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REVIEW ARTICLE

Cardiovascular risk in the postnatal life of children born to women with systemic lupus erythematous

Riesgo cardiovascular en la vida posnatal de hijos de mujeres con lupus eritematoso sistémico

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Abstract

Systemic lupus erythematous (SLE) is an autoimmune disease with clinical manifestations in multiple organs, primarily striking women of reproductive age. Women with SLE can became pregnant such as any other healthy woman and carrier their pregnancy to term due to the improvement of health systems, but their specific inflammatory conditions could affect the microenvironment in which the fetus grows, and influence the development of placenta and the fetal heart. Until now, there is very little evidence of any increased risk of postnatal cardiovascular disease (CVD) in the apparently healthy children from women with SLE, but it is this great variability in the effects of lupus on pregnant products is related to.

Keywords: *Systemic lupus erythematous. Maternal inflammation. Pregnancy. Offspring. Children. Cardiovascular disease. Heart.*

Resumen

El lupus eritematoso sistémico (LES) es una enfermedad autoinmune que presenta diversas manifestaciones clínicas en múltiples órganos, y afecta principalmente a mujeres en edad reproductiva. Las mujeres con LES se pueden embarazar y llevar a término su embarazo, sin embargo, las condiciones inflamatorias específicas de la madre pueden modificar el microambiente en el que el embrión y el feto se desarrollan y afectar la formación y desarrollo de la placenta y el corazón fetal. Hasta ahora hay muy poca evidencia de que haya un mayor riesgo de enfermedad cardiovascular (ECV) en hijos aparentemente sanos de madres con LES, a pesar de que se sabe que hay un mayor riesgo de alteraciones cognitivas y neuronales, así como de desarrollar enfermedades autoinmunes en esos niños. El objetivo de esta revisión fue realizar una búsqueda bibliografía cruzando palabras clave acerca la enfermedad cardiovascular en hijos sanos de mujeres con LES. La evidencia mostró que la autoinmunidad materna puede favorecer la predisposición para el desarrollo de ECV en sus hijos, por medio de la modificación de señales que alteran el microambiente durante la gestación, lo que puede afectar la respuesta inmunitaria y cambios epigenéticos durante la vida posnatal.

Palabras clave: *Lupus eritematoso sistémico. Inflamación materna. Embarazo. Descendencia. Enfermedad cardiovascular. Corazón.*

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Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease characterized by a loss of immunological tolerance and an increase in the production of autoantibodies[1]. SLE affects up to 1.5 out of every 1000 women aged 18-44 years[2]. This group represents 90% of the total cases of SLE, thus it is considered to be a disease almost exclusively of women of reproductive age. We now know that the fertility of women with SLE is similar to that of healthy women[3]. Nevertheless, the risk of clinical manifestations that affect the mother as well as the child during pregnancy has not decreased, despite the use of new treatments[4]. Through a search of reports on the incidence of complications during gestation in the children of pregnant women with SLE, it was found that premature birth and fetal death were the most frequent (Table 1), which were related to placental alteration[5-14].The main disorders reported in children born to women with SLE were eczema, asthma and learning disabilities[15-21], but incidence of cardiac alterations in these children is almost 6 times greater compared to children of healthy mothers (Table 2).

The heart is an organ that begins its formation and function in the beginning of the third week of gestation, and therefore is more susceptible during the first trimester of pregnancy[22]. Nevertheless, sensitivity of the cardiovascular system is maintained all through life and the risk of damage has been linked to pro-inflammatory states. Due to this, our goal is carry out a search of the scientific literature, regarding the effect that maternal inflammatory states and the placental transference may have on the development and health of the hearts of children from mothers with SLE, and how this relates to their postnatal life. The methodology is shown in the table 3.

Table 1. Fetal complications frequency in SLE pregnant women

Complication	Cases	Frequency (%)
Fetal Death	17	8.3
	107	8.0
	105	11.1
	86	23.3
	73	7.0
	338	11.2
Placental/Congenital	105	7.0
Malformations	509	5.1
	73	5.0
	338	1.3
	240	6.0
Preterm Birth	105	34.6
	17	33.3
	1010	14.0
	59	37.0
	86	25.0
	338	28.7
IUGR	17	13.6
	107	14.0
	59	29.0
	86	17.4
	73	15.8
	338	12.7
	1010	28.5
	105	28.9
	338	10.0
Oligohydrammios	107	3.0
	59	8.0
Neonatal death	105	3.6
	73	3.0

SLE: systhemic lupus erythematosus; IUGR: intrauterine growth restriction.

The placenta and the heart in communication

The placenta acts as a selective barrier between maternal and fetal circulation, in addition to providing oxygen and nutrients to the fetus. Both the placenta and the heart are the first organs to be differentiated and they maintain a close interaction during gestation, through the umbilical-placental circulation. This, in turn, directly influences the processes of remodeling and septation in the heart[23]. The vascular endothelial growth factor (VEGF) and its receptors are needed for vasculogenesis, angiogenesis, and normal maintenance of the endothelial function. Therefore, variation in the expression or concentration of these may lead to faulty angiogenesis, which is correlated to cardiovascular disease (CVD)[24] and to placental alterations[25]. Through

Table 2. Reported alterations in children from SLE women

Alteration	Result
Hearth Diseases	More risk to develop heart malformations (SLE 7.5% vs. healthy1.3%) Auricular and ventricular septal anomalies (SLE 5.1% vs. healthy 1.9%)
Neonatal Lupus	NL alterations: hepatobiliary, skin and hearth disorders and cytopenia. Development of AV block due to the presence of anti-Ro and anti-La (Risk 2-3%)
Neurological Diseases	Autism and other neural disorders (SLE 1.4% vs. healthy 0.6%) Learning disabilities (SLE 21.6% vs. healthy 9.3%)
Autoimmune Diseases	Autoimmune diseases (SLE 1.11% vs healthy 0.48%) Susceptibility for intestinal and thyroid diseases in male children
Atopic Diseases	Eczema and asthma (SLE 43.9% vs. healthy 38.1%) Asthma and premature birth related to smoking mothers (SLE 27-28% vs. healthy14-20%)

SLE: systemic lupus erithematosus; AV: atrioventricular.

Table 3. Methodology

STEP
1. A search was conducted on the published scientific literature indexed using https://www.ncbi.nlm.nih.gov/pubmed database
2. Keywords were identified according to the objective and using PUBMED MESH:
a) Child, Children, Offspring and Newborn
b) Mother, Maternal and pregnancy
c) Lupus, Neonatal Lupus, Systemic Lupus Erythematous
d) Inflammation
e) Cardiovascular diseases, Heart diseases
Combination between keywords was made looking for reviews, abstracts, case report, and investigation articles looking through 1990-2020
3. When the search was complete and all duplicate documents were thrown out, the abstracts of the remaining articles were carefully checked to ensure that they address our review question
4. Selected documents were analyzed and summarized and the findings from the articles and reviews were integrate them into the writing as appropriate way

the cardiac development, an over-expression of VEGF-A and VEGF-B favors cardiomyocyte hypertrophy and protects them from apoptosis, while in the placenta, VEGF-A is expressed in the decidual membrane and interacts with the trophoblast that expresses VEGFR-1, which contributes to communication between the maternal and embryonic/fetal tissues[26]. Despite the role of VEGF/VEGFR during cardiovascular development is still not clear, they could contribute to a higher risk of vascular alteration in patients with LES, and to placental malformation during pregnancy[27].

The placenta has an active role in the regulation of the maternal immune system, to support the pregnancy. For example, it expresses the toll-like receptors (TLRs), which recognize pathogens. Over time, these receptors show a pattern of expression in the maternal-fetal interface that protect and favor the adequate development of the placental barrier[28,29]. In turn, the trophoblast invasion into the endometrium is regulated by the decidua, by inhibiting the activation of NK cells[30]. More than 20% of women with SLE have been described as having an adverse pregnancy, due to placental alterations which have been related to alterations in the plasma levels of factors sFlt1, PlGF, and soluble endoglin[31], associated with vascular disorders and with a greater risk of preeclampsia.

Placental transfer and cardiovascular complications in children of mothers with SLE

Transfer of immunoglobulins

The immunoglobulins (Ig) G (IgG), whose molecular mass is approximately 160 kDa, use the specific transporter neonatal Fc receptor (FcRn) to transfer from maternal to fetal circulation[32]. The passage of Ig through the placenta starts at week 13 of gestation and increases proportionally with gestational age. It peaks at the beginning of the third trimester[33], coinciding with the period when the thickness of the placental barrier diminishes. The presence of the fraction Fab (fragment and antigen binding), the fraction Fc (fraction, crystallizable), and the complete IgG of maternal origin, has been detected in fetal circulation[34], while FcRn has been shown in the syncytiotrophoblast[35]. This is correlated with greater levels of Fc and complete IgG, compared with Fab. It is known that these transporters have a ubiquitous distribution, since they are also found in the blood-brain barrier, in the endothelium of the renal glomerulus and in the intestinal epithelium, whose function is to promote the host's defenses and to control the deposit of immune complexes[36].

Under normal conditions, newborn babies maintain the IgG of maternal origin in their circulation for approximately 6 months, but in newborn babies of women with SLE, it could be longer, since IgGs form immune complexes and these may participate in organic damage

mainly related to maternal autoantibodies, such as the case of fetal heart block[37]. Table 4 shows the frequency with which circulating autoantibodies characteristic of women with SLE are identified, being the anti-dsDNA antibodies the most abundant[38,39]. Almost all autoantibodies that can cross the placental barrier, attach themselves to the NMDA (N-Metil-D-Aspartate) receptors present in cortical cells[40], inducing apoptosis in these cells in the fetus. This has been related to the development of neurological disorders in postnatal life[41]. Despite the fact that large amounts of anti-dsDNA antibodies have been found circulating in the children of mothers with SLE, there does not seem to be any correlation with the development of CVD. However, an association has been found with these antibodies and the risk of CVD in adults with SLE, such as thromboembolic events and atherosclerosis. This discrepancy may be related with the disease activity or with a particular inflammatory response characterized by enhancement of the expression of pro-inflammatory molecules (VCAM1, ICAM1, metalloproteinases, and chemoattractant molecules)[42].

The maternal autoantibodies anti-Ro/SSA and anti-La/SSb are detected in the fetal circulation from weeks 18 to 24 of gestation and are associated with atrio-ventricular blockage (AV block), due to affectation of the AV node. This can occur in babies born to mothers with SLE, Sjögren's syndrome, or even asymptomatic carriers. Even though AV block is the primary cardiac alteration described in children of mothers with SLE, it occurs in only 2% of cases with maternal anti-Ro/SSA antibodies positivity and 3% of cases with both anti-Ro/SSA and anti-La-SSB antibodies positivity[43]. The apoptosis of cardiomyocytes occurs normally during the formation of the heart but it could be increased in mothers with SLE and positive anti-Ro and/or anti-La antibodies. In the other hand, it is known that these antibodies bind to intracellular antigens Ro52, Ro60, and La48, which could be over-expressed in the embryonic cells, and thus form immune complexes, coupled with de fact that cardiomyocyte apoptosis can also result in expression of Ro/SS-A and La/SS-B on the cell surface. The immune complexes are captured by FcYRIIA receptors in the phagocyte and are transported to the endosomic compartment, where they are recognized by TLRs.[44]. As a consequence, pro-inflammatory cytokines such as INF-γ, TNF-α, and IL-6 could be released. In addition, there can be an increase in the production of STAT1 dependent molecules which are able to cause the trans differentiation of cardiac cells to fibroblasts[45], which will finally produce fibrosis of the AV node[46]. This mechanism also can explain the development of other alterations related to cardiogenesis, such as endocardial fibroelastosis and dilated cardiomyopathy[47].

Table 4. Antibodies frequency in pregnant women serum with SLE

Frequency (%)	Year	
Antibody	2005	2017
Anti-Nucleosome	78.6	24.1
Anti-DNA	75.0	69.7
Anti-Histone	44.0	21.5
Anti-Sm	36.9	15.2
Anti-NRP	32.1	19.0
Anti-SSA (Ro)	54.8	48.1
Anti-SSB (La)	14.3	11.4

SLE: systemic lupus erithematosus. Frequency has been taken from two relevant studies.

Nevertheless, these are not the only autoantibodies related to fetal heart block. This is also associated with other antibodies that modulate several cellular pathways such as anti-calreticulin antibodies, which recognize calreticulin, a protein involved in the storage of intracellular calcium, anti-muscarinic acetylcholine receptor M1 antibodies, as well as anti-αFodrin antibodies which recognize fodrin, a membrane protein related to apoptosis[48,49].

The antiphospholipid antibodies (aPL) present in SLE are associated with obstetric complications such as recurrent miscarriages and preeclampsia, as well as affectation of postnatal cognitive development. The main target of aPL is the β2-glycoprotein-I located in endothelial cells[50] and platelets[51]; they are associated with prothrombotic events and repeated fetal losses, but they also interact with fetal neuronal antigens, causing alterations in postnatal cognitive behavioral development[52]. Likewise, an increase in aPL is related to changes in the circulating concentrations of fms-tyrosine-like kinase-1 (sFlt-1), placenta-like growth factor (PlGF) and soluble endoglin (sEng), and other placental factors that could be working together affecting vascular endothelium development and, as a consequence, placental-mediated vascular insufficiency, and hypoxia may be present[53].

The fetal cardiovascular system is in constant change, and the effect of maternal autoantibodies mainly targets the placenta, but does not seem to match with early developing heart. Cardiac septation occurs around the

sixth week of gestation[54], and the transplacental movement of IgG starts in the 13th week thus, one possible explanation of why maternal autoantibodies do not produce frequent morphological alterations in the fetal heart, is due major organogenesis of the heart happens before the placenta can permit the transference of Ig.

Placental transference of cytokines

The elevated concentration of pro-inflammatory cytokines in the circulation of patients with SLE, allows one to consider the possibility that these cytokines cross the placental barrier. Nevertheless, there exists great controversy on this issue. In a model of perfusion, bidirectional transference of IL-6 was observed in the placenta of pregnancies at term[55], but another study did not find IL-6 to be capable of crossing the placental barrier of healthy women, nor was transference of TNFα, IL-1β[56] or IL-8[57] detected. In one rat model treated with lipopolysaccharide (LPS) through intraperitoneal injection at the end of the gestation period, only a minimal transference of maternal IL-1 to the fetus was observed[58]. There are not studies that clearly show the passage of cytokines from the mother to the fetus throughout pregnancy rather this has been studied only at the end of pregnancy. Given this, and due to the fact that placental barrier structure is being constantly modified, it is not possible to dismiss the idea that cytokines may be able to be transferred to the fetus during the first and second trimester of gestation. The existing verified evidence only shows that at the end of the pregnancy, there is some transference of maternal cytokines to the fetus, but it remains in controversy. Therefore, it has been difficult to confirm the role of maternal cytokines in the prenatal baby and if they could have any influence on the children postnatal development. In addition, when a case of inflammatory process is identified, it is not clear whether this was generated by the tissues of the product itself[59], or whether it was secondary to the passage of maternal cytokines or another inflammatory stuffs.

Placental transference of cells

Microchimerism refers to the trafficking of cells or DNA molecules in the circulation that are genetically different from the host's own. This phenomenon is observed during pregnancy and is due to a bidirectional transference of maternal and fetal cells that are able to continue existing in the circulation for years[60,61]. The "alien" cells can exist without being perceived by the host immune system and without generating any apparent alteration; however, they could also be associated with the development of autoimmune diseases such a systemic sclerosis. This paradoxical response seems to depend particularly on the extent of similarity between the HLA antigen of the chimeric cells and those of the host[62]. The maternal cells are similar to immune grafts and persist in the circulation of children with severe immunodeficiencies[63]. These have also been observed in the pancreas of patients with Neonatal Lupus (NL) and Type I Diabetes[64]. In a study carried out in necropsies of newborn babies with NL who died due to arrhythmia secondary to the illness, cells of maternal origin were found attached to the fetal cardiomyocytes[65]. It is possible that this conditions the development of a local inflammatory response which later favors fibrosis of the conduction system. This may then manifest as AV Block or may generate apoptosis in the cardiomyocytes of any region. One possible explanation is that the presence of maternal cells in the host (child) may result in a rupture of the immune tolerance. Another possibility is that a small population of these cells may regulate a decrease in the immune response of the host, which over the long run generates a reaction of rejection. It appears that fetal microchimerism can persist silently for decades, and may gradually initiate pathological processes related to autoimmunity[66].

Inflammatory profile of children of mothers with SLE and its effect on the heart

Endothelial fetal cells are the ones that first establish contact with the maternal antibodies and inflammatory molecules that cross over the placental barrier. However, there is still limited evidence regarding the effect of this on fetal inflammatory states and of the response of these cells to the presence of such substances. In a research carried out by our group, we studied the expression of pro-inflammatory molecules in human umbilical vein endothelial cells (HUVEC) of healthy children of mothers with SLE, and the results showed a lower expression of IL-8, TLR9 and of adhesion molecules (E-Selectin, I-CAM, and V-CAM), compared to the HUVEC of healthy children of healthy mothers. However, there were no differences in the expression of IL-6[67]. Nevertheless, when the HUVEC were stimulated with TNF-alfa, the response was proportionally similar in both groups. This indicates that despite being basally depressed, the HUVEC of SLE had not lost the capacity to become activated in pro-inflammatory conditions. It is important to consider that

both genetic background and regulation due to environmental conditions affect the activation of the endothelium in postnatal life. In another study that looked at the family history of heart disease in healthy pregnant women whose children were healthy on birth, it was observed that the basal expression of pro-inflammatory cytokines in HUVEC was greater in women with some family history of CVD, than those with little or no history of CVD[68]. This shows that the inflammatory response in children from mothers with pro-inflammatory conditions, or with some risk of maternal illness, enhances the risk in the short or long term to develop some degenerative or autoimmune disease, with consequences in adult life. Furthermore, in other study with the goal of investigating the inflammatory profile of children of mothers with SLE and their association with alterations in cognitive and neurological development, it was observed that they had a greater incidence of autoimmune diseases such as glomerulonephritis, asthma, thyroid diseases, vitiligo, and cryoglobulinemia compared to children of healthy mothers. They also showed greater levels of IL1β, IL2, IL4, IL5, IL6, IL10, INFγ, and TNFα[69]. Since these patients were between the ages of 8 and 17 at the time of this study, it is hard to know if there was any relationship with the interaction with maternal environment during gestation or due to placental transference; however, it still confirms the pro-inflammatory situation suffered by children of mothers with SLE, over the long term and this may also cause a predisposition to the development of CVD. The evidence shows that the main cardiac affectation of children from mothers with SLE is AV blockage; however, we cannot dismiss other alterations that may affect cardiac function over the medium to long range. The administration of LPS in animal models allows for a simulation of maternal pro-inflammatory states, as it has been shown in female pregnant rats, LPS produces a decrease of the contractile function and increased remodeling of the left ventricle of the pups[70], and in rats, the offspring presents cardiomegaly, myocardial fibrosis, and hypertension[71,72]. It is known that LPS is an activator of the innate immune system and its effects are mediated through its interaction with receptors of the TLR family[73]. Most of the cells of the cardiovascular tissue present receptors for TLRs, and the TLR activity has been related to diseases such as atherosclerosis, cardiac dysfunction in sepsis, and congestive heart failure[74]. Therefore, fetal cardiomyocytes may be an important target during gestational heart development. There are still no studies on the mechanisms of action of TLR in the development of heart disease in children from women with SLE, but the action of these receptors could favor the synthesis and secretion of cytokines, adhesion molecules, chemoattractants, and reactive species of oxygen, which, in turn, promote the activation of endothelial cells and leukocytes in patients with SLE[75].

On studying the structure and function of the myocardium in children with active SLE, a high frequency of global dysfunction of the left ventricle was observed, even in the absence of clinical symptoms or signs of heart diseases. However, this is different in adults with active SLE, where there is a predominance of coronary artery disease due to premature atherosclerosis, hypertension, heart failure, and valvular disease[76]. This allows for the observation that age, environment, and history of the disease, can have distinct effects on the development of cardiac disease. In a longitudinal study carried out for over 20 years, the accelerated development of CVD was observed in patients diagnosed with SLE, in comparison with control groups. Nevertheless, there were no differences in associated risk factors such as cholesterol levels or blood glucose[77]. Likewise, their risk of developing subclinical atherosclerosis is similar to that of patients with rheumatoid arthritis and diabetes mellitus, which are associated with the activation of the P38-MAPK pathway, leading to the activation of NFkB as a response to the signals induced by aPL[78].

The inflammatory state of a woman with SLE may be the result of environmental interaction with the state of the disease itself, which implies a great variability in clinical manifestations. Epigenetics is the study of changes in genetic expression that are not related to mutations in the underlying DNA sequence, but rather to changes in DNA methylation, the modification of histones and the expression of miRNA, all of which are regulated by environmental conditions. In studying the transcription and methylation of the genome of PBMC cells of patients with SLE, various genes were found to be over- or under-expressed, and these are correlated to the state of methylation[79]. Differential analysis revealed a significant affectation of the signaling pathways of INF and TLRs, such as the expression of MX1, GPR84, and E2F2 molecules which are related to pro-inflammatory signaling pathways in macrophages. These were found to be increased in patients who already had lupus nephritis, in comparison with those who did not, while the serum levels of the cytokines IL17A, IP-10, bFGF, TNF-α, IL-6, IL-15, GM-CSF, IL-1RA, IL-5, and IL-12p70 were found to be elevated in all patients. In addition, it was observed that the over-regulation of IL-15 was correlated with hypomethylated sites in the promoter region of this gene[80]. It is known that apoptotic DNA is hypomethylated and produces an increase in the immune response through

signaling by TLR9. This culminates with the production of anti-dsDNA antibodies and lupus nephritis in rats[81].

Other environmental factors such as exposure to UV rays can cause a significant reduction in the global methylation of the DNA of peripheral blood mononuclear cells, phenomenon that is exaggerated in patients with SLE. Endogenous retrovirus can be reactivated through the hypomethylated state present in SLE, where the retroviral elements imitate autoantigens that induce a response from autoantibodies. Therefore, this state favors epigenetic modifications that can have repercussions throughout postnatal life, enhancing the susceptibility to develop cardiovascular and autoimmune diseases.

Conclusion

The available evidence from recent years suggests that maternal autoimmunity is a relevant risk factor in embryonic fetal development. This may condition a predisposition or biological programming toward CVD in children. This great variability in the effects of SLE on gestational products is related to individual genetic susceptibility, conditioned by therapeutic management, maternal metabolism, and the clearance of molecules that cross over the placental barrier and have contact with the fetus, or the structural changes in this barrier that affect maternal-fetal exchange. We may conclude that multiple signals form complex networks of interactions that program the prenatal immune system and trigger its homeostatic regulation. Maternal diseases, particularly infectious or autoimmune diseases, modify these signals and can also alter immunity in the early life of their children. An understanding of maternal programming in the newborn baby's immune system could provide the basis for timely interventions that promote health of children.

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Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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