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Polish Society of Nephrology Working Group — management of the pregnant woman with chronic kidney disase (part II)

Abstract

This recommendations present diagnosis and management kidney diseases in pregnancy primary and secondary glomerular diseases, acute kidney injury, hypertension, urinary tract infections, inherited kidney disordes, kidney transplantation.

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

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PREGNANCY IN GENETIC KIDNEY DISEASES

Genetic kidney diseases are a heterogeneous group of nosological entities including cystic kidney diseases, Alport syndrome (AS), inherited tubulopathies, and congenital nephrotic syndromes. *The most common genetic kidney disease is the autosomal dominant polycystic kidney disease (ADPKD) followed by the Alport syndrome. As in all nephropathies, maternal and infantile prognosis in patients with genetic kidney disease depends mainly on GFR* (glomerular filtration rate) proteinuria, and arterial hypertension values [1, 2]. Nonetheless, due to their specifically systemic character, genetic diseases are characterized by additional, frequently disease-specific pregnancy complications, as well as the risk of the disease being transmitted to the progeny [2]. This places a particular responsibility on physicians and requires multidisciplinary and personalized care. The task is even more difficult as the experience in the management of pregnant patients with genetic kidney diseases, rare as they are, is very limited and therefore no evidence-based recommendations are available in this respect.

CYSTIC KIDNEY DISEASES

At least 95 genes have been identified as responsible for the development of cystic kidney diseases. Ciliopathies, including autosomal dominant polycystic kidney disease (ADPKD), autosomal recessive polycystic kidney disease (ARPKD), nephronophthisis (NPHP), Bardet-Biedl syndrome (BBS), Meckel-Gruber syndrome (MKS), and Joubert syndrome. Renal cysts are also encountered in tuberous sclerosis complex (TSC) and von Hippel-Landau syndrome (VHL). Although all these diseases are classified as rare due to their low incidence, their total accumulated risk amounts to approximately 1:1000 live births.

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Autosomal dominant polycystic kidney disease (ADPKD) is the most common ciliopathy and the most common genetic kidney disease. Family history and the high availability of imaging studies are conducive to early diagnosis, and as the result, numerous patients receive nephrological treatment before the onset of any disease complications. This is the most preferred situation from the point of view

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of pregnancy planning. Early stages of CKD (G1 and G2) are usually not associated with complications during pregnancy, nor do they increase the risk of renal disease progression. However, multiparity of four or more pregnancies is considered to contribute potentially to the deterioration of kidney function.

PREGNANCY PLANNING AND PREPARATION

Potential parents should be notified of the 50% risk of the disease being transmitted to the progeny. If partners wish to obtain genetic counseling including an overview of possible options for prenatal (or preimplantation) diagnostics, they should be referred to a clinical genetics specialist. More detailed information can be found in the recommendations of the Working Group of the Polish Society of Nephrology (PTN): "Principles for the management of patients with autosomal dominant polycystic kidney disease and other cystic kidney diseases: molecular diagnostics and genetic counseling in ADPKD" [3].

In the case of concomitant polycystic liver disease (PLD), patients should be informed of the risk of disease worsening upon exposure to exogenous estrogens and progesterone found in hormonal contraceptive agents. There is no evidence suggesting that the route of administration of these agents is relevant to the risk of PLD progression, but the choice of transdermal route is reasonable if the patient insists on the use of this method of contraception [4].

Patients should be informed of the risks of possible pregnancy, both in relation to their health and to the health of the child. The risk depends on the stage of chronic kidney disease (CKD) and the status of arterial hypertension, proteinuria, and other ADPKD complications (e.g. urolithiasis, aneurysmal disease of the aorta and cerebral vessels, heart valve malformations). Females with ADPKD and renal insufficiency are, as women with renal insufficiency due to other etiological factors, at an increased risk of early loss of pregnancy, face difficulty in controlling the arterial pressure and risk accelerated loss of renal function.

The most common early complication of ADPKD is arterial hypertension, and therefore preparation for planned pregnancy should include ambulatory blood pressure monitoring (ABPM) measurements. This should facilitate the correct diagnosis of pregestational AH rather than that of pregnancy-induced hypertension.

It is necessary to analyze the pharmacological history and preemptively discontinue any renin–angiotensin–aldosterone system inhibitors (RAA system, teratogenicity, the risk of acute renal failure in the child). Patients planning pregnancy should take folic acid at the dose of 400 μg/day.

Pre-pregnancy abdominal ultrasound examination is recommended for indicative evaluation of total kidney volume (TKV) and total liver volume (TLV) (or at least the degree of the enlargement of both organs), as well as to exclude urolithiasis and complicated cysts.

Inclusion of cerebral vessel imaging examination, usually an magnetic resonance imaging (MRI) scan without contrast, as part of pregnancy preparation, is a matter of dispute. Despite its obvious costs, the modality has the advantage of being safe for pregnant women. Nonetheless, cerebral MRI scans are not performed in pregnant women unless clearly indicated. An MRI scan performed before conception is a reasonable decision as it facilitates exclusion of any lesions requiring intervention and or posing potential risks associated with natural labor. The controversy may be because the results of MRI scans without contrast enhancement are not 100% certain in exclusion of subarachnoid bleeding (SAH) and the probability of detecting aneurysms in patients with no relevant family history is low. However, it is important to remember that most cases of SAH occur with no preceding symptoms, and therefore is the role of MRI screening should not be underappreciated?

COMPLICATIONS DURING PREGNANCY

ARTERIAL HYPERTENSION

The management of arterial hypertension in patients with ADPKD does not differ from the regular management of hypertension in pregnancy.

Our experience shows that ambulatory blood pressure monitoring performed at least once per trimester is particularly helpful. ABPM facilitates therapeutic decision-making and allows an earlier initiation of treatment as compared to measurements taken in the physician's office. Late initiation of treatment of arterial hypertension during the pregnancy usually leads to higher doses of medication and more difficulties in controlling the pathology.

In women with ADPKD in whom pharmacotherapy is required in the management of hypertension, a significant increase in blood

pressure is to be expected in late pregnancy. An increase to values of ≥ 170/110 mmHg should be considered as an indication for emergency hospitalization.

Small doses of aspirin (75–150 mg/day) as recommended since gestation week 12 in hypertension-complicated pregnancies to reduce the risk of preeclampsia are controversial in ADPKD patients. The impact of this treatment on the risk of SAH and on the risk of bleeding to the kidney cysts is unknown. Decisions in this regard should be made on a case-by-case basis.

PROTEINURIA

Albuminuria and low proteinuria are parts of the clinical presentation of ADPKD and may be present before the pregnancy. On the other hand, nephrotic syndrome (NS) is unusual for ADPKD.

Reduced albuminemia, increased cholesterol, and swelling may develop in advanced physiological pregnancy. The onset of these symptoms in addition to the previously observed proteinuria, which increases in late pregnancy due to increased intraabdominal pressure dependent on the TKV and TLV, may result in the clinical presentation of typical NS that should be differentiated from preeclampsia.

URINARY TRACT INFECTION

Line in women without ADPKD, urine culture should be performed in the first trimester to exclude and treat any significant bacteriuria.

Cyst infection is a serious complication with a tendency to recur. The use of cyst-penetrating quinolone antibiotics s is contraindicated in pregnant women. The second choice is trimethoprim-sulfamethoxazole, which is absolutely contraindicated in the first trimester due to folic acid antagonism. It should also not be administered before delivery as it may cause kernicterus in the child. When making the treatment choice (usually on an empirical basis), the severity of infection should be considered. Antibiotics considered safe during pregnancy include cephalosporin or a combination of amoxicillin/clavulanic acid; carbapenems may also be used in specific situations. Microorganisms responsible for cyst infections are multi-resistant (most commonly Gram-negative bacilli), and conservative therapy in the infection of cysts > 5 cm in diameter usually ends in a failure.

BLEEDING TO CYSTS

Bleeding to cysts is a common complication and may also occur in pregnancy. It is usually manifested by pain with micro- or macroscopic hematuria. In most cases, the disease is self-limiting and resolves within 2–3 days, the treatment of choice includes staying in bed and the use of analgesics. Exclusion of concomitant infections (CRP, urine culture) is very important.

UROLITHIASIS

Urolithiasis is a frequent complication of ADPKD, with renal colic possibly also occurring during pregnancy. Factors contributing to the development of urolithiasis include slow urine stream and metabolic factors (e.g. reduced urinary content of calcification inhibitors such as magnesium and citrates). Pregnancy intensifies these risk factors while increasing calciuria and uricosuria. This promotes the accumulation of new deposits, as well as the growth of deposits already present before pregnancy.

RENAL PAIN

Renal pain is a characteristic complication of ADPKD and is usually exacerbated during pregnancy. The treatment of renal pain is problematic as chronic pain therapy is contraindicated in this period. The current guidelines for pain management in patients with ADPKD do not apply to pregnant patients. In such cases, rest and physical therapy should be recommended, accompanied by low acetaminophen doses in selected cases.

RENAL FAILURE

One should keep in mind that the formulas for the estimation of glomerular filtration rates are unreliable in pregnant women and should not be used in CKD staging or therapeutic decision-making. The increase in GFR of up to 50%, as characteristic for normal pregnancy, may not be observed in females with more advanced stages of CKD.

ADPKD IN THE PRENATAL PERIOD

Prenatal manifestations of ADPKD in the form of fetal kidney cysts are observed in less than 1% of cases, with the most common form consisting of increased corticomedullary differentiation. Therefore, detailed differential diagnostics is required for prenatal kidney

An increase to values of ≥ 170/110 mmHg should be considered as an indication for emergency hospitalization

cysts in the children of parents with ADPKD. Urinary stasis and caliectasis must be considered in differential diagnostics as these causes of renal impairment are potentially reversible and may require surgical intervention. Such presentation is quite likely as ciliopathies are associated with a higher incidence of CAKUT. Kidneys of the unborn child with ADPKD may be enlarged, but never as much as in ARPKD. No changes in the amount of amniotic fluid are observed in typical cases.

DELIVERY

ADPKD is not a contraindication for a natural delivery. Final decisions are made on a case-by-case basis by attending obstetricians.

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE

ARPKD is an autosomal recessive disease. The symptoms of the disease are the consequence of mutations within both alleles of the *PKHD1* gene responsible for fibrocystic production. Prenatal manifestation of ARPKD is very common and is usually observed as early as gestation week 20. Both fetal kidneys may be massively dilated and hyperechogenic, with no clear corticomedullary differentiation. No other lesions are detected prenatally in ARPKD. The concomitance of polydactyly, anomalies within the nervous system, facial skeleton, and reproductive system should raise the suspicion of other causes of polycystic disease (Bardet-Biedl and Meckel-Gruber syndromes, both inherited in autosomal recessive pattern). Oligohydramnios is a strong prognostic factor for renal failure at birth.

ARPKD is a disease with a severe prognosis with up to 30% of newborns dying due to respiratory failure. Renal insufficiency requiring renal replacement therapy usually develops in childhood. ARPKD is characterized by concomitant liver pathologies manifested by fibrosis, frequently complicated by portal hypertension.

Cases of uncomplicated pregnancies in patients with ARPKD were described in the literature, albeit the disease was abnormally mild in most of these cases, presenting with relatively minor renal impairment and no portal hypertension [5]. In patients with ARPKD having undergone renal transplantation, the maternal and infantile prognosis is determined not only by the function of the transplanted kidney, the history of hypertension, and acute rejection but also by the presence of portal hypertension. Pregnancy increases the volume of circulating blood and leads to an increase in portal hypertension and the risk of bleeding from esophageal varices. In women diagnosed with esophageal varices, the risk of bleeding during pregnancy is as high as 25%.

TUBEROUS SCLEROSIS COMPLEX

TSC is an autosomal dominant disease, and therefore the risk of the disease being transmitted to the progeny is 50%. The disease is caused by a loss of function mutation within the *TSC1* or *TSC2* gene. Mutations within the *TSC2* gene responsible for the production of tuberculin, are more common and involve a more severe course of the disease. The shared location of the *TSC2* and *PKD1* genes on chromosome 16 is conducive to the concomitance of TSC and ADPKD, which occurs in approximately 2% of cases.

Manifestation of the disease can be extremely different in members of the same family. In addition, numerous cases are caused by *de novo* mutations, and therefore patients may present with no family history. The diagnosis of TSC should be based on diagnostic criteria published e.g. in the "Principles for the Management of Patients with Renal Manifestations of Tuberous Sclerosis: Position of the Tuberous Sclerosis Working Group of the Polish Society of Nephrology" [6].

Renal injury in TSC occurs in 48 to 80% of patients. Renal manifestations of TSC, including angiomyolipomas (AML) and kidney cysts, are more common at adult age and are the second most common cause of premature mortality associated with the disease. End-stage renal failure may also develop in the course of TSC.

PREGNANCY PREPARATION IN TSC PATIENTS

Pregnancy-planning patients diagnosed with TSC or classified as having a high risk of TSC should be referred to genetic counseling. As part of the counseling, potential parents should be provided with information on the available options for prenatal and preimplantation diagnostics. The diagnostic procedure in potential mothers does not differ from that recommended by the PTN Working Group for all TSC patients. A multidisciplinary approach should be used. In patients with asymptomatic AMLs > 8cm in size or patients with an increased risk of bleeding (e.g. microaneurysms),

preventive measures (surgical or endovascular) are recommended before the planned pregnancy. This should also be considered in cases of asymptomatic AMLs > 4 cm in size. In each case, decisions should be made by interdisciplinary teams, and patients should be informed of the risks and the possible failure of such procedures.

Another important element of pregnancy preparation consists in the modification of potentially teratogenic antiepileptic therapies, and discontinuation of RAA system inhibitors and/or mTOR inhibitors. Although cases of unremarkable course of pregnancy were reported in patients receiving mTOR inhibitors, none of the available preparations were approved for use in pregnant patients. Medication should be discontinued at least 8 weeks before the planned conception.

Just as in patients with PLD, hormonal estrogen-containing contraception is not recommended in TSC patients. The use of these agents might increase the risk of angiomiolipoma (AML) rupture and/or (lymphangioleiomyomatosis) LAM progression.

MANAGEMENT OF PREGNANCY

There are no recommendations regarding pregnancy management in patients with TSC.

The available literature suggests that pregnancy in a TSC patient is to be considered a high-risk pregnancy [7]. Complications may occur in as many as 43% of cases and include preeclampsia, oligo- or polyhydramnios, inhibition of intrauterine fetal growth, premature rupture of membranes, premature placental abruption, and intrauterine fetal death.

In mothers with normal or slightly reduced GFR pregnancy does not seem to accelerate the progression of CKD.

AML rupture is TSC-specific and a complication in pregnancy. Pregnancy is conducive to this complication and therefore, it should be considered in every case of hypotonia, abdominal pain, or shock. Embolization and subsequent steroid therapy are the treatment of choice in case of AML bleeding.

Estrogens also exacerbate the course of pulmonary lymphangioleiomyomatosis (LMA), which is present in as many as approximately 80% of patients with TSC. This results in an increased risk of spontaneous edema and lymphorrhea within the pleural or peritoneal cavity, potentially leading to respiratory failure [8].

Patient care must be provided by multidisciplinary teams consisting of obstetricians and nephrologists, as well as neurologists, pneumologists, radiologists, ophthalmologists, and anesthesiologists.

PRENATAL DIAGNOSIS OF TSC

Prenatal diagnosis of TSC is made on the basis of rhabdomyoma detected in fetal echocardiography. Fetal MRI should also be considered to exclude the presence of brain lesions. Since the presence of a rhabdomyoma increases the risk of generalized fetal edema, weekly ultrasound monitoring of the fetus is recommended in such cases.

VON HIPPEL-LINDAU SYNDROME

VHL is an autosomal dominant disease, which, like in the case of ADPKD and TSC, results in a 50% risk of the disease being transmitted to the progeny. In 20% of cases, the disease may result from *de novo* mutations, which may delay diagnosis due to the absence of positive family history. Sometimes, the first diagnosis is made during pregnancy due to hormonally-accelerated growth of hemangioblastomas within the central nervous system [9].

VHL occurs at an incidence rate of 1:53 000. Clinical manifestations within the urinary tract include numerous foci of renal cell carcinoma (RCC), and therefore patients are referred to the attention of the nephrologist. There are two types of VHL that differ in the risk of pheochromocytoma development. VHL type 1 is present in families without pheochromocytoma (ca. 90%). In some cases, adrenal tumors are the first manifestations of VHL type 2, presenting a very high risk for potential pregnancies. If possible, pheochromocytoma should be treated by surgical means before conception. In untreated cases, the control of arterial hypertension during pregnancy poses a major challenge. As a rule, α-blockers should be used in the perinatal period as maternal and fetal mortality may reach up to 48%. In other cases, the prognosis for pregnancy in patients with VHL is much better, with child survival of 96.4% and maternal complications rate of 5.4%.

Patients with VHL require multi-specialist care including regular eye fundus examinations, non-contrast-enhanced MRI scan of the CNS acquired at about gestation week 16, as well as assessments of blood and urine catecholamine levels in each trimester.

There are no clear recommendations regarding the preferred method of delivery

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and usually, each case is treated individually. Vaginal delivery is not recommended due to the risk of uncontrolled arterial hypertension, increased intracranial pressure, and bleeding into the CNS.

ALPORT SYNDROME

Alport syndrome is related to the essential development advanced risk of chronic stages kidney disease in women too

The disease may be inherited in X-linked, autosomal recessive, or autosomal dominant patterns. The most common form (about 80% of cases) of the Alport syndrome (AS) consists of the mutation of the *Col4A5* gene with a sex-linked inheritance pattern. Until recently, the disease was wrongly believed not to develop or to develop with a very mild course only in female carriers of the abnormal genetic variant. Today, AS is known to be associated with the risk of advanced CKD stages in women with a mutation in the *COL4A5* gene being as high as 40%. As a result, the term "carrier" has been withdrawn from use in the most recent classification. In families with autosomal recessive (*COL4A3*) and autosomal dominant (*COL4A4*), inheritance patterns, fully symptomatic disease also develops in women.

Like in other nephropathies, the prognosis for pregnant AS patients depends on GFR, as well as the proteinuria and arterial hypertension status. Experience in this area is very limited; however, pregnancy complications were observed in all patients with fully symptomatic disease. All cases involved elevated proteinuria observed after gestation week 20, the requirement for accelerated delivery, and the associated low birth weight. A case of acute kidney failure and placental dysfunction before gestation week 25 resulting in stillbirth was also reported. The impact of pregnancy on the progression of CKD in SA patients is unknown.

If planning to be pregnant, patients with SA should be informed of the potential maternal and infantile risks, as well as of the risk of transmitting the disease to their progeny [10].

INHERITED TUBULOPATHIES

Inherited tubulopathies are a heterogeneous group of rare diseases with a spectrum of symptoms resulting from abnormal function of renal tubules. Abnormal tubular function leads to electrolyte balance, acid-base balance, and bone metabolism disorders, as well as abnormal osmoregulation and blood pressure control. The disease is usually diagnosed in childhood. In physiological pregnancy, changes in tubular function result in glucosuria, increased loss of bicarbonates leading to mild metabolic alkalosis, calciuria, and decrease in urine osmolality. All of these changes may exacerbate the course of tubulopathy and result in milder cases being diagnosed, for the first time, during pregnancy [11].

BARTTER AND GITELMAN SYNDROMES

Both syndromes have a similar clinical presentation and lead to urinary loss of sodium and hypokalemia. One should keep in mind that the increased demand, hemodilution, increased GFR, as well as nausea and vomiting associated with pregnancy, may increase hypokalemia and hypomagnesemia. Hypokalemia may have serious consequences since sudden cardiac deaths and rhabdomyolysis were described in both syndromes. The strict control of electrolyte levels, as well as potassium and magnesium supplementation, are required in the management of patients with Bartter and Gitelman syndromes.

It also seems that both syndromes may be associated with an increased risk of oligohydramnios; however, no complications are encountered in most carefully supervised pregnancies [12].

GORDON SYNDROME

The pathogenic factor in Gordon syndrome consists in increased activity of the sodium-chloride cotransporter (NCC) as manifested by hyperkalemia, arterial hypertension, hypercalciuria, mild metabolic acidosis, and low aldosterone levels (pseudo-hypoaldosteronism type 2). Hypertension is drug-refractory and, in principle, sensitive to thiazide diuretics. Regardless of the controversy over the use of thiazide diuretics in pregnancy, they appear to be a reasonable therapeutic choice in Gordon syndrome, and the treatment should not be interrupted.

NEPHROGENIC DIABETES INSIPIDUS

Nephrogenic diabetes insipidus is a rare disease caused by X-linked mutation in the vasopressin receptor V2 gene or, less frequently, an autosomal recessive mutation in the aquaporin 2 gene. If the symptoms of diabetes insipidus (polydipsia, polyuria, dehydration, hypernatremia) develop for the first time during the pregnancy, acquired causes of diabetes in-

sipidus, including pregnancy-induced diabetes insipidus, should be excluded first [13].

If nausea and/or vomiting occur, as well as while preparing for medical procedures (cesarean section) and during labor, intravenous hydration with hypotonic solutions should be provided to the mother. Monitoring of arterial pressure, heart rate, fluid balance, body weight, and electrolyte metabolism is also required.

FANCONI SYNDROME AND HEREDITARY HYPOPHOSPHATEMIC RICKETS

Most of the genetically determined pathologies of the proximal tubules lead to Fanconi syndrome as characterized by glucosuria, phosphaturia, calciuria, aminoaciduria, uricosuria, and metabolic acidosis. Chronic phosphaturia leads to bone demineralization and, consequently, to rickets or osteomalacia, depending on the patient's age. A similar clinical presentation is observed in hypophosphatemic rickets, i.e. in a spectrum of disorders leading to hyperphosphaturia as a result of phosphatonin (FGF23)-dependent and independent mechanisms. It is inherited in an X-linked, autosomal recessive, or autosomal dominant, manner. Pregnancy in hypophosphatemic patients usually requires intensification of phosphate supplementation and the delivery of calcitriol. The latter is used cautiously apart from pregnancy due to the risk of hypercalcemia.

GENETICALLY DETERMINED CONGENITAL NEPHROTIC SYNDROMES

These are rare disorders caused by the disturbed structure of renal glomeruli. They are associated with poor prognosis and lead to end-stage renal failure in childhood. The most common type of these disorders is the congenital nephrotic syndrome (CNS) of the Finnish type, associated with the improper structure of nephrin, a protein present within the slit diaphragm of the glomerular basement membrane. The disease follows the autosomal recessive inheritance pattern (the risk of disease in the child amounts to 25%) and is caused by the mutation in the *NPHS1* gene. Less common mutations may occur in *PLCE1*, *WT1*, *NPS2*, and *LAMB2* genes.

Due to the grave prognosis, no experience has been reported to date in relation to pregnancy in patients with congenital nephrotic syndrome.

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ACUTE KIDNEY INJURY IN PREGNANCY

INTRODUCTION

Acute kidney injury (AKI) is an acute/sudden deterioration/loss of kidney function leading to the retention of urine and other nitrogen-based metabolic products, as well as dysregulation of extracellular fluid volume and electrolyte balance. The term "acute kidney injury" replaced the previously used term "acute renal failure" (ARF) leaving space for separate consideration of small reductions in kidney function resulting in no apparent organ failure. yet being of significant clinical importance and leading to increased morbidity and mortality. AKI in the course of pregnancy may be caused by any of the disorders leading to AKI in the general population. However, AKI may also be associated with certain pregnancy complications specific to each pregnancy trimester [1, 2].

A number of consensus-based definitions of AKI were developed for use in the general population so that a unified, quantitative definition of the disorder could be used. These include the RIFLE (R — risk, I — injury, F — failure, L — loss, E — end stage renal disease) and the Acute Kidney Injury Network (AKIN) definition, as well as the "Kidney Disease: Improving Global Outcomes (KDIGO)-modified AKIN definition. " However, it is not clear whether the AKI consensus criteria apply for pregnant patients. This is because the glomerular filtration rate (GFR) is significantly increased (by about 50%) in pregnancy, which results in a reduction of the baseline serum creatinine level as compared to similarly healthy, non-pregnant individuals. No routine measurements of serum creatinine levels are carried out by obstetricians either before pregnancy or in early pregnancy. Therefore, the apparently "normal" serum creatinine concentrations (e.g. 0.7 to 0.9 mg/dL) may represent a significant increase from the baseline value which remains unrecognized at the time of presentation.

EPIDEMIOLOGY

AKI during pregnancy is rare in the developed world. The actual prevalence is difficult to estimate due to differences in diagnostic criteria. Most reviews estimate that in countries with adequate pre-partum care, only about 1 in 20 000 pregnant patients suffer from an AKI of severity requiring renal replacement therapy (RRT) [3]. The prevalence rates may be significantly higher in countries where pre-partum care is less available and where illegal abortions are performed [4]. Although some single-center studies from India and Africa reported rates as high as 10 to 20 percent, an Egyptian survey reported an AKI rate corresponding to dialysis being required in only 0.6 percent in the population of 5600 subjects [5].

ETIOLOGY

The most common causes of AKI in pregnancy depend on the trimester. AKI in early pregnancy (< week 20) is most commonly due to:

— prerenal disease due to hyperemia ;
— acute tubular necrosis (ATN) resulting from septic abortion;
— AKI related to viral infection (e.g. influenza), bacterial infection, and/or sepsis.

Some disorders may be conducive to AKI in later pregnancy or after childbirth [1, 2]. These include

— severe preeclampsia;
— severe preeclampsia with HELLP syndrome;
— thrombotic thrombocytopenic purpura (TTP, acquired or hereditary) or complement-mediated hemolytic uremic syndrome (HUS);
— acute fatty liver of pregnancy (AFLP) (see "Acute fatty liver of pregnancy");
— ATN or acute cortical necrosis (premature placental abruption, intrauterine fetal death, or amniotic fluid embolism);
— AKI related to non-steroidal anti-inflammatory drugs (NSAIDs).

In addition to these conditions, acute pyelonephritis and, less commonly, urinary tract obstruction were associated with AKI in pregnant women.

Pregnancy-related AKI may also develop in the post-partum period. It may be due to the above-mentioned reasons that had been present during pregnancy delivery and did not disappear following the delivery (e.g. preeclampsia, HELLP). Atypical pregnancy-related HUS usually develops in the post-partum period, although some patients may experience preeclampsia during pregnancy. AKI secondary to ATN may develop due to hemodynamic stress associated with hemorrhage or sepsis.

Preeclampsia with or without HELLP — preeclampsia is the most common cause of AKI during pregnancy. Preeclampsia refers to

a *de novo* onset of hypertension and proteinuria or other systemic symptoms (including thrombocytopenia, elevated liver enzymes, AKI, pulmonary edema, cerebral and/or visual disorders), usually after gestation week 20 in a female with normally low blood pressure.

Preeclampsia is observed in 3 to 5 percent of all pregnancies; the risk is increased in women with hypertension, diabetes, or chronic kidney disease (CKD) from any causes [6].

In most women with preeclampsia, the GFR is decreased on average by only 30 to 40 percent, resulting in only a slight increase in serum creatinine levels [7]. AKI requiring renal replacement therapy (RRT) is rare except in patients with very severe preeclampsia (e.g. with severe arterial hypertension, thrombocytopenia, elevated liver enzymes, pulmonary edema, cerebral and/or visual disorders) and when associated with hemorrhage and ischemic acute tubular necrosis. HELLP refers to the variant involving hemolysis, low platelet counts, and elevated liver enzymes. AKI is more likely to occur when preeclampsia is accompanied by HELLP [7]. In such cases, AKI is often multifactorial since, in addition to renal lesions characteristic of preeclampsia, such as edema and endothelial cell damage, coagulopathy is observed, which may potentially lead to bleeding, placental abruption, and ATN.

Both the thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are characterized by the presence of fibrin and/or platelet micro clots in multiorgan systems, particularly kidneys and the brain. Presenting signs include thrombocytopenia and microangiopathic hemolytic ischemia with no other evident etiological factor. In many patients, these are accompanied by neurological and/or renal disorders [8, 9]. TTP or HUS may be triggered by pregnancy [10–12].

TTP is caused by the acquired or constitutive deficiency of ADAMTS13, the protein which processes the von Willebrand factor [13]. Pregnancy was shown to cause the onset or recurrence of TTP due to ADAMTS13 deficiency [7].

TTP and HUS differ by onset times. ADAMTS13 deficiency-related TTP usually develops in the second and third trimesters [12]. The levels of ADAMTS13 are usually decreasing in the last two trimesters of pregnancy, potentially contributing to the course of TTP [13–16].

AKI may be present in both pregnancy-related TTP and HUS although it is more common in patients with HUS [12, 13].

TTP or HUS initially developing in pregnant women may recur in subsequent pregnancies, or the recurrent disease may develop in subsequent pregnancies [12, 15, 17, 18]. In general, the diagnosis is based on clinical characteristics. Renal biopsy is usually not performed, at least initially, due to the increased risk of bleeding associated with thrombocytopenia.

Plasma exchange is an important element of the treatment of AKI associated with pregnancy-related TTP or HUS. In pregnancy-related HUS, if no improvement in the AKI is observed, three to five plasma exchange procedures, with eculizumab — a monoclonal, humanized immunoglobulin G (IgG) inhibiting complement activation — may prove effective [7]. Since HUS is usually observed in the post-partum period, fetal toxicity of eculizumab is not a significant problem.

AKI is managed by means of supportive treatment. In addition to plasma exchange and maintenance care, induced labor may be indicated in pregnant patients, particularly if the diagnosis is not reliable. This is because the main differential diagnosis is usually preeclampsia with HELLP which improves after the delivery. If elevated liver enzymes are observed, the diagnosis of HELLP-related AKI is more likely. However, most patients require dialysis in the post-partum period, and therefore RRT considerations are similar to those in non-pregnant adults with AKI.

Renal cortical necrosis was once an important cause of AKI associated with catastrophic obstetrical complications such as placental abruption with massive hemorrhage or amniotic fluid embolism [7]. However, renal cortical necrosis is generally considered to be rather rare in developed countries and responsible for as little as 1 to 2 percent of all AKI cases [7].

Patients with cortical necrosis present with a sudden onset of oliguria or anuria, frequently accompanied by abundant hematuria, side pain, and hypotension [35, 36]. The oliguria/anuria, hematuria, and side pain symptom triad are rare in AKI developing in pregnant patients from other causes.

The diagnosis can usually be established by ultrasound or computed tomography (CT) scans which show hypoechogenic or hypodense regions in the renal cortex [19].

No specific therapy has been demonstrated to be effective in this disorder. Many patients require dialysis, but between 20 and 40 percent of them experience partial recov-

ery with creatinine clearance stabilizing in the range 15 and 50 mL/min [20].

Urinary tract obstruction — relaxation of the smooth muscles of the urethra and compression by the heavy uterus — lead to a mild extension of the collecting system [21, 22].

This functional hydronephrosis, more pronounced on the right, is detectable by ultrasound but usually not associated with renal impairment.

In some cases, compression by the uterus is sufficient to cause renal failure [21]. For some patients, diagnosis may be established on the basis of kidney function being normalized in the lateral horizontal position (which reduces uterine compression) and recurrence of obstruction in the supine position. Cases of AKI were reported as caused by urinary tract obstruction resulting from the enlargement of uterine myomas during pregnancy [23].

Obstructive AKI usually resolves with the elimination of obstruction. This can be achieved using a ureteral stent or childbirth [22].

Post-partum NSAID-related AKI — NSAIDs are routinely used in post-partum analgesia, particularly following the cesarean section. AKI may develop, albeit rarely, in these patients if certain predisposing factors, such as reduced volume or preeclampsia, are present.

The diagnostic approach to pregnant AKI patients is similar to that to non-pregnant patients at all stages of pregnancy.

Firstly, non-pregnancy-related causes of AKI including glomerulonephritis, interstitial nephritis, or acute tubular necrosis (ATN) caused by toxins, medications, or hemodynamic stress should be excluded. Causes of prerenal AKI (such as severe hyperemia) or ATN/acute cortical necrosis in the bark (such as sepsis or hemorrhage related to obstetric complications, including placental abruption, prolonged intrauterine fetal death, or amniotic fluid embolism) may also be suggested by medical history.

The following tests should be carried out:

— urinalysis with urine sediments;
— quantitative protein excretion (24-hour urine collection or protein/creatinine ratio);
— urine culture;
— hemoglobin concentration and platelet count with peripheral blood smear to evaluate microangiopathic hemolysis and thrombocytopenia;
— total direct and indirect bilirubin, haptoglobin, and lactate dehydrogenase (LDH) for evaluation of hemolysis;
— serum aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT);
— renal ultrasound scan.

TREATMENT

Treatment should target the specific cause of the AKI. Indications for dialysis therapy are based on normal criteria for non-pregnant patients.

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Alicja Dębska-Ślizień

PREGNANCY IN KIDNEY TRANSPLANT RECIPIENTS

Numerous female kidney transplant (KT) recipients hope to become pregnant. Becoming pregnant is possible for many of these patients as the recovery of hormonal function is observed within several months after the procedure. Nearly one-half of female TK recipients are of reproductive age, and therefore preconception counseling and appropriate pregnancy management are important elements of education and care provided to these patients. The following is an up-to-date overview of the information available on this topic based on the recommendations of the Pregnancy Study Group of the Italian Society of Nephrology (2018) [1], Kidney Disease: Improving Global Outcomes (KDIGO) (2009) [2], and EBPG Expert Group on Renal Transplantation European best practice guidelines for renal transplantation (2002) [3].

BASIC BIOCHEMICAL AND CLINICAL MARKERS EVALUATED BEFORE PREGNANCY

GFR of > 90 mL/min and GFR of 60–90 mL/min define the proper and good function of the transplanted kidney, respectively. Before the TK, renal function should be assessed using the creatinine clearance or the CKD-EPI formula (4).

Absence of proteinuria: proteinuria of < 300 mg/24h, UPCR < 300 mg/g of creatinine; proteinuria between 300–500 mg/24h is considered a "gray zone."

Arterial blood pressure: optimum arterial blood pressure is < 130/80 mmHg; < 140/90 is considered a "gray zone".

INFORMATION FOR THE PATIENT

Patients with worsening renal function or renal failure presenting with arterial blood pressure and proteinuria values exceeding the above limits are advised not to become pregnant as pregnancy is associated with the risk of severe arterial hypertension, increased proteinuria, progressing renal failure, and premature birth with consequences for the child [5, 6]. However, if the patient is determined to have a child, an ethical problem occurs. While the benefits of having a child are obvious, they are at odds with the potential harm to the mother, her kidneys, and her child. Therefore, both the patient and, preferably, also the potential father should be aware of the risks and understand them as they will be the ones to make the final decision in current social circumstances.

The patient should be aware that even with slightly less than optimal values of the above markers (GFR < 90 mL/min, arterial pressure >130/80 mmHg, proteinuria > 300 mg/24h), the risk of complications is increased.

Risk of maternal death negligible and difficult to quantify based on available evidence.

The patient should be aware that even with slightly less than optimal values of the above markers (GFR < 90 mL/min, arterial pressure >130/80 mmHg, proteinuria > 300 mg/24h), the risk of complications is increased

The risk of deteriorating kidney transplant function is low in normal or good kidney function (CKD 1 and 2) and significantly increased in higher stages of CKD as in the case of transplant-naive patients [7]. Renal function should not be evaluated solely based on creatinine concentration. The calculation of glomerular filtration rates using the MDRD or CKD-EPI formulas is unreliable during pregnancy. It is important to assess the dynamics of changes, preferably on the basis of creatinine clearance within 24-hour urine collection.

A de novo onset of proteinuria or an increase in previously observed proteinuria are frequently observed. No uniform standards are available for the assessment of proteinuria (e.g. 24-hour urine collection, UPCR in morning spot urine test) and interpretation of results obtained in the context of KT, but an increase above the pre-pregnancy baseline is a poor prognostic factor. An evaluation of the dynamics of proteinuria in the pre-pregnancy period is also helpful.

Risks to the fetus consist mainly in preterm birth. Premature birth (i.e. birth before gestation week 37) and preterm birth (birth between gestation week 22 and gestation week 37) are more frequent in pregnant women after kidney transplantation (KT). The risk to the fetus increases with the progression of renal failure in the transplant-recipient mother [8]. Potential mothers should be informed of potential complications associated with preterm delivery, such as perinatal death of the child, retinopathy, neurological disorders, and increased risk of arterial hypertension and cardiovascular diseases in adult age [9]. Children born from mothers after KT usually have low birth weight. Intrauterine fetal growth inhibition may be the result of, among other factors, the use of beta-blockers and calcineurin inhibitors.

Fetal malformations are not more common unless the background maternal disease is a congenital abnormality of the kidneys and the urinary tract (CAKUT) or autosomal dominant polycystic kidney disease (ADPKD) and unless teratogenic medications are used in the mother.

Data from the general population suggest that multiple pregnancies in CKD patients are associated with a higher risk of complications [10]. The risk of maternal and fetal complications increases in pregnancies resulting from *in vitro* fertilization [11].

Few reports are available on the long-term development of children. The available data suggest that it is unremarkable except for cases initially complicated with neurological disorders.

"OPTIMUM CANDIDATES" FOR PREGNANCY

Table 1 presents the characteristics of an optimum candidate for pregnancy.

Best results are observed in patients with normal renal function without proteinuria or arterial hypertension. In general, the risk profile is similar to that in CKD patients not receiving a kidney transplant. **Pregnancy in a patient with different characteristics is a considered high-risk pregnancy.**

Abnormal kidney function, proteinuria, and hypertension are defined as independent risk factors for an adverse pregnancy course.

Table 1. Characteristics of an optimum candidate for pregnancy

Kidney function	Proper or good (GFR > 60ml/min, CKD-EPI, creatinine clearance from 24-h urine collection). Creatinine clearance from 24-h urine collection is recommended as this is a recognized method of graft function monitoring in pregnancy.
Proteinuria	None or negligible < 300–500 mg/24h (24-h urine collection — mg/24h, or UPCR mg/g creatinine)
Arterial blood pressure	Normal (< 130/30) or well-controlled (treated with monotherapy, no organ damage)
Low doses of immunosuppressive drugs	Medications allowed: steroids, calcineurin inhibitors, azathioprine
Time since transplantation	Two years; recently reduced to one year; successful pregnancy outcomes were described in the first weeks after transplantation
Patient characteristics	No transplant rejection before conception (non-uniformly specified as 6 months or 1–2 years) Absence of recurrent urinary tract infections Discontinuation of potentially teratogenic drugs at least 6 weeks earlier Age of < 35 years Correct body weight Not diagnosed with diabetes Single pregnancy from natural conception

The simultaneous presence of proteinuria and arterial hypertension increases the risk of premature delivery even if the kidney function is considered to be proper (GFR > 90 mL/min) or good (GFR > 60 mL/min).

An individualized approach should be adopted in patients with borderline risk factor values, i.e. GFR of 60–90 mL/min, arterial pressure of < 140/90 mmHg, and proteinuria of < 500 mg/day.

During pregnancy, the creatinine levels are physiologically reduced; an increase, particularly in the second trimester, is an adverse prognostic factor. In the third trimester, hyperfiltration is reduced, and therefore creatinine level may be slightly increased as compared to the second-trimester values. The glomerular filtration rate and creatinine levels usually return to the pre-pregnancy values within two weeks after completion.

CAUSES BEHIND THE REDUCED RENAL FUNCTION

Acute kidney injury (AKI) — due to the reported variations in creatinine levels, it may be difficult to diagnose AKI during pregnancy [12]. The most common causes of AKI include

1. Post-partum bleeding may cause acute tubular necrosis (ATN). ATN should be differentiated from acute cortical necrosis, especially when bleeding was extensive, and anti-hemorrhagic medications (e.g. tranexamic acid, fibrinogen, recombinant factor VII) were used [12]. Tranexamic acid at cumulative doses of 1–2 g appears safe although dosing should be adapted to the kidney function and limited in the case of anuria [13]. Doppler ultrasound and magnetic resonance imaging (MRI, particularly T2-weighted with gadolinium contrast) help evaluate blood flow in renal cortex vessels.
2. Preeclampsia (PE) is clinically defined as arterial hypertension and proteinuria developing after gestation week 20. PE-related glomerular endotheliosis probably reduces the glomerular capability to induce gestational hyperfiltration, and therefore no typical GFR increase and creatinine reduction are observed in the second trimester in women developing preeclampsia. Severe PE may induce AKI. The disease burden of the pregnant patient, including pre-pregnancy arterial hypertension and diabetes, is further conducive to the development of PE (the so-called maternal PE, as opposed to placental PE).
3. Thrombotic microangiopathy (TMA) must be considered in a patient with renal impairment. TMA in pregnancy may be due to a variety of causes and differentiation between TMA in the course of PE or the HELLP syndrome (TMA affecting the liver), and a TMA episode in the course of TTP (ADAMTS 13 deficiency) or HUS (including aHUS) is very difficult. PE-related TMA usually resolves quickly after pregnancy. The absence of TMA remission should trigger further diagnostics screening for TTP and an HUS, which is particularly important in patients with no known etiology or renal insufficiency or patients with a history of TMA [14].
4. Amniotic fluid embolism is often a fatal pregnancy complication with AKI being one of the characteristics of multiorgan damage.
5. Urological complications — damage to the ureter of the transplanted kidney or the urinary bladder during obstetric procedures.

Kidney transplant rejection may occur either during or after pregnancy. A sudden loss of the placenta (tolerance) in the postpartum period may theoretically induce rejection [15]. In a meta-analysis of 2412 pregnancies carried out by Deshpande et al., transplant rejection was observed in a total of 4.2% of cases. Similar data were obtained in different world regions such as Asia (4%), Europe (3%), North America (3%), South America (5%), with a somewhat higher percentage being observed in the Middle East (8%). According to the authors of this meta-analysis, transplant loss occurred in 5.8% of 103 patients followed up for one year after pregnancy [16]. Transplant rejection during pregnancy and in the post-partum period may follow a particularly aggressive course. It is recommended that patients are thoroughly monitored in this period.

Urinary tract infections occur frequently during pregnancy following KT. Monitoring of pregnant patients is recommended including frequent urine culture assessments (as frequently as twice per month)[17].

Other factors affecting the course of pregnancy:

— age — the older the patient, the higher the risk of PE and premature labor;
— obesity — the risk of arterial hypertension and diabetes;
— type 1 diabetes — the risk of arterial hypertension and congenital malformations (frequently heart-related).

Table 2. Immunosuppressive drugs for chronic use in pregnant kidney transplant recipients [1, 17]

Medication	Key features	FDA classification
Considered safe		
Azathioprine	Teratogenic in an animal model. Not teratogenic in humans, most likely due to the inability of the fetal liver to activate the medicine. The KDIGO and EBP Guidelines suggest switching MMF to azathioprine before pregnancy.	D
Ciclosporin	No risk of teratogenicity. Fetal growth inhibition and preterm birth are considered to be related to maternal disease and non-specific to this medicine. Blood levels may vary. Adverse effects such as increased arterial blood pressure reduced control of glycemia and reduced kidney function should be monitored.	C
Tacrolimus	Effects similar to those ciclosporin, less experience in use.	C
Steroids	Most commonly used and best-studied medications. Short-acting: prednisone, methylprednisolone, and prednisolone; long-acting: betamethasone and dexamethasone No serious malformations have been observed; the risk of labiopalatoschisis should be taken into account. A higher risk of premature rupture of membranes was reported. Other adverse effects include increased risk of infection and gestational diabetes.	C
Use to be avoided		
Mycophenolate	Severe fetal malformations were reported, particularly within the circulatory system and the head, such as malformation or absence of outer and/or middle ear, cleft palate and cleft lip, micrognation. It is recommended to discontinue the drug 6 weeks before the planned pregnancy. It is recommended to inform the patient that the use of MMF by the potential child's father may be teratogenic (see the characteristics of mycophenolate-containing medicinal products).	D
mTOR inhibitors	Teratogenic in an animal model. KDIGO recommends discontinuing the drug when planning pregnancy.	C

Food & Drug Administration (FDA) classification: A — no risk demonstrated in adequately controlled studies in humans; B — no data on potential risks in available studies; C — risk not to be excluded; D — data suggesting that risks are possible; X — contraindicated in pregnancy

IMMUNOSUPPRESSIVE THERAPY

Table 2 presents immunosuppressive medications for use in pregnant women.

Azathioprine, ciclosporin, tacrolimus, and steroids are considered safe. mTOR inhibitors are considered teratogenic (animal experiments), although isolated reports on healthy children being born from by mothers using this group of medicines during pregnancy have been published [18]. Mycophenolate may cause a characteristic syndrome known as MMF embryopathy; the drug should be discontinued at least 6 weeks before attempting to become pregnant [19].

FREQUENCY OF CHECKUPS AND TESTS

Pregnancy in a TK recipient should be considered a high-risk pregnancy even in patients with the optimum characteristics as presented above.

Pregnancy in a TK recipient should be considered a high-risk pregnancy even in patients with the optimum characteristics as presented above

The objective of extensive monitoring consists of early identification of potential complications including acute rejection, arterial hypertension, proteinuria, anemia, urinary tract infection, or coagulation disorders.

Table 3 presents the schedule of visits and additional studies as proposed by the Pregnancy Study Group of the Italian Society of Nephrology [1, 17] and revised by the PTN Working Group. The frequency and nature of the checkup visits depend on the CKD stage as determined from the creatinine clearance in a 24-hours urine collection since eGFR indicators (MDRD and CKD-EPI) are not validated in pregnancy. It is recommended that proteinuria be assessed from the same urine collection sample.

According to Table 3, a patient with good renal function, creatinine clearance of 60 mL/min, no hypertension, and no protein-

Table 3. The schedule of visits and additional examinations during pregnancy after kidney transplantation [1, 17]

CKD stage	CKD 1	CKD 2	CKD 3	CKD 4
Frequency of visits (minimum)	2–4 weeks	2–4 weeks	1–3 weeks	1–2 weeks
Essential biochemical assays	Urinalysis, peripheral blood counts, urine culture, Na, K, Ca, P, albumin, creatinine, urea, uric acid, creatinine clearance, and proteinuria in 24-hour urine collection	As in CKD 1	As in CKD plus, a 24-hours urine collection for the determination of creatinine clearance and proteinuria at least once a month	As in CKD plus, a 24-hours urine collection for the determination of creatinine clearance and proteinuria twice a month
Imaging studies	Doppler ultrasound of the kidney if not performed before pregnancy	As in CKD 1	As in CKD 1	As in CKD 1
Other	Nutritional markers: albumin, total protein, ferritin, folic acid, B12, vit. D	As in CKD 1 Every 10–12 weeks	As in CKD 1 Monthly in patients on a diet	As in CKD 1 Monthly in patients on a diet
Drug levels	It is recommended that the drug levels are determined at least 2x a month in early pregnancy and once a month thereafter Dose adjustment may be necessary			

uria should be seen by a nephrologist every 2–4 weeks; a co-existence of several risk factors should result in visits being held every week. The more severe the impairment, the higher the proposed frequency of check-ups. Patients should be monitored for adverse effects of immunosuppressive therapy and the adequacy of this therapy at the same time (blood drug levels)

Calcineurin inhibitors usually require a dose increase in pregnancy due to an increase in the extracellular fluid volume (about 30%). Many patients require a dose increase by a factor as high as 2. The drug levels can be maintained at low patient-appropriate reference levels as determined before pregnancy.

TREATMENT OF ARTERIAL HYPERTENSION

Although arterial hypertension present before TN should be closely monitored, excessive lowering is not recommended (20). Based on the results of the Control of Hypertension in Pregnancy Study (CHIPS), aiming at the ideal pressure of < 130/8 mmHg, with the values of < 140/90 mmHg being acceptable is recommended in CKD patients under strict supervision [21]. Table 4 lists medications used in pregnancy along with their potential toxicities. The teratogenicity of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) are still a subject of debate. Nonetheless, preemptive discontinuation of these drugs is recommended as of today in patients with no proteinuria, with discontinuation upon the first positive result of pregnancy test (gestation week 4–6) being recommended in patients with proteinuria.

Hypertension and proteinuria developing during pregnancy should be differentiated from the PE. Low doses of acetylsalicylic acid may be used to prevent PE if not contraindicated.

MANAGEMENT OF PROTEINURIA

Data on the management of proteinuria in pregnant KT recipients are limited. Albumins infusions should be avoided. Hyperfiltration can be prevented by limiting protein-rich foods and applying moderate protein restriction as supervised by a dietitian and guided by nutrition markers (Tab. 3).

Special attention is required for patients with proteinuria and arterial hypertension as PE may develop. Low doses of acetylsalicylic acid are indicated in patients with proteinuria, impaired renal function, and arterial hypertension [22]. ASA may prevent PE. The timing of treatment initiation is a matter of dispute. Early initiation (after a positive pregnancy test result) may facilitate the placental formation,

Table 4. Antihypertensive drugs and their potential toxicity to the fetus [1, 17]

Medication	Action	FDA classification
First-line medications		
Methyldopa	Widely used, short-acting medication No negative impact on the fetus and the subsequent growth was observed May not be effective in severe hypertension	B
Nitrendipine (not available in Poland)	Long-acting calcium channel blocker. May cause peripheral edema in CKD patients	C
Labetalol (not available in Poland) — available for direct import	Usually well-tolerated In randomized studies comparable in methyldopa.	C
Second-line medications		
Beta-blockers	Fundamental disadvantage consists in the relationship with fetal growth restriction; atenolol is frequently associated with this complication. Effective in severe hypertension May induce hypoglycemia, hypotension, and bradycardia during labor.	B Pindolol C Metoprolol D Atenolol
Clonidine	A sudden increase in blood pressure after discontinuation is a common symptom. Fetal growth retardation was reported.	C
Alpha-blockers	No studies were carried out, hence not recommended.	C
Diuretics	Usually, to be avoided. Thiazides can be continued.	B Hydrochlorothiazide
Medications that should be avoided		
Nifedipine	Short-acting calcium channel blocker. Contraindicated by FDA, RCOG, and AIPE due to the risk of a rapid drop in blood drop and harmful effects on placental blood flow.	D
ACEis ARBs	Risk of serious malformations, particularly in the 2nd and 3rd trimester of pregnancy.	C 1st trimester D 2nd and 3rd trimester

RCOG — Royal College of Obstetricians and Gynaecologists; AIPE — Associazione Italiana Preeclampsia

while late (2nd trimester) initiation is safer in terms of the risk of bleeding and miscarriage. The matter should be discussed within an interdisciplinary team. Recent studies suggest that including ASA at a minimum dose of 100 mg before gestation week 16 is beneficial in terms of early PE prevention [23].

MANAGEMENT OF IMPAIRED RENAL FUNCTION

When deciding to initiate dialysis therapy, the clinical condition of the patient should be considered including the presence of disturbances that can be modified during dialysis (better control of arterial pressure and hydration status). The dynamics of parameter growth, particularly in relation to blood urea nitrogen (BUN), is much more important than any specific value of creatinine clearance. There is no specific BUN threshold at which dialysis should be started. However, BUN level is a recognized predictor of pregnancy outcomes after the initiation of dialysis treatment (maintenance < 50 mg/dL). Pregnancy should be taken into account when deciding to start dialysis, i.e. the risk and benefits of dialysis should be balanced against the risk of preterm birth in late pregnancy (> 26 weeks or even > 34 weeks). If dialysis is necessary, it should be delivered in an extensive manner (Kt/V should not be taken into account when assessing the adequacy). The percentage of live births was shown to be significantly higher for dialyzes delivered over a total of 36 hours per week as compared to dialyzes delivered over 20 hours per week. The experience with peritoneal dialyzes in pregnant TK recipients is very limited.

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The above recommendations are based on the data obtained in the population of CKD patients [24].

MANAGEMENT OF UNEXPECTED PREGNANCY

This relates to situations where potentially teratogenic drugs have been used dur-

ing the first weeks of pregnancy. It should be noted that none of the medications listed in Tables 2 and 4 is 100% teratogenic, allowing for a case-by-case approach being used. Ultrasound scans are now widely used, and the imaging quality facilitates the detection of numerous malformations at very early stages of pregnancy.

In the case of an unexpected pregnancy in the first year after the KT, patients should be aware of the risks associated with the use of potentially teratogenic drugs and the risk of rejection in the event of a sudden change in treatment. The patient is responsible for the decision regarding the pregnancy.

MULTIPLE PREGNANCY MANAGEMENT

Multiple pregnancies are considered high-risk pregnancies in the general population; likewise, they are considered high risk in CKD patients. Isolated reports on successful outcomes of multiple pregnancies following KR were published in the literature. Multiple pregnancy after KT requires special supervision by an interdisciplinary team.

PREGNANCY FOLLOWING *IN VITRO* FERTILIZATION

In the general population, in vitro fertilization is associated with a higher risk of PE, multiple pregnancy, intrauterine fetal growth retardation, and preterm birth with all its consequences. IVF-assisted pregnancy is possible in patients after KT [25]. Very close supervision is required from an interdisciplinary team of physicians. IVF techniques that are more likely to result in single pregnancy are recommended.

PREGNANCY IN A PATIENT AFTER KIDNEY AND PANCREATIC TRANSPLANT

In a patient with two transplanted organs within the pelvis minor, pregnancy may be associated with an additional risk to the mother and the child [26]. A greater risk of complications such as miscarriage, preterm birth, fetal malformation, and deteriorated function of both organs even following uncomplicated childbirth have been described. Fetal growth inhibition and low birth weight are more pronounced following kidney and pancreatic transplantation as compared to KT alone [27]. The pregnant patient should remain under strict supervision and the multidisciplinary team should include a contribution from a diabetologist even in the case of normoglycemia. The course of pregnancy is burdened by less risk for scheduled pregnancies (at least one year after pancreatic transplantation), normal arterial blood pressure, absence of proteinuria, normoglycemia, and stabilized immunosuppressive treatment.

CONCLUSION

Pregnancy in a recipient of a kidney transplant is possible following the return of hormonal function. In the general population, more than 10% of pregnancies are complicated by hypertension (including 3–5% of cases of preeclampsia) or gestational diabetes [27]. These events are more frequent in patients with CKD starting with the early stages of the disease; this also applies to patients with KT. In addition, pregnancies following KT are associated with the risk of teratogenicity of immunosuppressive medications and transplant rejection. Children are more often born prematurely and present with low birth weights.

The ideal profile for a pregnancy-planning patient includes proper or good kidney function (GFR > 60 mL/min, no or negligible proteinuria < 500mg/dL), normal or well-controlled arterial pressure (monotherapy and no organ lesions), no recent rejection, compliance with recommendations, low doses of immunosuppressive drugs, absence of potentially teratogenic therapies, and an interval of 1–2 years after kidney transplantation. In such an ideal recipient, the risk of renal impairment is negligible, and the chances of a successful outcome are high. In patients becoming pregnant shortly after the transplantation, patients with poorly controlled arterial hypertension, or patients with progressively worsening kidney function the risk of pregnancy complications is increased.

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URINARY TRACT INFECTIONS IN PREGNANCY

Urinary tract infection (UTI) is one of the most common infections in pregnant patients. It is estimated that 5–10% of pregnant women develop one of the various forms of UTI. Urinary stasis and reflux are promoted by physiological changes occurring in pregnancy, such as smooth muscle relaxation and the associated pelvic and ureteral widening, reduced ureteral peristalsis rates, an increased bladder capacity (up to 450–650 mL), and functional failure of the valvular mechanism. In addition, the compression by the enlarged uterus, changes in urinary pH (increase) and urine osmolality (decrease), as well as aminoaciduria and glycosuria, contribute to bacterial growth. The risk factors of UTI in pregnancy are the same as in the general population and include diabetes, urolithiasis urinary tract defects (vesicoureteral reflux), renal diseases, hypertension, immunosuppressive treatment. The most common etiological factors of UTI in pregnancy include E. coli (70% of infections), the others including Klebsiella (3%) and Enterobacter (3%), Proteus (2%), and gram-positive bacteria including group B streptococci (10%). UTIs in pregnancy are always considered complicated. Three clinical forms of pregnancy-related UTI are known, including asymptomatic bacteriuria, acute cystitis, and acute pyelonephritis [1, 2].

ASYMPTOMATIC BACTERIURIA

Asymptomatic bacteria is defined as significant bacteriuria in a subject without any symptoms of urinary tract infection. The same microorganism is detected in urine cultures of 2 consecutive urine samples in a titer of ≥ 105 CFU/mL. Leukocyturia coexisting with asymptomatic bacteriuria is not an indication for antimicrobial treatment. Asymptomatic bacteriuria occurs in 2.5–15% of pregnant women, not more frequently than in non-pregnant women. However, when untreated, it may lead to acute pyelonephritis in the last trimester of pregnancy in about 30–40% of patients, increasing the risk of preterm birth and low neonatal birth weight. Treatment of asymptomatic bacteriuria reduces the occurrence of symptomatic UTIs in pregnancy by 70–80%. It is recommended that all pregnant women are examined for asymptomatic bacteriuria at gestation week 12–16 or at the first prenatal care visit. If positive results are found, a urine culture test should be repeated routinely every month until the completion of pregnancy. If the first urine culture test is negative, further screening is indicated only in risk groups (diabetes, urinary tract defects). A urinary tract infection in pregnancy carries the risk of maternal complications such as anemia, hypertension, preeclampsia, as well as fetal complications including preterm birth, low birth weight, and perinatal mortality. Therefore, it is recommended that asymptomatic bacteria be treated in pregnant women [3, 4].

The treatment of asymptomatic bacteriuria may include:

— amoxicillin 500 mg every 8 hours for 3–7 days;
— cefalexin 500 mg every 12 hours for 3–7 days;
— phosphomycin 3 g (single dose);
— amoxicillin/clavulanic acid 500 mg every 8 hours for 3–7 days;
— nitrofurantoin 100 mg every 12 hours for 5 days in the 2nd and 3rd trimester (furazidin-furagin available in Poland);
— trimetoprim 100 mg bid for 5 days, to be avoided in the 1st trimester and the pre-partum period.

A follow-up culture test should be performed 7 days after the completion of treatment and repeated once a month thereafter. In 30% of pregnant women, failure of asymptomatic bacteriuria treatment is observed, with the disorder persisting or recurring. If the same pathogen is present in the repeated culture, a repeated, longer treatment or a switch in the therapeutic agent is recommended. If asymptomatic bacteriuria persists after 2–3 courses of treatment, chronic treatment with nitrofurantoin 50–100 mg at night is recommended for the whole pregnancy period.

In the case of recurrent bacteriuria — first culture after treatment positive with different pathogenic species or the follow-up culture-negative and the subsequent culture-positive with the same or different pathogenic species, treatment should follow the first-line regimen with no prophylaxis of potential recurrence (no data) [4, 5].

Particular attention should be paid during pregnancy to infections with group B streptococci (GBS), in particular, *Streptococcus agalactiae*. Colonization with *Streptococcus agalactiae* is observed in 10–30% of pregnant women within the vagina, rectum, and urethra. About 40–70% of infected women will pass GBS to the fetus which may lead to prema-

▶▶The most common etiological factors of UTI in pregnancy include E. coli (70% of infections), the others including Klebsiella (3%) and Enterobacter (3%), Proteus (2%), and gram-positive bacteria including group B streptococci (10%)◀◀

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ture rupture of membranes and preterm delivery. GBS infection will develop in 1–2% of children posing a risk to their life (early form detected within in the first week, late in weeks 2–15). GBS is found in urine cultures of 2–7% of women. Significant bacteriuria should be treated with amoxicillin or cefalexin, whereas non-significant bacteriuria should not be treated until delivery. Regardless of the CFU/mL, intravenous antibiotic (penicillin, cefazolin, clindamycin, vancomycin) is administered during labor. Due to the risk of life-threatening neonatal infection being transmitted during labor, screening for group B *streptococci* (vaginal swab and rectum culture) is recommended in women between gestation weeks 35 and 37 [6].

ACUTE CYSTITIS

Acute cystitis is observed in 1–4% of pregnant women, which is not more frequent than in non-pregnant women. On the other hand, asymptomatic bacteriuria may develop into symptomatic infection 3–4 times more often in pregnant women as compared to non-pregnant women. Clinical signs include painful urination with urgency and increased frequency of micturition, hematuria and *de novo* urinary incontinence or worsened pre-existing incontinence. In an uncomplicated pregnancy, symptoms such as tachycardia, urgency, and non-specific abdominal pains are observed frequently, and therefore the diagnosis of UTI may be delayed. Antimicrobial treatment should be administered for 3–7 days. Medications recommended for the treatment of cystitis in pregnant women are the same as those used for the treatment of asymptomatic bacteriuria. Empirical treatment is delivered on the basis of clinical presentation and urinalysis. A follow-up culture test? should be performed 7 days after the completion of treatment, and repeated once a month thereafter. Prophylaxis of relapses should include nitrofurantoin at the dose of 50–100 at night either in a chronic setting or after sexual intercourse; alternatively, cefalexin may be used at the dose of 250–500 mg at night [5].

ACUTE PYELONEPHRITIS

Acute pyelonephritis is more common in pregnant women (ca. 1–4% of all pregnancies) than in non-pregnant women and develops in women with asymptomatic bacteriuria (13–40% with) more frequently than in non-affected women (0.4%). Usually, acute pyelonephritis develops in the second half of pregnancy (2nd and 3rd trimester) and is **promoted**?? by difficult urinary outflow and changes within the urinary tract. The natural history of the infection is typical (fever, chills, lumbar pain and abdominal pain, nausea, vomiting, headache, and lumbar tenderness upon shaking movements). Severe complications such as septic shock, anemia, acute renal failure, ARDS, or preeclampsia are reported in 20% of pregnant women. Diagnosis is based on clinical signs, urinalysis (pyuria), and positive urine culture. Patients require hospitalization, with empirical treatment being introduced including broad-spectrum beta-lactam antibiotics [5, 7–9].

TREATMENT OF MILD TO MODERATE DISEASE:

— ceftriaxone 1.0 g every 12 hours;
— cefepim 1.0 g every 24 hours;
— amoxicillin/clavulanic acid 1.2 g/12 h;
— aztreonam 1.0 g every 8–12 hours.

TREATMENT OF SEVERE DISEASE:

— ticarcillin/clavulanic acid 3,0 g every 6 hours;
— piperacillin/tazobactam 3.375 g every 6 hours;
— meropenem 0.5 g every 8 hours;
— ertapenem 1.0 g every 24 hours;
— doripenem 1.0 g every 8 hours.

Forty-eight hours after the body temperature is normalized, the treatment may be switched to oral antibiotics administered for 10–14 days, with a follow-up urine culture test? after the treatment and monthly thereafter or prophylaxis being administered in a chronic setting until pregnancy completion. Recurrence of acute pyelonephritis is observed in 6–8% of pregnant women.

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