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VIA MEDICA

Polish Society of Nephrology Working Group — management of pregnant women with chronic kidney disease

ABSTRACT

This report presents the diagnostic and therapeutic management of pregnant women with chronic kidney disease. The progression of primary and secondary nephropathies, acute kidney injury during pregnancy, immunosuppressive treatment, hypertension treatment, and management in genetically-determined diseases were discussed. Pregnancy management in kidney transplant recipients was presented. The diagnosis and treatment of urinary tract infections during pregnancy were described.

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Key words: pregnancy, chronic kidney disease, primary and secondary nephropathy, immunosuppressive drugs, hypertension, urinary tract infections, renal transplantation, genetic disorders of the kidney, acute kidney injury

INTRODUCTION

Magdalena Durlik

URINARY TRACT ALTERATIONS IN THE COURSE OF PREGNANCY

Significant hemodynamic changes occur during a normal pregnancy. The increase in the circulating blood volume, decrease in systemic vascular resistance and increase in heart ejection occur. The increase in the concentration of vasodilator substances (nitrogen monoxide, relaxin) and relative resistance towards vasoconstrictor substances (angiotensin II) is observed. Blood pressure is decreased — usually, the lover values are observed in the 20th week of pregnancy. Hence, mild/average hypertension in the early pregnancy may be hidden by physiological changes. Glomerular filtration increases by 50% (hyperfiltration) and serum creatinine level decreases (0.4–0.6 mg/dL is considered a normal range). These physiological changes may hide the second/third stage of chronic kidney disease (CKD) in the early pregnancy. Evaluation of renal function by means of creatinine clearance calculated on the basis of 24-hour urine collection is recommended. The formula for estimated glomerular filtration rate (eGFR) should not be used (MDRD, *Modification of Diet in Renal Disease*; CKD-EPI, *Chronic Kidney Disease Epidemiology Collaboration*). Smooth muscles relaxation (influenced by progesterone) and mechanical pressure of the growing uterus may cause physiological hydronephrosis. The excretion of protein with urine in a normal pregnancy increases from 60–90 mg/d. to 180–250 mg/d. The assumed maximum value of normal proteinuria is 300 mg/d. The increase in proteinuria is caused by hyperfiltration, but it may also be connected with alterations in permeability of the glomerular capillary membrane. In some observations, tubular proteinuria was indicated, resulting from an increase in the concentration of retinol-binding protein. The measurement of urine protein to creatinine ratio (UPCR) is recommended during pregnancy as screening. If the UPCR values are increased, the measurement of proteinuria in 24-hour urine collection is recommended. Proteinuria above 500 mg/d occurring before the 20th week

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of pregnancy indicates a renal disease present before the pregnancy. It may be accompanied by active urine sediment, hypertension, worsening of kidney function, risk of pre-eclampsia (30%), especially if hypertension occurs and proteinuria and hypertension increase in the third trimester. Nephrotic syndrome developing during pregnancy, even with normal blood pressure and preserved kidney function, is a risk factor for complications for the mother and the fetus. Attention should be paid to the fact that 15% of pregnant women have isolated proteinuria defined as elevated UPCR without hypertension and renal disease [1, 2].

CHRONIC RENAL DISEASE

CKD leads to disorders of the hypothalamic-pituitary-ovarian axis, which results in menstrual disorders, infertility and sexual dysfunction. Despite these reproductive limitations, pregnancy may occur at any stage of CKD. In the case of CKD, the pregnancy should be planned and the woman should be under interdisciplinary specialist care [3].

Chronic renal disease occurs in 0.15–0.25% of pregnant women. Kidney disease influences the course of the pregnancy and the pregnancy influences the progression of kidney disease. Hypertension, proteinuria and impairment of filter function of kidneys are independent risk factors for the mother and the fetus; their negative influence on the course of pregnancy is totalized. The worse the kidney function before the pregnancy, the higher the risk of increase in proteinuria, worsening the control over blood pressure, premature birth, intrauterine fetal growth restriction (IUGR), pre-eclampsia and worsening of kidney function. Piccoli et al. indicated that even the early stage of CKD influences the occurrence of complications for the mother and the fetus [4]. Meta-analysis of 23 observational studies among pregnant women in stages 1–4 of CKD showed a higher complication risk in pregnancies of women with CKD than women without CKD. Higher frequency of pre-eclampsia, premature birth, low birth weight, cesarean section and pregnancy failure [5]. The prognosis for the mother and the fetus in the case of CKD depends on [6]:

— stage of CKD;
— underlying kidney disease and its activity;
— co-occurrence of hypertension;
— occurrence of anemia;
— co-occurrence of urinary tract infections;
— treatment used;
— occurrence of complications typical of pregnancy.

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IMMUNOSUPPRESSIVE TREATMENT IN PREGNANT WOMEN

Magdalena Durlik

During pregnancy, the exposure to immunosuppressants is altered due to the increased volume of circulating blood, increased glomerular filtration and placental metabolism. Immunosuppressants pass the placenta; therefore, it is necessary to modify the schemes of therapy and drug doses to minimize the risk of fetal harm. Rules of classification of immunosuppressants into safety categories in pregnant women according to the Food and Drug Administration (*FDA*) are presented in Table 1.

In December 2014, the FDA published new recommendations that determined how the safety of using drugs in pregnant women should be considered and how the division into categories A, B, C, D, X was nullified. It was assumed that relying only on this classification and just following the affiliation to specific categories is insufficient. All available data concerning the possible effect on the pregnancy and the child should be analyzed [1].

Table 1. Classification of immunosuppressants used in pregnant women according to FDA

Category	Definition
A	Studies with the control group did not show the risk for a fetus in the first trimester and the possibility of fetal harm seems unlikely
B	Studies on animals do not indicate a risk for the fetus, but studies on humans with a control group were not conducted, or studies on animals showed adverse effects on the fetus, but studies on a group of women did not confirm it.
C	Studies on animals showed teratogenicity and lethal effects for the fetus, but studies with a control group of women were not conducted, or no adequate studies on neither animals nor humans were conducted
D	There is proof for an adverse effect of the drug on the fetus, but in some clinical situations, the potential benefits of its use exceed the risk (e.g., in life-threatening situations or in case of diseases for which other, safe treatment either cannot be used or us ineffective).
X	Studies conducted on animals and humans showed fetus abnormalities in the course of treatment with the particular drug, or there is proof for the adverse effect of the drug on the human fetus and the risk significantly exceeds the potential benefits of its use.

Table 2. Immunosuppressants — risk categories for the fetus

Immunosuppressant	FDA category
Drugs deemed safe	
Azathioprine	D
Cyclosporine	C
Tacrolimus	C
Glucocorticosteroids	B
Drugs not recommended in pregnancy	
Belatacept	C
Mycophenolic acids derivatives	D
mTOR inhibitors	
Sirolimus, everolimus	C
Cyclophosphamide	D
Methotrexate, leflunomide	X
Drugs used in induction and treatment of the rejection process	
Basiliximab	B
Polyclonal anti-thymocyte antibodies	C
Rituximab	C
Intravenous immunoglobulin (IVIg)	C
Eculizumab	C

Despite the changes introduced, FDA classification is still used in research papers. However, it should be remembered to become familiar with the threats connected with the use of the particular drug, which are listed in the summary of product characteristics.

Cyclosporine A or tacrolimus with or without glucocorticosteroids, as well as azathioprine, may be used as an immunosuppressive treatment in pregnant recipients. Mycophenolate mofetil, sodium mycophenolate, sirolimus and everolimus are not recommended. At least 6 weeks before getting pregnant, the mycophenolic acid and proliferation signals inhibitors (mTOR) should be discontinued.

IMMUNOSUPPRESSANTS

GLUCOCORTICOSTEROIDS

Glucocorticosteroids (GS) are used in many primary and secondary nephropathies as well as autoimmune diseases. Prednisolone, prednisone and methylprednisolone are most frequently used. GS inhibit the expression of genes of pro-inflammatory cytokines [interleukin IL-1, IL-2, IL-3, IL-6, tumor necrosis factor α *TNF-*α), interferon (IFN-y)]. They cause numerous adverse effects such as osteoporosis, aseptic necrosis of bones, decreased immunity to infections, cataract, diabetes, hyperlipidemia, hypertension, and mental disor-

ders. The use of GS during pregnancy is safe. These drugs go through the placenta, which metabolizes 90% of the mother's dose and, therefore, the fetus is protected against the GS. It is recommended that the dose of prednisone for pregnant women did not exceed 15 mg/d. Glucocorticosteroids may also be administered in large doses (pulses) if clinical indications occur. Occasionally, inhibition of the adrenal cortex development was observed in infants, especially when the mother received high doses of GS. Exposure to GS in breast milk amounts to 0.1% of the mother's dose. In the case of daily dosage not exceeding 20 mg, breastfeeding is safe [2, 3].

CALCINEURIN INHIBITORS (CNI) — CYCLOSPORINE A (CSA), TACROLIMUS

The mechanism of action of cyclosporine and tacrolimus, despite the differences in the chemical structure, is the same and consists in the inhibition of the serine-threonine phosphatase – calcineurin. Cyclosporine A is a cyclic peptide isolated from *Tolypocladium fungus*, while tacrolimus is a macrolide antibiotic isolated from *Streptomyces tsukubaensis,* inhibiting the calcineurin stronger than CsA. Calcineurin is a phosphatase dephosphorylating the nuclear factor of activated T-cells (*NFAT*), which activates gene promotors for many cytokines activating T-lymphocytes, among others IL-2, IL-4, IFN-γ, TNF-α. The inhibition of activation and clonal expansion of T-lymphocytes occurs. Classic tacrolimus of an immediate release is administered two times a day. Tacrolimus with the modified release (tacrolimus MR) and prolonged-release tacrolimus LCPT (Envarsus®) are available. The last two products, unlike the classic form of tacrolimus, are administered once a day. Both calcineurin inhibitors (CNI*)* are metabolized by cytochrome P450 3A (CYP3A) in the microsomal systems of the intestines and liver. Both drugs are also substrates of glycoprotein P. The metabolism in the intestines by means of glycoprotein P and CYP3A constitutes the so-called first-pass metabolism. The liver is the main place of metabolism of drugs, but the metabolism in the intestines constitutes as much as half of CNI transformations. Both drugs are mainly excreted with bile and, to a small extent, with urine. Therefore, there is no need to modify their doses in CKD patients. Calcineurin inhibitors are drugs with a narrow therapeutic index. They are also characterized by significant inter-and intra-individual variability. Hence the monitoring of their concentration in blood is obligatory. The monitoring of the trough level (C_0) right before the administration of the next dose is recommended. The interactions of CNI with many other drugs require monitoring of their concentrations in blood and foreseeing the potential consequences. Each drug that affects the activity of CYP3A, is a substrate of glycoprotein P and interferes with the drug which influences it, should be considered in the context of interaction with CNI. Food that influences the intestinal or hepatic CYP3A enzymes, fruit such as grapefruit, pomelo, carambola, spices such as turmeric and ginger as well as herbs such as St. John's wort should not be ingested. CNI may cause hyperkalemia, hypomagnesemia, hypocalcemia and hyperchloremic acidosis. These drugs are nephrotoxic, neurotoxic and diabetogenic. Hypertension and hyperlipidemia occur in the majority of patients more often in patients receiving CsA.

It is assumed that the use of CNI is safe for pregnant women. Calcineurin inhibitors cross the placenta to fetal circulation. It was proven that the concentration of tacrolimus in cord blood amounted to 70% of the mother's concentration. The lower concentration in the child is explained by active transport of tacrolimus from the fetus to the mother by placental glycoprotein P and the difference in morphology of the child's and mother's blood. Pharmacological research of the concentration of tacrolimus in the whole blood of pregnant women showed a decrease in the second trimester and the need to increase the dose of tacrolimus by 20–25% in order to maintain the therapeutic concentration of the drug in the blood. It is usually recommended to maintain the concentration of immunosuppressants in whole blood at least at the level equal to the level before the pregnancy. It should be remembered that tacrolimus binds with protein and red blood cells (85–95%). In pregnant recipient with anemia [red blood cells (*RBC*) < 3.5 mln/μL], hypoalbuminemia (< 3.0 g/dL) free (biologically active) tacrolimus concentration increases and so does the risk of toxicity (nephrotoxicity, infection, high blood pressure, pre-eclampsia, low birth mass). In patients with anemia and hypoalbuminemia, failure to adjust the dose means that the unchanged concentration of free tacrolimus is not maintained. The adjustment of the dose in order to maintain its therapeutic concentration may mean the doubling of the

concentration of free tacrolimus. In clinical practice, the determination of free or serum tacrolimus concentration is unavailable. The suggested management is to maintain the dose until the concentration lowers by more than 50% or below the minimum standard range. Then, the dose should be increased.

The increased frequency of congenital disabilities in children of mothers treated with CNI in comparison to the general population was not reported. However, tacrolimus may cause reversible nephrotoxicity and hyperkalemia in newborns. The concentration of the drug in the mother's milk is minimal (< 1% of the mothers' dose) [2–4].

AZATHIOPRINE

Azathioprine is an antimetabolite, a purine analog that builds into the cellular deoxyribonucleic acid (DNA), which results in the inhibition of purine nucleotides as well as the proliferation of lymphocytes and other bone marrow cells. The drug's concentration in blood does not have to be monitored. The drug is not excreted through the kidneys. The most common complication connected with the use of azathioprine is its myelotoxicity which may cause hepatitis and cholestasis. In the case of co-administration of azathioprine and allopurinol, the dose of azathioprine should be reduced by 50–75% or the drug should be discontinued to avoid severe bone marrow damage [2, 3].

Despite the qualification to the D category, azathioprine may be used in pregnant women. The drug's penetration through the placenta amounts to 50–90% of the mother's concentration. However, the fetus's liver does not show any activity of inosine pyrophosphorylase, an enzyme converting azathioprine to its active form, which is 6-mercaptopurine. The recommended dose of azathioprine should not exceed 2 mg/kg/d, the optimum is 1 mg/kg/d. Breastfeeding is safe; 1% of the mother's dose is reported in child.

MYCOPHENOLATE MOFETIL AND SODIUM SALT OF SODIUM MYCOPHENOLATE

Mycophenolate mofetil (MMF) and mycophenolate sodium (MPS) are prodrugs. The active component they release is the mycophenolic acid (MPA). MPA is a reversible inhibitor of the inosine-5'-monophosphate dehydrogenase enzyme (IMPDH). IMPDH is the crucial enzyme participating in the *de novo* synthesis of purines and catalyzing the production of new guazine nucleotide from inosine. The decrease in the formation of guanosine nucleotides by means of MPA constitutes a relatively selective anti-proliferation action concerning lymphocytes. To a larger extent than other cells, lymphocytes depend on *de novo* purine production and do not have an alternative path of guazine nucleotides synthesis. Therefore, a selective anti-metabolic action of the drug is observed. MPA inhibits the T- and B-lymphocytes. MPS is an enteral form of mycophenolic acid, while MMF absorption occurs in the stomach (with pH < 5.0). After the absorption, the agents are immediately hydrolyzed to the active molecule, mycophenolic acid, obtaining the maximum concentration in the blood within 1–2 hours. Subsequently, MPA undergoes glucuronidation to the inactive form of mycophenolic acid glucuronide (MPAG). Enterohepatic circulation and deglucuronidation of MPAG to MPA in the intestines with intestinal microbes may cause the second MPA peak after around 5–6 hours. The modification of drug doses in case of kidney damage is not necessary. The majority of adverse effects concern the digestive system, with diarrhea occurring in 30% of patients. Nausea, bloating, dyspepsia and vomiting are also observed. Symptoms of bone marrow damage (anemia, leucopenia, and thrombocytopenia) are also reported. However, MPA is not nephrotoxic, neurotoxic or hepatotoxic. Mycophenolates are not recommended in pregnancy. They are teratogenic in humans and cause miscarriages and congenital disabilities. In 45–49% of cases, exposure to mycophenolates in the mother's womb results in miscarriages, whereas in 23–27%, the exposure causes congenital disabilities. Before starting the treatment with MPA, obtaining a negative result of a pregnancy test is necessary. Mycophenolates should be discontinued at least 6 weeks before the conception [2, 5].

MTOR INHIBITORS — SIROLIMUS, EVEROLIMUS

The mTOR enzyme is a kinase regulating the process of cell division. Sirolimus and everolimus — mTOR kinase inhibitors — inhibit the progression of the cell cycle from G1 to S phase and, therefore, lower the cell proliferation dependent on the cytokines. Sirolimus is administered once a day and everolimus is administered twice a day. The strength of immunosuppression of mTOR inhibitors correlates with MPA derivatives. They show weaker immunosuppressive effects compared

with CNI. mTOR inhibitors inhibit angiogenesis, endothelial cell proliferation and show anti-cancer properties. They are metabolized by the system of microsomal enzymes, CYP3A, and show drug interactions similar to CNI. These are drugs with a narrow therapeutic index. The monitoring of their concentration in blood is necessary (C_0). They cause hypokalemia, hypomagnesemia, delayed wound healing as well as lymphorrhea, hypercholesterolemia, hypertriglyceridemia, peripheral edema, proteinuria, mouth ulceration, and reversible spermatogenesis disorder. mTOR inhibitors have a teratogenic potential

Mycophenolates and mTOR inhibitors should be discontinued while planning pregnancy. These drugs may be replaced by azathioprine.

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HYPERTENSION IN PREGNANT WOMEN WITH CHRONIC KIDNEY DISEASE

Marcin Adamczak

Taking into consideration the differences in pathophysiology and clinical picture, hypertension during pregnancy, like in the general population, in chronic kidney disease (CKD) patients is divided into two clinical conditions: chronic hypertension (that is occurring before the pregnancy or diagnosed before the 20th week of pregnancy) and hypertension disorders of the pregnancy (that is diagnosed after 20th week of pregnancy) [1, 2].

Chronic kidney disease increases the risk of hypertension in pregnant women [3]. Hypertension occurs in around 20–50% of pregnant women with CKD. The frequency increases with the stage of CKD [4]. Data concerning the different pathophysiology of hypertension in pregnant women with CKD were obtained in research conducted on animals as well as clinical studies, including small groups of pregnant women. They show that the leading cause of hypertension in pregnant women with CKD is the inability of damaged kidneys to physiologically adapt to the pregnancy, that is, to increase the glomerular filtration by 50%. This results in sodium retention in the organism as well as hypervolemia and, in consequence, an increase in blood pressure [5]. Moreover, it may be assumed that increased activity of the sympathetic nervous system and renin-angiotensin system participates in the pathogenesis of hypertension, similarly to CKD in women who are not pregnant.

The risk of pregnancy complications increases with the stage of CKD and increase in blood pressure. The prognosis for the fetus and the mother is also worse. The following occur more often in women with CKD and hypertension: miscarriage, pre-eclampsia, eclampsia and premature birth. Moreover, newborns are more often characterized by low birth mass (resulting from the delayed growth of the fetus, IUGR) and are characterized with the higher risk of hospitalizations in the intensive care units. Perinatal mortality is also higher [7, 8].

The definition of hypertension in pregnant women with CKD, like in the general population, is based on the office blood pressure measurement. The measurement should be done according to recommendations of the Polish Hypertension Society [1]. Hypertension is diagnosed when systolic blood pressure is ≥ 140 mm Hg and/or diastolic blood pressure is ≥ 90 mm Hg. Hypertension during pregnancy is described as mild (140–159/90–109 mm Hg) or severe (≥ 160/110 mm Hg) [1, 2, 9]. The diagnosis of mild hypertension should be confirmed with out-of-office blood pressure measurement (that is 24-hour ambulatory blood pressure monitoring [ABPM] or home measurements). If this is not available, the diagnosis should be confirmed during two independent visits. The diagnosis of hypertension has to be confirmed within 7 days in the first trimester and within 3 days in the second and third trimester, The same blood pressure values as in the general population should be used in the diagnosis of hyperten-

Chronic kidney disease increases the risk of hypertension in pregnant women

sion during pregnancy [2], that is the mean of 24-hour blood pressure measurements and average blood pressure in-home measurements ≥ 135 and/or ≥ 85 mm Hg or a mean of night measurements in 24-hour blood pressure measurement ≥ 120 and/or ≥ 70 mm Hg. In the case of measurements done in the office and at home, an automatic blood pressure monitor with proper recommendations is preferred. The list of recommended automatic blood pressure monitors for consulting rooms and home use is published on the web page http://bhsoc.org/bp-monitors/bp-monitors/. The correct size of the cuff is vital for the conect blood pressure measurements. If the perimeter of the middle part of the arm is larger than 33 cm, a large cuff should be used [1, 10]. Rigorous monitoring of blood pressure is necessary in pregnant CKD patients (home measurements — twice a day, that is in the morning and in the evening; in the morning on an empty stomach, before taking drugs; in the evening before a meal and taking the drugs). In pregnant women with CKD because of the abnormal diurnal BP profile (lack of nocturnal BP lowering), which is common in CKD, 24-hour BP recording should be preffered, if possible, both for the diagnosis of hypertension and for monitoring the effects of antihypertensive treatment.

Once hypertension is diagnosed, antihypertensive treatment should be given to every pregnant woman with CKD. BP targets in pregnant women with CKD are similar to those in pregnant women without CKD, i.e., pregnant women with hypertension and CKD should aim for a target diastolic pressure of 81–85 mm Hg [11–14]. This target diastolic blood pressure was established by the CHIPS (*Control of Hypertension in Pregnancy Study*) [11], the only randomized trial to evaluate the benefits of more or less intensive antihypertensive treatment during pregnancy. This study showed that more intensive reduction of diastolic blood pressure (to 81–85 mm Hg) was associated with a lower incidence of severe hypertension. The presence of severe hypertension, on the other hand, increases the rate of maternal and fetal complications. To date, there have been no studies evaluating the optimal systolic blood pressure range in pregnant women. The authors of the present opinion, similarly to the authors of the recently published joint recommendations of the Polish Society of Hypertension, the Polish Cardiac Society and the Polish Society of Gynecologists and Obstetricians (PTNT/PTK/PTGiP), stated that it is reasonable to consider systolic blood pressure values within the range of 110–139 mm Hg as the target values [2]. If treatment results in blood pressure values are below target (i.e., systolic blood pressure < 110 mm Hg or diastolic blood pressure ≤ 80 mm Hg), the intensity of antihypertensive therapy should be reduced, as too intensive reduction of blood pressure may impair placental blood flow and fetal well-being. If therapy results in blood pressure values are higher than the target (i.e., systolic blood pressure > 140 mm Hg or diastolic blood pressure > 85 mm Hg), intensification of antihypertensive treatment is recommended.

An emergency condition requiring referring a pregnant patient to a hospital is the persistence of arterial pressure ≥ 160/≥ 110 mm Hg (in several consecutive measurements within 15–30 minutes) [2, 14].

Non-pharmacological management in pregnant women with hypertension and CKD should consist on smoking and alcohol intake cessation [15]. However, there are no recommendations on the amount of salt consumed. It seems that in pregnant women with CKD, in contrast to the general population, no significant reduction in the dietary salt intake should be recommended.

The same principles should be used in the the selection of antihypertensive drugs in pregnant women with CKD as in pregnant women without renal disease [2]. Most of the studies evaluating the efficacy and safety of particular antihypertensive drugs during pregnancy were completed in the last decades of the last century. The drugs most commonly evaluated in these studies were methyldopa, labetalol, and nifedipine. Other antihypertensive drugs have been the subject of only a small number of studies, the results of which do not establish whether their use is safe in pregnant women. The above fact justifies the recommendation to prefer methyldopa, labetalol, and extended-release nifedipine over other antihypertensive drugs in pregnant women.

Methyldopa is a centrally-acting drug that reduces sympathetic nervous system activity (α_2-adrenergic receptor agonist in the central nervous system). Methyldopa has documented safety in terms of developmental assessment of prenatally exposed children at 7-year follow-up [16, 17]. Factors limiting its use include sedative effects, peripheral edema, dry mouth, sleep disturbances, and feelings of fatigue. Dose: 250 mg 2–3 times daily,

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up to a dose of 2 g/24h (maximum 3 g/d., orally) [18]. Methyldopa is excreted primarily by the kidney; the daily dose of the drug should be reduced in patients with impaired renal function. It is recommended to increase the interval between doses to 8 hours when eGFR is in the range of 60–89 mL/min/1.73 m^2, to 8–12 hours when eGFR is in the range of 30–59 mL/min/1.73 m^2, and to 12–25 hours when eGFR < 30 mL/min/1.73 m^2. Methyldopa is eliminated from the body during hemodialysis. Therefore, to prevent an increase in blood pressure after the hemodialysis procedure, a supplemental dose of 250 mg is recommended after the procedure.

Labetalol is a β- and α-adrenergic receptor antagonist (it has no intrinsic sympathomimetic activity and is not cardioselective). This drug has shown antihypertensive efficacy and is safe in pregnant women. It was used as the recommended first-line drug in the CHIPS trial [11, 19]. Dosage: 100 mg twice daily, up to 800 mg/d. (Maximum 1200 mg/d in 2–4 divided doses, orally). It should be emphasized that the use of this drug may be associated with a risk of maternal and fetal bradycardia and should not be administered in women with impaired left ventricular systolic function, second- or third-degree atrioventricular block, or asthma [18].

Nifedipine sustained-release-oral (*nifedipine*) is a calcium channel antagonist that is the first-line drug alongside methyldopa and labetalol due to its demonstrated safety in pregnant women. Note that administration of extended-release nifedipine together with magnesium sulfate may lead to excessive BP lowering [20]. Dosage: 30–120 mg/d orally in 2 divided doses. The most common side effects of this drug are: excessive lowering of blood pressure, headaches and dizziness, redness of the facial skin with a feeling of heat, and swelling of the lower extremities.

In the case when the monotherapy is ineffective, combination therapy with two and then with three mentioned-above drugs (that is, the combination of methyldopa, labetalol and nifedipine with extended-release) should be indicated. In the CHIPS study, combination therapy was administered to around 35% and 30% of women from study groups who underwent more and less intensive anti-hypertensive treatment, respectively.

Labetalol and nifedipine with the extended-release are available in Poland only after direct impact the request for targeted importation and following the instructions published by the Drug Policy Department of the Ministry of Health (http://www2.mz.gov.pl/wwwmz/index).

Emergency in which intensive anti-hypertension treatment is recommended is blood pressure persisting on the level ≥ 160/≥ 110 mm Hg. In such cases, antihypertensive treatment should be administered within 60 minutes [18]. Emergency antihypertensive therapy should be managed in a way that allows obtaining the initial decrease in blood pressure by 25%. Further intensive lowering of blood pressure to target values for intensive antihypertensive treatment < 160/110 mm Hg should be obtained within few hours [12]. Having obtained this blood pressure value, oral medication described above, recommended in chronic antihypertensive therapy in pregnant women, should be used. It should be underlined that a too quick decrease in blood pressure may cause severe complications in the mother and the fetus. Drugs recommended for pregnant women to treat emergency hypertension include labetalol (intravenous), nifedipine (oral), and hydralazine (intravenous).

In pregnant women with CKD, despite kidney disease, the use of nephroprotective drugs (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists and aldosterone receptor antagonists), which are recommended in non-pregnant women with CKD, is contraindicated.

The use of diuretics to lower blood pressure in pregnant women is not recommended due to the possibility of decreasing the amount of amniotic fluid and the occurrence of electrolyte imbalance in the fetus. Nevertheless, exceptionally in pregnant women with CKD (especially in advanced stages), indications for the use of loop diuretics may occur. The administration of loop diuretics may be considered in case of extensive edema, usually in the course of nephrotic syndrome [3]. It should be remembered that, firstly, pregnant women with CKD should be recommended to rest with their lower limbs elevated, as well as use of elastic stockings. Diuretics are absolutely contraindicated in pre-eclampsia when lower plasma volume is observed.

Apart from antihypertensive treatment, pregnant women with CKD and hypertension should start taking acetylsalicylic acid in the dose 100–150 mg/d before the 16th week of the pregnancy, as it decreases the risk of pre-eclampsia, premature birth, and intrauterine growth restriction (IUGR) [24].

In the case when the monotherapy is ineffective, combination therapy with two and then with three mentioned-above drugs (that is, the combination of methyldopa, labetalol and nifedipine with extended-release) should be indicated

Apart from antihypertensive treatment, pregnant women with CKD and hypertension should start taking acetylsalicylic acid in the dose 100–150 mg/d before the 16th week of the pregnancy

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PREGNANCY IN PRIMARY GLOMERULOPATHY

Ilona Kurnatowska

THE EPIDEMIOLOGY OF PRIMARY GLOMERULONEPHRITIS IN PREGNANCY AND THE INFLUENCE OF THE DISEASE ON THE COURSE OF PREGNANCY

There are little data concerning the epidemiology of primary glomerulonephritis in pregnant women [1]. This paper includes data concerning primary glomerulopathies occurring during the pregnancy: IgA nephropathy, focal segmental glomerulosclerosis (FSGS), minimal change and membranous nephropathy.

IgA nephropathy is the most frequent glomerular disease in young people and the most frequent glomerulonephritis in pregnant women

IGA NEPHROPATHY

IgA nephropathy is the most frequent glomerular disease in young people and the most frequent glomerulonephritis in pregnant women. Relatively the biggest amount of data concerning the influence of glomerulonephritis on the course of pregnancy concerns nephropathies. Hypertension complicates around 9–40% of pregnancies in patients with IgA nephropathies. The majority of the described pregnant women with this type of glomerulonephritis are characterized by good excretory activity of kidneys (1–3 stage of CKD). 70–100% of pregnancies end with the birth of a living child (12 publications, analyzing 10–136 pregnancies). The number of successful pregnancies increased after 2000. The average birth weight of babies amounts to 3.2 kg. The occurrence of pre-eclampsia complicates 25% of pregnancies. The recently published observational study in which the clinical course of IgA nephropathy of pregnant and non-pregnant women was compared showed that the pregnancy of 1–3 stage of CKD does not accelerate the course of the renal disease. However, pregnancies of these patients are connected with a higher risk of: miscarriage, premature birth, low birth weight and pre-eclampsia. The risk factors of complications occurrence as well as the possible worsening of the excretory function of the mother's kidneys are eGFR < 60 mL/min/1.73 m^2, proteinuria > 1 g/d. and the co-occurrence of hypertension. However, the risk of adverse events in pregnant women with IgA nephropathy is lower than in women with lupus nephritis or diabetes [2].

Minimal change is a rarely described nephropathy in pregnant women. It is manifested by nephrotic syndrome with low albumin concentration in plasma. It should be treated with glucocorticosteroids

The majority of IgA nephropathy patients do not require immunosuppressive treatment. Before the pregnancy, women usually receive angiotensin convertase inhibitors/angiotensin II receptor antagonism as nephroprotection, which should be discontinued right before getting pregnant or right after its confirmation. Glucocorticosteroids should be used during the pregnancy in the active form of the disease [3].

Membranous nephropathy during the pregnancy has a secondary nature

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

There are little data concerning glomerulopathy, including FSGS. Similarly to IgA nephropathy, the course of pregnancy and prognosis for the mother and the fetus depends mainly on the level of proteinuria, the excretory function of the kidneys and good blood pressure control [4]. In the observational study, which included 64 pregnant women with glomerulonephritis (patients with IgA nephropathy, patients with mesangial proliferative glomerulonephritis, patients with FSGS, patients with membranous nephropathy and with minimal change), the course of pregnancy and results were compared with 100 pregnancies of healthy women. The factor increasing the risk for the mother was proteinuria > 3.5 g/d, whose consequences include lowering of the albumin concentration in plasma, the occurrence of swelling, worse blood pressure control and propensity for thrombosis. Concurrently, complications include the worsening of blood flow through the placenta, hypoperfusion and IUGR. Proteinuria > 3.5 g/d. was also a risk for the fetus, similarly to hypertension (≥ 160/110 mm Hg) and increased concentration of uric acid (≥ 363 μmol/L) [4]. In the case of FSGS diagnosis, differential diagnosis of its secondary forms should also be conducted. Primary FSGS usually manifests by the occurrence of nephrotic syndrome, while secondary FSGS is most often manifested by subrenal proteinuria and deterioration of kidney function. In the treatment of FSGS in pregnant women, the use of glucocorticosteroids and/or CNI should be considered [3, 5].

MINIMAL CHANGE AND MEMBRANOUS NEPHROPATHY

Minimal change is a rarely described nephropathy in pregnant women. It is manifested by nephrotic syndrome with low albumin concentration in plasma. It should be treated with glucocorticosteroids. In case of recurrence, which may happen during the pregnancy, azathioprine or CNI may be used [3].

Membranous nephropathy during the pregnancy has a secondary nature. It occurs in

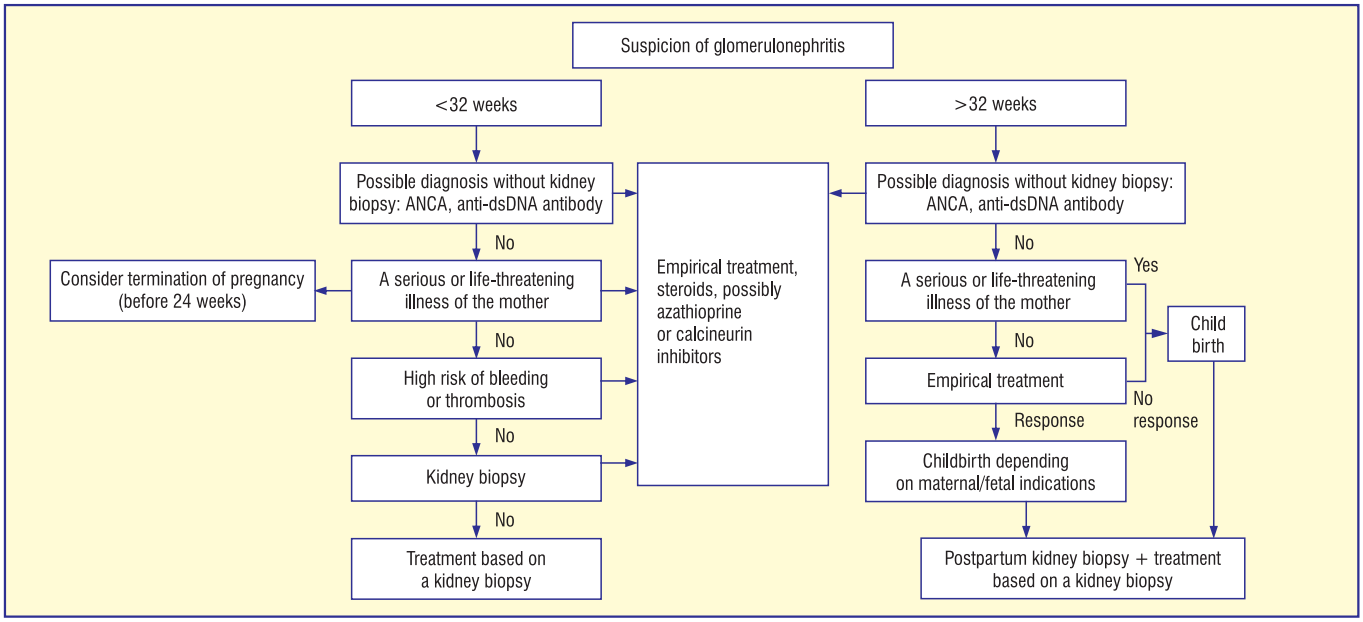

Figure 1. A suggested approach to diagnosis and management of glomerular disease in pregnancy

lupus erythematosus, may be a complication of misuse of non-steroidal anti-inflammatory drugs or biological treatment, an effect of viral hepatitis type B or C, syphilis or (less frequently in pregnant women) accompanying neoplasms. Drugs that may be prescribed to treat the primary membranous nephropathy in pregnant women include glucocorticosteroids and CNI. In the severe course of nephropathy, administration of rituximab may be considered [3].

In comparison to pregnancies of healthy women, the pregnancies of women with glomerulonephritis resulted more frequently in pre-eclampsia, miscarriage, premature birth and giving birth to a baby with lower birth weight, IUGR. Differences in the prognosis for the course of the pregnancy in relation to the type of glomerulonephritis were not observed [6].

PROTEINURIA DIAGNOSIS AND GLOMERULONEPHRITIS IN PREGNANT WOMEN

Proteinuria and worsening of kidney function are the main indicators of kidney damage in the course of glomerulonephritis. Its acceptable level during the pregnancy amounts to 300 mg/d due to physiological hyperfiltration. The following screening tests are recommended to diagnose proteinuria: protein to creatinine concentration in an accidental morning urine sample (UPCR) or albumin/creatinine ratio (ACR). The value of UPCR > 500 mg/g or ACR > 300 mg/g in a pregnant woman without diabetes is a risk factor for the occurrence of pre-eclampsia and premature birth. However, it may be incorrect in around 15% of pregnant women without the renal disease [7]. Each elevated UPCR/ACR result is a recommendation to evaluate the 24-hour excretion of proteins with urine. Isolated proteinuria may occur intermittently during the pregnancy and be treated as "pregnancy-induced proteinuria". It may precede pre-eclampsia or indicate primary or secondary disease of glomeruli. Proteinuria, even if isolated, indicates the risk of adverse results of pregnancies, including growth limitation and premature birth [8, 9]. Therefore, it is significant to determine whether the proteinuria is pregnancy-induced or caused by primary or secondary glomerular diseases, and also whether it is an indicator of pre-eclampsia.

Therefore, careful monitoring of proteinuria in the course of pregnancy is vital and its increasing levels are a challenge for the doctor. The influence of pregnancy on the progression of primary glomerulonephritis is not apparent. In early pregnancy, the increase in proteinuria require a diagnostic procedure, similar to a non-pregnant woman. There is no data concerning the usefulness of marking biomarkers, such as phospholipase A2 receptor antibodies (anti-PLA2R) during pregnancy [1, 7]. The pregnancy constitutes a specific acute-phase response; therefore, the concentrations of complement component in the diagnosis of

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the causes of glomerulonephritis may remain within the normal range [1]. The suggested diagnostic-therapeutic procedure in the case of glomerulonephritis suspicion is presented in Figure 1.

KIDNEY BIOPSY

In connection with the threat of complications to the mother, but also a danger to the fetus, performing a biopsy is recommended if its result may be significant to the treatment. The biopsy should be performed in the case of significant proteinuria or *de novo* nephrotic syndrome, sudden deterioration of kidney function or high probability of glomerulonephritis in early pregnancy (first/second trimester). The procedure is relatively safe. Complications were described in around 4.5–7% of biopted pregnant women, where the majority of them were not clinically significant (backache, hematuria). In a more advanced pregnancy (23^{th}–26^{th} week), significant bleeding after the biopsy was described. This connected to with premature birth or even fetal necrosis. Kidney biopsy is not recommended in pre-ecclampsia, due to high coocurrence of coagulation disorders and it not being a required diagnostic criterion. Moreover, it will not be possible for the patients in advanced pregnancy to assume the correct position for the procedure. In such a case, a biopsy in a sitting position should be performed and the diagnosis of the type of glomerulonephritis in the 32^{nd}–36^{th} week of the pregnancy will not influence the treatment and prognosis. Therefore, in late pregnancy (> 30^{th} week), the procedure is not recommended, but it should be underlined that each case should be treated individually. If the biopsy performance is postponed to the postnatal period, it is advisable to wait 4–6 weeks until the physical endothelial alterations subside [7].

THE TREATMENT OF PRIMARY GLOMERULONEPHRITIS IN PREGNANCY — GENERAL RECOMMENDATIONS

PLANNING OF THE PREGNANCY, CONTRACEPTION IN GLOMERULONEPHRITIS PATIENTS

Pregnancy in a patient with glomerulonephritis (GNC) should be planned. A conversation concerning contraception with the patient is recommended. Patients with primary and secondary glomerulonephritis should not take estrogen-based contraceptives. These products deteriorate blood pressure control, may increase proteinuria and the risk of thrombosis. Contraceptives containing progesterone in the form of pills and intramuscular progestagen in the form of *depo* may be used. Intrauterine devices may be recommended (more often in multiparas). Therefore, mechanical measures are less effective and are not recommended as the only birth control method [9].

The pregnancy should be planned in a patient who has been in remission for at least 3–6 months and in whom potentially teratogenic drugs were discontinued, including immunosuppressants, or they were replaced by drugs that can be safely used during pregnancy. In connection with the use of angiotensin convertase inhibitors/ angiotensin II receptor antagonist, the data come only from few studies conducted on pregnant women with diabetic nephropathy. Their use since conception (they show teratogenicity in the second/third trimester) stabilized proteinuria and increased the baby's birth mass. However, there are no observations based on patients with primary glomerulonephritis. Teratogenic drugs, e.g., lipid-lowering drugs, should be discontinued [7].

Strict blood pressure control constitutes an approved way of lowering proteinuria and inhibiting the progression of kidney disease. So far, consistent recommendations concerning blood pressure values in pregnant women with glomerulonephritis were determined. It is suggested that the "perfect" goal is < 135/85 mm Hg (acceptable level: < 140/90 mm Hg) [8].

SYMPTOMATIC TREATMENT OF NEPHROTIC SYNDROME IN PREGNANT WOMEN

The typical symptoms of nephrotic syndrome include: hypoproteinemia, hypercoagulability and lipid disorders. If it is possible, causal and symptomatic treatment should be introduced. The sooner the nephrotic syndrome occurs, the bigger the danger for the course of pregnancy (the prognosis is better if it develops in third than in the first or second trimester) [7].

Patients with swelling in the course of nephrotic syndrome should be recommended to wear pressure stockings, avoid prolonged standing, resting with elevated lower limbs and limiting the salt intake. Symptomatically, in patients with significant swelling, loop diuretics may be used. Nevertheless, attention should be paid to the possibility of lowering the volume of amniotic fluid and electrolyte imbalance in the fetus. Patients with severe hypoproteinemia may receive albumin infusion [7]. Hypoproteinemia increases the risk of thrombo-

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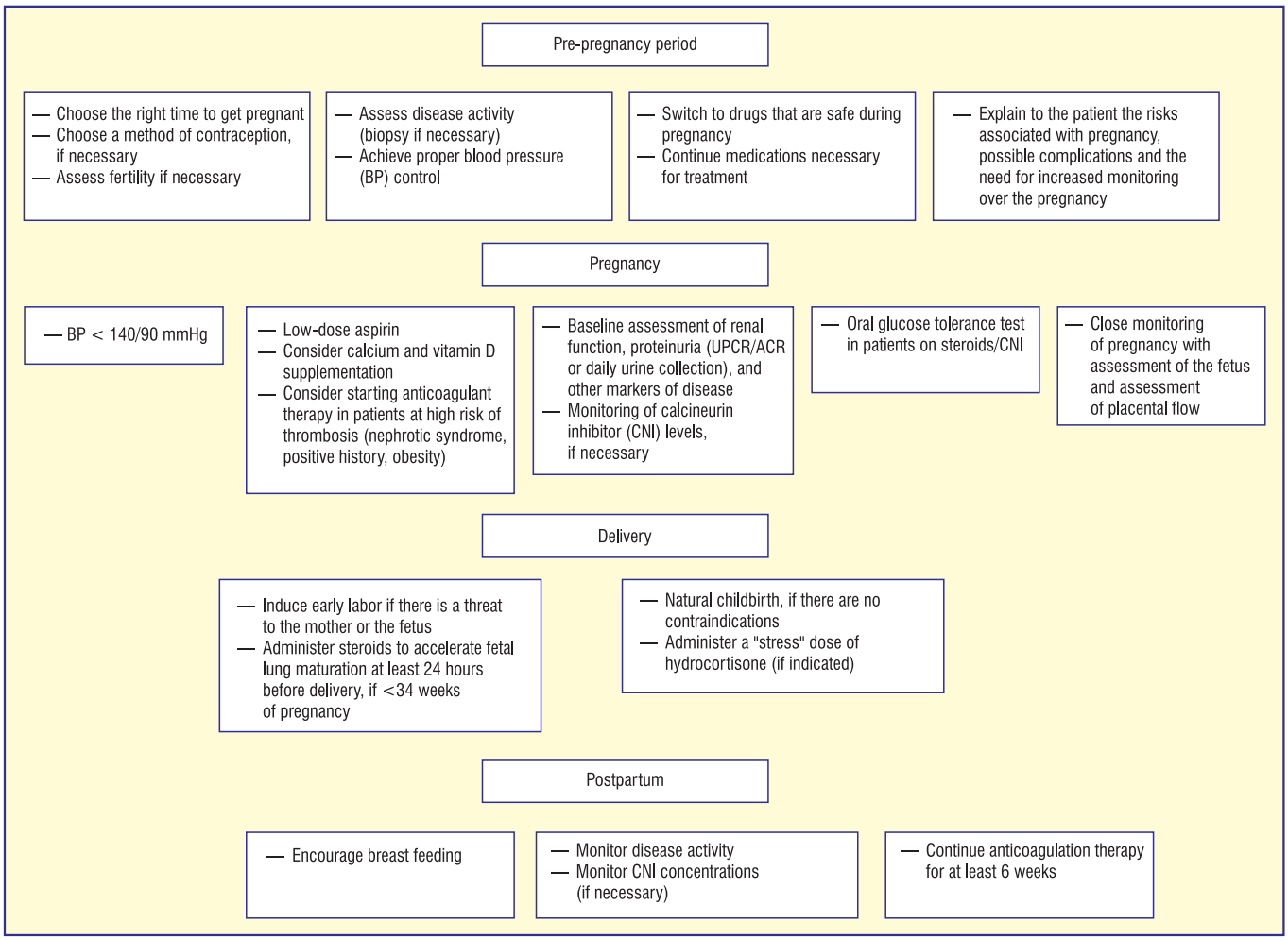

Figure 2. Management of glomerulonephritis before, during and after pregnancy [1]. BP — blood preasure, CNI — calcineurin inhibitors

sis and the pregnancy itself is prothrombotic [10]. Since in the case of severe nephrotic system, when the albumin concentration reaches < 20–25 g/dL, anti-thrombotic prophylaxis is crucial. Some authors recommend it in increased hypoproteinemia but in co-occurrence with risk factors, such as obesity, immobilization or membranous nephropathy. The drug recommended for pregnant women is subcutaneous low molecular weight heparin. Warfarin penetrates the placenta and may cause bone and central nervous system disorders [7, 11]. Anti-thrombotic prophylaxis should be discontinued right before the labor to avoid excessive bleeding but re-administered after the childbirth and continued for the first 6 weeks, during which severe pro-thrombotic promptitude occurs [12].

Pregnancy alone increases total cholesterol by about 43%, low-density lipoprotein (LDL) fraction cholesterol by 36%, but most importantly triglycerides by 2.7-fold; the presence of nephrotic syndrome definitely exacerbates lipid disorders. Statins used to treat hyperlipidemia have been deemed teratogenic by the FDA and are not recommended during pregnancy, although recent publications indicate that this group of drugs is safe for pregnant women (no official guidelines yet). The use of fibrates, ezetimibe, and niacin is controversial. The only class of drugs that have been found to be safe are bile acid binders. Given the lack of safe drugs to administer in pregnant women, hyperlipidemia associated with nephrotic syndrome during pregnancy is usually not treated [7, 13].

If nephrotic syndrome associated with primary GN is present during pregnancy, there are indications for prompt initiation of immunosuppressive therapy. Methylprednisolone infusions and plasmapheresis can be considered rescue treatment when symptomatic management is insufficient while waiting for a response to the implemented immunosuppressive treatment [7].

If the biopsy performance is postponed to the postnatal period, it is advisable to wait 4–6 weeks until the physical endothelial alterations subside

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Contraceptives containing progesterone in the form of pills and intramuscular progestagen in the form of depo may be used. Intrauterine devices may be recommended (more often in multiparas). Therefore, mechanical measures are less effective and are not recommended as the only birth control method

The pregnancy should be planned in a patient who has been in remission for at least 3–6 months and in whom potentially teratogenic drugs were discontinued, including immunosuppressants, or they were replaced by drugs that can be safely used during pregnancy

Methylprednisolone pulses are a rescue therapy in severe nephrotic syndrome in GN during pregnancy. The safe immunosuppressive drugs in pregnant are also: azathioprine, cyclosporin and tacrolimus.

It is recommended to include low-dose acetylsalicylic acid (75–150 mg/d) from the 12th week of pregnancy, which significantly reduces the incidence of pre-eclampsia, IUGR, and the risk of preterm delivery [1, 8, 9]. Low-dose acetylsalicylic acid should also be recommended during breastfeeding [9]. Calcium supplementation of at least 1 g/d has also been shown to reduce the risk of pre-eclampsia, so calcium testing and supplementation are necessary for pregnant women with GN [8, 9]. Recommendations for the management of a pregnant woman with GN are included in Figure 2.

IMMUNOSUPPRESSANTS

Glucocorticosteroids. Drugs in this group are used to suppress the inflammatory immune response in autoimmune diseases and are also the mainstay of treatment after organ transplantation. A placental 11-β-hydroxysteroid dehydrogenase metabolizes prednisone to inactive cortisone (dexamethasone administered to accelerate lung maturation is not inactivated and reaches a fetal concentration of approximately 30% of the maternal dose). It is considered a fairly safe drug in pregnancy, although it increases the risk of developing gestational diabetes, worsening of blood pressure control, weight gain, preterm labor, and infections, including urinary tract infections. Therefore, steroids should be used at the lowest effective doses. Parenteral administration of perioperative steroids should be considered in women who have received > 7.5 mg/d of prednisone for more than 2 weeks, whereas it is recommended at a dose > 20 mg used for more than 3 weeks (usually hydrocortisone). There are no pregnancy-specific dose recommendations, although most authors do not recommend exceeding 15 mg/d of prednisone for maintenance therapy. Doses of 1 mg/kg orally or intravenous infusions (500 mg/d for 3 consecutive days) should be reserved for severe disease exacerbations. During steroid treatment, calcium supplementation and vitamin D (400–2000 IU/d) should be considered to prevent osteopenia. Prednisone passes into breast milk (approximately 1%). No adverse effects of steroids were observed in breastfed children by mothers treated with these drugs at that time [14].

Azathioprine. It is ofthen the first choice drug in maintenece therapy of GN. Its teratogenic effects have not been demonstrated, although the dose should not exceed 2 mg/kg/d. The fetal liver lacks the enzyme inosine pyrophosphorylase, whose presence is required for the conversion of azathioprine to its active metabolite, 6-mercaptopurine. Due to myelotoxicity during treatment, monitoring of blood count and transaminase levels is indicated (2 weeks after starting the drug, every 3 months at a stable dose) [7, 9, 14].

Calcineurin inhibitors — cyclosporine (CsA) and tacrolimus. These drugs are safe to use during pregnancy and breastfeeding [14]. The transplantologists have significant experience with these drugs in pregnant women, as they are routinely used after transplantation, also in pregnant women [15]. Both drugs require the monitoring of their concentration in the blood. CNI concentration monitoring every two weeks in the first and second trimester, and once a week in the third trimester and one week after childbirth is recommended [16]. The CNI doses usually require increasing the dosage during the pregnancy by 20–25% in order to maintain the same concentration in blood as before the pregnancy, possibly due to the increase in hepatic metabolism. After the end of pregnancy, re-modification of doses is required [17], Tacrolimus is strongly connected to plasma proteins and erythrocytes. Anemia and hypoproteinemia increase physiologically during the pregnancy, so does creatinine clearance, which may influence the concentration of the free form of the drug. The low concentration of the drug shown in the total blood may not correspond to the real concentration of the free, active fraction. Therefore, the changes in dosages should be introduced very carefully in order to avoid too low drug concentrations and their toxic influence [18]. Calcineurin inhibitors, especially tacrolimus, predispose the patients to the development of diabetes. Therefore, pregnant women should be closely monitored for this complication, especially after the 28th week of pregnancy [9].

Drugs from the CNI group penetrate the placenta, filtering to the fetal circulation. It was reported that the concentration of tacrolimus in the fetus reaches 71% of the mother's concentration. It may be connected to the active transport of the drug in the placenta through P-glycoprotein [19]

Rituximab (Rtx). It is a monoclonal antibody that opsonizes and destroys B lymphocytes by binding to the CD20 receptor and is increasingly used to treat primary and secondary forms of GN. Its half-life is about 22 days, but B-lymphocyte depletion takes about 6 months [20]. The fetus may therefore be

exposed to it even though the drug was given before pregnancy. The antibody is easily transmitted across the placenta but has no toxic effects on the fetus. Depletion of B lymphocytes exposed to Rtx during pregnancy has been described, but no congenital disabilities were observed in these children. Thus, the use of the drug seems safe in pregnant women, especially in the first trimester, when the drug is passively transmitted across the placenta [21]. It is important to remember that children who have been exposed to Rtx during pregnancy cannot be vaccinated with live vaccines before the age of 6 months [9]. However, the long-term effects of Rtx in children exposed to the drug during the fetal period are unknown.

Cyclophosphamide and mycophenolate mofetil/sodium. These are teratogenic drugs and should be avoided during pregnancy. It is necessary to withdraw them from treatment regimens at least 3 months before the planned pregnancy [7, 9].

BREASTFEEDING

Women should be encouraged to breastfeed. Most of the drugs considered safe during pregnancy can also be used during breastfeeding despite the information about contraindications to breastfeeding in the SmPC [7–9]. Prednisone and azathioprine pass into breast milk in minimal amounts. As for CNI, CsA was usually not present in breast milk, while tacrolimus was present in a minimal fraction compared to maternal blood concentrations [1, 22]. However, it is important to keep in mind the need to carefully monitor maternal concentrations of these drugs and to readjust dosages due to physiologically changing absorption and metabolic processes after pregnancy.

Few data indicate that Rtx absorbs into breast milk in small amounts, although absorption is unlikely; the drug should be digested in the infant's gastrointestinal tract. Hence, breastfeeding is not contraindicated after the administration of this antibody [9].

Breastfeeding is contraindicated in the case of exacerbation of the course of GN and the need for cyclophosphamide or mycophenolates. The use of diuretics, which cause dehydration, is also not recommended in nursing women and may reduce the amount of breast milk. Enalapril, captopril, and quinapril can be safely used during lactation; they can be started soon after pregnancy, especially with coexisting proteinuria [1, 7].

SUMMARY

Nephrologists and gynecologists should jointly monitor the pregnancy of patients with GN. The prognosis in primary GN is better than in secondary forms. The main risks to mother and fetus include miscarriage, preterm delivery, pre-eclampsia, intrauterine fetal stunting, low birth weight, and deterioration of maternal renal excretory function. Risk factors for these complications include uncontrolled hypertension, proteinuria, and impaired renal function at baseline. Thus, blood pressure, proteinuria, serum creatinine and uric acid levels should be carefully monitored in pregnant patients with GN. If proteinuria increases in early pregnancy, renal biopsy should be considered, and empirical treatment should be instituted in advanced pregnancy. Multidisciplinary care and close clinical observation are the cornerstones of maternal and fetal care.

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Women should be encouraged to breastfeed. Most of the drugs considered safe during pregnancy can also be used during breastfeeding despite the information about contraindications to breastfeeding in the SmPC

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Historically, pregnancy was expected primarily in women with type 1 diabetes (most women with diabetes and childbearing potential suffer from diabetes type 1), but current epidemiologic trends increasingly allow pregnancy to be expected in women with type 2 diabetes as well

PREGNANCY IN PATIENTS WITH SECONDARY NEPHROPATHIES

Tomasz Stompór

DIABETIC KIDNEY DISEASE

The risk of pre-eclampsia, preterm delivery and perinatal death is approximately 2–4 times higher in patients with type 1 or type 2 diabetes compared with the general population. Historically, pregnancy was expected primarily in women with type 1 diabetes (most women with diabetes and childbearing potential suffer from diabetes type 1), but current epidemiologic trends increasingly allow pregnancy to be expected in women with type 2 diabetes as well. One in 250 pregnancies involves a woman with type 1 or type 2 diabetes, with the proportion of pregnant women with type 2 diabetes rising steadily. For example, among all women with diabetes who become pregnant in the UK, the proportion of women with type 2 diabetes has increased from 27% to over 40% in a decade. The epidemiological dimension of diabetic kidney disease (DKD) in pregnant diabetics has not been reliably assessed, but some estimates suggest that the prevalence of this complication in pregnant women is declining (currently, 3–7% of diabetic women who become pregnant) [1, 2]. On the other hand, DKD is arguably the most common cause of chronic kidney disease (CKD) in pregnant women [3]. Predicting future trends seems to be a difficult challenge: optimization of diabetes treatment, improvement of patient prognosis, and introduction of new drugs for the treatment of this disease will promote a further decrease in the risk of developing DKD and delay its onset, but a further delay in the age at which women (including those with diabetes) will conceive should probably be expected.

EFFECT OF PREGNANCY ON THE COURSE OF DIABETIC KIDNEY DISEASE

At first, it should be noted that the medical literature allowing conclusions on the impact of pregnancy on the health of women with diabetes and renal complications is limited and is based on observational studies of groups of several dozen (maximum several hundred) women. The most common comparison is between the outcome of women with DKD of similar severity and stage who had a pregnancy or multiple pregnancies and those who had not become pregnant. For DKD, analyses are fur-

ther complicated by the different definitions of this entity (e.g., any proteinuria, albuminuria ≥ 30 mg/d, ≥ 200 mg/d, ≥ 300 mg/d, etc.).

The presence of DKD with normal GFR (and therefore limited to albuminuria), given optimal anti-hypertensive therapy before and during pregnancy, was not associated with a greater risk of worsening of renal function or worsening of distant prognosis compared with women with DKD who did not become pregnant. Pregnancy is not considered to have an adverse effect on renal function if it occurs in a diabetic woman with a creatinine level of less than 1.4 mg/dL, proteinuria < 1 g/d, and well-controlled blood pressure. On the contrary, the risk of progression of kidney damage as well as complications during pregnancy increases dramatically if the pregnancy involves a woman with creatinine levels greater than 2 mg/dL, nephrotic proteinuria, and poor blood pressure control [2, 3]. While diabetes and DKD alone do not accelerate the rate of DKD progression after the end of pregnancy (under conditions of good prognosis described above), such progression (including significantly increased risk of end-stage renal disease after many years of follow-up) can be expected in those women with diabetes and DKD who develop pre-eclampsia [4].

The course of pregnancy itself with coexisting DKD is very often complicated by hypertension (in about 1/3 of women, hypertension occurs before pregnancy; in the third trimester, 60–80% of women require hypotensive treatment). Moreover, it is estimated that up to 50–75% of women with DKD in the third trimester of pregnancy should expect an increase in proteinuria to a range meeting the definition of nephrotic syndrome; in most cases, however, the increase in proteinuria is not accompanied by a loss of GFR [1]. This risk is significantly reduced in women treated with drugs that block the renin-angiotensin-aldosterone (RAA) axis prior to pregnancy (see below).

Proteinuria exceeding 3 g/d (regardless of the cause of kidney damage) and eGFR < 50 mL/min/1.73m^2 at the time of conception are universal factors for progression of CKD — in about 40% of women, irreversible deterioration of kidney function during pregnancy should be expected. All women with renal disease, irrespective of the underlying disease, should be counseled regarding fertility and the consequences of pregnancy for the kidneys; this rule is particularly applicable to those in whom the above-mentioned risk factors of poor prognosis are present [4].

THE INFLUENCE OF DIABETIC KIDNEY DISEASE ON THE COURSE OF PREGNANCY

At the beginning, it should be mentioned that CKD is not a risk factor for an increased frequency of congenital disability of the fetus. The risk depends on impaired metabolic control of diabetes. Achieving therapeutic goals is more difficult in the case of CKD. It is estimated that the risk of the development of congenital disabilities increases up to 30% for each 1% of HbA_1c increase [1]. The risk of fetal death also largely depends on the metabolic control of diabetes (reaching 10% of women with HbA_1c > 10%) and is not correlated directly with the presence and stage of CKD. The modern, integrated, multidisciplinary care (obstetrician, diabetologist, nephrologist-hypetensiologist) allows to achieve good pregnancy outcomes in 95% of pregnancies in women with CKD, that is the delivery of a healthy child [2].

Long-term psychomotor development of children born from mothers with CKD may be slightly delayed, mainly due to complications such as pre-eclampsia and premature birth (before the 24th week of pregnancy) or low birth mass and prematurity [2]. Pre-eclampsia in women with CKD is very frequent. It occurs in 30–60% of pregnancies of women with albuminuria at the moment of conception (pre-eclampsia occurs in around 10–15% of pregnant women with diabetes without CKD and in 2–8% of the general population of women). Its occurrence is facilitated especially by: renal impairment, proteinuria and poorly controlled hypertension before the pregnancy (*superimposed pre-eclampsia*) [4]. Microalbuminuria also increases the risk of the development of pre-eclampsia. Independently of the presence of CKD, the occurrence of pre-eclampsia is also facilitated by high values of HbA_1c, mainly in the first trimester [3]. The biggest challenge is the differentiation between the progression of CKD in the late stages of pregnancy and pre-eclampsia (the same difficulty concerns the differentiation between pre-eclampsia and relapse of lupus nephropathy or other primary and secondary glomerulopathies). Unfortunately, the determination of potentially useful biomarkers, such as placental growth factor (PIGF) or soluble fms-like tyrosine kinase-1 (sFlt-1) or their ratio (sFlt-1/PlGF ratio), in the differentiation of these diseases has

▶▶ The presence of DKD with normal GFR (and therefore limited to albuminuria), given optimal anti-hypertensive therapy before and during pregnancy, was not associated with a greater risk of worsening of renal function or worsening of distant prognosis compared with women with DKD who did not become pregnant ◀◀

▶▶ It should be mentioned that CKD is not a risk factor for an increased frequency of congenital disability of the fetus ◀◀

not been validated in patients with diabetes or CKD.

Pre-eclampsia is an independent risk factor of many complications for the mother and the fetus. The occurrence of pre-eclampsia increases the risk of premature births in women with type 1 diabetes and microalbuminuria — these disorders have been reported in 45% of pregnancies.

Experts indicate the benefits resulting from RAA blockade "until the last moment," that is, until getting pregnant

THE MANAGEMENT IN THE PERIOD BEFORE AND DURING THE PREGNANCY IN WOMEN WITH CKD — SELECTED ASPECTS

One of the most controversial aspects concerning the management of women with diabetes who plan on getting pregnant is the approach to the therapeutic blocking of RAA axis. Some groups of experts claim that due to possible adverse effect on the developing fetus, drugs from the groups: angiotensin converting enzyme inhibitors and angiotensin II AT1 receptor antagonists (sartans) should not be used at all in sexually active women of childbearing potential (and if the therapy with these drugs is necessary, these women should use the most effective contraception). This is the opinion of, among others, *the American Diabetes Association* [5]. Meanwhile, studies show that the use of a drug blocking the RAA axis in women with CKD for 6 months before conception and discontinuing them once the pregnancy is confirmed (that is, immediately after a positive pregnancy test) increases the chance for the pregnancy to be successful (inter alia, by reducing the risk of premature births). The data on the teratogenic effect of angiotensin converting enzyme inhibitors/sartans in early pregnancy (an almost threefold increase in the risk of congenital disabilities) are currently questioned. The harmfulness of their use in the third trimester now is underlined (at that time, they negatively influence the development of the fetus's heart and kidney and facilitate the occurrence of oligohydramnios). The opinion that the RAA axis blockade is not absolutely contraindicated in the second and third trimester is more and more frequent. Hence, termination of pregnancy motivated by the concern for congenital disabilities connected with the exposure to angiotensin converting enzyme inhibitors/sartans during the period of organogenesis is not recommended [3]. According to the current state of knowledge, the above-mentioned drugs should be absolutely discontinued after obtaining a positive result of a pregnancy test, whereas, according to the present knowledge, there are no good reasons for forbidding their use in the period before the conception (what is more, there is a growing body of evidence that such treatment is recommended in proteinuric CKD patients who plan on getting pregnant). Experts indicate the benefits resulting from RAA blockade "until the last moment," that is, until getting pregnant. Specific indications in this group of patients include: performing frequent pregnancy tests by women being sexually active in order to be able to diagnose pregnancy early (especially in women with irregular periods). It should be underlined that the above-mentioned deliberations are fully based on the opinions of experts, which in turn may have been formed on the basis of low quality evidence, as assessed according to the Evidence-Based Medicine (EBM) proofs hierarchy. An alternative for RAA blockade during pregnancy with CKD is the following (the same as in any case of hypertension during pregnancy): methyldopa, labetalol, some beta-blockers and calcium antagonists as well as (in cases of extreme overhydration, taking into account the possible serious adverse effects connected with their use) diuretics. The issue was discussed in detail in other parts of this paper.

Studies show that the use of a drug blocking the RAA axis in women with CKD for 6 months before conception and discontinuing them once the pregnancy is confirmed (that is, immediately after a positive pregnancy test) increases the chance for the pregnancy to be successful

Blood pressure target levels during a pregnancy complicated with hypertension, diabetes or CKD was not defined precisely. However, it seems that patients with diabetes and CKD have benefits in the form of less frequent obstetric complications and better prognosis for the fetus from lowering the blood pressure < 130/80 mm Hg and proteinuria < 300 mg/d. in the period before the conception [2].

Although oxidative stress is an extremely significant factor in the pathogenesis of endothelium dysfunction in diabetes as well as in pre-eclampsia, so far, substances that are thought to posses antioxidative potential (vitamins C and E) had not any positive effect on the reduction of this complication in pregnant women with diabetes.

As it was already mentioned, glycemic control is a significant therapeutic goal during pregnancy. This issue, perfectly defined in diabetic women, was not addressed by any specific recommendations in case of CKD. Yet, it seems that good glycemic control should result in the percentage of HbA_1c not exceeding 7% or even 6% [3]. The Polish Diabetes Association recommends HbA_1c < 6% as long as striving for this value is not connected with an

increased risk of hypoglycemia [6]. The American Diabetes Association perceives the HbA_1c value < 6% as perfect but allows — in order to avoid the threat of hypoglycemia — the value of 7% [5]. The discussion of the hypoglycemic treatment of diabetes during pregnancy goes beyond the scope of paper. The reader should consult the recommendations of diabetes associations. It should be underlined that no special recommendations have been developed for the management of pregnant women with diabetes and CKD. None of the above-mentioned recommendations concern this topic and all the recommendations are universal to all diabetic patients.

Among the commonly used medication, statins should be discontinued during pregnancy (due to potential teratogenicity). In the case of every high-risk pregnancy, including diabetes and CKD, low doses of acetylsalicylic acid (LDA, low-dose aspirin), that is 75 mg starting at 12th week of pregnancy (or according to some experts, it should be administered before the 16th week and discontinued around a week before the planned childbirth) are claimed to be beneficial. The exact age of the pregnancy, when LDA should be administered (yet it should be before 16th week) has not yet been determined. Women taking acetylsalicylic acid before the pregnancy may continue the therapy after getting pregnant [2].

The higher frequency of the development of the neural tube defect in fetuses, observed in type 1 diabetes, predisposes this group of women to taking supplementation with folic acid.

In women of childbearing potential, who are sexually active but do not plan a pregnancy, prostagen-based contraception is recommended (due to increased risk of thromboembolic complications, cardiovascular risk and the possibility of increasing albuminuria, estrogen-based contraception is not recommended) [1].

Summing up, the results of meta-analysis in which the influence of the course of pregnancy on kidney disease and the influence of kidney disease on the pregnancy were analyzed should be presented. It included 23 observational studies in which cases of 506,340 pregnant women (with or without CKD) were described. In 7 out of 23 studies, the analysis included only patients with CKD (type 1 or 2 diabetes). In many other studies, these patients were also included. Different definitions of CKD and knowledge concerning the etiology of kidney damage which is not often available, allowed only a general comparison of patients with diabetic and non-diabetic renal disease to be conducted. The risk of pre-eclampsia and premature birth rendered lower in women with diabetic renal disease in comparison to chronic renal disease of different origin. What is interesting, the pregnancy did not negatively influence the kidney function in diabetic renal disease and chronic renal disease of another origin (in the study included in the meta-analysis there were few women whose creatinine concentration at the time of conception exceeded 1.2 mg/dL). The universal factor of obstetric complications (independent of the etiology of the disease) was overt proteinuria [7].

▶▶ The risk of pre-eclampsia and premature birth rendered lower in women with diabetic renal disease in comparison to chronic renal disease of different origin ◀◀

DIABETIC RENAL DISEASE AND PREGNANCY — SUMMARY

The available literature causes certain disorientation, as in the majority of reference materials, it is claimed that diabetic renal disease is not a significant, independent risk factor of pregnancy complications and worsening of the prognosis for the mother and the fetus. These factors include: poorly controlled diabetes and hypertension, massive proteinuria and the occurrence of pre-eclampsia. All these aggravating circumstances are certainly more frequent and more severe in diabetic renal disease in comparison with the general population of pregnant women and those who have diabetes without renal complications. This means that **the occurrence of renal complications of type 1 or type 2 diabetes is a serious danger for the pregnancy.**

▶▶ Pregnancy did not negatively influence the kidney function in diabetic renal disease and chronic renal disease of another origin ◀◀

LUPUS NEPHRITIS (LN) AND ANTIPHOSPHOLIPID SYNDROME (APS)

Systemic lupus erythematosus (SLE) and lupus nephritis (LN) are diseases occurring in a vast majority young women (in the procreative period). Therefore, the issues of infertility and pregnancy in this group of patients require special attention and are better known and described than other autoimmune diseases, "secondary" nephropathies and "primary" glomerular diseases. The antiphospholipid syndrome does not always occur in SLE patients. It may have many secondary causes and an idiopathic character. The majority of sources discuss the fertility issues and pregnancy of women with SLE/LN and antiphospholipid syndrome (APS) jointly and such aaproach was also adopted in this paper. Pregnancy in

women with SLE was discussed more broadly, underlining the aspects connected to LN. Analyzing the course of pregnancy, its complications and the risk of congenital disabilities in newborns (connected with the disease itself and its treatment), the "basic risk" should be remembered. In the general population of women, spontaneous miscarriage occurs on average in 10–15% of cases and around 2–5% of children have congenital disabilities. However, in relation to the treatment itself, it is crucial (and difficult) to balance the risk resulting from pharmacotherapy and exposure to drugs and the risk connected with uncontrolled base disease.

Active LN at the moment of conception (or even the history of LN) is the most serious factor of a bad prognosis for the mother and the fetus

THE INFLUENCE OF SLE, LN AND APS ON THE COURSE OF PREGNANCY AND THE ACTIVITY OF THE UNDERLYING DISEASE

The fertility of women with SLE is a subject of discussion. Some authors claim that SLE and the presence of antiphospholipid antibodies themselves do not impair the fertility itself. On the other hand, the opinion that active lupus, especially lupus nephritis, make getting pregnant difficult is common [8].

SLE patients are generally characterized by 2–4 times higher risk of obstetric complications. This concerns: pre-eclampsia, premature birth, fetal growth disorders (IUGR), fetal death and the death of a newborn. The risk of death of pregnant woman may be 20 times higher in lupus patients than in the general population of women. Two major causes of death of women with SLE during pregnancy include LN and infectious complications. On the other hand, significant progress in this area should be underlined: in the 1980s, around 40% of pregnancies were lost in women with SLE, now it concerns around 15–20% (with the population average at the level of 10–15%). Not all factors were equally improved. For example, the number of premature births in this group of patients in the United States has remained at the level > 30% over the decades, while in the population averages only 10–12%; analogically, the data from Norway amount to 22% in SLE patients and 6% of the general population. The percentage of intrauterine growth retardation (IUGR) and the low birth mass is also 3 times higher in women with lupus [8, 9].

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Active SLE or relapse in the period of 6–12 months before getting pregnant increases the risk of relapse during the pregnancy (twofold or more), the occurrence of pre-eclampsia (almost two times), as well as miscarriage (almost 6 times) fetal growth disorders (3.5 times) and premature birth (over 6 times). Each of these events will happen additionally two–three times more often, if the active disease or relapse affects kidneys (LN). A renal relapse before or during the pregnancy facilitates more severe complications such as pre-eclampsia and HELLP syndrome. On the basis of reference materials, it may be concluded that active LN at the moment of conception (or even the history of LN) is the most serious factor of a bad prognosis for the mother and the fetus. Independently of the clinical symptoms, the risk of complications during the pregnancy increases in patients with serological manifestations of the activity of the disease (decrease in the concentration of C3 and C4 component of the complement, increase in anti-dsDNA antibody titer). It was shown in the PROMISSE study devoted to the analysis of the course of pregnancy in women with SLE that the predictor of obstetric complications in SLE is also the platelet count < 100 000/μL [10]. Some data suggest that various constellations of serologic indicators have slightly different predictive value for the occurrence of relapse during the pregnancy: low concentration of C3 and high titer of antibodies against double-stranded DNA (anti-dsDNA) at the beginning of the pregnancy indicate the risk of LN relapse in any time of the pregnancy, while low concentration of C4 and high titer of antibodies against the C1q complement component (anti-C1q) indicate the risk of LN relapse in the first and second trimester. The frequency of occurrence of early (first and second trimester) and late (third trimester) relapses is similar [11, 12]. The presence of anti-SSA or anti-SSB antibodies (Sjögren A, B) may lead to the development of congenital heart block (CHB in around 1–2% of fetuses of women with these antibodies) and the development of *neonatal lupus*. The prognosis for pregnancy with SLE usually improves with subsequent pregnancies (hence, the highest risk is connected with the first pregnancy).

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Profiles of patients with the best and the worst prognosis for the course of pregnancy were identified in the PROMISSE study. The first group consisted of White (but not Hispanic) women with negative lupus anticoagulant (LAC) who did not require hypotensive medication, with platelet count > 100 000/μL. In this group, the risk of obstetric complications amounted to 7.8% and the loss of the preg-

nancy or the death of a newborn occurred in 3.9% of cases. On the other hand, the highest risk was observed in the non-White and Hispanic ethnical groups with positive LAC and necessity of hypotensive treatment. Pregnancy complications concerned 58% of them and the mortality of fetuses and newborns amounted to 22%. It has to be noted that the PROMISSE study did not include patients who were using prednisone in the dose of 20 mg or higher with proteinuria > 1.2 mg/dL, diabetes and blood pressure exceeding 140/90 mm Hg. Hence, the underlying disease of the study participants was stable and overall prognosis was good [10].

In connection with APS, the highest risk of pregnancy complications concerned women who had thrombosis. The course of pregnancy is usually worse in patients with APS with co-occurrence of SLE (compared with to primary APS) and in patients with SLE and antiphospholipid antibodies (aPL) (compared with SLE without these antibodies). The frequency of pregnancy complications in the PROMISSE study concerned 15.4% of pregnancies of patients with SLE but without aPL and as much as 43.8% of patients with both SLE and aPL [10]. Positive LAC, the presence of several antibodies and a high titer of aPL were the factors that increase the risk of thrombotic complications by more than 12 times, pre-eclampsia two times and IUGR with low birth mass almost 5 times [13].

The basic rule when planning the pregnancy in the case of SLE is to achieve remission for at least 6 months before the conception. Active disease (relapse) during the 6 months before conceiving results in a four times higher risk of losing the pregnancy (SLEDAI scoring system ≥ 4 in the evaluation conducted during 6 months before the conception is a cut-off point at which the risk of relapse increases significantly) [8]. Moreover, getting pregnant when the disease is active is connected with a 60% increase in the risk of relapse during the pregnancy (average risk amounts to 10–20%, around 25% of relapses meet the criteria of "severe" relapse). The activity of the disease during the pregnancy is evaluated by means of a modified SLEDAI scale (SLEPDAI, SLE Disease Activity Indices in Pregnancy). According to one of the meta-analyses, the relapse occurred on average in 25.6% of women with LN, while premature birth and intrauterine dystrophia in 39.4% and 12.7% of women, respectively [9]. In so far the largest observational study concerning pregnant women with SLE (PROMISSE), it was shown that the severity of the disease considered mild or moderate occurred in 12.7% of patients, and severe in 2.5% of patients in 20th–30th week of pregnancy, while between 32 and 35 the percentage amounted to 9.6% and 3%, respectively [10]. Renal relapses were the most common among the severe relapses. Statistics show that LN relapses during pregnancy occur in 15–30% of women with an LN history. The fact that no more than 10% of relapses are of renal character (with significant worsening of kidney function) and that the vast majority have nephrotic but not nephritic character (with the significant increase in proteinuria and relatively stable kidney function) should be considered relatively beneficial [14]. In the PROMISSE study, quoted here multiple times, 32% of patients with lupus had a history of LN (the majority was confirmed with biopsy). Renal relapse during the pregnancy occurred in 11% of women with a history of LN (in 6.4% of women without a history of LN). The most important predictors of renal aggravation of SLE during pregnancy were LN before the pregnancy and the low level of the C4 component of the complement. However, the risk of relapse was not connected to the high titer of anti-dsDNA antibodies. Intrestingly, in this study, renal SLE relapse and LN *de novo* manifestation were not connected with the increase in obstetric complications [15].

Proteinuria during pregnancy in women with LN is a factor of unfavorable prognosis. It was shown that for each 1 g of protein per 1 g of creatinine excreted with urine, the risk of premature birth increases by 15%. According to predictions, the presence of II and IV class LN is connected with a higher risk of pre-eclampsia in comparison to class II and V. This is related mainly to more serious prognosis in these classes. The relation between the histological form of LN and prognosis for the pregnancy has not yet been confirmed by all analyses [16]. The type of relapse which may occur during the pregnancy is largely determined by the course of SLE before the pregnancy. As it was mentioned before, in women included in the PROMISSE analysis with the history of LN before the pregnancy, 11% of relapses concerned kidneys (renal relapses occurred only in 1.6% of women without LN before the pregnancy). Both in women without a history of LN and in the majority of those with previously diagnosed LN, the most frequent forms of relapse of SLE are non-renal

The basic rule when planning the pregnancy in the case of SLE is to achieve remission for at least 6 months before the conception

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forms: cutaneous, articular and hematological (with dominant thrombocytopenia). The same rule applies during 1 year after childbirth, which is considered a period of increased risk of relapse [8].

The activity of the disease in women who plan pregnancy leads to aggressive therapy under the cover of contraception. The preparation for a planned pregnancy includes, apart from remission, the optimization of maintenance therapy. The rules for the use of immunosuppressants during pregnancy were discussed separately. It should only be mentioned here that the pregnancy should not occur sooner than 3 months after the last exposure to cyclophosphamide and 6 weeks from the last exposure to MMF. It should be remembered that in around 10–12% of women who are scheduled to switch MMF to azathioprine, a relapse of the underlying disease should be expected due to the decrease in "the strength" of immunosuppression [8, 14].

In long-term observations (up to 10 years), it has been not proven that pregnancies in women with LN unfavorably affect further activity of the disease and long-term prognosis. Conversely, women with LN who got pregnant had better kidney function and better blood pressure control after 10 years

The greatest challenge in the course of renal diseases in general and especially in LN is the differentiation between LN relapse after the 20th week and pre-eclampsia. The common features of both are include: the increase in proteinuria, worsening of kidney function and blood pressure control as well as decreased platelet count. Different types of neurological manifestations also belong to the clinical picture of both pre-eclampsia (eclampsia) as well as SLE with the involvement of the peripheral and central nervous system. Pre-eclampsia is evidenced by a lack of changes in urine sediment, increased liver enzymes and abdominal pain. Hyperuricemia, which is typical for pre-eclampsia, may also be present in LN. Serological test results are helpful: normal levels of C3 and C4 component of the complement and stable titer of anti-dsDNA suggest pre-eclampsia. Other symptoms of SLE indicate the relapse of LN. These include joint pain, the appearance of new, typical changes on the skin, and fever. Although difficult, differential diagnosis is crucial due to disparate therapeutic procedures [8, 9, 17]. It should also be added that kidney biopsy during pregnancy is connected with a higher frequency of adverse events; however, they are almost exclusively moderate. Nevertheless, performing a biopsy during pregnancy should be reserved only for the most severe cases in which the evaluation of the morphology of biopsy is indispensable, that is in the case when the biopsy result will in all likelihood influence the management [16].

Going through pregnancy without or with little complications is a kind of "certificate" proving the stability of the disease in women with SLE and LN

Pregnancy should not occur sooner than 3 months after the last exposure to cyclophosphamide and 6 weeks from the last exposure to MMF

It should be underlined that in long-term observations (up to 10 years), it has been not proven that pregnancies in women with LN unfavorably affect further activity of the disease and long-term prognosis. Conversely, women with LN who got pregnant had better kidney function and better blood pressure control after 10 years. It should be remembered that the results refer to the group of women in which >90% of pregnancies were planned, so in the preconception period, the clinical state and treatment were optimized [18]. Therefore, it may be assumed that pregnancy is protective towards kidneys, although it is more possible that going through pregnancy without or with little complications is a kind of "certificate" proving the stability of the disease in women with SLE and LN. Relatively healthier women get pregnant and go through it successfully.

APS symptoms are inextricably connected with pregnancy. Therefore, the course of pregnancies in the past defines the disease itself. Its diagnosis is highly probable in women who lost at least three consecutive pregnancies before the 10th week or at least 1 pregnancy after the 10th week or in the case of the occurrence of premature birth before the 34th week of pregnancy due to intrauterine dystrophia (IUGR) threat to the fetus's life or pre-eclampsia. Serological criterion is the detection of one or more among aPL: LAC, anticardiolipin antibodies or anti-beta2-glycoprotein I (*aβGPI*). APS cases with concurrent SLE and those in which the presence of LAC, high titer of other antibodies, the simultaneous presence of all three aPL as well as low concentration of the components of the complement have a very poor prognosis. The prognosis is especially unfavorable at a young age and in women with APS and a history of thrombotic events [8, 9].

THE PRINCIPLES OF MONITORING AND TREATMENT OF SLE, LN AND APS DURING PREGNANCY

Observations show that 80% of women with LN, who get pregnant with creatinine concentration < 1.2 mg/dL and proteinuria < 1 g/g of creatinine, do not experience any significant complications during the pregnancy and the frequency of relapse does not exceed 2.5% in second and 3% in the third trimester [16]. Apart from the rule that conception should occur after 6 months from remission, the second very important management rule, which is beyond any doubt, is the use of hydroxychlo-

roquine (HCQ) before getting pregnant and during the entire pregnancy. It was indicated that HCQ significantly lowers the risk of obstetric complications (e.g., premature births, low birth mass and IUGR), as well as SLE/LN relapse during the pregnancy. Discontinuation of HCQ in the preconceptive period or during the pregnancy increases the risk of all above-mentioned complications (both mother-fetal and connected with SLE relapse) [8]. In the case of relapse, all drugs deemed safe in pregnancy may be used, that is, non-fluorinated steroids (prednisone, methylprednisolone, in special cases also in high IV doses) as well as azathioprine and CNI. Steroids are generally deemed safe. Yet, they should be administered in the minimal effective dose, because apart from "typical" (but potentially serious in pregnancy) adverse effects (increase in mother's body mass, increase in the risk of gestational diabetes, hypertension), they also impair the fetus's growth and facilitate premature births. The reports about the increased risk of cleft palate in children of mothers using steroids were not confirmed. The "last choice" treatment for pregnant women is the administration of intravenous immunoglobulins (IVIg). This is *ultima ratio* management which, according to the majority of authors, does not show a positive influence in controlling lupus relapse. However, it is recommended during pregnancy due to the lack of other, safe medication. IVIg do not raise significant objections in regard to their safety for the fetus [9].

In the case of APS, the standard is the simultaneous use of LDA with heparin (data suggest that non-fractioned heparin is better, but from the practical point of view, it is usually low molecular weight heparin). Such management is recommended, despite the fact that prospective randomized studies did not confirm that adding low molecular weight heparin to LDA significantly decreases complications during pregnancy. Heparin should be discontinued around 10–12 hours before the planned delivery and re-administered no sooner than 4–6 hours after it. Women taking vitamin K inhibitors as chronic anticoagulation should also discontinue the treatment (with a change for low molecular weight heparin) before or right after getting pregnant [17].

The use of HCQ is a standard in APS (also in primary cases, not connected to lupus). Also in this disease, the long-term use of HCQ during the pregnancy significantly increases the percentage of living births, decreasing the risk of potential complications connected with the presence of aPL [8, 9].

The safety of immunosuppressants in pregnant women was discussed in another part of this paper. However, a medication which is increasingly used in nephrology in severe cases of lupus nephritis and membranous nephropathy (although these are still off-label uses) and — which is in accordance with the registered indication — in small vessel inflammation with anti-neutrophil cytoplasmic antibodies (ANCA), should be remembered. I mean rituximab. Despite general contraindication to use this drug during pregnancy, the number of women with different diagnoses who get pregnant (the pregnancy is usually unplanned) during or after taking rituximab increases. These experiences show that exposure to rituximab was connected with the risk of congenital disabilities. In all likelihood, the majority of biological drugs based on immunoglobulin G (IgG) in their structure, are not transferred through the placenta before the 12th week of pregnancy. On the other hand, the cases of lymphopenia and infectious complications in children of mothers exposed to rituximab during the pregnancy were described. Currently, the manufacturer recommends that the period between the last dose of the drug and conceiving should last 12 months. Experts lean towards shortening this period to 6 months, which should constitute a sufficient safety measure. Considering the available case studies, there is no reason to deem the only registered biological drug for SLE — belimumab — as teratogenic [8, 9, 17]. HCQ, which was mentioned several times above, transfers through the placenta, but significant toxicity for the fetus was not stated so far [14].

As it was already mentioned, there are few recommendations concerning pregnancy and childbirth in relatively rare renal diseases described here. This results from the fact that there are no data of good quality in the EBM hierarchy, which does not allow recommendations to be made. Therefore, two documents concerning fertility and pregnancy in women with SLE and APS should be referred to: EULAR recommendations published in 2017 and the opinion of the *Italian Study Group on Kidney and Pregnancy* published in 2016 [13, 14].

For the sake of clarity, when discussing the EULAR recommendations, the strength of the recommendation was not given. Those which evidence level was low were marked. According to EULAR recommendations, the

▸▸ Apart from the rule that conception should occur after 6 months from remission, the second very important management rule, which is beyond any doubt, is the use of hydroxychloroquine (HCQ) before getting pregnant and during the entire pregnancy ◂◂

▸▸ HCQ significantly lowers the risk of obstetric complications as well as SLE/LN relapse during the pregnancy ◂◂

Drugs used in the prophylaxis of SLE/LN relapse during pregnancy are: HCQ, steroids, azathioprine, cyclosporine and tacrolimus. Mycophenolate mofetil (MMF), cyclophosphamide, methotrexate and leflunomide should not be used

Low molecular weight heparin should be included in the therapy of every pregnant woman whose albumin concentration in plasma is below 20–25 g/L, no matter what is the cause of renal disease

highest risk for the pregnancy of a woman with SLE is the active disease at the moment of conception or relapse during the pregnancy, especially LN relapse. The special risk factors are also the history of LN and the presence of aPL and APS [13]. Key risk factors of failure during pregnancy with just APS are: the presence of "high risk" antibodies (LAC, simultaneous presence of aPL antibodies, high titer of aPL antibodies), the concurrence of SLE, the history of vascular and thrombotic complications, and previous complicated pregnancies. In the preconceptive period, the following issues are of crucial importance: remission achievement, optimal blood pressure control, supportive treatment with a minimal, effective dose of steroids as well as necessary use of HCQ and possibly other drugs deemed safe during pregnancy (see: immunosuppressants accepted for the use during pregnancy). The monitoring of blood pressure and thrombosis prophylaxis with the use of the antiplatelet drug (acetylsalicylic acid) are necessary for patients with SLE and APS.

The issue of contraception is are considered regulated by the use of contraception in intrauterine devices as the safest method for women with SLE/APS, provided there are no gynecological contraindications. Hormonal methods should be used carefully and only in women with inactive SLE or very stable course of the disease as well as when aPL titer is negative. In each case, prostagen-based contraception should be preferred and only after a thorough analysis of the risk of thrombotic events.

The issues of exposure to alkylating medication in the context of possibilities of future conception should be discussed with women with SLE. In women who undergo therapy with cyclophosphamide, administration of gonadoliberin analog may be considered to lower the risk of infertility. In women with stable or inactive lupus, assisted reproductive technologies, like ovulation stimulation and *in vitro* fertilization, may be used. The recommendation strength of these statements was weak. Limited sources indicate that during ovulation stimulation, relapses were observed in 8–30% of women, which does not prove that the procedure increased the risk of relapse [8].

Low doses of acetylsalicylic acid should be used in all women with SLE (especially with LN or presence of aPL) as pre-eclampsia prophylaxis. Apart from LDA, during the pregnancy, anticoagulation with low molecular weight heparin should be used in patients with aPL and APS. Drugs used in the prophylaxis of SLE/LN relapse during pregnancy are: HCQ, steroids, azathioprine, cyclosporine and tacrolimus. Mycophenolate mofetil (MMF), cyclophosphamide, methotrexate and leflunomide should not be used [17]. Although this recommendation is not supported by a prospective study, it is claimed that low molecular weight heparin should be included in the therapy of every pregnant woman whose albumin concentration in plasma is below 20–25 g/L, no matter what is the cause of renal disease [16].

The intensification of obstetric folllow-up albo surveillance in the form of frequent analysis of biometric parameters and Doppler evaluation (especially in the third trimester to identify any disorders of the placenta) is essential during pregnancy. It is vital to perform fetal echocardiography if arrhythmia or myocarditis is suspected (this also concerns women with anti-Ro/SSA and anti-La/SSB antibodies) [13].

Another document quoted is the statement of *the Italian Study Group on Kidney and Pregnancy*. Its contents are in majority very similar to the above-presented recommendations. Experts list the absolute contraindications to pregnancy in SLE: severe forms of lung involvement (pulmonary restriction), severe pulmonary hypertension, advanced heart failure, and a history of severe pre-eclampsia (HELLP syndrome) in an earlier pregnancy. A creatinine level > 2.5 mg/dL was considered a relative contraindication. The authors consider IVIg therapy for lupus flares during pregnancy to be safe (which is true) and effective (for which there is no evidence). They emphasize the necessity of increasing the doses of steroids in the perinatal period in women with lupus and stress the necessity of intensified monitoring of women after delivery, considering the subsequent 6–12 months as a period of increased risk of disease recurrence [14].

THE INFLUENCE OF SLE, LN AND APS ON FETUSES AND NEWBORNS

The most important consequences of aPL presence are prematurity and low birth weight secondary to intrauterine dystrophy. APLs have been shown to pass through the placental barrier, but thrombotic complications in fetuses and neonates are infrequent. The consequences of anti-Ro/SSA and anti-LA/SSB antibodies are also a rare complication. It has been reported that < 2% of infants born to women with these antibodies may develop CB,

while 7–20% may develop extracardiac manifestations of lupus (neonatal lupus; NLE). Grade III atrioventricular block is inflammatory and develops on the basis of an infiltrate composed of macrophages and giant cells within the atrioventricular node, with its secondary fibrosis and calcification (there are no valvular or other structural abnormalities in the heart that could explain the conduction disturbances). Neonatal lupus usually presents with transient and fully reversible increases in transaminase activity, asymptomatic cytopenias (most commonly thrombocytopenia), and skin lesions. Because of the risk of CB, repeated fetal cardiac echocardiography between 18 and 28 weeks of gestation is extremely important, and treatment with fluorinated steroids should be started, which are able to easily cross the placental barrier and thus exert anti-inflammatory effects in the fetus (such steroids are dexamethasone and betamethasone). HCQ, IVIg, and plasmapheresis have also been proposed (none of these methods have been objectively verified for their effectiveness in reducing CB risk). Cardiostimulation is necessary for more than 75% of babies born with this abnormality [8, 9, 17].

PREGNANCY IN WOMEN WITH SMALL VESSEL VASCULITIS (SVV)

Most cases of vasculitis affect women over the age of 40 (except for non-renal Takayasu's arteritis). In younger women, the intensity of life-saving immunosuppressive treatment (with exposure to high doses of cyclophosphamide) often compromises the chances of pregnancy. This means that pregnancies in women with *small vessel vasculitis* (SVV) are rare events. Similarly, as in the case of SLE, a relatively good prognosis is associated with those cases in which pregnancy occurs in persons with long-lasting remission (such cases are usually published and from these reports, we gain knowledge about the course of pregnancy in SVV) [14, 17, 19]. The infrequent occurrence of pregnancies in women with SVV (which occur at a rate of a few cases per million people) makes it challenging to find reliable statistics on the risk of individual complications. A number of cases have been described of the occurrence of disease flares and the first (*de novo*) manifestations of SVV during pregnancy. ANCA-positive vasculitis SSV manifests for the first time during pregnancy more frequently compared to other autoimmune diseases [19]. It is estimated that exacerbations of ANCA-positive vasculitis SSV can affect up to 35–45% of pregnancies in this group of patients, preterm deliveries are found in 23–36% of cases, and data on pregnancy loss are highly variable (from 5 to nearly 30%). Flare-ups are manifested, among others, by severe pulmonary hemorrhages, rapidly progressive nephritis, polyneuritis, myocarditis, heart failure (several case reports described exacerbation or *de novo* manifestation of the disease which ended in the death of the pregnant woman) [17]. Toward the end of pregnancy, women with granulomatosis with polyangiitis are relatively more likely to develop potentially life-threatening subglottic stenosis.

In the treatment of SVV during pregnancy, no EBM-based guidelines can be given. Clinical remission at the time of pregnancy seems to offer hope for an uncomplicated course of pregnancy. Thus, general principles of immunosuppression, similar to those discussed for lupus (and with the same drug groups), should be used. In the prevention of complications, acetylsalicylic acid given chronically should always be considered. Steroids, azathioprine, IVIg, and plasmapheresis are available for SVV flares [14]. Nevertheless, in severe, life-threatening SVV flares, it sometimes becomes necessary to administer cyclophosphamide (being aware of the risk to the fetus). Maternal and fetal deaths caused by the primary disease have been described — due to pregnancy, the treatment of SVV was limited to steroids and azathioprine, which were proved to be insufficient. It seems that rituximab (otherwise formally registered for the treatment of SVV) is currently the best choice in these most dramatic cases of the disease [17]. The prognosis is particularly unfavorable in polyarteriitis nodosa, in which a very high rate of death during and shortly after pregnancy has been described, with many cases of the disease being diagnosed only at autopsy [19].

More recent summaries allow for greater optimism in determining the prognosis for pregnancy in women with SVV. Analysis of 51 pregnancies in 29 women with vasculitis (Takayasu's disease, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, Behçet's disease) revealed that although the duration of pregnancy was significantly shorter compared with the control group matched for a number of pregnancies, demographic characteristics, ethnicity, age, *body mass index* (BMI), smoking, and other features

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(36 weeks 2 days *vs.* 40 weeks 2 days; $p < 0.03$), and birth weight of babies was significantly lower (median 3000 *vs*. 3800 g; $p = 0.004$), the rates of miscarriage, live births, obstetric complications, and even episodes of preeclampsia did not differ between groups. The recurrence rate was 31% (including 1 patient with granulomatosis with polyangiitis in the third trimester who required surgery due to the development of critical subglottic stenosis). However, it should be emphasized that only in one of the analyzed pregnancies the diagnosis of the disease was established during the pregnancy, whereas in the remaining patients, the median time from diagnosis to pregnancy was 3 years and all women were in remission at the time of pregnancy [20].

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