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Lupus science and medicine: dialogue

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Because of improved treatment and pregnancy management, many patients with systemic lupus erythematosus (SLE) now have safe, successful pregnancies. Prior studies have led to identified specific risk factors for poor pregnancy outcome, among them antiphospholipid antibody (aPL), severe disease flare and kidney disease. Adverse pregnancy outcomes that still do occur in patients with SLE include fetal death, pre-eclampsia, preterm delivery and small for gestational age infants. Thus many surviving babies are at risk for the later life physical complications and neurodevelopmental delays associated with early gestational age and small size. While numbers vary from study to study, preterm birth and low birth weight probably occur in up to a quarter of SLE pregnancies overall. Risk of damage to their children is an area of concern for women with lupus and for their physicians.

Some have suggested that the risk for neurodevelopmental delay is even greater than the risk imposed by low gestational age and birth size alone. In 1988 Lahita reported (from the mother's statement) a prevalence of learning disabilities (LDs) of 45% in 55 male offspring of patients with SLE.[1] Recent studies, directly examining the children, confirm normal global intelligence but an increased incidence of LD[2]

In this issue of *Lupus Science and Medicine*, Marder *et al*[3] present compelling data that support the association of aPL (specifically lupus anticoagulant) and the antiphospholipid syndrome (APS) with increased use of special education (SE) services by SLE offspring. For Marder *et al*, SE use being a real world, clinically relevant end point and an appropriate starting point for further large-scale studies, is a proxy for poor neurodevelopmental outcome.

The study presented data on 60 offspring of 38 mothers with SLE, of whom 15 received SE support. Maternal disease duration, nephritis flare and pre-eclampsia were not associated with SE referral, nor, surprisingly, were gestational age, birth weight and small for gestational age status. Possible explanations for the lack of association include the small number of children who used SE or the dichotomous nature (SE or no SE) of the designation. Multivariate analysis showed that APS is associated with a threefold to eightfold increase in any use of SE services, consistent with a prior report of increased LD in offspring of patients with primary APS.[4]

Limitations of this report, a pilot observational study intended to spur further investigation, include possible recall bias, the relatively small numbers of affected children and the lack of a control group, although rates of SE use estimated from Michigan educational data (14% in the state vs 25% for SLE children) are cited for comparison. There may be additional reasons for increased SE use overall that are not accounted for in the analyses. For example, patients with SLE have a high average educational level (16 years), which might result in higher parental expectations; and chronic illness in the mother may cause more anxiety and hypervigilance regarding a child's developmental milestones or academic performance.

APL appears to be an independent contributing factor to risk for neurodevelopmental abnormalities. Since IgG maternal autoantibodies begin to cross the placenta after 12 weeks gestation, and since the fetal blood-brain barrier is not yet complete, aPL may react directly with fetal brain endothelial or neural tissue, analogous to the binding of maternal anti-Sjogren's syndrome-A (SS-A/Ro) antibodies to fetal cardiac tissue in neonatal lupus-associated congenital heart block. Many other factors may also contribute. Indeed, the same authors recently stated that azathioprine use during SLE pregnancy is associated with a high use of SE services in the surviving children.[5]

Long-term neuropsychological outcome of one's children is an important source of anxiety for any mother, especially when she has an underlying chronic illness such as SLE or APS. Identification of specific risk factors, such as aPL, beyond the diagnosis of SLE itself is critical, and would expedite greater efforts at therapy during pregnancy, more directed prenatal counselling, and early referral for formal evaluation and therapy of neurodevelopmental

abnormalities. This paper, together with previous reports, should spur long-term multicentre prospective studies of populations with SLE and APS to evaluate the relative contributions and mechanisms of prematurity, small birth size, severe disease activity, transplacental autoantibody and medication use during pregnancy.

Competing interests None.

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