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LETTER

On Exposure Definition and Temporal Interpretation in the Reported Association Between Number of Pregnancies and Rheumatoid Arthritis [Letter]

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Dear editor

We read with interest the cross-sectional NHANES analysis by Sheng et al, who reported that a higher number of pregnancies were associated with higher odds of self-reported rheumatoid arthritis (RA) among 2383 women, including an adjusted odds ratio of 1139 per additional pregnancy and a sharper increase beyond three pregnancies.[1] Their effort to address an important question at the interface of reproductive history and autoimmune disease is commendable. We nevertheless believe that several aspects of exposure definition and clinical interpretation would benefit from further clarification before the findings are used as a basis for a threshold-like or screening interpretation. This is particularly relevant because clinicians may intuitively read "number of pregnancies" as a proxy for parity or repeated postpartum exposure, which is not necessarily what the current variable captures.

Our first concern is that the study evaluates lifetime number of pregnancies, but much of the discussion interprets the results through mechanisms that are more closely linked to live birth or postpartum physiology. The authors appropriately acknowledge that pregnancy outcomes such as miscarriage and induced abortion were unavailable.[1] This matters because a broad pregnancy count is a heterogeneous construct, and the broader literature has not shown a consistent association between gravidity or parity and incident RA overall. In a systematic review and meta-analysis, Chen et al found no consistent evidence that either gravidity or parity was associated with RA development[2] More recently, a large prospective cohort reported no association for ever pregnancy, although women with four or more children had a modestly higher RA risk after extensive adjustment, suggesting that different reproductive phenotypes should probably not be assumed to be interchangeable.[3] For this reason, the reported "more than three pregnancies" threshold may be better framed as a hypothesis-generating pattern within a broad pregnancy-history measure rather than a definitive clinical or biological cut-point.

Second, the outcome was self-reported RA subtype rather than validated incident RA. This is not a trivial distinction. Validation studies in population cohorts have shown that self-reported RA alone has limited positive predictive value, and that accuracy improves substantially when medication data or medical-record confirmation are incorporated.[4,5] In this context, some misclassification between RA and other arthritides is plausible. Because the analysis included 143 RA cases, even modest misclassification may have influenced the magnitude of the observed odds ratios and the apparent dose-response pattern. We therefore wonder whether the discussion should more explicitly acknowledge that the study concerns self-reported prevalent RA rather than clinically adjudicated RA, and that this uncertainty may affect both the estimated effect size and the proposed threshold-like interpretation.

Third, the cross-sectional use of lifetime pregnancy count and lifetime RA history makes temporal interpretation more difficult. The timing of pregnancies relative to RA diagnosis was not reported in a way that resolves sequence.[1] Yet the literature suggests that reproductive timing matters: in the Swedish EIRA study, parity-related associations differed by age and ACPA status, with increased risk concentrated in younger women with ACPA-negative RA.[6] Likewise, incident RA has been reported to peak during the first 24 months postpartum.[7] These observations do not refute the authors'

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findings, but they do suggest that a lifetime pregnancy count may obscure time-sensitive patterns that could be relevant to RA onset. We therefore respectfully suggest softening causal language such as "independent risk factor" and emphasizing that the present analysis identifies an association between self-reported pregnancy history and self-reported RA within a cross-sectional survey.

These points do not diminish the value of the study. Rather, they may help align the conclusion more closely with what the dataset can support. Reframing the exposure as a broad pregnancy-history measure, tempering the "more than three pregnancies" threshold language, and foregrounding the uncertainty inherent in self-reported RA could make the message more robust and clinically useful. Prospective studies with adjudicated RA, clearer separation of pregnancy outcomes, and time-resolved reproductive histories will be especially important for determining whether the observed association reflects gravidity itself, specific pregnancy outcomes, postpartum timing, or residual confounding. Even a modest reframing along these lines may preserve the paper's clinical relevance while improving the precision of its message.

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