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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.

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

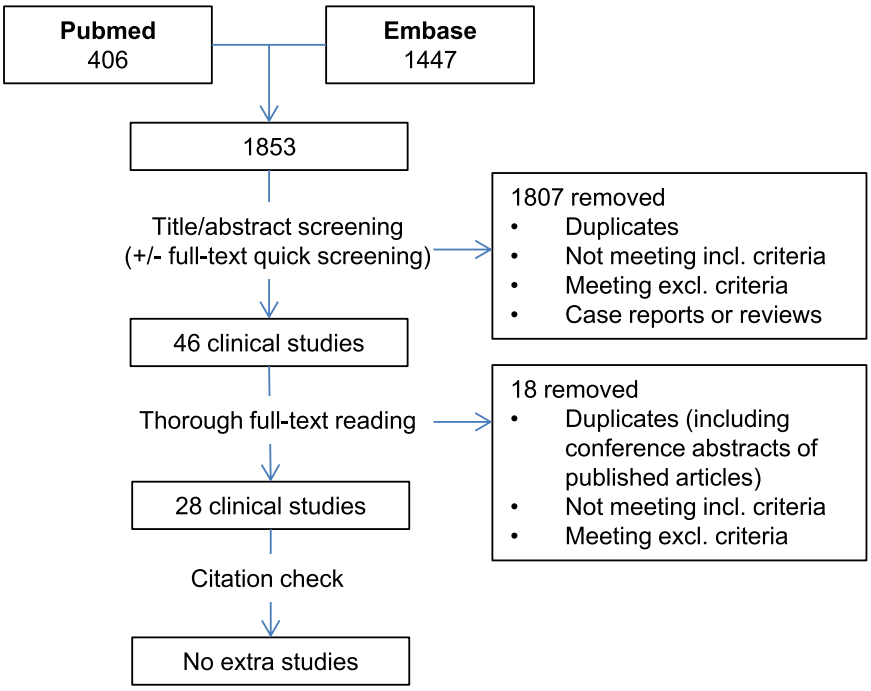

Fig. 1. Flowchart of the search strategy and results. During full text reading, references were also checked for missing relevant papers (citation check).

offspring in this study. Evidence level 4 was also used if only the abstract was available. In certain cases level 4* was assigned, indicating a moderate quality study (e.g. *a controlled study that lacked controls specifically for our research question because the main study topic differed from the topic of this review*). Besides these evidence levels, a self-made checklist was used to describe critical appraisal in more detail (Supplementary Table 2).

3. Results

The search yielded 28 relevant clinical studies after initial screening of 1853 hits (Fig. 1). A summary of the evidence levels and quality of these 28 studies is shown in Table 1. Eleven studies were classified with an evidence level 4 and another 4 studies evidence level 4*. Three individual case control studies scored 3b and only 10/24 individual cohort studies scored 2b.

In the next sections, the different areas of development will be discussed and Tables 2 and 3 structure the results. The findings on each outcome are summarized at the end of the corresponding paragraph.

3.1. Physical development

There was one study each that reported on cardiac functioning and general development, and five reported on growth (Table 2). All studies except one (score 2b) had low evidence levels (4 or 4*). Studies on cardiopulmonary functioning, which is a good marker of overall health [8], are lacking. The English abstract of one study (in Polish) reports no systolic left ventricular dysfunction in 38 SLE offspring compared to controls aged 3–18 years (mean 12 years). Subclinical left-sided diastolic impairment was reported in 8 subjects (control percentage unknown) [9].

A study with evidence level 4* reported on the health of 176 children from 143 women with connective tissue diseases (77% SLE). Data were retrieved from mothers, general practitioners and/or pediatricians, and were often based on the maternal report of state-mandatory infant health assessments. Visus, hearing, growth and general development were all found normal in these children at a mean age of 26 months (range 12–108 months). Neither premature childbirth, maternal APS (28/143 mothers), maternal positivity for anti-SSA/SSB antibodies (47%/20%), nor maternal treatment influenced the results [10].

Two Chinese studies of which only the English abstract could be assessed and one conference abstract reported impairment of growth in none, 4% and 27% of children from SLE patients [11–13]. However, in the only study on growth with evidence level 2b, no growth impairment was found in 26 children from Japanese SLE mothers. These children had been followed prospectively up to 12 years of age. Of note, 40% of the mothers had antiphospholipid antibodies and 35% anti-SSA antibodies. All 5 children (19.2%) with IUGR showed catch-up growth [14].

3.1.1. Summary

There are no studies in English on cardiopulmonary functioning in SLE offspring. Two published full length articles showed no growth impairment.

3.2. Neurocognitive development

The results for all studies on this topic are given in Table 2. Different aspects of neurocognitive development will be discussed one by one.

3.2.1. Global neurodevelopment

Six cohort studies (four with evidence level 2b and two with level 4) and three abstracts investigated the global neurodevelopment of SLE offspring. The number of SLE offspring included in these studies ranged from 11 to 60, except one abstract on 284 children. The mean age varied greatly between studies (*precise age information is given in* Table 2). In the United States (U.S.), 25% of 60 SLE offspring needed special educational services (SEdS), as reported by mothers (evidence level 4) [15]. Furthermore, in a study with evidence level 2b that used Swedish medical records, 31% of 36 children from anti-SSA positive SLE patients were affected, compared to only 10% of 78 children from anti-SSA positive mothers without SLE ($p < 0.01$) [16]. The frequency of neurodevelopmental impairment in these studies (25–31%) was twice the prevalence in the general U.S. population (15%) [17]. This trend was underlined by a Canadian study with evidence level 2b that

Table 1
Study quality.

Study reference	Sample size of cases	Adequately controlled	Measurement method	Blinding of tester	Appropriate statistics	Selection bias	Participation (response) bias	Information bias	Recall bias	Confounding & influencing factors	Evidence level	Further explanation of theassigned level of evidence
Cohort studies												
[9]	38	●	●	●	●	●	●	●	●	●	**4**	Abstract (article in Polish).
[10]	176	●	●	●	●	●	●	●	●	NA	**4***	No control group for the topic of this review because the study was aimed at HCQ. Information was retrieved from the mother, general practitioner and/or pediatrician.
[11]	35	●	●	●	●	●	●	●	●	●	**4**	Abstract (article in Chinese).
[12]	49	●	●	●	●	●	●	●	●	●	**4**	Abstract (article in Chinese).
[13]	11	●	●	●	●	●	●	●	●	●	**4**	Abstract.
[14]	26	●	●	●	●	●	●	●	●	NA	**2b**	
[15]	60	●	●	●	●	●	●	●	●	●	**4**	Method: maternal report.
[16]	114	●	●	●	●	●	●	●	●	●	**2b**	
[18]	57	●	●	●	●	●	●	●	●	●	**2b**	
[19]	284	●	●	●	●	●	●	●	●	●	**4**	Abstract.
[20]	12	●	●	●	●	●	●	●	●	NA	**2b**	No controls, but comparison with general prevalence.
[21]	133	●	●	●	●	●	●	●	●	NA	**4**	Follow–up was 50% after 2 years and 20% after 5 years. Of 18 SLE offspring, it is unclear how many were tested at age > 1 y.
[23]	47	●	●	●	●	●	●	●	●	●	**2b**	
[24]	58	●	●	●	●	●	●	●	●	●	**2b**	
[26]	90	●	●	●	●	●	●	●	●	●	**4***	Questionnaire, but the majority was verified by standardized tests.
[28]	154	●	●	●	●	●	●	●	●	●	**4***	Method: questionnaire, validation of which is unclear.
[35]	719	●	●	●	●	●	●	●	●	●	**4**	Abstract (preliminary results).
[37]	40	●	●	●	●	●	●	●	●	●	**2b**	
[38]	16	●	●	●	●	●	●	●	●	NA	**2b**	
[39]	30	●	●	●	●	●	●	●	●	●	**4**	Not all study details were provided in the article.
[43]	719	●	●	●	●	●	●	●	●	●	**2b**	
[45]	114	●	●	●	●	●	●	●	●	NA	**2b**	No controls, but comparison with normal developmental milestones.
[46]	104	●	●	●	●	●	●	●	●	●	**4***	Method: questionnaire, validation of which is unclear.
[47]	184	●	●	●	●	●	●	●	●	●	**4**	Abstract.
Case–control studies												
[40]	1227	●	●	●	●	●	●	●	●	●	**3b**	Correction for relevant confounders, but none of those mentioned in Supplementary Table 2.
[41]	80	●	●	●	●	●	●	●	●	●	**3b**	
[48]	45	●	●	●	●	●	●	●	●	●	**4**	No information on confounders.
[49]	2431	●	●	●	●	●	●	●	●	●	**3b**	Maternal serum was drawn years after pregnancy.

Study quality assessment using the evidence level based on the Oxford CEBM's guidelines and a self-made checklist (Supplementary Table 2). Evidence level 4* is explained in Section 2. Legend: black = unknown. Red = low quality, yellow = medium quality, green = high quality. For bias, these colors indicate high risk, medium risk and low risk respectively. Adequately controlled: red = not controlled, yellow = comparison with the general population or normal score in standardized tests, green = adequate control group. Measurement method: red = not validated questionnaire, yellow = physical examination or medical records, green = validated test/questionnaire (and for case-control studies also antibodies measurement in maternal serum). Confounding & influencing factors: 5 relevant factors were checked (Supplementary Table 2), red = none of these were analyzed, yellow = 1 was analyzed, green ≥ 1 were analyzed, NA = not applicable because there was no effect on the outcome and therefore no confounder analysis. HCQ = hydroxychloroquine.

detected increased neurodevelopmental impairment by standardized tests in 81% of 57 children of SLE mothers compared to 65% of 49 controls matched for age, sex, race and socio-economic status ($p = 0.07$). Comparison with other studies was difficult, because development was considered abnormal when one test of the test battery employed on that domain was aberrant, resulting in high frequencies [18]. A meeting abstract in 2013 mentioned 7.1% of 274 SLE progeny (<17 years) had development delay, special (educational) needs or attention deficit disorder (maternal report) [19]. Finally, no abnormalities were detected in three cohort studies (two with evidence level 2b) and two abstracts, which used small populations (n = 11–35) and diverse outcome measures (physical examination, clinical records or standardized tests) [11,13,14,20,21]. Assessment of only young children (age 3–48 months) [20] and high loss-to-follow-up [21] may explain the absence of diagnoses in these studies.

In the studies that found affected children, azathioprine exposure influenced the results of one study ($p < 0.05$), but significance of the relation with the immunosuppressant was lost in multivariate regression with lupus nephritis, SLE flare and corticosteroid use ($p = 0.097$). Antiphospholipid syndrome was a confounder in this study ($p < 0.05$), but the APS-exposed population was small (n = 7) [15,22]. Maternal socioeconomic (SE) status and disease activity (e.g. nephritis, flares) were not associated with problems [15,18], nor were steroids, anti-DNA, anti-SSA/Ro and anti-SSB/La antibodies [16,18]. However, high-dose or

Table 2
Studies describing the effect of maternal SLE on physical (orange), neurologic (grey), psychiatric (blue) and motor development (green) in offspring.

Disorder	Ref	Evid–ence Level	Study type	Population Children, *maternal condition in italic*	Age	Outcome measure ‡ *(Outcome in Italic)*	Results *P–values or 95% CI in italic*
Cardiac functioning	[9]	4	C†	38 *SLE* 38 controls	Mean 12 y (range 3–18)	Physical examination *(arterial blood pressure, ECG, echocardiogram with Doppler, treadmill test according to Bruce's protocol)*	All children were in good cardiological condition, except for not precisely specified rhythm abnormalities. No systolic left ventricular dysfunction. Subclinical diastolic impairment in 8 subjects (control % unknown).
General develop–ment	[10]	4*	C	176 offspring of 110 mothers with CTD *(77% with SLE)*	Follow–up from birth: mean 26 months (range 12–108)	Report by mothers +/– pediatrician or general practitioner *(state–obligatory inspections for development, visus and hearing)*	No developmental delay or problems in visus or hearing.
Growth	[10]	4*	C	176 offspring of 110 mothers with CTD *(77% with SLE)*	Follow–up from birth: mean 26 months (range 12–108)	Report by mothers +/– pediatrician or general practitioner *(state–obligatory growth inspections)*	None affected.
	[14]	2b	C	26 *SLE*	Mean 6.6 y (range 6 months–12 y)	Physical examination *(height, weight)*	None affected (including 19.2% that had suffered from IUGR).
	[11]	4	C†	35 *SLE*	Unknown	Unknown *(growth)*	None affected.
	[12]	4	C†	49 *SLE*	Unknown	Physical examination *(height, weight)*	4% in the lower limit for height or weight.
	[13]	4	C†	11 *SLE*	> 6 y	Unknown	27% below 25th percentile (all exposed to corticosteroid therapy during pregnancy).
Global neurodeve–lopment	[20]	2b	C	12 *SLE*	Follow–up from birth: median 9 months (range 3–48)	Medical records *(growth and neurodevelopment)*	None affected.
	[14]	2b	C	26 *SLE*	Mean 6.6 y (range 6 months–12 y)	Standardized tests *(MDI, PDI, intelligence, achievement, behavior)*	None affected.
	[21]	4	C	18 *SLE + APS (total 130 APS)*	Follow–up from birth: 5 y	Clinical examination *(development milestones)*	None affected, but follow–up was low (for all children in the study 48% at 2 y and 20% at 5 y).
	[18]	2b	C	57 *SLE* 49 controls	2–26 y	Standardized tests *(learning and memory, language, visuospatial skills, sensorimotor functions, executive skill, attention, behavior, intellectual function and academic skills)*	81% cases vs 65% controls scored low on at least one subtest for 9 tested domains *(p = 0.07)*. ¥
	[15, 22]	4	C	60 *SLE*	Median = 5.7 y (IQR = 3.4–9.2)	Maternal report *(development delay or need for SEdS)*	25% affected, mainly speech delay. Confounded by AZA exposure ($p < 0.05$) and APS ($p < 0.05$)
	[16]	2b	C	114 *anti–SSA (36/114 SLE)*	Median 13.0 y (IQR: 8.2–17.5)	Medical records (*behavior, learning, attention, speech, motor development*)	31% of 36 SLE offspring and 10% in the remaining anti–SSA exposed children were affected *(p<0.01)*.
	[11]	4	C†	35 *SLE*	Unknown	Unknown *(mental development abnormalities)*	None affected.
	[13]	4	C†	11 *SLE*	> 6 y	Standardized test *(IQ)*	None affected.
	[19]	4	C†	284 *SLE*	< 17 y	Questionnaire *(development delay, attention deficit, special needs)*	7.1% affected.
Learning disabilities (LD)	[14]	2b	C	26 *SLE*	Mean 6.6 y (range 6 months–12 y)	Standardized tests *(intelligence, achievement)*	None affected.
	[23]	2b	C	14 *SLE*	Mean 9.5 y (range 7–14)	Standardized tests *(IQ, locomotor, personal–social, hearing and speech, coordination, performance, practical reasoning, reading)*	LD were tested in only 14/47 children. LD in 21.4% (1 was a border–line case). Maternal aPL in 100% of 3 affected children and 18% of the 11 others *(p < 0.02)*.
	[26]	4*	C	90 *SLE*	Unknown	Questionnaire +/– medical records *(LD)* or standardized test *(IQ)*	LD in 30%. (45% in males, 8% in females).
	[24]	2b	C	58 *SLE* 58 controls	Mean 9.3 y (8–15 y)	Standardized tests *(IQ, reading, writing, calculation, oral reading quotient)*	LD in 26% vs 7% in controls. Anti–SSA was independently associated with more LD in SLE offspring: OR = 5.74 *(1.32–23.74), as was maternal disease flare (OR = 9.43 [95% CI = 1.32–67.24])*.
Dyslexia	[26]	4*	C	90 *SLE*	Unknown	Questionnaire +/– medical records *(dyslexia)* or standardized test *(IQ)*	24.4% (40% of 55 boys, 0% in 35 girls).
	[23]	2b	C	14 *SLE*	Mean 9.5 y (range 7–14)	Standardized tests *(IQ, locomotor, personal–social, hearing and speech, coordination, performance, practical reasoning, reading)*	Dyslexia was tested in only 14/47 children. 2 males (14.3%) were affected (both exposed to maternal aPL).
	[24]	2b	C	58 *SLE* 58 controls	Mean 9.3 y (8–15 y)	Standardized tests *(IQ, reading, writing, calculation, oral reading quotient)*	Reading disability in 19.0% vs 6.9%. *(p unknown)*.
	[28]	4*	C	153 *SLE* 150 controls	Mean 13.8 y (range 8–20)	Questionnaire *(reading problems)*	Reading disorders in 21.6% vs 9.3% *(p < 0.01)*. OR for maternal SLE and reading disorders = 4.06 *(1.67–9.87)* in males.
Attention disorders	[16]	2b	C	109 *anti–SSA*	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(attention deficit)*	Attention deficit in 13.9% of 36 children with maternal SLE vs 1.4% of 73 remaining anti–SSA exposed children *(p < 0.05)*.
	[14]	2b	C	26 *SLE*	Mean 6.6 y (range 6 months–12 y)	Standardized tests (*MDI, PDI, intelligence, achievement, behavior)*	None affected.
	[15]	4	C	60 *SLE*	Median = 5.7 y (IQR = 3.4–9.2)	Maternal report *(ADHD)*	ADHD in 5%.
	[28]	4*	C	153 *SLE* 150 controls	Mean 13.8 y (range 8–20)	Questionnaire *(attention deficit, hyperactivity)*	Attention disorders: 15.7% cases vs 6% of controls. *(p <0.01)*. OR for maternal SLE and attention deficit = 3.08 *(1.08–9.79)* in males. Hyperactivity: 13.1% vs 1.3% respectively. *(p < 0.01)*. OR for maternal SLE and hyperactivity = 7.24 *(1.53–34.37)* in males.
	[35]	4	C†	719 *SLE* 8493 controls	Mean follow–up time 9.1 y (Sd = 5.8)	Healthcare database *(ADHD)*	ADHD in 9.9% of cases and 6.1% of controls, HR = 1.73 *(1.25–2.40)* for SLE group. When maternal drug treatments were included, HR lowered to 0.97.
Speech disorders	[16]	2b	C	114 *anti–SSA (36/114 SLE)*	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(speech problems)*	9% affected. 15% of 36 SLE offspring vs 5% in the remaining anti–SSA exposed children *(ns)*.
	[28]	4*	C	153 *SLE* 149 controls	Mean 13.8 y (range 8–20)	Questionnaire *(stuttering, pronunciation)*	Stuttering in 5.2% vs 2.0% *(ns)*. Pronunciation problems in 9.2% vs 4.7% *(ns)*.
	[15, 22]	4	C	60 *SLE*	Median = 5.7 y (IQR = 3.4–9.2)	Maternal report *(development delay or need for SEdS)*	Speech delay in 20%. Confounded by AZA and APS.
Autism spectrum disorders (ASD)	[41]	3b	CC	80 autistic children 80 controls	3–12 y	Determinant measure: Questionnaire verified with medical records *(familial autoimmunity)*	Maternal autoimmunity was seen in 11/80 (13.8%) of cases and in 0% controls. 2 case mothers (2.5%) had SLE.
	[40]	3b	CC	1227 ASD children 30693 controls	Cases diagnosed ≤ age 10	Determinant measure: parents' medical records in registry *(autoimmune diagnosis)*	OR for maternal autoimmunity in cases = 1.6 *(1.1–2.2)*. OR for maternal SLE in cases = 3.1 *(0.7–13.6)*.
	[20]	2b	C	12 *SLE*	Follow–up from birth: median 9 months (range 3–48)	Medical records *(ASD)*	None affected.
	[43]	2b	C	719 *SLE* 8493 controls	Mean follow–up time 9.1 y (Sd = 5.8)	Healthcare database *(ASD)*	ASD in 1.4% vs 0.6% of controls, OR = 2.25 *(1.13–4.45)*.

(continued on next page)

Behavior disorders	[16]	2b	C	114 *anti-SSA* (36/114 *SLE*)	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(behavior problems)*	4% affected, consisting of 8.3% of 36 SLE offspring and 1.4% of 73 remaining anti-SSA exposed children *(ns).*
	[18]	2b	C	57 *SLE* 49 controls	2–26 y	Standardized tests *(behavior)*	39.2% affected vs 20.9% of controls *($p = 0.06$).* #
	[14]	2b	C	26 *SLE*	Mean 6.6 y (range 6 months–12 y)	Standardized tests *(behavior)*	None affected.
Motor impairment	[16]	2b	C	114 *anti-SSA* (36/114 *SLE*)	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(motor development)*	8% affected. Of 36 SLE offspring, 13.9% was affected, compared to 5.5% of the remaining anti-SSA exposed children *(ns).* 4/5 affected SLE offspring had CHB and 4/5 were born preterm.
	[14]	2b	C	26 *SLE*	Mean 6.6 y (range 6 months–12 y)	Tests *(psychomotor development index)*	None affected.
	[45]	2b	C	114 *autoimmune (41 SLE)*	Follow-up from birth: 24 months.	Physical examination and motor quotient (MQ) *(motor impairment)*	None affected (MQ > 85) until age 2.
	[15]	4	C	60 *SLE*	Median = 5.7 y (IQR = 3.4–9.2)	Maternal report *(development delay or need for SEdS)*	5% needed SEdS for motor impairment (2% for gross motor and 3% for fine motor skills).
	[18]	2b	C	56 *SLE* 47 controls	2–26 y	Tests *(motor impairment)*	Sensorimotor dysfunction in 30.4% of cases and 22.5% of controls affected *($p = 0.36$).* #

C = cohort study. CC = case-control study. † = only the abstract was available. SLE = systemic lupus erythematosus. APS = antiphospholipid syndrome. aPL = antiphospholipid antibodies. CTD = connective tissue disease. NL = neonatal lupus. y = years. IQR = interquartile range. Sd = standard deviation. ECG = electrocardiogram. IUGR = intra-uterine growth restriction. IQ = intelligence quotient. LD = learning disabilities. SEdS = special educational services. AZA = azathioprine. ADHD = attention deficit hyperactivity disorder. CHB = congenital heart block. ns = not significant (p-value not given). OR = odds ratio. HR = hazard ratio. MQ = motor quotient. Sometimes population numbers may differ within the same study, as some outcomes were not measured in all subjects.

‡Standardized tests consisting of questionnaires are referred to as standardized tests. Questionnaire refers to non-standardized questionnaires.

#Frequencies for disorders were high in the study by Urowitz et al. as a neurodevelopmental domain was considered abnormal if the score on one subtest was low.

fluorinated steroids were of influence in another study ($p < 0.01$) [15]. Finally, preterm birth associated with global neurodevelopment impairment in one study ($p < 0.01$) [16], but not in another [15].

3.2.1.1. Summary. Based on the evidence level 2b studies by Skog et al. and Urowitz et al., SLE offspring seem to have a 1.25-3-fold higher prevalence of global neurodevelopment impairment. However, this was not undisputable because smaller studies that assessed mostly younger children found no impairment.

3.2.2. Learning disorders

Learning disorders (LD) encompass a discrepancy between intellect and academic achievement in certain areas: mainly reading (dyslexia), writing (dysgraphia) or math (dyscalculia). Three studies with evidence level 2b and one with level 4* reported on these problems. Using standardized tests, an increased rate of LD (21.4–26%) was reported in a total of 72 SLE offspring aged 7–15 years when compared to 58 matched controls (7%, *p not given*) [23,24] and the U.S. general population (8%) [25]. These abnormalities were associated with maternal disease flare ($OR = 9.43$ [95% $CI = 1.32–67.24$]), anti-SSA positivity ($OR = 5.74$ [95% $CI = 1.32–23.74$]) [24] and aPL (3/3 affected children vs 2/11 others, $p < 0.02$) [23]. In line with these studies, the study with evidence level 4* found that 30% of 90 SLE offspring of unknown age suffered from LD, as reported by parents (partly verified by medical records or tests) [26]. In contrast, one study in 26 Japanese children reported no LD, but the sample size, lower subject age (0.5–12 years, mean 6.6) and the exclusion of patients with serious disease manifestations (e.g. nephritis) may have contributed to the lack of LD [14]. The definition and assessment tools of LD differed between studies, ranging from any discrepancy of verbal and performance IQ [26] to a difference between academic achievement and IQ as determined by a variety of standardized tests [23,24]. However, the diversity of definitions of LD is evident and constitutes a problem for studies on LD in general [27].

3.2.2.1. Summary. Based on high quality studies that used standardized tests at adequate age, LD were present in 21.4–26% of SLE offspring. These frequencies exceeded those in matched controls (7%) and the general U.S. population (8%). Maternal disease flares, anti-SSA and aPL were associated with LD.

3.2.3. Dyslexia

Four cohort studies of moderate (evidence level 4*) to good quality (level 2b) report an increased prevalence of reading problems and dyslexia in children of SLE patients. Amongst those reports, two uncontrolled studies found that 24.4% of 90 (test: questionnaire) and 14.3% of 14 SLE offspring (standardized tests) had dyslexia. The assigned evidence levels were 4* and 2b respectively [23,26]. Moreover, two studies with matched controls substantiated these findings: reading disorders were found in 19.0% of 58 SLE offspring compared to 6.9% of 58 controls (*p unknown*, standardized tests, evidence level 2b) [24] and in 21.6% of 153 versus 9.3% of 150 controls ($p < 0.01$, questionnaire, evidence level 4*) [28]. The association between maternal SLE and child reading problems was independent of maternal drug treatment, maternal SE status, premature birth and birth weight [24,28]. However, maternal anti-SSA, disease flares [24] and aPL were significantly associated with LD, including reading disorders (see Section 3.2.2.) [23]. The age was similar between these studies (combined range 7–20 years) and corresponds with the appropriate age for dyslexia assessment of 8 years and above [29].

These four studies also specify a higher risk for dyslexia to occur in *male* SLE offspring. Across these studies, 25%, 27%, 30%, and 40% of male SLE offspring were dyslectic, compared to respectively 0%, 11%, 12%, and 0% of females [23,24,26,28]. These ratios (♂:♀ > 2.5) exceed the male predominance for dyslexia in the general population across 4 studies in New Zealand and the United Kingdom (♂:♀ = 1.5–3) [30].

3.2.3.1. Summary. The prevalence of dyslexia and reading problems is increased in children of female SLE patients: 14.3–24.4% of altogether 315 SLE offspring were affected compared to 6.9–9.3% of matched controls and 5–17.5% in the general population [31]. Predominantly males were affected.

3.2.4. Attention disorders

Four studies with evidence levels 2b, 4* or 4 and one abstract discussed attention disorders. In the study assigned level 4*, attention disorders and hyperactivity were seen in respectively 15.7% and 13.1% of 153 SLE offspring, significantly more than in 150 controls (6% and 1.3%, $p < 0.01$) when tested at a mean age of 13.8 years (range 8–20 years) by questionnaires [28]. Furthermore, in the study assigned level 2b, data retrieved from Swedish medical records of children with a mean age of 13 years revealed that 13.9% of 36 children of anti-SSA positive SLE mothers had attention problems: 4 males and 1 female, all known with congenital heart block (CHB). This was significantly higher than in 73 children from anti-SSA positive mothers without SLE, where 1.4% was affected ($p < 0.05$) [16]. The frequencies in these two studies also exceed the general prevalence of attention deficit hyperactivity disorder (ADHD) amongst U.S. (10%) and Swedish (3.7%) residents [25,32]. In contrast, attention disorders were seen in only 0–5% of 86 SLE offspring in two cohort studies with evidence level 2b and 4 [14,15]. It is noteworthy that the studies that found

Table 3
Studies describing the effect of maternal auto-antibodies on physical (orange), neurologic (grey), psychiatric (blue) and motor development (green) in offspring.

Disorder	Ref	Evid–ence Level	Study type	Population Children, *maternal condition in italic*	Age	Outcome measure *(Outcome in Italic)*	Results *P–values or 95% CI in italic*
Growth	[46]	4*	C	104 *anti–SSA* 22 controls	Mean 14.5 y (range 5–39)	Questionnaire *(height, weight)*	Differences in height or weight were not significant (*ns*).
	[47]	4	C†	184 *anti–SSA (110 with NL and 74 unaffected siblings)*	0 – > 20 y	Questionnaire *(height, weight)*	Low height or weight (not precisely defined) in 11% of 110 NL children and 12% of unaffected siblings.
Global neurodevelopment	[37]	2b	C	40 *anti–SSA*	6–16 y	Standardized tests *(IQ, visual perception and motor integration, attention, verbal and visual learning and memory, behavior)*	None affected.
	[38]	2b	C	16 *anti–SSA*	Mean 5 y (range 2–12)	Standardized tests *(IQ, locomotor, personal–social, hearing and speech, coordination, performance, practical reasoning, reading)*	None affected (although a minor LD in 1 child, 6.3%).
	[16]	2b	C	114 *anti–SSA (36/114 SLE)*	Median 13.0 y (IQR: 8.2–17.5)	Medical records (*behavior, learning, attention, speech, motor development*)	14% affected. 31% of 36 SLE offspring and 10% in the remaining anti–SSA exposed children *(p<0.01).*
	[46]	4*	C	104 *anti–SSA* 22 controls	Mean 14.5 y (range 5–39)	Questionnaire (*attention, behavior, learning, hearing, speech, development delay*)	40% cases vs 27% controls *(p=0.34).*
	[39]	4	C	30 *SLE or APS, aβ2GPI positive*	Median = 9y	Standardized tests *(behavior, intelligence),* home–made questionnaire and clinical examination	Normal neuropsychological exam and intelligence. Mild behavior disorders in 10% (all with a history of epilepsy).
Learning disabilities (LD)	[46]	4*	C	104 *anti–SSA* 22 controls	Mean 14.5 y (range 5–39)	Questionnaire *(learning problems)*	9.6% affected vs 9.1% of controls *(ns).*
	[24]	2b	C	58 *SLE* 58 controls	Mean 9.3 y (8–15 y)	Standardized tests *(IQ, reading, writing, calculation, oral reading quotient)*	LD in 26% vs 7% in controls. Anti–SSA was independently associated with more LD in SLE offspring, OR = 5.74 *(1.32–23.74).*
Dyslexia	[48]	4	CC	45 dyslectic children 262 controls	Unknown	Unknown *(IQ, reading age)* Determinant measure: maternal serum *(anti–SSA)*	Anti–SSA positivity: 9% in mothers of cases, 0.4% in mothers of controls *(p < 0.01).*
Attention disorders	[37]	2b	C	40 *anti–SSA*	6–16 y	Standardized tests *(auditory and visual attention)*	All scores in normal range, although scores on attention were low (mean 6.6, 7.7 and 9.4 for different subtests, normal mean = 10 [Sd = 3]).
	[16]	2b	C	109 *anti–SSA*	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(attention deficit)*	Attention deficit in 13.9% of 36 children with maternal SLE vs 1.4% of 73 remaining anti–SSA exposed children *(p < 0.05).*
	[46]	4*	C	104 *anti–SSA* 22 controls	Mean 14.5 y (range 5–39)	Questionnaire *(attention problems)*	20.1% cases vs 4.5% controls *(p=0.120).* The small control group size possibly contributed to the high p value.
	[47]	4	C†	184 *anti–SSA (110 with NL)*	0 – > 20 y	Questionnaires *(ADHD)*	ADHD in 5% of 110 NL children and 8% of unaffected siblings
Speech disorders	[46]	4*	C	104 *anti–SSA* 22 controls	Mean 14.5 y (range 5–39)	Questionnaire *(speech problems)*	13.5% affected vs 15% of controls *(ns).*
	[16]	2b	C	114 *anti–SSA (36/114 SLE)*	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(speech problems)*	9% affected. 15% of 36 SLE offspring vs 5% in the remaining anti–SSA exposed children *(ns).*
Autism spectrum disorders (ASD)	[47]	4	C†	184 *anti–SSA*	0 – > 20 y	Questionnaires *(autism)*	Autism in 3% of 110 NL children and 3% of unaffected siblings.
	[49]	3b	CC	2431 mothers of ASD children 653 control mothers	Unknown	Determinant measure: maternal serum *(anti–brain antibodies, ANA)*	Anti–brain antibodies (Ab–ab) in 10.7% of cases and 2.6% of controls *(p < 0.01). This finding was confirmed in 318 additional case sera (8.8% positive).* 53% of Ab–ab positive mothers were ANA positive, compared to 13.4% of Ab–ab negative subjects *(p < 0.01) and 15% of controls.* In cases, SLE was present in 5/233 (2.22%) of Ab–ab positive cases and 1/622 (0.16%) of Ab–ab negative cases *(p < 0.01).*
Behavior disorders	[38]	2b	C	16 *anti–SSA*	Mean 5 y (range 2–12)	Standardized tests *(behavior)*	None affected.
	[37]	2b	C	40 *anti–SSA*	6–16 y	Standardized tests *(behavior)*	None affected.
	[46]	4*	C	104 *anti–SSA* 22 controls	Mean 14.5 (range 5–39)	Questionnaire *(behavior problems)*	10.6% affected vs 4.5% of controls *(ns).*
	[16]	2b	C	114 *anti–SSA (36/114 SLE)*	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(behavior problems)*	4% affected, consisting of 8.3% of 36 SLE offspring and 1.4% of 73 remaining anti–SSA exposed children *(ns).*
Depression	[46]	4*	C	104 *anti–SSA* 22 controls	Mean 14.5 (range 5–39)	Questionnaire *(depression)*	4.8% affected vs 0% of controls *(ns).*
Motor impairment	[16]	2b	C	114 *anti–SSA (36/114 SLE)*	Median 13.0 y (IQR: 8.2–17.5)	Medical records *(motor development)*	8% affected. Of 36 SLE offspring, 13.9% was affected, compared to 5.5% of the remaining anti–SSA exposed children *(ns).* 4/5 affected SLE offspring had CHB and 4/5 were born preterm.
	[47]	4	C†	184 *anti–SSA* (110 with NL)	0 – > 20 y	Questionnaire *(motor development milestones)*	Motor development delay in 3% of 74 non–NL subjects, compared to 12% of 110 NL subjects *(p = 0.027).*

C = cohort study. CC = case-control study. † = abstract only. SLE = systemic lupus erythematosus. y = years. IQR = interquartile range. Sd = standard deviation. ns = not significant (p-value not given). NL = neonatal lupus. IQ = intelligence quotient. SEdS = special educational services. AZA = azathioprine. ADHD = attention deficit hyperactivity disorder. NL = neonatal lupus. CHB = congenital heart block. OR = odds ratio. Sometimes population numbers may differ within the same study, as some outcomes were not measured in all subjects. ‡Standardized tests consisting of questionnaires are referred to as standardized tests. Questionnaire refers to non-standardized questionnaires.

more attention disorders assessed children at roughly twice the age of the studies that did not. This might contribute to the difference in prevalence, considering that in up to 50% of ADHD patients no symptoms are reported before 7 years of age [33] and a shift of the age of onset criterion from 7 to 12 years in the DSM-V resulted in a 1.5-fold increase in prevalence (from 7.4% to 10.8%) [34]. Finally, preliminary results of a Canadian study describe ADHD in 9.9% of cases and 6.1% of controls, HR = 1.73 (1.25–2.40) for the SLE group, which did not withstand adjustment for in-utero drug exposure (HR 0.97 [0.41–2.28]) [35]. However, maternal SLE remained significantly associated after multivariate analysis including treatment during pregnancy in two above-mentioned studies [16,28].

3.2.4.1. Summary. Based on the studies by McAllister et al. and Skog et al. that compared SLE offspring with controls and assessed children at the most appropriate age, maternal SLE increases the risk for attention disorders. CHB was also significantly associated with attention deficit.

3.2.5. Speech disorders

Speech disorders were investigated in three studies with evidence level 2b, 4* and 4. The speech disorder frequency in the U.S. is 5% in the first grade [36]. In an American study assigned level 4, 20% of SLE offspring of a similar age (n = 60, median age 5.7 years) needed SEdS for speech problems as reported by their mothers. Interestingly, azathioprine exposure was significantly ($p < 0.05$) associated with use of SEdS [15]. Furthermore, in a large Canadian population (n = 153), pronunciation problems (9.2%) and stuttering (5.2%) were roughly twice as prevalent, but statistically not significantly different compared to 149 controls (respectively 4.7% and 2.0%) at the age of 13.8 years with data obtained by a questionnaire (level 4*) [28]. Finally, in the level 2b

study, 15% of 36 children of anti-SSA positive female SLE-patients had speech problems, whereas only 5% of 78 other maternal anti-SSA (bot not SLE) exposed children were impaired (*not significant*). Prematurity, CHB and steroid exposure were not significantly associated with speech disorders [16].

3.2.5.1. Summary. These three studies suggest that children of SLE patients are at increased risk for speech disorders, as the prevalence was increased compared to the general population and 2–3 times higher than in controls, albeit not statistically significant.

3.2.6. IQ

IQ scores were unambiguously normal in SLE offspring across several studies [13,14,23,24,37–39].

3.3. Psychiatric development

The results for psychiatric development are given in Table 2.

3.3.1. Autism spectrum disorders

The association between SLE and autism spectrum disorders (ASD) has been investigated in two case-control studies (evidence level 3b) and two cohort studies (level 2b) that used medical records. Maternal SLE was associated with a threefold higher risk of ASD in a case-control study in 1227 children with ASD (odds ratio 3.1, 95% *CI* = 0.7–13.6). This result was not significant, probably because of a lack of power for SLE, which was present in only 2/1227 case mothers and 18/30693 control mothers [40]. An Egyptian case-control study confirms this trend: 2.5% of 80 autistic children had mothers with SLE, in contrast to none of 80 controls (*p not given*) [41]. The actual frequency of SLE amongst mothers of children with ASD therefore varied between 0.16% and 2.5%, clearly surpassing controls (0–0.06%) in these studies and matching or exceeding the general SLE prevalence in U.S. women (0.16–0.41% depending on ethnicity) [42]. Moreover, in a large population-based cohort identifying mothers with SLE and children with ASD using diagnostic codes in the Canadian healthcare system, ASD were more than twice as prevalent in 719 SLE offspring compared to 8493 matched controls: 1.4% versus 0.6% had ASD, univariate OR = 2.25 (95% *CI* = 1.13–4.45). This OR withstood correction for maternal education and age as well as child race and sex in a multivariate analysis. Multivariate analysis including these factors and obstetric complications yielded an OR of 1.97 (95% *CI*: 0.95–4.08). Information on in-utero drug exposure was available for 22% of the SLE group and 21% of controls and had no influence on ASD [43]. In contrast, no ASD were found in a cohort of 12 infants from SLE patients, which has to be interpreted with caution because the median age was 9 months [20].

3.3.1.1. Summary. Based on the findings by Vinet et al., we conclude that ASD are over 2-fold more frequent in children of SLE patients. Vice versa, two case-control studies indicate increased SLE prevalence in mothers of children with ASD as well.

3.3.2. Behavior

Three cohort studies assigned level 2b described behavior problems. Using standardized tests, abnormal scores on behavior were seen more often in 57 Canadian SLE progeny compared to 49 controls (39.2% vs 20.9%, $p = 0.06$) [18]. Based on medical records, 8.3% of 36 children of anti-SSA positive mothers with SLE had behavioral problems versus 1.4% of controls exposed to anti-SSA but not SLE (*not significant*) [16]. No abnormal behavior was seen in 26 Japanese children (different set of standardized tests) [14].

3.3.2.1. Summary. A statistically not significant trend towards more behavior disorders in SLE offspring was seen in two studies.

3.4. Motor development

Motor development (Table 2) was never the main study topic, but was mentioned in 5 cohort studies. All studies had evidence level 2b, except one (level 4). Across different countries, 5–8% of school-aged children have development coordination disorder [44]. Motor deficit was reported by mothers in 5% of 60 SLE offspring in the U.S. study with evidence level 4 [15]. Medical records of 36 SLE and anti-SSA exposed children describe that 13.9% had underdeveloped motor skills, whereas this occurred in only 5.5% of 78 other anti-SSA exposed children (*not significant*). However, CHB and preterm birth were present in 4/5 affected SLE offspring and preterm birth was significantly associated with motor impairment in all subjects ($p < 0.001$) [16]. Sensorimotor abnormalities were found by tests in 30.4% of 56 SLE progeny and 22.5% of 47 controls ($p = 0.36$) [18]. No motor deficit was seen in two other studies using physical examination and tests (combined n = 67) [14,45].

3.4.1. Summary

There is no increased prevalence of motor development abnormalities in SLE offspring. Prematurity and CHB may be associated with motor disorders.

3.5. Maternal autoantibodies

Maternal SLE-related autoantibodies were specifically included in the search string (Supplementary Material). The studies on this topic are summarized in Table 3.

3.5.1. Physical development

A cohort study with evidence level 4* reported no growth impairment in 104 anti-SSA exposed children at a median age of 14.5 years (range 5–39 years) [46], whereas an abstract described low height or weight (not defined) in 11% of 110 anti-SSA exposed children with neonatal lupus and 12% of 74 unaffected siblings [47].

3.5.2. Neurocognitive development

Global neurodevelopment was assessed in 4 cohort studies: three with evidence level 2b. One study with level 4* reported a not significant difference in impairment between 104 anti-SSA exposed children and 22 controls (respectively 40% versus 27% affected, $p = 0.34$) [46]. In 78 Swedish anti-SSA (but not SLE) exposed children, 10% were impaired: less than the U.S. general prevalence of 15% (unfortunately data on global neurocognitive impairment in Swedish children lacked) [16,17]. Furthermore, none of in total 56 anti-SSA exposed children displayed neurodevelopmental problems in two other studies that used standardized tests [37,38].

Considering specific antibody associated disorders, anti-SSA (but not anti-Sm and anti-RNP) was independently associated with LD in 58 SLE offspring: OR = 5.74 (1.32–23.74) (standardized tests, evidence level 2b) [24]. No such effect was measured by maternal report on 104 anti-SSA exposed children (24% had a mother with SLE): 9.6% was affected vs 9.1% of 22 controls (level 4*) [46]. Anti-dsDNA antibodies were present during pregnancy in the mothers of 1/3 children with LD, compared to 8/11 unaffected offspring (*not significant*) in a study assigned level 2b [23]. One case-control study (level 4) found anti-SSA in 9% of mothers of 45 dyslectic children and 0.4% of mothers of 262 non-dyslectic children ($p < 0.01$): a 22,5-fold difference [48].

Attention disorders were investigated in a level 4* study by asking parents of 104 anti-SSA exposed children if an official (doctor, nurse, teacher) had suspected such problems: this was reported in 20.1% versus 4.5% of 22 controls ($p = 0.120$) [46]. However, no problems were detected by standardized tests amongst 40 exposed children in a study with evidence level 2b [37]. In this line, an abstract reported ADHD in 5% of 110 anti-SSA exposed children with neonatal lupus and 8% of 74 unaffected siblings, not exceeding the general U.S. prevalence (10%) [25,47].

Finally, anti-SSA was also not associated with speech disorders in two studies with respectively level 2b and 4* [16,46].

3.5.3. Psychiatric development

In 184 anti-SSA exposed children, 3% had autism (abstract) [47]. Information about a possible association between maternal SLE and autism in the offspring was also obtained in a study with level 3b that analyzed anti-brain antibodies (ab-ab) in the sera of 2431 mothers of children with ASD and 653 control mothers. Ab-ab were present in 10.7% of the cases, significantly more than in controls (2.6%, $p < 0.01$). Of the ab-ab positive mothers, 53% were ANA positive and 2.22% had SLE. Both ANA and SLE presence were significantly more frequent compared to ab-ab negative cases ($p < 0.01$) and ANA prevalence also exceeded controls ($p < 0.01$) [49]. Another noteworthy finding was that ab-ab preferentially targeted the cerebellum, hippocampus and frontal cortex. These are known ASD-associated areas [49,50]. Caveats include that autoimmune disorder prevalence was based on self-report and that control women were not checked for autoimmunity or parenthood. Also, ab-ab positivity during pregnancy was uncertain as blood samples were drawn years after gestation.

Behavior abnormalities were present in 10.6% of 104 anti-SSA exposed children and 4.5% of 22 controls, a not significant difference (evidence level 4*) [46]. Furthermore, only 1.4% of 73 anti-SSA exposed children from healthy mothers or mothers with connective tissue diseases other than SLE were affected (level 2b) [16] and no behavior abnormalities were seen in 56 anti-SSA exposed children across two other studies (level 2b) [37,38].

A single paper with evidence level 4* reported depression in 4.8% of 104 children born to anti-SSA positive mothers (mean age 14.5 years), compared to 0% in 22 controls (*not significant*) [46].

3.5.4. Motor development

A cohort study (level 2b) found that 8% (9 children) of 114 Swedish children from anti-SSA positive mothers (36/114 SLE offspring) had motor problems (6/9 affected children had CHB) [16]. In an abstract on 184 anti-SSA exposed children, motor impairment was found in 12% of 110 children with neonatal lupus and 3% of 74 unaffected siblings ($p = 0.027$) [47].

3.5.5. Summary on antibodies

There is no evidence that exposure to maternal anti-SSA influences child growth, global neurodevelopment, attention disorders, speech disorders, ASD and behavior problems. However, anti-SSA was significantly associated with LD in SLE offspring in one high quality study. Motor disorders were more prevalent in children with anti-SSA/SSB mediated CHB.

Other auto-antibodies were seldom investigated. Anti-brain antibodies were much more prevalent in the serum of mothers of ASD children and require further investigation.

3.6. Antiphospholipid antibodies

APS often accompanies SLE and some studies considered the influence of aPL (lupus anticoagulant, anti-cardiolipin, anti-β2-glycoprotein I *[aβ2-GPI]*) in SLE patients. During a prospective 5-year follow-up on 130 children born to aPL positive mothers, autism, language delay and hyperactivity were found in one child each. However, the true rates of these disorders remain uncertain because only 48% of subjects were tested above age 2 and only 20% at age 5 [21]. In 14 SLE offspring, all 3 children with LD had aPL positive mothers [23]. In addition, aPL (especially lupus anticoagulant) exposure was associated with the use of SEdS, mainly for speech delay, in 60 SLE offspring ($p < 0.05$, odds ratio 5.1, 95% $CI = 1.2$–22.6) [22]. One Italian study investigated children (median age 9) born to 30 aβ2-GPI-positive mothers with SLE or APS. Ten percent had minor behavior disorders (all known with focal epilepsy), matching the prevalence of 8.7–14.7% in Italian school children when measured with the same test [39,51]. Finally, normal neurodevelopment was found using standardized tests in 10 aPL-exposed SLE offspring [14].

3.6.1. Summary

Exposure to maternal aPL was associated with speech delay and LD in one study each.

4. Discussion

This systematic review was conducted to provide a complete overview of the available evidence on the long-term physical, neurodevelopmental, psychiatric and motor development of children born to SLE patients. Important conclusions are that *maternal SLE was associated with learning disorders (especially dyslexia), autism spectrum disorders and attention problems.*

Generally, almost half of the studies scored a high evidence level: 2b or 3b. Consequently, half received evidence level 4 or 4*, indicating that the results should be interpreted with caution. Shortcomings included small sample sizes (resulting in insufficient statistical power), lack of control groups, use of not-standardized measurement methods and assessment at low age. Furthermore, comparison between studies was complicated by variability in outcome definitions, examination methods and report measures. A meta-analysis was therefore impossible. Another limitation of this review was the risk for publication bias. It should be noted that some of these shortcomings arose because the information retrieved for this review was not the main study topic and therefore not represented inherent study problems.

Learning disorders (LD) were roughly three times more prevalent in SLE offspring. Although the definitions of LD varied widely across different studies, comparable frequencies were reported in SLE offspring. Different aspects of maternal SLE possibly mediated the association with LD, as the presence of maternal anti-SSA or antiphospholipid antibodies (aPL), as well as active disease during pregnancy were associated with LD.

The most consistent learning disability found in children from mothers with SLE was dyslexia, where a clear male predominance was seen. A possible explanation for this phenomenon might be the so-called immunoreactivity theory which suggests that the Y chromosome contains antigens that provoke a maternal antibody response against the male fetus, resulting in more neurodevelopmental abnormalities in males compared to females [52].

Likewise the occurrence of autism spectrum disorders (ASD) and speech disorders was consistently increased in children of SLE mothers [15,16,28,43]. More divergent findings were reported for global neurodevelopmental impairment, attention disorders and behavior problems. Mainly large studies that used controls reported associations between maternal SLE and these abnormalities, whereas studies that found no association were mostly smaller and assessed children at a lower age. Measurement at lower age results in fewer diagnoses, which is also seen in the general population [17,25,33,34].

Finally, IQ and motor skills were not influenced by maternal SLE. Data on cardiopulmonary functioning and mood disorders lacked and should be generated.

One hypothesis for this review was that transplacentally transferred maternal autoantibodies damage the fetus and influence child development later in life. The Ro antigen is found not only in the heart, but also in the brain, suggesting that anti-SSA/SSB antibodies cause brain damage as well [53]. However, the adverse effects of anti-SSA on child development were limited and seemed to mainly encompass an association with LD [24]. On the other hand, most studies on anti-SSA were limited by small sample sizes, a lack of controls or a small control group. Furthermore, a few important studies for the above-mentioned associations between maternal SLE and several developmental problems did not report on these antibodies [15,28,43]. Therefore, the role of anti-SSA cannot be discarded based on these results. Nonetheless, anti-SSA exposed SLE offspring had more developmental problems than other anti-SSA exposed children [16], suggesting that other facets of SLE

(e.g. other autoantibodies, cytokines, disease activity, pregnancy complications) contribute to a greater extent.

In this respect, anti-dsDNA is an autoantibody of interest, as it is known to cross-react with brain NMDA receptors [54]. These antibodies can enter the fetal brain because the blood-brain barrier is not yet developed until around birth [55]. In an animal model, these auto-antibodies caused histological brain damage, followed by cognitive impairment in the offspring [56]. Accordingly, a similar effect on the neurodevelopment of children of anti-dsDNA positive SLE patients seems possible. Unfortunately, anti-dsDNA was only investigated in one study of 14 children, where no effect on IQ or LD was seen [23].

Another interesting aspect is the presence of anti-brain antibodies (ab-ab) in the sera of mothers of children with ASD [49]. This finding should be confirmed in a new study with samples drawn during gestation, followed by a prospective study aimed at proving a causal relationship with ASD.

Two factors that are known to influence child development are preterm birth and low birthweight (LBW), complications that are present in respectively 31% and 23% of SLE pregnancies [57]. A substantial amount of long-term follow-up studies and reviews on premature, very premature (<32 weeks) and very low birth weight (VLBW, <1500 g) children report increased frequencies of neurocognitive, psychiatric and motoric problems during childhood and adolescence [58–64]. Nonetheless, some major studies in this review found that premature birth and LBW were of little influence on the reported associations between maternal SLE and LD, dyslexia, ASD, attention and speech disorders [15,16,24,43]. Several factors may contribute to the discrepancy between the expected influence of preterm birth and LBW and the actual effect in these studies. First, most premature children in these studies were born at a gestational age between 32 and 37 weeks and most children with LBW weighed >1500 g [15,16,43]. These groups are at lower risk for neurodevelopmental problems than very preterm and VLBW children [65–67]. Secondly, the statistical power was lower for prematurity, as only 15.8–38.3% of the mostly moderately sized populations was affected across these studies [15,16,24,43]. Altogether, the influence of maternal SLE on child development withstood correction for these pregnancy complications [15,16,43] and was still present when compared to controls with similar rates of preterm birth [24]. Therefore the magnitude of the effect of maternal SLE on child development apparently extends beyond the sequelae of preterm birth and low birth weight.

5. Conclusion and future goals

In conclusion, SLE during pregnancy is a risk factor for long-term developmental problems in offspring, in particular learning disabilities (especially dyslexia in male progeny), attention disorders, autism spectrum disorders and probably speech disorders. A contributing role for anti-SSA was not consistently seen in most of these associations..

For future studies, a large-scale, controlled, prospective setup with follow-up through childhood and adolescence using internationally accepted standardized tests assessing the different developmental areas covered in this review is needed. Furthermore, a complete maternal autoantibody profile, maternal disease activity, in-utero exposure to medication, gestational age and birth weight should be registered and corrected for.

Take-home messages

- Maternal SLE is associated with neurodevelopmental problems in offspring.
- Specific disorders include learning disorders, autism spectrum disorders, attention deficit and probably speech problems.
- These associations are not solely explained by sequelae of pregnancy complications.

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