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Review

The development of offspring from mothers with systemic lupus erythematosus. A systematic review

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ABSTRACT

Objective: To analyze published data on the influence of maternal systemic lupus erythematosus (SLE) on different aspects of child development.
Methods: A systematic review was conducted using PubMed and Embase searches for SLE or SLE-related antibodies and physical, neurocognitive, psychiatric or motor development outcomes in children.
Results: In total 24 cohort and 4 case-control studies were included after initial screening of 1853 hits. Learning disorders (LD) were reported in 21.4–26% of SLE offspring, exceeding the prevalence in the general population. Four studies reported that dyslexia and reading problems were present in 14.3–21.6% of lupus offspring with a clear male predominance. Furthermore, a twofold increased rate of autism spectrum disorders (ASD) (n = 1 study) and a two- to threefold increased risk for speech disorders (n = 3 studies) were reported in lupus offspring compared to controls, although the latter was not statistically significant. More divergent results were found for attention deficit (n = 5 studies) and behavior disorders (n = 3 studies). In two large controlled studies attention disorders were more prevalent and a trend towards more behavior disorders was reported in 2 of 3 studies analyzing this subject. Finally, IQ and motor skills were not affected in respectively 7 and 5 studies. Cardiopulmonary functioning and mood disorders were scarcely investigated (both n = 1). Maternal anti-SSA antibodies were associated with LD in offspring in one study. Other SLE-related antibodies were rarely studied.
Conclusion: This systematic review suggests that maternal SLE is associated with LD (specifically dyslexia), ASD, attention deficit and probably speech problems in offspring. However, over half of the studies were assigned a low or moderate evidence level. Therefore, further research is necessary to substantiate the found evidence and expand the scope to lesser researched areas such as cardiopulmonary functioning.
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Contents

Abbreviations: aβ2-GPI, anti-β2-glycoprotein I; ab-ab, anti-brain antibodies; anti-dsDNA, anti-double stranded DNA; ANA, antinuclear antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; ADHD, attention deficit hyperactivity disorders; ASD, autism spectrum disorders; AZA, azathioprine; CHB, congenital heart block; HCQ, hydroxychloroquine; IQ, intelligence quotient; IUGR, intra-uterine growth restriction; LD, learning disorders; MQ, motor quotient; NL, neonatal lupus; SE, socioeconomic; SEdS, special educational services; SLE, systemic lupus erythematosus; U.S., United States.

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1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with heterogeneous manifestations. Hallmark of the disease is the presence of autoantibodies, such as antinuclear antibodies (ANA), antibodies to double stranded DNA (anti-dsDNA) and antibodies to extractable nuclear antigens, including those against the Sm, Ro/SSA and La/SSB antigens. The disorder exhibits a female predominance and usually manifests itself in childbearing age. Therefore, pregnancy is a relevant topic for many patients. It is well recognized that in these patients pregnancy and the postpartum period should be regarded as risky for both mother and child. Apart from exacerbations of the disease itself, pregnant women with SLE have significantly increased risks of severe preeclampsia, infections, thrombo-embolic complications and mortality. Risks for the child are increased rates of fetal loss, intra-uterine growth restriction (IUGR), preterm birth and neonatal death [1,2]. Furthermore, neonates are at risk for the neonatal lupus syndrome (NL), which is caused by the transfer of maternal IgG class anti-Ro/SSA or anti-La/SSB autoantibodies across the placenta during the second and third trimester of pregnancy. Manifestations of NL are usually transient and include cutaneous manifestations, cardiomyopathy, hepatobiliary disease and cytopenia. The most feared manifestation is a persistent and potentially fatal congenital heart block (CHB) [2]. Central nervous system involvement in NL has been mentioned in case-reports. These refer to imaging abnormalities, rarely accompanied by neurological symptoms like paresis, seizures or macrocephaly [3].

Risk factors for poor pregnancy outcome have been identified and include active disease during pregnancy or within 6 months before, SLE onset during gestation, hypertension, thrombocytopenia, proteinuria, presence of antiphospholipid antibodies (aPL) or the antiphospholipid syndrome (APS) and presence of anti-Ro/SSA or anti-La/SSB antibodies. However, with proper counseling and a multidisciplinary approach in which rheumatologists, obstetricians and pediatricians cooperate before, during and after pregnancy, live birth rates of 85–90% can be achieved [2,4]. In this line, the European League against Rheumatism has recently published recommendations on family planning, pregnancy and delivery in SLE patients [5].

Besides the impact of SLE on the immediate pregnancy outcome, the question whether their disease will influence the long-term general health and development of their children is often raised by SLE patients who wish to conceive. This was the reason for the current literature study in which we collected data on the influence of maternal SLE during pregnancy on a wide spectrum of developmental domains including physical, neurocognitive, psychiatric and motor development. Furthermore, we explored the influence of maternal SLE-related antibodies on these developmental aspects.

Although previous reviews have given insight into some facets of the long-term development of SLE offspring [6], this is the first comprehensive *systematic* review on this subject covering many different aspects of development separately. A broad search strategy and detailed quality judgement were combined to provide a complete and up-to-date perspective on the development of children from SLE patients.

2. Methods

A systematic search was conducted using both the PubMed and Embase databases. Summarized, the search string consisted of the disease and synonyms *OR* SLE-related autoantibodies *AND* pregnancy and synonyms *OR* maternal and synonyms *OR* offspring and synonyms *AND* outcomes (physical fitness, motor performance, psychomotor performance, psychiatric development and illnesses, development, cognition, intelligence, learning disorders) and synonyms. The complete search strings can be found in the Supplementary Material. The search was performed on 07-08-2016 and updated on 11-02-2017. The search results and consequent steps are shown in Fig. 1. Inclusion and exclusion criteria are stated in Supplementary Table 1. The goal of this review was to analyze development on the long-term and not perinatal manifestations such as in neonatal lupus. Studies in which all patients were aged <1 year were therefore excluded. Articles in languages other than English were included only when an abstract in English was provided. As the scope of this article was to investigate the effects of SLE and not APS on child development, we included only papers of SLE patients with APS or aPL, and did not include the aPL as separate search item.

Study quality was assessed using the Oxford Centre for Evidence-Based Medicine's Levels of Evidence (2009) for a systematic review on etiology (Supplementary Table 2) [7]. This category was chosen as maternal SLE is considered the cause of developmental problems in

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