INTRODUCTION

It is a well-known fact that rheumatic disease (RD) has been associated with an increased risk of developing complications during pregnancy. RD has limited spread, and therefore their effect on the course of pregnancy has been studied extensively in the population of women with the most common diseases in this group: systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Other systemic connective tissue disorders (SCTD) also increase the risk of complications in pregnancy, especially when disease activity is high, antibodies are detected, or organ complications occur.

Retrospective data have shown that pregnancy complications such as hypertension during pregnancy, preeclampsia, fetal growth restriction and premature delivery were observed significantly more frequently in patients with RA than in healthy pregnant women. Moreover, these pregnancies require more frequent Cesarean delivery [1-3]. A meta-analysis of 2001-2016 studies including 3395 SLE patients demonstrated almost double the relative risk increase for hypertension during pregnancy and preeclampsia, more than three times the risk for premature delivery and more than four times the risk of child growth retardation [4].

Pregnancy is a condition characterized by major physiological cardiovascular structural and hemodynamic changes such as increased cardiac output, stroke volume, increased LV size and mass, while peripheral vascular resistance is decreased. These mechanisms contribute to the adaptation of the circulatory system of the pregnant woman. These changes have a different effect on the RD activity. Patients with RD may present a challenge during pregnancy as disease exacerbation may be incorrectly interpreted as pregnancy complications or physiological changes. This is because some symptoms of RD may overlap with normal physiological changes during pregnancy. The distinction between these different processes is very important. Therefore, pregnancy in a patient diagnosed with SCTD is a condition that requires close cooperation between rheumatologists and gynecologists for a normal pregnancy and reduced risk of complications [5].

MODERN GUIDELINES FOR PREGNANCY AND RHEUMATIC DISEASES MANAGEMENT

Fertility and contraception

Studies have shown that RD does not negatively affect fertility [6, 7, 8]. Women with RD can use most types of birth control without major concerns about side effects. For example, an intrauterine device such as a hormone-releasing IUD (with low risks of infection) and progesterone-based therapy
methods are effective and safe options for long-term contraception to be used [9, 10]. However, the discussion of a possible pregnancy in RD patients is very important because women taking teratogenic medicines such as cyclophosphamide, methotrexate, leflunomide, and mycophenolate mofetil require effective contraception to prevent pregnancy. In addition, women with RD should be informed that in case of emergency contraception, the use of progesterone-only tablets is safe and effective when taken within 72 hours after unprotected intercourse.

The appropriate time interval for conception

For patients who have SCTD, the proper conception time is of crucial importance [11]. This should be a period of low disease activity achieved through medical therapy, which in turn can be safely continued during pregnancy [12]. In general, a six-month interval for maintaining the disease in remission can be assumed to be a sufficient period after which conception can be carried out [13]. For this reason, the discussion of pregnancy in women with RD should be started before conception with appropriate risk stratification and pregnancy planning [14]. Patients with significant organ damage should be consulted about the relevant risks prior to conception. A further step shall include an assessment of the organ dysfunction associated with RD. If the woman has a history of organ damage (even if there is temporary normalization of organ function), this fact significantly increases the risk of complications for both the mother and the fetus [15]. In cases of pulmonary hypertension, interstitial lung lesions, heart failure, renal failure or hypertension during a previous pregnancy, a multidisciplinary group of specialists should decide on pregnancy planning due to the increased risk.

Specifics of the RD control pharmacotherapy

One of the main features in treating patients with pregnancy and RD is specific pharmacotherapy. Maternal disease control during pregnancy is associated with successful delivery and lower maternal and fetal complications risk. An important element of the preparation is the correct analysis of the medicines used by the patient and the possibility of continuing treatment during pregnancy. For example, it is essential to advise those women taking medicines such as methotrexate and mycophenolate mofetil that these medicines are not safe during pregnancy and that the use of reliable contraception in these cases is of great importance. Modification of medication therapy is also required in both patients planning pregnancy and women who are already pregnant. The objectives of pharmacotherapy are to suppress the activity of the current RD and to ensure the possibility of using medication that is safe and compatible with normal embryonic and fetal development [16, 17, 18, 19]. Discontinuation of therapy used before conception may induce an exacerbation of RD, resulting in pregnancy complications. On the other hand, inappropriate use of teratogenic medicines would cause irreversible damage to the developing fetus.

Data indicate that discontinuing hydroxychloroquine in therapy in patients with SLE is a significant risk factor for underlying disease exacerbation and adverse pregnancy outcomes [20, 21, 22]. Therefore, all pregnant lupus patients should receive hydroxychloroquine unless it is contraindicated. Medicines to control the disease with a known teratogenic effect, which should be discontinued before pregnancy, are methotrexate – three months; cyclophosphamide $ three months; mycophenolate mofetil – six weeks [23, 24, 25]. It is also recommended to stop taking medicines whose effects on pregnancy have not been sufficiently studied at least one month before the planned pregnancy. These include target synthetic disease-modifying anti-rheumatic drugs [23]. In the case of the use of biological medicines, their ability to penetrate the fetal circulation is different. Therefore, only some of them have been approved for use during pregnancy [26]. Nevertheless, the continuation of some TNF inhibitors during pregnancy is acceptable, and the recommended time for their discontinuation prior to scheduled delivery depends on the given medicine's half-life. This is done to prevent the medicine from being available in the child’s body during birth, as the drug can be a risk factor for infections [27].

Assessment of antibody status

Another important aspect to be noted in pregnancy planning is assessing the presence of anti-SSA and anti-SSB antibodies. Anti-Sjogren syndrome-associated antigen-A antibodies (anti-SSA)/RO and anti-SSB/LA antibodies can be detected not only in Sjogren patients but also in other SCDT patients [28]. These antibodies actively penetrate the placental barrier at approximately 16 weeks of gestational age (g.w.), which may cause fetal atrioventricular (AV) block or neonatal lupus [29]. In most cases, a heart block develops between 18 and 24 gestation weeks. The risk of complete AV block in the fetal heart with an SSA or SSB-positive mother is 2%, but it is increased to 18% if the unit has already occurred in a previous pregnancy [30]. The complete AV block in the fetus’s heart is the most dangerous complication that almost always requires cardiostim-
ulation in the newborn due to irreversible changes in the electrical properties of the heart's drive line system.

Determining the anti-SSA or anti-SSB status of the mother at the planning of the pregnancy or its early stages allows for accurate monitoring – the ultrasound assessment of atrioventricular conduction in the fetus's heart. In addition, steroid therapy penetrating the placental barrier (dexamethasone, betamethasone) should be administered early in cases where AV block is detected [31]. However, the effectiveness of this treatment has not been clearly demonstrated.

The use of hydroxychloroquine has been associated with a proven reduction in the incidence of atrioventricular block in fetuses of anti-SSA-positive and anti-SSB-positive mothers, as well as with a reduced incidence of this complication in subsequent pregnancies [32, 33, 34]. The skin, hematological and liver manifestations of neonatal lupus generally resolve within six to nine months of life when maternal antibodies stop circulating in the child [35].

Patients with SLE, a history of recurrent spontaneous abortion or other severe pregnancy complications should be evaluated for the presence of antiphospholipid antibodies (aPL) [36]. Low doses of aspirin are recommended for women with aPL to reduce the risk of preeclampsia [37]. After becoming pregnant, patients with a prior history of thrombotic antiphospholipid syndrome (APS) require therapeutic/prophylactic use of low molecular weight heparin (LMH) or unfractionated heparin, depending on their risk stratification [38, 39]. It is important to note that the administration of NHS for the prevention of thromboembolism also depends on the presence of risk factors for venous thromboses, such as BMI>30, immobilization, chronic cardiovascular or pulmonary diseases, varicose veins, etc.

**Obstetric anamnesis**

An essential element in preparation for pregnancy is a detailed analysis of the obstetric anamnesis of a woman with SCTD. The patient should also be informed that proper preparation increases the chances of a successful pregnancy. The following factors should be considered:

- Previous pregnancy failures that meet one of the clinical criteria for APS require confirmation of this diagnosis by laboratory testing before the patient becomes pregnant again. For this reason, it is appropriate to test the woman for the aPL [40].
- The presence of anti-cardiolipin antibodies doubles the risk of venous thrombosis in patients with systemic lupus. The risk is six times higher for women with positive results from the lupus anticoagulant test compared to patients with lupus without these antibodies [41].
- In patients with APS, anticoagulant prophylaxis with LMH is recommended throughout pregnancy and the post-natal period.
- As regards the case of anti-SSA/anti-SSB antibodies, it is always necessary to ask these patients about the occurrence of atrioventricular block or neonatal lupus in their children.

**Pregnancy monitoring**

The current guidelines for monitoring pregnant women with SCTD recommend that the monitoring shall be carried out by a multidisciplinary team including a rheumatologist, obstetrician-gynecologist and, depending on the organ involvement, specialists from other fields of medicine. The systematic monitoring of disease activity markers conducted by the rheumatologist enables early detection of exacerbations and the potential for modification of pharmacotherapy. The tracking of each patient should be individualized according to the presence of relevant risk factors determined prior to conception. In addition to the obstetric and gynecological examination and blood pressure measurements performed at each visit, laboratory tests should be performed to assess renal function (creatinine, urine analysis, urine protein present), liver function (ASAT, ALAT) and complete blood count. If arterial hypertension occurs, it should be controlled regularly by the 24 hours Holter, monitoring of the blood pressure and/or home blood pressure measurements to optimize antihypertensive therapy.

All pregnant patients with SCTD are at high risk of developing preeclampsia. This is particularly true in the case of lupus erythematosus. Therefore, the precautionary use of low doses of acetylsalicylic acid (≤ 150 mg) [13, 42] is recommended. The recommended time for starting prophylactic therapy is in the 12-16 gestation week. Factors further increasing the risk of preeclampsia in lupus patients included active disease six months before conception, lupus nephritis, hypertension, antiphospholipid antibody presence, low complement component levels and thrombocytopenia [43].

Non-invasive arterial wine examination using Doppler ultrasound is an important method both in the assessment of fetal and placental circulation as well as in the prediction of fetal status and pregnancy outcome. The placental vascular impedance is usually expressed by pulsatility index (PI), resistance index
and systolic/diastolic relationship and UIA. It is well known that the doppler ultrasound is an invaluable tool for monitoring high-risk pregnancies. Doppler imaging allows non-invasive assessment of uterine-placental circulation. The clinical value of doppler velocimetry of the uterine artery (UIA Doppler is important in predicting adverse outcomes in women at high risk for the development of preeclampsia. UIA Doppler is a method recommended to be used during the second trimester. Abnormal doppler ultrasound between 23 and 25 gestation weeks is associated with a decreased venous volume of umbilical blood flow, and it is an indicator of reduced placental perfusion. Such a result is a predictor of hypertension during pregnancy and the development of preeclampsia [44].

Specific conditions
The distinction between preeclampsia and lupus nephritis presents a significant challenge in the follow-up of patients with SLE. This is due to the fact that in both cases, the clinical expression may include proteinuria, edema, impaired renal function, hypertension, and thrombocytopenia. Lupus nephritis is characterized by reduced concentrations of complement components C3 and C4, increased anti-dsDNA antibody titers, pathological urine sediment and other dermatological, joint and hematological symptoms of disease flare. There is evidence that in preeclampsia C3 and C4 components of the complement system are usually increased [45]. In cases where both conditions cannot be clinically differentiated, renal biopsy may be necessary. In severe preeclampsia and life-threatening symptoms for the mother and fetus, the only effective solution is the premature birth of the child.

For patients with APS, the risk of thromboembolism during pregnancy is elevated and therefore, anticoagulant prophylaxis with LMH is recommended [46]. Such pregnant patients, as well as women with systemic lupus, should take anti-platelet therapy with low doses of aspirin.

For patients who are positive for anti-SSA and anti-SSB antibodies, foetal ultrasound of atrioventricular conduction time should be monitored. The flow time can be measured in the M-mode ultrasound imaging, pulse Doppler and tissue Doppler [47]. The American Cardiac Association recommended the initiation of foetal monitoring per patient positive for anti-SSA or anti-SSB antibodies in 16 gestation week. Measurements must be carried out weekly until the 24th gestation week.

Post-natal monitoring
During the post-natal period, the mother's body undergoes substantial hormone and physiological changes again until it recovers from birth and adapts to breastfeeding. This period is further complicated by some stressful situations for the mother, such as the reduction in sleep time, which inevitably comes with caring for the baby. All these factors may contribute to increasing the risk of post-natal exacerbation of RD. Therefore, a rapid re-evaluation of therapy is necessary to minimize this risk.

The 2016 European League Against Rheumatism (EULAR) consensus recommended using medicines during the post-natal period [48]. The American College of Rheumatology (ACR) guidelines from 2020 include a special section on the use of medications after birth and during breastfeeding, highlighting specific therapeutic options that can be safe for nursing women while optimizing disease control [38].

Highlights
• Prior to pregnancy, the woman should be informed about potential complications, the control of the RD activity, screening for hypertension and renal impairment, switching off pulmonary hypertension and modifying therapy.
• During pregnancy, it is essential to monitor all aspects of disease activity such as renal impairment as well as possible pregnancy complications such as intrauterine limitation of fetal growth, thromboembolic disease and preeclampsia, especially in patients with SLE, APS, vasculitis and systemic sclerosis.
• After pregnancy, the mother should be consulted on specific post-natal problems, breastfeeding and contraception. In addition, possible post-natal exacerbations of RD should be monitored and managed as they often occur during this period.

Conclusion
Pregnant women with rheumatic diseases are a high-risk population with potentially adverse consequences for the fetus and mother. Rheumatic diseases during pregnancy require early intervention because changes in immune system function induced by pregnancy may affect the underlying disease's activity. Active monitoring, regular reviews, maintenance of healthy weight, and medication shown can prevent pregnancy complications. In addition, interdisciplinary monitoring performed by obstetrician-gynecologist and rheumatologist and patient's monitoring before, during and after pregnancy significantly reduces the risk of developing short- and long-term mother and fetal damage.
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