Jansen-McWilliams L, et al. Age-specific Incidence Rates of Myocardial Infarction and Angina in Women with Systemic Lupus Erythematosus: Comparison with the Framingham Study. Am J Epidemiol 1997;145:408-15.

10. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E, et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011-8.

11. Zahid S, Mohamed MS, Wassif H, Nazir NT, Khan SS, Michos ED. Analysis of Cardiovascular Complications During Delivery Admissions Among Patients With Systemic Lupus Erythematosus, 2004-2019. JAMA Netw Open 2022;5:e2243388.

12. Zahid S, Mohamed MS, Khan MZ, Rajendran A, Minhas AA, Nazir N, et al. Abstract MP73: Cardiovascular Complications During Delivery Admissions Associated With Rheumatoid Arthritis: A National Inpatient Sample Analysis (2004-2019). Circulation American Heart Association; 2023;147:AMP73-AMP73.

13. Dhital R, Baer RJ, Bandoli G, Guma M, Poudel DR, Kalunian K, et al. Maternal Cardiovascular Events in Autoimmune Rheumatic Diseases and Antiphospholipid Syndrome Pregnancies. Am J Obstet Gynecol MFM 2024;101319.

14. Wu L-S, Lin Y-S, Lin C-P, Chu P-H, Tang C-H, Hung S-T, et al. Major Adverse Cardiovascular Events and Mortality in Systemic Lupus Erythematosus Patients After Successful Delivery: A Population-based Study. Am J Med Sci Elsevier; 2014;347:42-9.

15. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy Characteristics and Women's Future Cardiovascular Health: An Underused Opportunity to Improve Women's Health? Epidemiol Rev 2014;36:57-70.

16. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, et al. Cardiovascular Disease-Related Morbidity and Mortality in Women With a History of Pregnancy Complications. Circulation American Heart Association; 2019;139:1069-79.

17. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ [Internet] British Medical Journal Publishing Group; 2007 [cited 2022 Dec 18];335:974. Available from: https://www.bmj.com/content/335/7627/974

18. Smith GD, Harding S, Rosato M. Relation between infants' birth weight and mothers' mortality: prospective observational study. BMJ 2000;320:839-40.

This accepted article is protected by copyright. All rights reserved.

Accepted Article

19. Parikh NI, Gonzalez JM, Anderson CAM, Judd SE, Rexrode KM, Hlatky MA, et al. Adverse Pregnancy Outcomes and Cardiovascular Disease Risk: Unique Opportunities for Cardiovascular Disease Prevention in Women: A Scientific Statement From the American Heart Association. Circulation American Heart Association; 2021;143:e902-16.

20. Talge NM, Mudd LM, Sikorskii A, Basso O. United States Birth Weight Reference Corrected For Implausible Gestational Age Estimates. Pediatrics 2014;133:844-53.

21. Jelliffe-Pawlowski L, Baer R, Blumenfeld Y, Ryckman K, O'Brodovich H, Gould JB, et al. Maternal characteristics and mid-pregnancy serum biomarkers as risk factors for subtypes of preterm birth. BJOG Int J Obstet Gynaecol 2015;122:1484-93.

22. Erton ZB, Sevim E, Jesús GR de, Cervera R, Ji L, Pengo V, et al. Pregnancy outcomes in antiphospholipid antibody positive patients: prospective results from the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ('Registry'). Lupus Sci Med Archives of Disease in childhood; 2022;9:e000633.

23. McIntire DD, Bloom SL, Casey BM, Leveno KJ. Birth Weight in Relation to Morbidity and Mortality among Newborn Infants. N Engl J Med Massachusetts Medical Society; 1999;340:1234-8.

24. Blake RA, Park S, Baltazar P, Ayaso EB, Monterde DBS, Acosta LP, et al. LBW and SGA Impact Longitudinal Growth and Nutritional Status of Filipino Infants. PLOS ONE Public Library of Science; 2016;11:e0159461.

25. Bernatsky S, Linehan T, Hanly JG. The Accuracy of Administrative Data Diagnoses of Systemic Autoimmune Rheumatic Diseases. J Rheumatol The Journal of Rheumatology; 2011;38:1612-6.

26. Hanly JG, Thompson K, Skedgel C. The use of administrative health care databases to identify patients with rheumatoid arthritis. Open Access Rheumatol Res Rev 2015;7:69-75.

27. Hanly JG, Thompson K, Skedgel C. Identification of patients with systemic lupus erythematosus in administrative healthcare databases. Lupus 2014;23:1377-82.

28. Bernatsky S, Joseph L, Pineau CA, Tamblyn R, Feldman DE, Clarke AE. A population-based assessment of systemic lupus erythematosus incidence and prevalence—results and implications of using administrative data for epidemiological studies. Rheumatology 2007;46:1814-8.

This accepted article is protected by copyright. All rights reserved.

Accepted Article

29. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Myocardial Infarction Diagnoses in Administrative Databases: A Systematic Review. PLoS ONE 2014;9:e92286.

30. Hsieh C-Y, Chen C-H, Li C-Y, Lai M-L. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. J Formos Med Assoc 2015;114:254-9.

31. Cozzolino F, Montedori A, Abraha I, Eusebi P, Grisci C, Heymann AJ, et al. A diagnostic accuracy study validating cardiovascular ICD-9-CM codes in healthcare administrative databases. The Umbria Data-Value Project. PLoS ONE 2019;14:e0218919.

32. Casez P, Labarère J, Sevestre M-A, Haddouche M, Courtois X, Mercier S, et al. ICD-10 hospital discharge diagnosis codes were sensitive for identifying pulmonary embolism but not deep vein thrombosis. J Clin Epidemiol 2010;63:790-7.

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Figure Legends

Figure 1. Adjusted risk ratios (aRRs) of the composite of adverse pregnancy outcomes and their individual components among pregnant individuals with ARDs, primary APS, and those without either condition based on the presence or absence of a cardiovascular event during pregnancy

APO: adverse pregnancy outcome; APS: antiphospholipid syndrome, ARD: autoimmune rheumatic disease, CVE: cardiovascular event, PTB: preterm birth, SGA: small-for-gestational-age

*aRR adjusted for age, race/ethnicity, primary payer, maternal education, pre-pregnancy BMI, clinical comorbidities (preexisting and gestational DM and HTN, pregnancy-induced HTN, hyperlipidemia, depression, alcohol, tobacco, and drug use during pregnancy

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Table 1. Maternal characteristics (n, %) of live births in the State of California (2005–2020) among individuals with ARDs, primary APS, and those without either condition, based on the presence or absence of cardiovascular events during pregnancy

		No ARD or APS (n= 7,004,334)			Any ARD (n=19,340)			Primary APS (n=7,758)		
		Without CVEs	With CVEs	p-value	Without CVEs	With CVEs	p-value	Without CVEs	With CVEs	p-value
Sample		**6,987,204 (99.7%)**	**17,130 (0.3%)**		**19,075 (98.6%)**	**265 (1.4%)**		**7,330 (94.5%)**	**428 (5.5%)**	
Maternal age (years)	< 18	151,239 (2.2)	269 (1.6)	< 0.0001	102 (0.5)	*	0.0402	29 (0.4)	*	0.0001
	18 – 34	5,461,429 (78.2)	12,492 (72.9)		13,332 (69.9)	183 (69.1)		4,685 (63.9)	318 (74.3)	
	35 - < 45	1,360,668 (19.5)	4,295 (25.1)		5,567 (29.2)	77 (29.1)		2,571 (35.1)	105 (24.5)	
	45+	13,660 (0.2)	73 (0.4)		74 (0.4)	*		45 (0.6)	*	
	Missing	208 (0.0)	*		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Race/ ethnicity	White, non-Hispanic	1,882,500 (26.9)	5,361 (31.3)	< 0.0001	6,358 (33.3)	73 (27.6)	< 0.0001	3,986 (54.4)	191 (44.6)	< 0.0001
	Hispanic	3,485,989 (49.9)	6,835 (39.9)		7,710 (40.4)	110 (41.5)		1,963 (26.8)	155 (36.2)	
	Black	344,175 (4.9)	2,045 (11.9)		1,223 (6.4)	39 (14.7)		342 (4.7)	31 (7.2)	
	Asian	940,438 (13.5)	1,763 (10.3)		2,441 (12.8)	25 (9.4)		570 (7.8)	22 (5.1)	
	Other	344,102 (4.8)	1,126 (6.6)		1,343 (7.0)	18 (6.8)		469 (6.4)	29 (6.8)	
Expected payer for delivery	Private	3,328,471 (47.6)	9,207 (53.8)	< 0.0001	11,921 (62.5)	125 (47.2)	< 0.0001	5,311 (72.5)	240 (56.1)	< 0.0001
	Public	3,242,681 (46.4)	7,227 (42.2)		6,264 (32.8)	125 (47.2)		1,701 (23.2)	170 (39.7)	
	Self-pay	182,152 (2.6)	188 (1.1)		149 (0.8)	*		72 (1.0)	*	
	Other	233,900 (3.4)	508 (3.0)		741 (3.9)	12 (4.5)		246 (3.4)	14 (3.3)	
Maternal education	< 12 years	1,453,614 (20.8)	3,050 (17.8)	< 0.0001	1,904 (10.0)	42 (15.9)	0.0006	533 (7.3)	55 (12.9)	< 0.0001
	12 years	1,709,674 (24.5)	4,645 (27.1)		3,994 (20.9)	60 (22.6)		1,147 (15.7)	96 (22.4)	
	> 12 years	3,541,295 (60.7)	8,693 (50.8)		12,313 (64.6)	144 (54.3)		5,296 (72.3)	258 (60.3)	
	Missing	282,621 (4.0)	742 (4.3)		864 (4.5)	19 (7.2)		354 (4.8)	19 (4.4)	
Pre-pregnancy BMI[a]	<18.5	248,624 (3.6)	456 (2.7)	< 0.0001	684 (3.6)	*	0.5291	207 (2.8)	12 (2.8)	< 0.0001
	18.5 to < 25	2,710,613 (38.8)	5,021 (29.3)		7,733 (40.5)	106 (40.0)		3,153 (43.0)	128 (29.9)	
	25 to < 30	1,504,920 (21.5)	3,238 (18.9)		4,293 (22.5)	61 (23.0)		1,590 (21.7)	103 (24.1)	
	> = 30	1,292,423 (18.5)	3,805 (22.2)		4,194 (22.0)	53 (20.0)		1,528 (20.9)	125 (29.2)	
	Missing[a]	1,230,624 (17.6)	4,610 (26.9)		2,171 (11.4)	38 (14.3)		852 (11.6)	60 (14.0)	
Hypertension	None	6,395,662 (91.5)	12,940 (75.5)	< 0.0001	15,231 (79.9)	145 (54.7)	< 0.0001	6,318 (86.2)	332 (77.6)	< 0.0001
	Preexisting or unspecified	135,183 (1.9)	1,351 (7.9)		1,236 (6.5)	34 (12.8)		305 (4.2)	39 (9.1)	
	Gestational	196,031 (2.8)	602 (3.5)		804 (4.2)	17 (6.4)		210 (2.9)	*	
	Preeclampsia[b]	260,328 (3.7)	2,237 (13.1)		1,804 (9.5)	69 (26.0)		497 (6.8)	47 (11.0)	
Diabetes mellitus	None	6,290,553 (90.0)	14,454 (84.4)	< 0.0001	16,506 (86.5)	220 (83.0)	0.0012	6,296 (85.9)	356 (83.2)	0.2920
	Preexisting	74,049 (1.1)	611 (3.6)		431 (2.3)	15 (5.7)		135 (1.8)	*	
	Gestational	622,602 (8.9)	2,065 (12.1)		2,138 (11.2)	30 (11.3)		899 (12.3)	63 (14.7)	
Hyperlipidemia[b]		2,4909 (0.4)	303 (1.8)	< 0.0001	275 (1.4)	*	0.5469	95 (1.30	12 (2.8)	0.0093
Smoking during pregnancy[a]		146,784 (2.1)	1,027 (6.0)	< 0.0001	853 (4.5)	26 (9.8)	< 0.0001	213 (2.9)	33 (7.7)	< 0.0001
Alcohol during pregnancy[b]		18,440 (0.3)	199 (1.2)	< 0.0001	120 (0.6)	*	0.0112	30 (0.4)	*	0.3675
Drug use during pregnancy[b]		115,333 (1.7)	1,234 (7.2)	< 0.0001	733 (3.8)	29 (10.9)	< 0.0001	113 (1.5)	32 (7.5)	< 0.0001
Depression		131,737 (1.9)	1,084 (6.3)	< 0.0001	1,267 (6.6)	31 (11.7)	0.0011	292 (4.0)	25 (5.8)	0.0592

*: n < 11; [a]Not available for 2005 and 2006; [b]Binary variable (yes vs no)

APS: antiphospholipid syndrome, ARD: autoimmune rheumatic disease, BMI: body-mass index, CVE: cardiovascular event

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Table 2. Risk differences of composite adverse pregnancy outcomes among individuals with ARDs, with and without cardiovascular events, compared to a reference group without ARD/APS and without a cardiovascular event

	Adverse pregnancy outcomes, n (row %)
	Unadjusted Risk Difference (95% CI) Adjusted Risk Difference (95% CI)
No ARD/APS, no CVE (n = 6,987,204), %	1,063,139 (15.2)
	Reference
No ARD/APS with CVE (n = 17,130) , %	4,822 (28.2)
	12.9 (12.1 - 13.7)
	7.8 (7.1 - 8.6)
ARD, no CVE (n = 19,075) , %	5,065 (26.6)
	11.3 (10.6 - 12.1)
	8.7 (8.0 - 9.4)
ARD with CVE (n = 265) , %	141 (53.2)
	38.0 (29.2 - 46.8)
	27.8 (19.3 - 36.3)

ARD: autoimmune rheumatic disease, CVE: cardiovascular event

Adverse pregnancy outcome: defined as the composite measure of preterm birth and small-for-gestational-age infant

**aRDs adjusted for age, race/ethnicity, primary payer, maternal education, pre-pregnancy BMI, clinical comorbidities (preexisting and gestational DM and HTN, pregnancy-induced HTN, hyperlipidemia, depression, alcohol, tobacco, and drug use during pregnancy*

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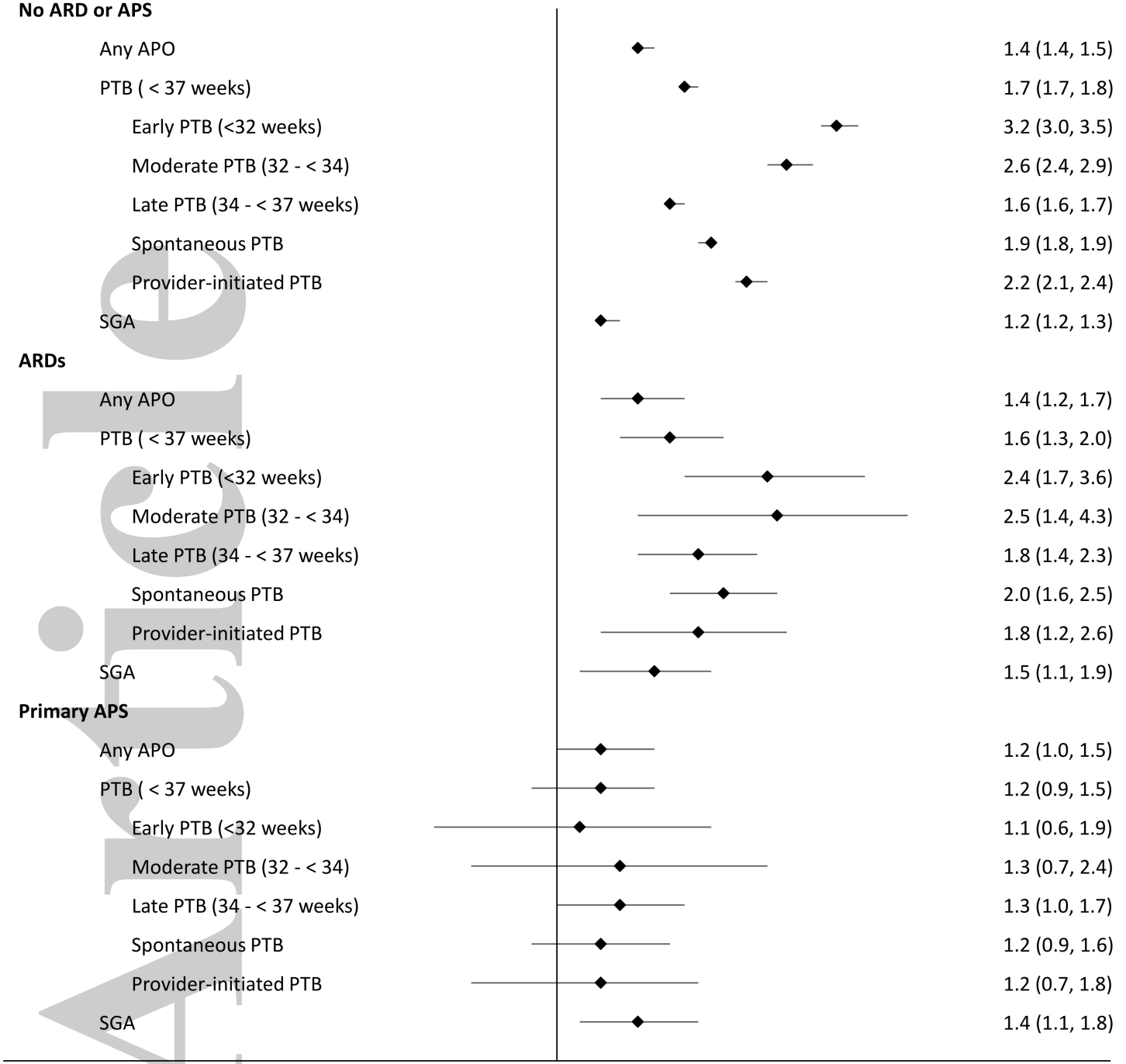

	aRRs	No CVE , n(%)	Any CVE, n (%)
No ARD or APS		**n= 6,987,204**	**n=17,130**
Any APO	1.4 (1.4, 1.5)	1,063,139 (15.2)	4,822 (28.2)
PTB (< 37 weeks)	1.7 (1.7, 1.8)	496,415 (7.1)	3,318 (19.4)
Early PTB (<32 weeks)	3.2 (3.0, 3.5)	50,204 (0.7)	655 (3.8)
Moderate PTB (32 - < 34)	2.6 (2.4, 2.9)	49,055 (0.7)	502 (2.9)
Late PTB (34 - < 37 weeks)	1.6 (1.6, 1.7)	387,199 (5.5)	2,035 (11.9)
Spontaneous PTB	1.9 (1.8, 1.9)	337,890 (4.8)	2,146 (12.5)
Provider-initiated PTB	2.2 (2.1, 2.4)	116,561 (1.7)	1,047 (6.1)
SGA	1.2 (1.2, 1.3)	622,522 (8.9)	1,948 (11.4)
ARDs		**n= 19,075**	**n=265**
Any APO	1.4 (1.2, 1.7)	5,065 (26.6)	141 (53.2)
PTB (< 37 weeks)	1.6 (1.3, 2.0)	2,978 (15.6)	109 (41.1)
Early PTB (<32 weeks)	2.4 (1.7, 3.6)	449 (2.4)	29 (10.9)
Moderate PTB (32 - < 34)	2.5 (1.4, 4.3)	347 (1.8)	14 (5.3)
Late PTB (34 - < 37 weeks)	1.8 (1.4, 2.3)	2,113 (11.1)	62 (23.4)
Spontaneous PTB	2.0 (1.6, 2.5)	2,042 (10.7)	79 (29.8)
Provider-initiated PTB	1.8 (1.2, 2.6)	824 (4.3)	27 (10.2)
SGA	1.5 (1.1, 1.9)	2,658 (13.9)	51 (19.3)
Primary APS		**n= 7,330**	**n=428**
Any APO	1.2 (1.0, 1.5)	1,517 (20.7)	131 (30.6)
PTB (< 37 weeks)	1.2 (0.9, 1.5)	946 (12.9)	84 (19.6)
Early PTB (<32 weeks)	1.1 (0.6, 1.9)	150 (2.1)	14 (3.3)
Moderate PTB (32 - < 34)	1.3 (0.7, 2.4)	121 (1.7)	11 (2.6)
Late PTB (34 - < 37 weeks)	1.3 (1.0, 1.7)	58 (13.6)	58 (9.0)
Spontaneous PTB	1.2 (0.9, 1.6)	653 (8.9)	60 (14.0)
Provider-initiated PTB	1.2 (0.7, 1.8)	268 (3.7)	22 (5.1)
SGA	1.4 (1.1, 1.8)	726 (9.9)	61 (14.3)

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