Outcomes in Children Born to Women with Rheumatic Diseases

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KEYWORDS

• Systemic lupus erythematosus • Rheumatoid arthritis • Pregnancy • Children
• Long-term outcomes

KEY POINTS

- Genetic factors and in utero exposure to maternal autoantibodies, cytokines, and medications, as well as obstetric complications, might predispose SLE and RA offspring to adverse health outcomes.
- Children born to women with SLE and RA are potentially at increased risk of neurodevelopmental disorders, congenital heart defects, and autoimmune diseases, compared with children from the general population.
- Although clinicians should probably be aware of this increased relative risk of adverse health outcomes, the absolute risk is small and women with SLE and RA should not be discouraged from having children.

INTRODUCTION

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are the most prevalent autoimmune rheumatic diseases, and predominantly occur in women during childbearing years. To date, research has mainly focused on assessing the risk of immediate complications during SLE and RA pregnancies, with studies documenting a higher risk of adverse obstetric outcomes, such as preterm births and infants small for gestational age (SGA). However, until recently, little was known regarding the long-term health of children born to affected women. SLE and RA offspring are potentially exposed in utero to maternal autoantibodies, cytokines, and drugs, as well as

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obstetric complications. This might result in developmental anomalies, congenital defects, and/or disease susceptibility. In the past few years, observational studies have suggested an increased risk of adverse health outcomes, including neurodevelopmental disorders, congenital heart defects (CHDs), hematological malignancies, and autoimmune diseases, in offspring born to mothers with SLE and RA. We present a review of the current evidence regarding the risk of adverse health outcomes in SLE and RA offspring, as well as potential mechanisms involved in their pathogenesis.

Neurodevelopmental Disorders

Epidemiologic data suggest that children born to women with SLE may have an increased risk of neurodevelopmental disorders compared with children born to healthy women. Several retrospective studies suggest that children, particularly sons, of mothers with SLE are at increased risk (up to 25%–45%) for learning disabilities.[1–3] In a small retrospective study using parental report, the prevalence of learning problems in offspring of mothers with SLE was more than twice that reported for controls.[2] A prospective study assessed the neurodevelopment of 57 children born to mothers with SLE and 49 controls using standardized tests.[4] Offspring of mothers with SLE had more than a threefold increase in anomalies related to learning and memory, as well as behavior. In a retrospective cohort study of 60 SLE offspring, in utero exposure to azathioprine conferred more than a sixfold increased risk of having special educational needs (used as a proxy for developmental delays), when adjusting for disease severity and obstetric complications.[5]

Although these previous studies support the hypothesis of an increased risk of neurodevelopmental disorders in offspring of mothers with SLE, the studies were marked by important methodological limitations: all had limited sample size; only one controlled for obstetric complications and medication exposures; and most used parental report, did not include a control group, and/or were retrospective in nature.

In 2015, investigators reported data from the Offspring of SLE Mothers Registry (OSLER), a large population-based cohort using Quebec's health care databases and including 719 children born to mothers with SLE, and a matched control group of 8493 children born to unaffected mothers.[6] SLE offspring were more frequently found to have a diagnosis of autism spectrum disorders (ASD) compared with unexposed children (frequency of recorded ASDs 1.4% [95% confidence interval (95% CI) 0.8–2.5] vs 0.6% [95% CI 0.5–0.8]), a difference of 0.8% (95% CI 0.1–1.9). The mean age at ASD diagnosis was younger in offspring of mothers with SLE (mean 3.8 years, 95% CI 1.8–5.8) compared with offspring of controls (mean 5.7 years, 95% CI 4.9–6.5). In multivariate analysis accounting for maternal characteristics and obstetric complications, SLE offspring had a substantially increased risk of ASD compared with controls (odds ratio [OR] 2.19, 95% CI 1.09–4.39). The younger age at ASD diagnosis could suggest either more severe cases or increased surveillance within the SLE population.

In addition to cohort evidence of an increased risk of neurodevelopmental disorders in offspring of mothers with SLE, numerous case-control studies have suggested an increased prevalence of SLE and other autoimmune diseases in mothers of children affected with neurodevelopmental disorders.[7–9] In a case-control study of 61 children with ASD and 46 healthy controls, affected children had more than an eightfold increase in the odds of having a mother with an autoimmune disorder (by self-report) than unaffected children.[9] SLE was observed in 13% of children with ASD, versus 4% of healthy controls. Another large population-based study showed similar results.[7] In this study, children with ASD were more likely than unaffected children to have a mother diagnosed with an autoimmune rheumatic disease (relative risk 1.56, 95% CI 1.08, 2.17), whereas

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