Evaluation of systemic lupus erythematosus activity during pregnancy

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Abstract: Pregnancy in patients with systemic lupus erythematosus (SLE) is considered a high-risk pregnancy. It is complicated by preeclampsia, premature labour and miscarriage more frequently than in the general population. Improved prognosis depends on low disease activity during conception and on appropriate medical care (SLE activity monitoring, selection of therapy safe for the mother and the developing foetus, advances in neonatology). Because symptoms of physiological pregnancy and SLE exacerbation are similar, their correct interpretation is essential for skin lesions, arthralgias, arterial hypertension or results of laboratory tests: proteinuria, thrombocytopenia or leucopenia observed in the patient. In order to standardise the assessment of SLE activity during pregnancy, scores of this activity are used. In the past, scores validated on non-pregnant populations (including male patients) were used: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure (SLAM), European Consensus Lupus Activity Measurment (ECLAM). Only recently have SLE activity scores been introduced that are specific for pregnant women: Lupus Activity Index In Pregnancy (LAI-P), Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI), modified – Systemic Lupus Activity Measure (m-SLAM) and a visual three-grade score modified – Physician Global Assessment (m-PGA). So far, only scores LAI-P and m-PGA have been validated. According to the LAI-P score, clinical data are divided into 4 groups. Group 1 includes mild clinical symptoms, group 2 – symptoms of involvement of internal organs, group 3 pertains to modifications of treatment and group 4 to laboratory parameters. Point values are ascribed to individual parameters depending on their intensity.

Key words: disease activity, pregnancy, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is mainly a female disease. Prevalence is the highest in the 15–40-year-old patients. Fertility of women suffering from SLE is not changed by the disease and is the same in the population of age-matched, healthy women [1,2]. Not infrequently, despite a chronic disease, female patients arrive at a decision of maternity.

Before glucocorticosteroids era pregnancy in SLE patients was contraindicated, since it was connected with high mortality of mothers [3]. In the 1970s loss of a foetus concerned 40% of cases [1]. Understanding the causes of obstetric complications, detection of antiphospholipid antibodies (aPL), introduction of treatment by acetylsalicylic acid and heparin, advances in neonatology as well as birth planning decreased frequency of spontaneous abortions and dead births.

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Received: March 23, 2007. **Accepted in final form:** June 28, 2007.
Conflict of interest: none declared
Pol Arch Med Wewn. 2007; 117 (7): 312-316

Nowadays, the frequency of alive births among SLE patients in specialized centers is the same as in the healthy women population [4-6]. Still, more frequent are: premature labour, eclampsia and pregnancy-induced hypertension [5, 7-10]. Moreover, there are more children with low birth weight, caesarean sections are used more frequent and hospitalizations after labour last longer comparing to healthy women [11].

There are several disadvantageous factors which are unfavorable for pregnancy and increase the risk of obstetric complications: active lupus nephritis [12,13], proteinuria [14], hypertension [14,15], aPL [9,16], cessation of hydroxychlorochine treatment during pregnancy [16], high activity of disease during conception [13,16,17].

SLE activity in pregnancy

Female SLE patients, while planning maternity, ask about the risk of lupus exacerbation during pregnancy. In recent 25 years several trials concerned this issue (Tab. 1). Reported frequency of SLE exacerbations during pregnancy is from several to 70%. The cause of this range could be due to different ways of disease activity estimation. Importantly, in most cases these exacerbations were mild: only skin lesions and arthralgias. In

Table 1. Frequency of SLE exacerbations in pregnancy and puerperium (based on chosen publications)

Authors (year)	Number of pregnancies (number of patients)	Type of trial	Definition of exacerbation	Frequency of exacerbations (%)	Effect on obstetrical results
Lockshin (1989)	80 (80)	prospective	– assessment by researcher – increasing dose of GCS – number of abnormalities in laboratory tests	13	NS
Nossent et al. (2000)	39 (19)	retrospective, control group: non-pregnant SLE female patients	clinical and laboratory assessment	71	NS
Petri et al. (1991)	40 (37)	prospective	increase of PGA by ≥1	60	NS
Lima et al. (1995)	108 (90)	prospective	clinical and laboratory assessment	57	NS
Ruiz-Irastorza et al. (1996)	78 (68)	prospective, control group: non-pregnant SLE female patients	LAI	65	NS
Huong et al. (1997)	62 (38)	prospective, only planned pregnancies	clinical and laboratory assessment	27	NS
Georgiou et al. (2000)	59 (47)	prospective, 2 control groups: – non-pregnant SLE female patients – healthy pregnant women	new SLE symptom during pregnancy	13.5	loss of a foetus ($p < 0.001$), premature labours ($p < 0.001$)
Cortes-Hernandes et al. (2002)	103 (60)	prospective	event requiring intensification of SLE treatment	33	NS
Molad et al. (2005)	29 (20)	prospective	SLEDAI	20*	NS
Clowse et al. (2005)	227 (203)	prospective	increase of PGA by ≥1	21	premature labours ($p < 0.001$)

GCS – glucocorticosteroids, LAI – Lupus Activity Index, NS – statistically non-significant, PGA – Physical Global Assessment, SLE – systemic lupus erythematosus, SLEDAI – Systemic Lupus Erythematosus Disease Activity Index

very rare cases severe complications occurred [13,18]. Changes of basic treatment were rare. In most trials there were no correlations between SLE activity and the course of pregnancy [5-7,9,16,19,20].

In 2005 the results of a prospective, multiyear trial with pregnant women suffering from SLE were published. This trial was performed between 1987 and 2002. The authors estimated the effect of disease activity on frequency of: spontaneous abortions, dead births, premature labours and labours with low newborn body weight. Activity of the disease was estimated by the visual three-grade score (Physician Global Assessment ≥2 meant high activity). In multifactorial analysis demographic data, lupus nephritis and antiphospholipid syndrome were considered. Two hundred and seventy-seven pregnancies were observed. High activity of SLE concerned 57 patients (21%). In this group a lower number of living births (77% vs. 88%, $p = 0.063$) and a higher number of premature labours ($p < 0.001$) were noticed. High activity of the disease in the first and the second trimesters was connected with the threefold increase in the risk of pregnancy complications [21].

Differentiation between symptoms of SLE exacerbation and physiological pregnancy

It must be remembered that in pregnancy there is a change in the meaning of clinical symptoms and laboratory tests. Symptoms and signs considered as SLE exacerbation could be a physiological state in pregnant women.

Good examples are skin lesions: angiogenic face erythema, palmar erythema, slight angiomas on the upper part of the body, disseminated chloasmas and melasmas after the exposition to sunlight. They can resemble the acute phase of SLE or vasculitis, but they often occur in healthy pregnant women as well.

Also hair loss, a sign of SLE activity, in women after birth is caused by a decrease in estrogenes level.

Another sign, often observed in pregnancy, is arthralgia, which is connected with physiological looseness of ligaments. There is often a small aseptic articular hydrops in a knee joint. If these changes are inflammatory and concern more than 2 joints they may be a sign of SLE exacerbation [22].

An important sign, requiring perceptive analysis, is proteinuria. It can be: a sing of SLE exacerbation, pregnancy complications or a fixed phenomenon in patients with previous renal disease [23]. In the case of SLE exacerbation, it is often accompanied by extrarenal signs of disease (skin lesions, arthralgia, increased titre of antibodies against double stranded DNA – anti-dsDNA). Usually proteinuria increases gradually and is accompanied by haematuria.

Proteinuria as a complication of pregnancy is a symptom of preeclampsia. Preeclampsia develops after the 20th week of pregnancy and in most cases disappears during 42 days after labour. It is accompanied by an increase in arterial blood pressure (systolic >140 mmHg or diastolic >90 mmHg) and proteinuria >300 mg/d. Organs are hypoperfused and there is a danger for a mother and a foetus [24]. These signs are often accompanied by headaches, blurred vision, epigastric pain and abnormalities in laboratory tests: thrombocytopenia as a cause of microangiopathic heamolytic anaemia and increased transaminases activity. Helpful symptoms in differentiation between active lupus nephritis and preeclampsia are shown in Table 2. Exacerbation of preeclampsia resulting in seizures is called eclampsia [25]. A clinical picture of preeclampsia differs in certain cases in the spectrum of symptoms and courses. Most often it develops slowly and is restricted to mild disturbances, however, in cases with a fulminant course in a few hours it can lead to eclampsia. The cause of preeclampsia is unknown. Its background consists of endothelial dysfunction, vascular hypersensitivity to vasoconstriction agents as well as the activation of coagulation, which lead to ischaemia of internal organs of a mother and a foetus. Described above phenomena can be additionally complicated by procoagulant aPL, thus preeclampsia could be more frequent in pregnant women suffering from SLE and antiphospholipid syndrome.

Another complication, requiring detailed diagnostics and often preterm delivery is hemolysis, elevated liver enzymes and low platelets syndrome, described for the first time in 1982. It can appear in every pregnancy, but it is suggested that it is more frequent and more intensive in pregnant patients with antiphospholipid syndrome [26].

Table 2. Differentiation between preeclampsia and SLE exacerbation in pregnancy

Parameter	Preeclampsia	SLE exacerbation
C_3, C_4, CH_{50}	could be decreased	usually decreased
erythrocyturia	rarely present	frequently present
onset of proteinuria	frequently sudden	frequently gradual
hypertension	always present	often
aminotransferase activity	frequently increased	rarely increased
anti-dsDNA	no changes	increase

anti-dsDNA – antibodies against double stranded DNA, C_3, C_4, CH_{50} – complement components, SLE – systemic lupus erythematosus

Interpretation of chosen laboratory tests

In progress of active SLE there can be abnormalities in laboratory tests: increased ESR, leucopenia, thrombocytopenia or low levels of complement components. In pregnant patients individual characters of these abnormalities should be considered in their interpretation. Increased ESR is a phenomenon typical of physiological pregnancy. Also a decreased number of blood platelets (100 000–135 000/mm^3) is revealed in 8% of normal pregnancies. Mild thrombocytopenia (70 000–100 000/mm^3) occurring before the 15th week of pregnancy, without concurrent symptoms and signs of SLE exacerbation, could be connected with the appearance of aPL and it disappears after aspirin treatment. Severe thrombocytopenia (often >10 000/mm^3) could be connected with idiopathic purpura.

In the third trimester of physiological pregnancy there is an increased number of leucocytes in peripheral blood, on average up to 15 000/mm^3. Its cause is an increased proliferation of neutrophils. An absolute number of lymphocytes is not changed. That is why lymphopenia, not leucopenia, is a sensitive indicator of SLE activity in pregnancy.

Increased estrogene-related synthesis of proteins in the liver is responsible for a rise in blood serum levels of fibrinogen, factor V, VIII, X and the von Willebrand factor. Activity of coagulation proteins as well as the level of fibrin degradation products, e.g. d-dimers, are also increased.

In physiological pregnancy there is a graduate increase in complement components: C_3, C_4, and an increase in total hemolytic activity CH_{50}, usually by 10–50% in relation to values before pregnancy. Therefore, a more competent test indicating SLE exacerbation is the detection in serum active complement components, e.g. C_{3a}.

Scores of SLE activity during pregnancy

In order to standardize the assessment of SLE activity during pregnancy, scores of this activity are used. In the past, the following scores were used: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Activity Measure (SLAM), European Consensus Lupus Activity Measurement (ECLAM). Since they have been validated on non-pregnant populations (including male patients), recently SLE activity scores have been introduced that are specific for pregnant women. In 1999 the following scores were introduced: Lupus Activity Index in Pregnancy (LAI-P), Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) and modified Systemic Lupus Activity Measure (m-SLAM) [22,27]. Petri et al. introduced a visual three-grade score, the modified Physician Global Assessment (m-PGA) [27], on

Table 3. Lupus Activity Index in Pregnancy

Group	Parameter	Point values				Values to calculate LAI-P
1	fever	0	1			mean (a)
	erythema	0		2		
	arthritis	0		2	3	
	serositis	0	1	2	3	
2	neurological symptoms	0			3	highest (b)
	renal involvement	0		2	3	
	lung involvement	0			3	
	hematological symptoms	0	1	2	3	
	vasculits	0			3	
	myositis	0		2		
3	prednison, NSAID, hydroxychlorochine	0	1	2	3	mean (c)
	immunosuppressive drug	0			3	
4	proteinuria	0	1	2	3	mean (d)
	anti-dsDNA	0	1	2		
	C_3, C_4	0	1	2		

point value of LAI-P = (a+b+c+d)/4
maximal value of LAI-P =2.6; exacerbation – increase by ≥0.25
Abbreviations: LAI-P – Lupus Activity Index in Pregnancy, NSAID – nonsteroidal antiinflammatory drugs, others – in Table 2

which a physician marks points, indicating a low, a mean and a high activity of the disease. So far, only the scores LAI-P and m-PGA have been validated [27,28].

According to the LAI-P score (Tab. 3), clinical data were divided into 4 groups. Group 1 includes mild clinical symptoms, group 2 the symptoms of involvement of internal organs, group 3 pertains to modifications of treatment and group 4 to laboratory parameters. Point values are ascribed to individual parameters depending on their intensity.

In group 1 to a fever of >38°C, after exclusion of infection or drugs as a cause, 1 point is ascribed. Skin lesions, if they are inflamed are assessed on 2 points. Point values are not ascribed to cicatricial changes, transient erythematous changes and pregnant dermatoses. Arthritis is essential for the assessment of SLE activity if it concerns more than 2 joints. If inflammation concerns up to 5 joints, or more than 5 joints, 2 points and 3 points are ascribed, respectively. Serositis is estimated from 1 to 3 points: 1 point if there is a chest pain, 2 points if it is confirmed by an additional test (echocardiography, ECG, chest X-ray), and 3 points if there are signs of tamponade.

In group 2, heavy organ and hematological complications are described. Neurological signs are: 1) psychosis; 2) organic changes; 3) seizures; 4) brain vascular event; 5) signs of retinopatia, scleritis and episcleritis. It is necessary to exclude eclampsia, preeclampsia, antiphospholipid syndrome and iatrogenic drug complications, e.g. after GCS.

Renal complications are ascribed to SLE exacerbation after exclusion of other causes of renal disease. They are characterized by proteinuria >0.5 g/d or doubling of proteinuria value before pregnancy, accompanied by active urinary sediment or a decrease in complement level in serum. If renal biopsy reveals class II and V changes by the WHO, 2 points are ascribed, if class III and IV – 3 points.

Involvement of lungs, defined as lung interstitial density, hemoptoe or indirect proofs of alveolar haemorrhagia are estimated at 3 points. Exclusion of infection is needed.

Haematological changes are significant if a number of platelets is less than 100 000/mm^3 and a number of leucocytes – 3000/mm^3. During deterioration of cytopenia, until thrombocytopenia <20 000/mm^3, leucopenia <1000/mm^3 and lymphopenia <100/mm^3, the number of ascribed points increases to 3 and 2, respectively. Three points are also ascribed to anaemia haemolytica, confirmed by the Coombs test and a decrease in haemoglobin level < 8g/dl. Myositis and vasculitis are ascribed to 3 and 2 points, respectively.

Changes in treatment are involved in group 3. Three points are ascribed to the addition of nonsteroidal antiinflammatory drugs, hydroxychlorochine or prednison at a dose of 0.25 mg/kg b.w./d or the inclusion of immunosuppressive drug.

In group 4 among laboratory parameters there are specified: proteinuria 0.5g/d – 1 point, 1–3 g/d – 2 points, >3g/d – 3 points. Anti-dsDNA antibodies or decreased complement level (1 point for 50–75% of normal, 2 points for >50%) are also significant.

The total value of LAI-P is an arithmetic mean of the following values: mean of groups 1, 3 and 4 and the highest from group 2 (max 3). The result is situated in a range between 0 and 2.6. Exacerbation is defined by an increase of at least 0.25 point in relation to the previous examination.

SUMMARY

Pregnancy in SLE is not contraindicated, however, it still remains a high risk pregnancy. The highest percentage of pregnancies ended in healthy childbirth was achieved in centers, in which rheumatologists, obstetricians and pediatricians were holding a common care. The importance of qualified specialists cooperation derives from the fact that collagenoses are rare and symptoms of SLE exacerbation and pregnancy complications of pregnancy display much similarities (onset of anaemia, thrombocytopenia, hypertension and proteinuria). A proper differentiation between these signs is crucial for the benefit of pregnancy and the mother health.

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