An ever-challenging relationship: lupus and pregnancy

Andra Bălănescu, Teodora Donisan, Dinu Bălănescu

University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

Abstract

Systemic lupus erythematous (SLE) is a chronic inflammatory disease with an unknown etiology and an autoimmune pathogenesis, and its clinical manifestations can involve multiple organs through polymorphic biological changes. Nowadays, pregnancy is possible for most patients with SLE, and good outcomes can be expected for both mother and child. This became possible as a consequence of increasingly better monitoring and treatment of pregnant women with SLE. The following article outlines the problems associated with fertility, course of pregnancy, and breastfeeding in women with SLE.

Key words: systemic lupus erythematosus, pregnancy.

Introduction

Systemic lupus erythematous (SLE) is a chronic inflammatory disease with protean manifestations, an unknown etiology, and an autoimmune pathogenesis; it is defined by the synthesis of autoantibodies (auto-Ab) directed against elements of the cellular nucleus, and its clinical manifestations can involve multiple organs through polymorphic biological changes [1]. Since the disease is prevalent in females of reproductive age and its pathogenesis involves the immune system and hormonal alterations, pregnancy-related issues are extremely important for the mother's disease course, as well as for fetal development. Previously, pregnancy was contraindicated for most patients with SLE; however, we are witnessing a major shift in this paradigm. Nowadays, pregnancy is possible for most patients with SLE and good outcomes can be expected for both mother and child, through a better understanding of the pathogenesis of the disease and due to advances in clinical management which triggered a widening body of evidence in relation to SLE-pregnancy association. Lately, there have been major changes in the management of pregnant women with lupus.

Systemic lupus erythematous and contraception

Women with SLE should be counseled about the use of effective contraceptive measures, based on their disease activity and thrombotic risk, especially for the prevention of unwanted pregnancies during high disease activity periods and intake of teratogenic drugs [2].

These patients have fewer contraceptive options because oral contraceptives contain estrogen and progesterone; these two hormones might trigger disease flares. Even though clinical trials have generated inconsistent results in this regard, it is recommended to avoid these hormone-containing contraceptives in SLE patients, especially if the disease is active [3]. However, in patients with inactive SLE and negative anti-phospholipid antibodies, combined hormonal contraceptives can be considered [2]. Additionally, estrogen use increases the risk for thrombosis in patients with antiphospholipid or nephrotic syndromes. An accepted alternative is progesterone, but its long-term use is limited by the risk of osteoporosis and must be carefully weighed against the risk of thrombosis [2, 4].

Due to these reasons, mechanical contraceptive methods are mainly recommended in patients with SLE, but even these are to be used with caution due to the increased risk of infection. Intrauterine devices (IUD), especially those covered only with copper, can be used for all patients with SLE and/or antiphospholipid syndrome free of any gynecological contraindication [2].

Systemic lupus erythematous and female fertility

There are reports showing that female patients with rheumatic inflammatory diseases, including SLE, have

a smaller number of children compared to age-matched controls from the general population [5]. This difference could be explained by reduced fertility, influenced by multiple factors, such as disease age of onset, disease activity, degree and severity of the visceral involvement and treatment. Other than the potential for reduced fertility, there is a higher risk of miscarriage and pregnancy-related disorders, influenced by immune factors represented mainly by the presence of anticardiolipin antibodies [6]. Another indirect indicator of fertility, "time to pregnancy", is prolonged in females with rheumatoid inflammatory diseases; multiple factors could explain this prolongation, and decreased fertility can be one major explanation [7].

Fertility is not altered in most female patients with SLE [8]. However, since SLE is a systemic inflammatory disease, which could involve any organ or system, there are some risk factors with a potential negative impact on female fertility. There are many mediators involved in reproductive processes such as pre-implantation or the blastocyst–endometrium interaction: inflammatory cytokines, chemokines or growth factors; the dysfunction of these mediators could explain reduced fertility. The most important factors with an impact on fertility are: the patient's age (decreased fertility after 35 years), disease activity, involvement of specific organs and some treatments [9]. Nonsteroidal anti-inflammatory drugs may interfere with ovulation, implantation and placentation because they inhibit prostaglandin synthesis. Glucocorticoids (e.g. high doses of prednisone, above 7.5 mg daily) may induce transient suppression of the hypothalamic-pituitary-ovarian axis. Therefore, these drugs can induce reversible infertility. Cyclophosphamide can cause irreversible infertility through ovarian failure caused by the cumulative effect of high doses [10]. Fertility preservation methods, especially GnRH (gonadotropin-releasing hormones) analogues, should be considered for all menstruating women with SLE who are going to receive alkylating agents [2].

Before conception

The most important strategy, which ensures positive outcomes for the mother and the baby, is planning the pregnancy.

The checklist of parameters to be considered for pre-conception counseling and risk stratification in women with SLE and/or antiphospholipid syndrome (APS) has been recently updated and published by EULAR (European League Against Rheumatism) [2].

Good planning includes a thorough pre-conception assessment, with emphasis on the following issues:
• factors with an impact on fertility (mentioned above),
• previous pregnancies and their possible complications,

• current disease activity and disease flares in the recent past; SLE activity/flares (in the last 6–12 months or at conception) are associated with increased risk for maternal subsequent flare during pregnancy and puerperium), hypertensive complications, fetal morbidity and mortality, preterm delivery [2],
• lupus nephritis (history or active at conception) is a strong predictor of poor maternal and fetal outcome(s) (fetal loss and preterm delivery) [2],
• potential irreversible organ damage,
• serological activity: low complement level, elevated anti-dsDNA Ab titers are associated with increased risk for maternal SLE flares during pregnancy and pregnancy loss [2],
• presence of APS/Ab is a strong predictor of adverse maternal and fetal outcomes, especially for patients with persistent moderate-to-high aPL titers, LA and multiple aPL positivity (high-risk aPL profile): increased risk of maternal vascular thrombotic events during pregnancy, (pre-)eclampsia, APS-related pregnancy morbidity, preterm birth [2],
• presence of anti-Ro or anti-La Ab is linked to development of neonatal lupus, including a low risk for congenital heart block (especially if there are moderate-to-high anti-Ro titers); weak association with other pregnancy complications [2],
• current usage of certain drugs (such as cyclophosphamide, methotrexate, mycophenolate, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, HMG-CoA reductase inhibitors) [4]; all drugs mentioned here should be stopped,
• smoking must be prohibited.

The ideal time for conception is during a prolonged remission (with a duration of at least 6 months). The patient should have normal blood pressure, no renal or neurological symptoms during the last year, no pulmonary hypertension, low titers of anti-dsDNA Ab, antiphospholipid or anti-Ro Ab, no hematological abnormalities, and no biological inflammatory syndrome. The patient should also receive corticosteroid therapy in doses < 15 mg daily and should not receive any teratogenic treatments (discussed further below) [11]. Remission of lupus nephritis is defined by normal values of creatinine and serum complement, proteinuria < 500 mg/24 h, < 5 red blood cells/field in urine. Pregnancy should be delayed if the patient does not fulfill all the criteria mentioned above.

However, there are relatively few circumstances when the pregnancy is contraindicated in a patient with SLE: pulmonary hypertension (systolic PAP > 50 mm), severe ventilatory functional restriction, severe cardiac failure, chronic renal disease in stages 4–5, previous pre-eclampsia or HELLP syndrome, stroke or severe flare of the disease in the previous 6 months [4].

Good planning of the pregnancy and the major advances made in the management of the pregnant patient with SLE led to a significant decrease in the abortion rate, from 43% in the 1960s to 17% in the 2000s [12].

Systemic lupus erythematous and pregnancy: pathogenetic characteristics

Because of the multi-organ involvement and the synthesis of a high number of Ab, SLE may have a complex influence on the pregnancy. However, the pathogenic mechanisms which form the basis of the clinical manifestations during pregnancy or which have an influence on the pregnancy evolution in SLE are not completely understood. The most often incriminated causes are pregnancy-specific hormonal changes (mainly increased levels of estrogens and prolactin) [13].

The developing placenta and embryo are foreign tissues for the mother and may trigger defense mechanisms. On the other hand, the product of conception must be defended from the mother's immunologic assault. Hence, the maternal immune system must adapt to this new circumstance, and the regulatory T cells play an important part in this process [3]. From this perspective, it is easy to understand that an autoimmune disease, such as SLE, can dramatically impair these mechanisms and can lead to the development of significant reproductive disorders. During the periods of disease activity, the regulatory T lymphocytes are decreased and their suppressive function is correspondingly altered.

In SLE, estrogens have a complex and diverse modulatory effect on the immune response. During pregnancy, the immune response is mainly Th2 type, while the cell-mediated immune response, the Th1 lymphocyte function, and the concentration of the cytokines produced by the Th1-cells: interleukins 2 and 12 (IL-2, IL-12), interferon γ (IFN-γ), tumor necrosis factor (TNF), are depressed (which is essential for the fetus survival). On the other hand, the production of cytokines by the Th2 lymphocytes (IL-4, IL-10) and the humoral response are exacerbated; these changes are reversible after birth, but may trigger disease flares [14]. Th17 lymphocytes are another type of cells with a seemingly important role during pregnancy. These cells produce IL-17, a cytokine with significant proinflammatory effects. High concentrations of IL-17 have been found in females with SLE with pre-eclampsia and recurrent abortions [15]. Another important cytokine produced in excess in SLE is IL-10, which leads to continuous, excessive stimulation of B lymphocytes [13].

Unlike other proinflammatory cytokines, the levels of IL-6 are decreased in SLE; also, during the last pregnancy trimester, IL-6 is increased in healthy pregnant women, but not in SLE. IL-6 stimulates angiogenesis, and alterations of its level may be associated with premature birth or with impaired placental and fetal growth.

Interleukin 33 is the most recent member of the IL-1 superfamily and a potentially important factor in the pathogenesis of SLE and other autoimmune diseases. This cytokine induces the activity of Th2 lymphocytes, mastocytes, macrophages and NK cells, enhancing the synthesis of type Th2 cytokines. Also, IL-33 facilitates the invasion of the trophoblast and the proper development of the placenta. Dysfunctions of this cytokine are associated with recurrent abortions [16].

Normal placental development is essential for a normal pregnancy. Disorders of placental vasculature are the main cause of abortion in this disease [17]. In over a third of pregnant SLE patients, the size of the placenta is reduced because of the placental vasculitis associated with ischemia. Ischemic changes may be aggravated by arterial thrombosis, especially when associated with APS. These alterations of the placental vessels may compromise the nutrition and the oxygenation of the fetus, delaying its growth and triggering premature rupture of membranes. Pregnancy-associated disorders are the hallmark of both primary APS and SLE-associated APS. Over half of pregnancies positive for antiphospholipid Ab end in abortion, especially in patients with previous abortions or fetal deaths. The major culprits for pregnancy-associated complications are thrombosis of placental vessels and subsequent placental infarctions. Furthermore, Ab have a direct effect on the trophoblastic cells from the placenta, thus reducing the invasive activity of the trophoblast, the cellular differentiation, the development of the syncytium and the synthesis of hCG (human chorionic gonadotropin) [14]. Exposure of amniotic phospholipids and/or of β2-glycoprotein on the surface of trophoblastic cells stimulates the binding of anti-phospholipid Ab to cardiolipin and explains placental tropism of these Ab. However, the activity of these Ab has an impact on the placentation process. Furthermore, the anti-phospholipid Ab has been proven to interfere with the process of endometrial angiogenesis.

In addition, the placental pathologic changes may cause an imbalance between the release of angiogenic and pro-inflammatory factors, followed by damage of the vascular endothelium and the onset of pre-eclampsia [14]. New results from the PROMISSE study and from other research have proved that angiogenic factors play an important predictive role for pre-eclampsia [18]. In pregnant women with or without SLE, pre-eclampsia may be anticipated by increased levels of soluble fms-like tyrosine-kinase, which inhibits the growth of placental blood vessels and by low levels of placental growth factor, which stimulates local angiogenesis.

Moreover, the placenta releases microparticles involved in oxidative stress, and the levels of circulating vascular endothelial growth factor (VEGF) and pro-angiogenic factors mentioned above are decreased even 4–5 weeks prior to the onset of clinical signs. If these results are clearly confirmed, the above-mentioned molecules may be considered biomarkers which can anticipate the onset of pregnancy complications in SLE patients [14]. Additionally, in some cases of pre-eclampsia, it was determined that lipid-rich foam cells accumulate in the walls of the uterine spiral arteries, similar to the early stages of atherosclerosis.

All these phenomena may cause miscarriage or pre-eclampsia or may impair fetal growth [19]. No abnormalities have been described in the aborted fetuses. However, some babies born to antiphospholipid Ab-positive mothers have been proven to have similar biological abnormalities [20].

Estrogens stimulate and control the release of prolactin, which, in turn, stimulates T-lymphocyte proliferation, B-lymphocyte maturation and Ab synthesis. Moreover, the level of prolactin appears to be correlated with disease activity in female patients with SLE.

Therefore, all the circumstances in which the estrogen levels are increased (pregnancy, hormone replacement therapy, estrogen-containing contraceptives) can induce disease flares.

Clinical particularities of systemic lupus erythematous during pregnancy

In most cases, there are no significant differences between the clinical picture of SLE in pregnancy and the usual one. If the disease onset overlaps with pregnancy (very rarely), joint manifestations and constitutional symptoms may sometimes be mistakenly considered to be pregnancy-related [21].

Joint pain and inflammation occur mainly in the hands, elbows, shoulders and knees. Joint pain is associated with stiffness, and the swelling is generally symmetrical, but the arthropathy is non-erosive and does not cause deformities [11].

Mucocutaneous manifestations are also common. The most specific ones are the following: butterfly malar rash (*vespertiglio*), generalized rash, photosensitivity, but also multiple nonspecific cutaneous manifestations: panniculitis, hives, vasculitis, livedo reticularis, oral ulcerations, circumscribed alopecia, and Raynaud phenomenon. Besides these acute signs, there are subacute manifestations such as polycyclic annular and papulosquamous (psoriasiform) lesions, and also chronic manifestations, such as discoid lupus and lupus profundus.

All these manifestations may be present during pregnancy, but the "butterfly" rash is rare in pregnant women and Raynaud phenomenon is uncommon during pregnancy [1]. It may be difficult to differentiate between cutaneous manifestations of SLE and melasma, the facial hyperpigmentation specific to pregnant women, which is also photosensitive. Also, alopecia, which may be induced by the disease or by the treatment, may occur independently from SLE during pregnancy or during the first months after delivery.

During pregnancy, pleuritis is the most common form of serositis (pericarditis and peritonitis occur very rarely).

Renal involvement is extremely important in pregnant women with SLE and represents the most important prognostic factor. All clinical trials have shown a significant increase in abortion and/or premature birth rates in pregnant women with SLE and renal involvement, compared to those without nephropathy [22]. Creatinine clearance < 65 ml/min/m^2 or proteinuria > 2.4 g/24 h are major risk factors for miscarriage and are associated with abortion in more than 50% of cases [22].

Apart from renal disease, **neuropsychiatric involvement** is one of the main prognostic factors. Neuropsychiatric disorders may be very diverse: headache, peripheral neuropathies, cranial nerve involvement, partial or generalized seizures, strokes, acute lymphocytic meningitis. Psychiatric involvement can also be very heterogeneous, ranging from mild memory, perception and orientation impairment up to psychosis. Although rare, estrogen-induced chorea can occur in pregnant women with SLE [17].

Cardiovascular disorders may consist of pericarditis, myocarditis, arrhythmias or conduction disorders, heart failure, nonbacterial verrucous endocarditis described by Libman and Sacks, and coronary disease caused by vasculitis or by increased atherosclerosis in patients receiving corticotherapy. Thrombosis, either venous (mainly in deep veins of lower limbs) or arterial, is another possible complication occurring in SLE patients and more common in pregnant patients [22]. Hypertension is more common in SLE patients during pregnancy: 25% of pregnancies are associated with hypertension in SLE patients, especially if they received corticotherapy or had previous nephritis [11].

Pregnant SLE patients have a higher risk of other medical complications, such as gestational diabetes and infections, compared to healthy pregnant women, and maternal mortality is higher in this population of patients [22].

Effect of pregnancy on systemic lupus erythematous

The flares of SLE are 3 times more common in the first trimester of pregnancy, 1.5 times more common

in the second and third trimesters, and 6 times more common postpartum [3]. The rate of the flare episodes depends on the activity of the disease at the time of conception [23]. Disease flares occur during pregnancy in 7–33% and 56–65% of cases if the disease was inactive or active, respectively.

Effect of systemic lupus erythematous on conception and pregnancy

In SLE women (with or without APS), prematurity, preeclampsia and HELLP syndrome (eclampsia/Hemolysis, Elevated Liver enzyme levels, Low Platelet count) rates approximate 25–35%, 10–15% and 1.0–1.5%, respectively [2].

So, SLE can have an impact on the pregnancy course during any of the trimesters as well as in the postpartum period. The disease can be associated with a higher risk of abortion and premature births (caused by pre-eclampsia, premature rupture of membranes, placental insufficiency, or high doses of corticosteroids), perinatal deaths caused by exacerbations of renal disease and infections, intrauterine growth restriction and neonatal lupus [14]. Increased levels of ferritin caused by the inflammatory process and decreased levels of estradiol, suggestive for placental insufficiency, are associated with higher risk of premature birth [24].

The PROMISSE study (Predictors of Pregnancy Outcome: Biomarkers in APL Syndrome and SLE), a multicentric, prospective trial that enrolled 492 pregnant women with SLE, showed the occurrence of severe adverse pregnancy outcomes (pre-eclampsia before the gestational age of 34-weeks, fetal/neonatal death, abortion, premature birth before 30 weeks of gestation) in 12% of patients and moderate adverse pregnancy outcomes (pre-eclampsia after the gestational age of 34-weeks, premature birth between 30 and 36 weeks of gestation, or intrauterine growth restriction) in 10% of cases [18]. Moreover, the study led to the identification of certain biomarkers – circulating angiogenic factors (soluble fms-like tyrosine kinase, soluble endoglin), which were associated with severe adverse events.

The normal pregnancy course in SLE patients can be affected by factors linked to the clinical and biological activity of the disease during the previous 6–12 months before conception (especially renal function, serum levels of complement, anti-dsDNA Ab); therefore, planning the pregnancy and choosing the most appropriate timing are of paramount importance. Hence, previous renal dysfunction is associated with a high rate of maternal complications, antiphospholipid Ab are associated with an increased risk of spontaneous abortion and anti-Ro and anti-La Ab are predictive for the risk of neonatal

lupus [25]. Other pathologies linked to a reserved prognosis for the pregnancy in women with SLE are lupus nephritis with hypertension, diabetes mellitus, thrombosis, pre-eclampsia, urinary tract infections, premature rupture of membranes, previous pregnancies not carried to term (although pregnancies can have different courses in the same SLE patient) or treatment (high-dose corticoids, immunosuppressive agents) [26].

Laboratory diagnosis in pregnancy

Anemia is more common in pregnant women with SLE because the iron requirements are increased, but also because of the usual causes of anemia associated with SLE (simple chronic anemia, hemolytic anemia, iron deficiency anemia caused by treatment-induced digestive losses of iron). During pregnancy, the decreased white blood cell count specific to SLE may be absent; moreover, slight leucocytosis may be observed in some cases, even in the absence of concomitant infections or corticosteroid therapy [27]. Usually, the platelet count is normal in pregnant women with SLE, but severe thrombocytopenia can occur in certain situations, e.g. during disease flares, HELLP syndrome, APS, or pre-eclampsia.

Inflammatory markers are usually increased during pregnancy, and because of this they are no longer an appropriate measure for disease activity. However, ESR values over 50 mm/h cannot be explained by pregnancy and should raise concern for the obstetrician. Moreover, the complement levels are increased because estrogens enhance its hepatic synthesis; therefore, if the disease is not very active, the serum complement can be normal in pregnant SLE patients. Nevertheless, decreased complement levels are suggestive for an increased risk of premature birth (only 16% of pregnant women with SLE and decreased complement levels have a term delivery) [25].

Renal function and urinalysis should be assessed on a monthly basis in SLE pregnant women, and any suspicion of renal involvement should be confirmed by measuring proteinuria over 24 hours.

Pre-eclampsia is a complication of pregnancy occurring in 20% of pregnant women with SLE, compared to 7% in patients without this disease [25]. It is more common in patients with lupus nephropathy. This complication is sometimes difficult to distinguish from an SLE flare, since both clinical entities have multiple similar traits: proteinuria, arterial hypertension, persistent elevated BUN, edemas, and thrombocytopenia. There are cases when both conditions can be present at the same time [22]. The diagnosis of pre-eclampsia is more probable when the onset of proteinuria occurred after 20 weeks of gestation, in cases with isolated proteinuria without other alterations of urinalysis, in cases with seizures and

in patients with previous pre-eclampsia. Furthermore, many of the clinical signs of SLE are absent in pre-eclampsia, such as arthritis and cutaneous involvement; on the other hand, pre-eclampsia is more commonly associated with HELLP syndrome, increased serum levels of uric acid or decreased urinary calcium levels. Proteinuria with hematuria and urinary casts, decreased serum complement levels (C3 and C4), and positive anti-nuclear antibodies are more suggestive for lupus nephritis.

Presence of anti-dsDNA Ab in pregnant women with SLE is associated with renal dysfunction and an increased risk for premature delivery. SS-A and anti-Ro antibodies are present in 30% of SLE cases and in Sjögren syndrome [27]. These Ab are important because they are associated with certain subtypes of the disease (subacute cutaneous lupus) with some particular clinical manifestations (photosensitivity), and especially with neonatal lupus. SS-B or anti-La Ab (also identified in Sjögren syndrome) are always accompanied by the previously mentioned Ab: they can be identified in 15% of patients and are usually missing in those with nephropathy. Anti-Ro and anti-La Ab must be tested before and during pregnancy: if the results are positive, a fetal echocardiogram must be performed weekly during weeks 16–24 of gestation. Anti-cardiolipin Ab are associated with an increased risk of abortion or premature birth; therefore, they must be monitored carefully throughout the pregnancy [28].

Pregnancy monitoring

EULAR recommendations also include pregnancy monitoring. Women with SLE and/or APS should undergo supplementary fetal surveillance with Doppler ultrasonography and biometric parameters, particularly in the third trimester to screen for placental insufficiency and small for gestational age fetuses [2].

Fetal echocardiography is recommended in cases of suspected fetal dysrhythmia or myocarditis, especially in patients with positive anti-Ro/SSA and/or anti-La/SSB Ab, when supplementary fetal surveillance between week 16 and week 24 is recommended [2, 27].

Systemic lupus erythematous treatment during pregnancy

In 2016, EULAR published an extensive analysis of the data associated with the use of antirheumatic drugs during pregnancy and breastfeeding. In this paper, EULAR defined 4 overarching principles which should guide the therapy in such situations [29]. These principles are as follows:
– "Family planning should be addressed in each patient of reproductive age and adjustment of therapy considered before a planned pregnancy.

– Treatment of patients with rheumatic disease before/during pregnancy and lactation should aim to prevent or suppress disease activity in the mother and expose the fetus/child to no harm.
– The risk of drug therapy for the child should be weighed against the risk that untreated maternal disease represents for the patient and the fetus or child.
– The decision on drug therapy during pregnancy and lactation should be based on agreement between the internist/rheumatologist, gynecologist/obstetrician and the patient, and including other healthcare providers when appropriate".

Based on this analysis, EULAR divided the antirheumatic drugs into the following categories:
• Antirheumatic drugs proven compatible with pregnancy, which should be continued in pregnancy for maintenance of remission or treatment of a disease flare:
– hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus
• Drugs with teratogenic effect which should be withdrawn before pregnancy:
– methotrexate, mycophenolate mofetil and cyclophosphamide
• Drugs which can be considered in pregnancy if needed to control active disease symptoms
– NSAIDs should be restricted to the first and second trimesters
– corticosteroids in low doses
• Drugs which should be considered only in severe, refractory maternal disease during pregnancy:
– methylprednisolone pulses, intravenous immunoglobulin, or second or third trimester use of cyclophosphamide
• Drugs with insufficient documentation concerning use in pregnancy, which should be avoided until further evidence is available:
– leflunomide, selective COX-2 inhibitor, belimumab.

Generally, the types of medications used in SLE which can be considered during pregnancy are NSAIDs, corticosteroids, immunosuppressive agents, and biological agents [30].

NSAIDs are widely used in less severe cases, characterized mainly by serositis and cutaneous or articular manifestations. An increasing trend in the number of abortions has been reported in women who have used NSAIDs around the time of conception. Acetaminophen and aspirin are the most used NSAIDs during pregnancy. Since these two drugs cross the placenta, they can inhibit prostaglandin synthesis and are occasionally associated with premature closure of the ductus arteriosus and fetal pulmonary hypertension. Therefore, aspirin

and other NSAIDs should be used in lower doses than usual and should be avoided during the last trimester. However, lately, it is recommended that low doses of aspirin should be administered throughout the pregnancy because it can have positive effects for the mother by preventing arterial hypertension and pre-eclampsia [31]. Many studies have proven that aspirin has no teratogenic effects. In high doses, it can cause prolonged labor, peripartum anemia and neonatal hemorrhage. Because of the limited data available so far about the use of COX-2 specific NSAIDs, it is recommended to avoid their use during pregnancy.

Corticosteroids are the main therapy for pregnant women with SLE, in severe cases, with renal or neurological involvement, where high doses (1–1.5 mg/kgc/day) or pulse-therapy with methyl-prednisolone may be needed. Prophylaxis with prednisone is not necessary if the patient is in remission. The risk of cortico-adrenal insufficiency caused by the suppression of the hypothalamic-pituitary-adrenal axis in the fetus is relatively low, because most corticosteroids are metabolized by specific enzymes from the placenta into inactive products; therefore, the fetal levels reach only 10% of the maternal plasmatic levels. Only the fluorinated corticosteroids (e.g. dexamethasone, betamethasone) can cross the placenta and end up in the fetal blood stream. Hence, these drugs should be chosen if the patient to be treated is the fetus (e.g. in cases of atrioventricular block). Doses up to 20 mg/day of prednisone are considered to be safe. Methylprednisolone can also be considered during pregnancy, because the rate of its placental transfer is similar to prednisone and it has a similar rate of placental transfer [32].

Pregnant patients receiving corticotherapy should be monitored regularly, because they may have a higher rate of pre-eclampsia, gestational diabetes, hypertension, premature rupture of membranes, fetal growth retardation and infections [3]. No cases of congenital malformations have been reported in exposed fetuses, except very rare cases of cleft lip [10]. Supplemental cortisone should be administered before delivery in patients who have received chronic corticotherapy, in order to prevent an Addisonian crisis during labor and delivery. After birth, the tapering of cortisone should be performed with caution, because of the high risk of disease flare.

Azathioprine is the only immunosuppressive agent allowed during pregnancy, in daily doses below 2 mg/kgc [32]. This treatment should be reserved for severe cases, where corticotherapy was ineffective or contraindicated [10]. This drug crosses the placenta and is transformed into an inactive metabolite, thiouric acid. Therefore, azathioprine has minimal effects on the fetus, although it

can cause fetal growth restriction, prematurity, transient neonatal immunosuppression, leukopenia or pancytopenia, and ovarian follicle disorders in female neonates, with a later impact on fertility. There is no increased rate of spontaneous abortion in patients treated with azathioprine.

Hydroxychloroquine is safe during pregnancy, as it is not associated with an increased rate of congenital malformations [10]. However, isolated cases of ocular (retinal pigment deposits) and auditory abnormalities, mental retardation and spontaneous abortions have been reported. Continuation of hydroxychloroquine treatment if the patient became pregnant is widely accepted, even though the disease might be in remission. Moreover, withdrawal of hydroxychloroquine is considered a risk factor for pregnancy [12]. HCQ may reduce the odds of CHB occurrence in fetuses exposed to maternal anti-Ro/SSA Ab, especially in mothers who have already had a child with congenital heart block [2].

Other immunosuppressive drugs, such as cyclophosphamide, mycophenolate mofetil, methotrexate, chlorambucil, and cyclosporine, may cause fetal abnormalities and are contraindicated in pregnant women.

Biological agents: The only biological agent approved currently for SLE treatment is belimumab (humanized monoclonal Ab anti-BLyS/BAFF, which inhibits B-lymphocyte activation). Experimental studies performed in monkeys showed that belimumab has no teratogenic effects and does not cause other adverse events, although it crosses the placenta and may cause a decrease in the count of B-lymphocytes in babies. Because there are no data available about the safety in humans, belimumab is currently contraindicated for pregnant women with SLE [10].

Research is currently underway to identify the best treatment for the pregnant patient with APS. Lately, corticotherapy has been replaced by a form of anticoagulant or antiplatelet therapy [19]. Current discussions regard the use of aspirin, heparin, or both. Administration of low doses of aspirin has decreased the rate of abortion in patients with APS. However, aspirin is not sufficient for those with previous thrombo-embolism or pre-eclampsia; in such cases, it is recommended to use in addition an anticoagulant agent, e.g. low molecular weight heparins (LMWH). Still, the ability of LMWH to prevent recurrent abortions in patients with previous miscarriages remains to be proven [22]. Even in patients with thrombophilia, there is much debate around the positive effect of LMWH on the pregnancy's outcome. Oral anticoagulant agents cannot be used because they can impair the development of the fetus, especially in weeks 6–12 of gestation. Therefore, women who were receiving oral anticoagulants before pregnancy must be switched to subcutaneous heparin.

The most difficult aspects of lupus therapy during pregnancy are related to the treatment of disease flares; usually, in such circumstances, a multidisciplinary team including a gynecologist, rheumatologist, and neonatologist must be involved.

Breastfeeding in systemic lupus erythematous

Traditionally, breastfeeding has been considered a trigger for SLE flares. However, recent data have shown that breastfeeding was not associated with an increase of the disease activity in patients with a reduced perinatal level of disease activity, without pregnancy-related complications and with an at-term delivery [33]. Most drugs can be identified in very small concentrations in the maternal milk.

EULAR's recommendations in relation to breastfeeding are as follows [29]:
- drugs compatible with breast feeding which can be considered for continuation during lactation:
  – hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, cyclosporine, tacrolimus, prednisone, immunoglobulin, non-selective NSAIDs and celecoxib. Maternal milk contains only 5–20% of the prednisone dose administered to the mother, and this concentration has no effects on the infant. If the prednisone dose exceeds 20 mg, breastfeeding should be delayed at least 4 hours after the intake of the drug,
- drugs with limited data on breast feeding which should be avoided:
  – methotrexate, mycophenolate mofetil, cyclophosphamide, leflunomide, other COX-2 selective NSAIDs, except celecoxib,
- drugs with very little data on breast feeding which should be avoided during lactation and can be used only if other therapy cannot control the disease:
  – belimumab.

How appropriate breastfeeding is should be carefully considered for each case in an individualized manner, considering the disease activity, the visceral involvement and the treatment received by the patient.

* * *

In summary, important advances have been made in the last few years with regards to understanding the pathogenesis of pregnancy in patients with SLE; therefore, the therapeutic management of these patients has been updated. The therapeutic progress led to an improvement in maternal and fetal prognosis, which is now similar to healthy pregnant women in certain SLE patients. However, planning the pregnancy is essential for the best maternal (no SLE flares) and fetal (birth of a healthy baby) outcomes. Planning should take into account the individual risk factors for the mother and the baby and should be followed by careful clinical, biological and therapeutic monitoring, before and during pregnancy and in the perinatal period, performed by an experienced multidisciplinary team.

References

1. Bălănescu A, Parvu M. Lupusul eritematos şi sarcina. In: Ginecologie, ed. Tratat de Chirurgie, Obstetrică si Ginecologie. Academiei Române, Bucuresti 2014; 789-801.
2. Andreoli L, Bertsias KG, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 2017; 76: 476-485.
3. Østensen M, Andreoli L, Brucatoc A, et al. State of the art: Reproduction and pregnancy in rheumatic diseses. Autoimmun Rev 2015; 14: 376-386.
4. Ruiz-Irastorza G, Khamashta MA. Lupus and pregnancy: integrating clues from the bench and bedside. Eur J Clin Invest 2011; 41: 672-678.
5. Clowse MEB, Chakravarty E, Costenbader KH, et al. The effects of infertility, pregnancy loss, and patient concerns on family size ofwomenwith rheumatoid arthritis and systemic lupus erythematosus. . Arthritis Care Res (Hoboken) 2012; 64: 668-674.
6. Carp HJ, Selmi C, Shoenfeld Y. The autoimmune bases of infertility and pregnancy loss. J Autoimmun 2012; 38: 266-274.
7. Jawaheer D, Zhu JL, Nohr EA, Olsen J. Time to pregnancy among women with rheumatoid arthritis. Arthritis Rheum 2011; 63: 1517-1521.
8. Singh AG, Chowdhary VR. Pregnancy-related issues in women with systemic lupus erythematosus. Int J Rheum Dis 2015; 18: 172-181.
9. Brouwer J, Hazes JM, Laven JS, RJ. D. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Ann Rheum Dis 2015; 74: 1836-1841.
10. Baldwin C, Avina-Zubieta A, Rai SK, et al. Disease-modifying anti-rheumatic drug use in pregnant women with rheumatic diseases: a systematic review of the risk of congenital malformations. Clin Exp Rheumatol 2016; 34: 172-183.
11. Dvorkina O, Ginzler EM. Clinical features of systemic lupus erythematosus. In: Hochberg M, Silman AK, Smolen J, et al. (eds.). Rheumatology. Elsevier Mosby, St Louis 2015; 1033-1044.
12. Schreiber K. Pregnancies in women with systemic lupus erythematosus and antiphospholipid antibodies. Lupus 2016; 25: 343-345.
13. de Jesus RG, Mendoza-Pinto C, Ramires de Jesus N, et al. Understanding and managing pregnancy in patients with lupus. Autoimmune Dis 2015; 2015: 943490.
14. Østensen M, Cetin I. Autoimmune connective tissue diseases. Best Pract Res Clin Obstet Gynaecol 2015; 29: 658-670.

15. Pernis A. Th17 cells in rheumatoid arthritis and systemic lupus erythematosus. J Inter Med 2009; 265: 644-652.

16. Salker MS, Nautiyal J, Steel JH, et al. Disordered IL-33/ST2 activation in decidualizing stromal cells prolongs uterine receptivity in women with recurrent pregnancy loss. PLoS One 2012; 7: e52252.

17. Salmon J, Pricop L, D'Agati V.Immunopathology of systemic lupus erythematosus. In: Hochberg M, Silman AK, Smolen J, et al. (eds.). Rheumatology. 6th ed. Elsevier Mosby, St Louis 2015; 1052-1067.

18. Kim MY, Buyon JP, Guerra MS, et al. Angiogenic factor imbalance early in pregnancy predicts adverse outcomes in patients with lupus and antiphospholipid antibodies: results of the PROMISSE study. Am J Obstet Gynecol 2016; 214: 1-14.

19. Khamashta M, Amigo MC. Antiphospholipid syndrome: overview of pathogenesis, diagnosis, and management. In: Hochberg M, Silman AK, Smolen J, et al. (eds.). Rheumatology. 6th ed. Elsevier Mosby, St Louis 2015; 1144-1145.

20. Ruffatti A, Tonello M, Visentin M, et al. Risk factors for pregnancy failure in patients with anti-phospholipid syndrome treated with conventional therapies: a multicentre, case-control study. Rheumatology (Oxford) 2011; 50: 1684-1689.

21. Bălănescu A. Bolile reumatice si sarcina. In: Vladareanu R (ed.). Afectiunile medicale asociate sarcinii. InfoMedica, Bucureşti 1999: 337-485.

22. Soh MC, Nelson-Piercy C. High-risk pregnancy and the rheumatologist. Rheumatology (Oxford) 2015; 54: 572-587.

23. Kavanaugh A, Cush JJ. Pregnancy: data, outcomes, and treatment paradigms. J Rheumatology (Oxford) 2015; 42: 1357-1358.

24. Clowse M, Wallace D, Weisman M, et al. Predictorsof preterm birth in patients with mild systemic lupus erythematosus. Ann Rheum Dis 2013; 72: 1536-1539.

25. Jakobsen IM, Helmig RB, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990–2010. Scand J Rheumatol 2015; 44: 377-384.

26. Kwok L, Tam L, Zhu T, et al. Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. Lupus 2011; 20: 829-836.

27. Chaudhary P, Clowse M. Systemic lupus erythematosus in the pregnant patient and neonatal lupus. In: Hochberg M, Silman AK, Smolen J, et al. (eds.). Rheumatology. 6th ed. Elsevier Mosby, St Louis 2015; 1127-1130.

28. Žigon P, Perdan Pirkmajer K, Tomšič M, et al. Anti-phosphatidylserine/prothrombin antibodies are associated with adverse pregnancy outcomes. J Immunol Res 2015; 2015: 975704.

29. Götestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis 2016; 75: 795-810.

30. Kavanaugh A, Cush JJ, Ahmed MS, et al. Proceedings from the American College of Rheumatology Reproductive Health Summit: the management of fertility, pregnancy, and lactation in women with autoimmune and systemic inflammatory diseases. Arthritis Care Res 2015; 67: 313-325.

31. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding – Part II: Analgesics and other drugs used in rheumatology practice. Rheumatology (Oxford) 2016; 55: 1698-1702.

32. Flint J, Panchal S, Hurrell A, et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding – Part I: Standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. Rheumatology (Oxford) 2016; 55: 1693-1697.

33. Noviani M, Wasserman S, Clowse ME. Breastfeeding in mothers with systemic lupus erythematosus. Lupus 2016; 25: 973-979.