Pr-AKI: Acute Kidney Injury in Pregnancy – Etiology, Diagnostic Workup, Management

Pr-AKI: Ursachen, Diagnostik und Therapie der akuten Nierenschädigung während der Schwangerschaft

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Authors

Florian G. Scurt[1], Ronnie Morgenroth[1], Katrin Bose[2], Peter R. Mertens[1], Christos Chatzikyrkou[3,4]

Affiliations

1 Klinik für Nieren- und Hochdruckerkrankungen, Diabetologie und Endokrinologie, Medizinische Fakultät der Otto-von-Guericke-Universität, Magdeburg, Germany
2 Universitätsklinik für Gastroenterologie, Hepatologie und Infektiologie, Medizinische Fakultät der Otto-von-Guericke-Universität, Magdeburg, Germany
3 PHV-Dialysezentrum, Halberstadt, Germany
4 Klinik für Nephrologie, Medizinische Hochschule Hannover, Hannover, Germany

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Correspondence

Dr. med. Florian G. Scurt
Klinik für Nieren- und Hochdruckerkrankungen, Diabetologie und Endokrinologie, Medizinische Fakultät der Otto-von-Guericke-Universität
Leipziger Straße 44, 39120 Magdeburg, Germany
florian.scurt@med.ovgu.de

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ABSTRACT

Despite significant improvements in inpatient and outpatient management, pregnancy-related acute kidney injury (Pr-AKI) remains an important risk factor for early and late maternal and fetal morbidity and mortality. There is a discrepancy between the incidence of Pr-AKI in developing and in developed countries, with the former experiencing a decrease and the latter an increase in Pr-AKI in recent decades. Whereas septic and hemorrhagic complications predominated in the past, nowadays hypertensive disorders and thrombotic microangiopathy are the leading causes of Pr-AKI. Modern lifestyles and the availability and widespread use of in-vitro fertilization techniques in industrialized countries have allowed more women of advanced age to become pregnant. This has led to a rise in the percentage of high-risk pregnancies due to the disorders and comorbidities inherent to or accompanying aging, such as diabetes, arterial hypertension and preexisting chronic kidney disease. Last but not least, the heterogeneity of symptoms, the often overlapping clinical and laboratory characteristics and the pathophysiological changes related to pregnancy make the diagnosis and management of Pr-AKI a difficult and challenging task for the treating physician. In addition to general supportive management strategies such as volume substitution, blood pressure control, prevention of seizures or immediate delivery, each disease entity requires a specific therapy to reduce maternal and fetal complications. In this review, we used the current literature to provide a summary of the physiologic and pathophysiologic changes in renal physiology which occur during pregnancy. In the second part, we present common and rare disorders which lead to Pr-AKI and provide an overview of the available treatment options.

ZUSAMMENFASSUNG

Die schwangerschaftsassoziierte akute Nierenschädigung (Pr-AKI) stellt trotz deutlich verbesserter ambulanter und stationärer Versorgungsmöglichkeiten noch immer ein hohes Risiko für Früh- und Spätkomplikationen sowohl für die werdende Mutter als auch für das Ungeborene dar. Erfreulicherweise konnte vor allem in den Entwicklungsländern ein deutlicher Rückgang der Inzidenz des Pr-AKI innerhalb der letzten Jahrzehnte verzeichnet werden, wohingegen sich in den Industrienationen anhand retrospektiver Daten leider ein Anstieg der Pr-AKI-Fälle zeigt. Während früher häufig septische Aborte, die Puerperalsepsis oder schwangerschaftsassoziierte Blutungen ein Pr-AKI verursachten, sind heute hypertensive Erkrankungen wie z. B. die Präeklampsie und thrombotische Mikroangiopathien führend in der Genese des Pr-AKI. Gründe hierfür sind zum einen die mit dem fortgeschrittenen mütterlichen Alter verbundene Zunahme der Risikofaktoren wie Bluthochdruck, Diabetes oder chronische Nierenerkrankungen und zum anderen die mit Reproduktionstechnologien verbundenen Mehrlingsschwangerschaften. Nicht zuletzt wegen der Heterogenität der Symptome, der teils überlappenden klinischen und laborchemischen Merkmale und der pathophysiologisch bedingten Veränderungen während der Schwangerschaft stellt das Pr-AKI den behandelnden Arzt vor eine Reihe komplexer Herausforderungen bez. weiterer Diagnostik und Behandlungsstrategien. Neben allgemeinen Maßnahmen, wie der Ursachenforschung, der intravenösen Flüssigkeitstherapie und – falls erforderlich – der sofortigen Entbindung des Fetus, erfordert ein jedes Krankheitsbild eine spezifische Behandlung zur Senkung der Komplikationsrate sowohl für die Mutter als auch für das Ungeborene. In der vorliegenden Übersicht konzentrieren wir uns zunächst – unter Verwendung der aktuellsten Literatur – auf die zugrunde liegenden pathophysiologischen Veränderungen der Nierenphysiologie während der Schwangerschaft. Im 2. Teil werden sowohl häufige als auch seltene Entitäten, die zu einer akuten Nierenschädigung in diesem speziellen Patientenkollektiv führen, beleuchtet und ein Überblick über therapeutische Möglichkeiten gegeben.

Introduction

Pregnancy-related acute kidney injury (Pr-AKI) encompasses numerous clusters of symptoms with very different causes which can significantly increase the risk of fetal or maternal complications both during pregnancy and post partum [1, 2]. Because of the pathophysiological changes occurring in pregnancy, the heterogeneity of symptoms and the sometimes overlapping clinical and laboratory characteristics, the diagnosis and management of Pr-AKI is a complex challenge for the treating physician. In addition to hyperemesis gravidarum, the most common causes of PR-AKI include pregnancy-related bleeding and septic complications. However, AKI can also develop from less common pregnancy-related causes (e.g., HELLP syndrome, thrombotic microangiopathies, lupus nephritis, antiphospholipid syndrome) or have a non-pregnancy-related etiology (e.g., medication, glomerulonephritis, genetic factors). Despite significant improvements in outpatient and inpatient care, retrospective data from Canada and the USA have shown a renewed increase in the incidence of Pr-AKI (from 1.7 to 2.7 and from 2.4 to 6.6 per 10 000 deliveries, respectively) in the last two decades, accompanied by increased maternal and fetal mortality rates, higher rates of renal failure requiring dialysis and a higher use of resources [3 – 5].

This review starts by outlining the underlying pathophysiological changes to renal physiology which occur during pregnancy. In the second part, we present both common and rare disease entities which lead to acute kidney injury in this specific patient population and provide an overview of the treatment options.

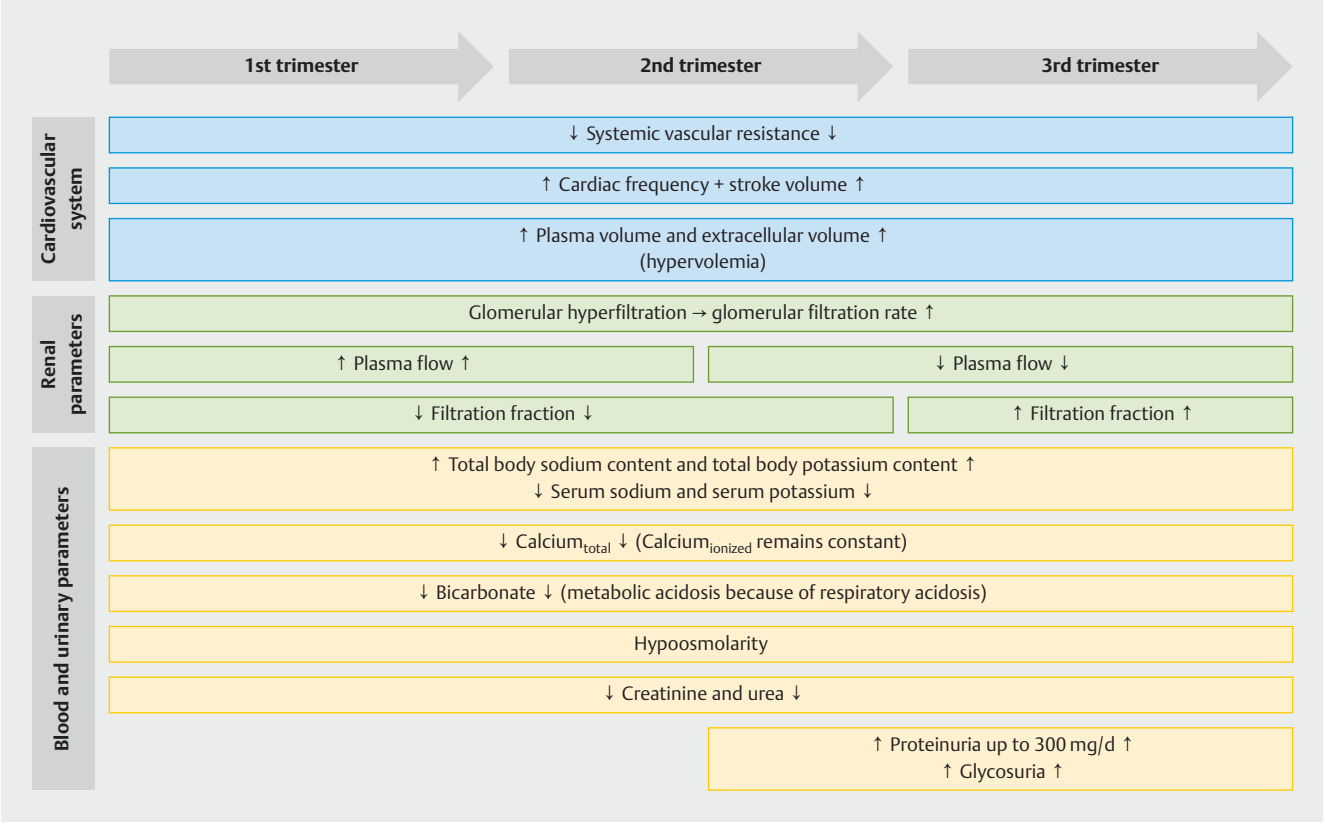
Pathophysiological Renal Changes During Pregnancy

During pregnancy, the female organism undergoes numerous changes which ensure fetal development and provide nutrition to the growing fetus. Although this process of adaptation affects all organ systems, the kidney plays a very central role (▶ **Fig. 1**) [6].

Effects of relaxin, endothelin and nitric oxide

The most obvious change occurring in this context is the change to the body's water balance. It is triggered by placental production of the hormone relaxin, which converts endothelin into its active form and has a nitric oxide-mediated vasodilatory effect [7, 8]. Cardiac frequency and cardiac stroke volume increase during pregnancy to mitigate against the dramatic drop in medium arterial blood pressure [9].

This is followed by decreased renal resistance and subsequently by an increase in renal plasma flow of up to 80 % as well as an increase in the glomerular filtration rate (GFR) by up to 60 %, meaning that pregnancy is characterized by glomerular hyperfiltration [10 – 13]. As both the afferent and the efferent arterioles of the glomeruli are affected, the increased plasma flow does not result in glomerular hypertension [9]. The increase in renal plasma flow and GFR remains roughly linear until the 20th week of gestation, after which the plasma flow decreases again to pre-pregnancy levels [14]. But glomerular hyperfiltration persists, due to the changes in transcapillary hydrostatic pressure and glomerular surface and glomerular permeability [15, 16].



▶ **Fig. 1** Pathophysiological changes during pregnancy.

Effects of the renin-angiotensin-aldosterone system

Decreased renal resistance leads to activation of the arterial baroreceptors, the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system with subsequent release of ADH (antidiuretic hormone, vasopressin) from the hypothalamus.

Although angiotensin is a strong vasoconstrictor and increased plasma levels during pregnancy are detected, only a weak vasoconstrictive effect occurs [17]. It is very likely that during pregnancy the expression patterns of angiotensin I und angiotensin II receptors shift towards increased expression of the more vasodilatory angiotensin II receptors [18]. Following estrogen and progesterone stimulation, the RAAS adapts to preserve both renal vasodilation and glomerular filtration [19, 20].

Fluid balance

The above-described mechanisms lead to the hypervolemia and hypoosmolar volume changes typically occurring in pregnancy [21]. Plasma volumes may increase by up to 60 % and extracellular volumes by up to 50 %, which corresponds to an additional volume of 6–8 l. Laboratory tests have shown concomitant dilution effects on creatinine and urea levels and a related increase in the eGFR (estimated glomerular filtration rate) [9, 22].

Aldosterone, which coordinates the increased absorption of water and sodium in the distal convoluted tubules and collecting ducts of the kidneys, plays a key role in this process [23].

Hypoosmolality is additionally increased through modulation of the thirst threshold and the release of ADH, which increases water retention through regulation of the water channel aquaporin-2 in the renal collecting duct [24, 25]. This culminates in a drop of the oncotic pressure of around 10 mOsmol/kg, as the number of cellular blood components (including erythrocytes, hemoglobin, hematocrit, thrombocytes) decreases [26]. This spreads to the glomeruli, which then leads to an increase in the GFR [23].

Adaptation of tubular function and proteinuria

Additionally to the glomerular changes which occur during pregnancy, tubular function is also affected by pathophysiological changes. In addition to increased excretion of bicarbonate and calcium (in consequence of the respiratory alkalosis caused by hyperventilation) glycosuria occurs in 10 % of all pregnant women even though they may have standard blood sugar levels [10, 27, 28]. Proteinuria increases to 200–300 mg/24 h in the 2nd half of pregnancy due to the increased glomerular filtration rate and the changes in tubular reabsorption [29, 30].

Changes in renal anatomy during pregnancy

Another consequence of the increased renal plasma flow is reflected in the renal anatomy. Its size increases by 1–1.5 cm over the course of pregnancy [31]. This is accompanied by dilation of the ureters, the renal pelvis and calyces, mainly due to the influence of progesterone and expansion of the gravid uterus [10]. Be-

cause the anatomical conditions (the ovarian artery and vein and the uterine artery pass under the ureter and the common iliac arteries and veins pass over the ureter) lead to compression of the ureter, mild physiological bilateral hydronephrosis (more prominent on the right side because the ureter crosses the ovarian vein and the uterus rotates to the right while the left ureter is partly protected by the sigmoid colon) is common in the advanced stage of pregnancy [32, 33].

Impact of pregnancy on electrolyte and acid-base homeostasis

The changes in hormone levels, renal volumes and glomerular filtration rate also require additional renal adjustment to deal with changes in electrolytes, pH and renal tubular cell function [22].

Increased filtration and sodium excretion through glomerular filtration is regulated by increased aldosterone expression and the conversion of progesterone to deoxycorticosterone. The effect of both hormones on the mineralocorticoid receptor is to reduce sodium excretion and increase the kaliuretic response [25]. Other influencing factors include progesterone as an aldosterone antagonist and atrial natriuretic peptide which increases sodium excretion [34, 35]. Although body stores of sodium and potassium rise during pregnancy, hypervolemia induces hyponatremia and hypopotassemia [22].

Around 30 g of calcium are additionally required during fetal development, most of which is provided through increased intestinal absorption [36, 37]. Placentally produced parathyroid hormone-related peptides stimulate vitamin D activation (1, 25), which in turn enables intestinal absorption [38]. Although the reduced albumin concentrations result in hypocalcemia, this does not affect ionized calcium levels [39].

In contrast, there is a decrease in overall magnesium levels and the percentage of ionized magnesium [40]. Glycosuria is observed in some pregnant women, but it has no pathological impact. It occurs despite the preservation of renal function and the absence of diabetes mellitus [28, 41, 42]. Likewise, there is also an increase in uric acid excretion, which leads to a decrease in uric acid concentrations until the 2nd trimester of pregnancy. Uric acid concentrations increase again in the 3rd trimester of pregnancy because of increased production by the growing fetus [43, 44].

During pregnancy, the acid-base balance tends to become more alkaline. This is the result of progesterone-induced hyperventilation which leads to respiratory alkalosis (decreased arterial CO_2 concentrations). This leads to reduced renal bicarbonate reabsorption and therefore to lower serum bicarbonate levels [45].

Differential Diagnostic Workup of Pr-AKI

The lack of a standard definition of Pr-AKI and the pregnancy-induced pathophysiological changes (40–50% increase in GFR, reduced vascular resistance, increased cardiac output) create serious challenges for outpatient and clinical care. Prompt diagnosis of Pr-AKI is difficult; moreover, normal renal retention parameters may already be hiding severe loss of renal function [46, 47].

The approach used to evaluate AKI in this patient cohort does not differ from that used for other groups. In addition to typical pregnancy-related renal disorders (e.g., preeclampsia, HELLP syndrome, acute fatty liver of pregnancy, hyperemesis gravidarum, embolisms, etc.), it is important to also be aware of non-pregnancy-related mechanisms of kidney injury (e.g., lupus nephritis, interstitial nephritis, necrosis caused by drug-induced nephrotoxicity, sepsis, surgical interventions, etc.) (▶ **Table 1**).

To detect AKI early on and determine renal retention parameters, which are usually unknown prior to pregnancy, laboratory tests to measure kidney function parameters should be carried out as soon as the pregnancy has been confirmed. Because values may deviate by 40 ml/min/1.73 m^2 compared to insulin clearance (gold standard), the MDRD formula (**m**odification of **d**iet in **r**enal **d**isease) and eGFR (estimated GFR) should not be used to calculate kidney function [48].

Serum creatinine concentrations are currently the only standard parameter which can be used to monitor renal function in pregnant women. Based on a nonpregnant reference interval of 45–90 µmol/l (0.51–1.02 mg/dl), a serum creatinine of more than 77 µmol/l (0.87 mg/dl) in pregnant women should already be considered pathological [48, 49]. Similarly, the absence of a physiological decrease in creatinine levels as the pregnancy advances can suggest a serious kidney injury, necessitating a search for the possible cause of AKI.

The timing when AKI occurs in pregnancy offers the first clues to its etiology (▶ **Fig. 2**). In addition to prerenal azotemia triggered by hyperemesis gravidarum, the most common causes of Pr-AKI in the 1st trimester of pregnancy are infectious complications (e.g., septic miscarriage). Postrenal kidney injury caused by compression of the ureters by the expanding uterus or infectious complications (e.g., urinary tract infection, pyelonephritis) occur more commonly in the 2nd and 3rd trimesters. Renal events which occur in late pregnancy are usually pregnancy-related. In addition to preeclampsia, HELLP syndrome and acute fatty liver of pregnancy, such events can include thrombotic microangiopathies such as thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. They are caused by the increase in risk factors such as hypertension, diabetes or chronic renal disease due to advanced maternal age as well as assisted reproductive technology-related multiple pregnancy.

During the differential diagnostic workup of AKI, it is important to be aware that both HELLP syndrome and thrombotic microangiopathies can occur several weeks after giving birth.

Specific Causes of Pr-AKI

Lupus nephritis

Systemic lupus erythematosus (SLE) is a rare autoimmune disease whereby various pathophysiological mechanisms lead to the production of pathogenic autoantibodies and immune complex disease. It has numerous organ manifestations [50–52]. The peak age at onset of disease is between 20 and 30 years of age, with women affected almost 9 times more often than men.

Kidney involvement (lupus nephritis) is the most common and in 25% of cases it is the first manifestation of SLE in solid organs [53]. However, the first symptoms of renal injury often only appear late in its clinical course. Depending on the course of disease, clinical or laboratory findings show either **nephrotic syndrome**

(proteinuria of more than 3.5 g/day, hypoproteinemia, hypercholesterolemia, edema) despite preserved excretory renal function (normal GFR), **nephritic syndrome with active urinary sediment** (persistent hematuria with increased numbers of dysmorphic erythrocytes and possibly erythrocyte cylinders) usually accompanied by decreased diuresis, a propensity to develop edema, and hypertension, or the **characteristics of thrombotic microangiopathy** (anemia, thrombopenia, elevated LDH and free Hb, low haptoglobin levels).

Depending on the study, the histological findings on kidney biopsy with response to therapy show progression to terminal kidney failure within 15 years in up to 40 % of cases, meaning that early diagnosis to plan therapy and slow progression is essential [54 – 56].

In addition to the above-listed symptoms, a first flare-up of SLE during pregnancy significantly increases the risk of pregnancy-associated complications. In addition to the potential consequences for the mother such as AKI, aggravation of lupus with multiorgan involvement, thromboembolic events (TVT, LAE) or the development of preeclampsia or HELLP syndrome, complications may also include fetal complications such as preterm birth or miscarriage, fetal growth restriction or the development of neonatal lupus [57 – 60].

Pregnant women newly diagnosed with SLE or with known SLE have high-risk pregnancies which require monitoring and care by an interdisciplinary team of medical specialists for a period which extends well after delivery of the baby, particularly if kidney involvement has been confirmed.

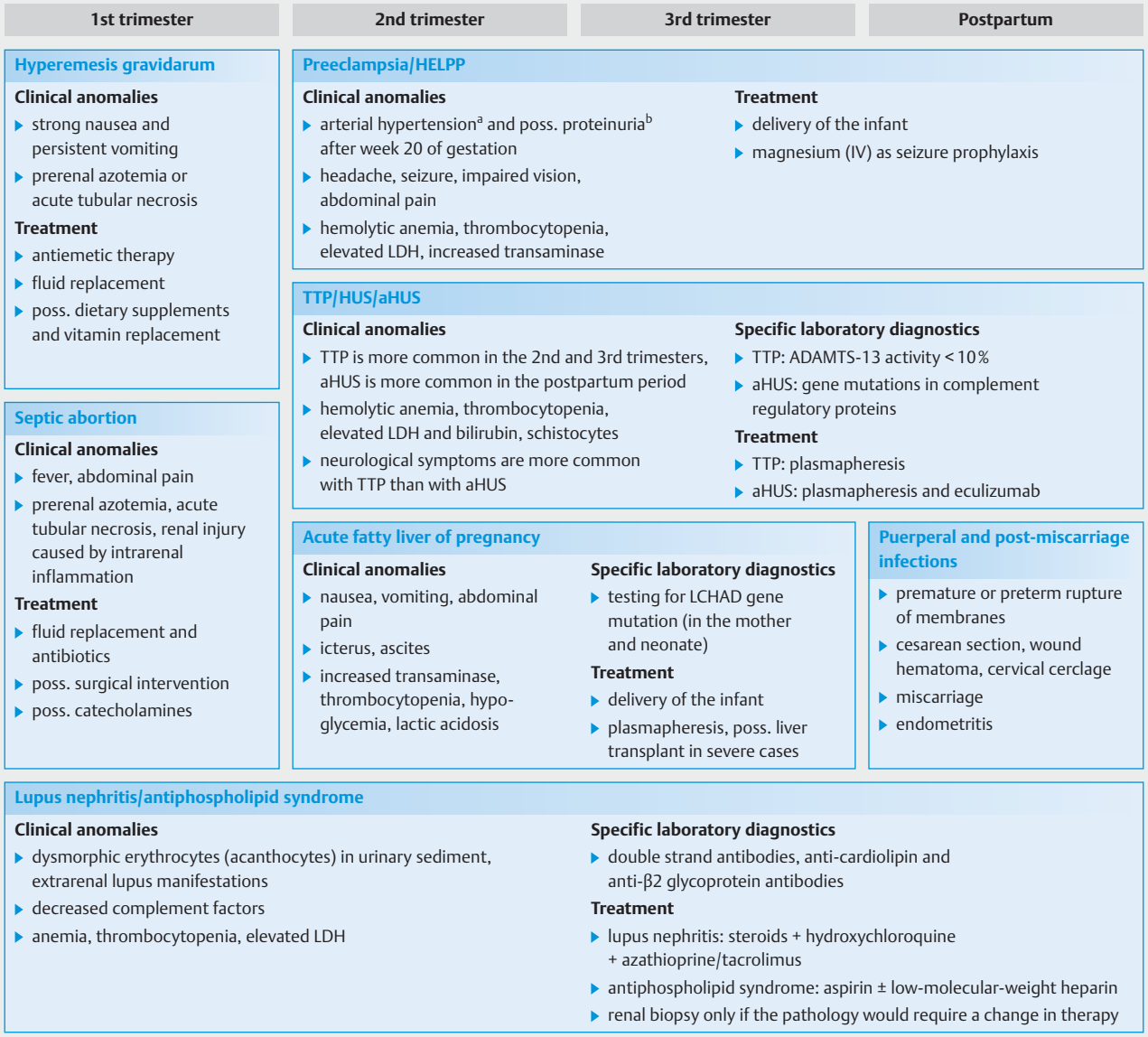
As it is still not known to date whether pregnancy should be considered as a possible risk factor which can trigger lupus or whether pregnancy leads to exacerbation of lupus nephritis, it is very difficult to predict the clinical course of SLE during pregnancy [61]. In two clinical studies, low C3 complement levels prior to pregnancy, known lupus nephritis, and lupus activity prior to pregnancy were identified as possible independent predictive factors for SLE or lupus nephritis activity flares during pregnancy [62, 63]. It is therefore recommended that patients with known SLE or lupus nephritis wait for at least 6 or 9 months from the last SLE or nephritis activity and trying for a planned pregnancy [64].

Because of the similarities in the clinical and laboratory data of lupus nephritis, preeclampsia and thrombotic microangiopathies, diagnosing lupus nephritis activity during pregnancy is a challenge for the treating physician (▶ **Table 2**). Confirmation of C3 and/or C4 complement levels, increased or rising levels of anti-double strand DNA (anti-dsDNA), anti-Smith (Anti-Sn) or SSA(Ro) autoantibodies, active urinary sediment, a urinary protein-to-creatinine ratio of more than 0.3 g/g or new onset of skin efflorescence may suggest the diagnosis [65 – 67]. It should be noted, however, that confirmation of a drop in complement factor levels may be disguised by pathophysiological increases during pregnancy [68].

In patients with known or newly confirmed SLE or lupus nephritis, the determination of sFlt-1 (soluble fms-like tyrosine kinase-1) concentrations or of the sFlt-1/PlGF (placental growth factor) ratio in the 12th to the 15th week of gestation can be used to predict complications [69]. In the prospective PROMISSE trial (Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody

▶ **Table 1** Pregnancy-related and non-pregnancy-related causes of AKI.

Extrarenal (hemodynamic AKI)
Intravascular volume depletion (hypovolemia)
▪ hyperemesis gravidarum
▪ ovarian hyperstimulation syndrome
▪ diarrhea
▪ hemorrhage from peripartum bleeding, miscarriage or surgical interventions
▪ diuretics
Reduced arterial blood pressure/reduced effective cardiac output
▪ infection-related
– pyelonephritis/urosepsis
– antepartum and postpartum infections
▪ acute and chronic cardiac insufficiency
Intrarenal
Glomerulonephritis
Interstitial nephritis
▪ infection-related
– pyelonephritis/urosepsis
– antepartum and postpartum infections
▪ ischemia-related (acute tubular necrosis/acute cortical necrosis)
– peripartum hemorrhage, miscarriage, surgical interventions
– placenta previa/placental abruption
– uterine rupture/uterine atony
Vascular nephropathy
▪ vasculitis
▪ HELLP syndrome
▪ thrombotic microangiopathies (TMA)
– thrombotic thrombocytopenic purpura (TTP)
– atypical hemolytic uremic syndrome (aHUS)
– disseminated intravascular coagulation (DIC)
▪ acute fatty liver of pregnancy (AFLP)
Lupus nephritis and/or antiphospholipid syndrome (APS)
Intrarenal vasoconstriction/disordered autoregulation of renal blood flow
▪ ACE inhibitors, angiotensin II receptor blockers
▪ nonsteroidal antirheumatics
▪ cyclosporine, tacrolimus
Pulmonary embolism, amniotic fluid embolism
With kidney transplants: acute rejection
Postrenal
▪ hydronephrosis caused by uterine compression of the ureter/bladder
▪ nephrolithiasis
▪ iatrogenic injury of the ureter, bladder, urethra during cesarean section or vaginal delivery
▪ spontaneous bladder or urethral injury during vaginal delivery



▶ **Fig. 2** Typical times for the occurrence and symptoms of specific entities of Pr-AKI.

Syndrome and Systemic Lupus Erythematosus), Kim et al. were able to show that both sFlt-1 concentrations and higher sFlt-1/PlGF ratios were associated with many complications over the course of the pregnancy (e.g., preeclampsia or fetal death after the 12th week of gestation independent of chromosomal abnormalities, anatomical malformations or congenital infections).

Scoring systems such as SLEPDAI (Systemic Lupus Erythematosus Pregnancy Disease Activity Index) should additionally be used to estimate SLE activity, and blood and urinary parameters should be regularly measured in every trimester of pregnancy [70].

The medication of women with known SLE planning to become pregnant must be switched to teratogenic immunosuppressive drugs such as mycophenolate mofetil (MMF), cyclophosphamide, mTOR inhibitors (e.g., everolimus), rituximab (RTX) or methotrexate (MTX) as soon as possible. Hydroxychloroquine is currently the best alternative to maintain remission of SLE and lupus nephritis because of its side-effects profile, lack of risks for fetal malformations or fetal or neonatal toxicity, the improvement in renal long-term outcomes and the up to 50% reduction in congenital heart block in infants born to anti-Ro-positive mothers, H [71–74]. Alternative options are listed in ▶ **Table 3**, but because individualized SLE therapy is essential, these alternatives should only be used after consultation with the treating nephrologist, dermatologist or rheumatologist [75, 76].

If the patient is already pregnant, clinical exacerbation of existing lupus nephritis or renal SLE involvement should be treated

▶ **Table 2** Overview of clinical and laboratory characteristics of different Pr-AKI entities with overlapping symptoms (table based on [46] und [47]).

	Preeclampsia/ HELLP	TTP/HUS	aHUS	AFLP	Antiphospholipid syndrome	Lupus
Timepoint	After the 20th week of gestation	In the 2nd and 3rd trimester (higher incidence in the 2nd trimester)	Higher incidence postpartum	In the 2nd and 3rd trimester (higher incidence in 3rd trimester)	In the 1st–3rd trimester and post partum	In the 1st–3rd trimester and post partum
Arterial hypertension (> 140/90 mmHg)	●●●	○○○ to ●●●	●●○	○○○ to ●●○	○○○ to ●●●	○○○ to ●●●
Neurological symptoms	○○○ to ●●●	●●○ to ●●●	○○○ to ●○○	○○○	○○○ to ●●●	○○○ to ●●●
Fever	○○○	●○○ to ●●●	○○○ to ●●●	○○○	●●○	●●○
Schistocytes (> 1 %)	○○○ to ●●○	●●●	●●○	○○○ to ●○○	●●○	○○○
Thrombocytopenia	○○○ to ●●●	●●○ to ●●●	●●●	●○○ to ●●○	●●○	●○○ to ●●○
Elevated trans-aminase levels	○○○ to ●●●	○○○ to ●○○	○○○ to ●○○	●●○ to ●●●	○○○ to ●○○	○○○
Hypoglycemia	○○○	○○○	○○○	●●○	○○○	○○○
Proteinuria[a]	●○○ to ●●●	●○○ to ●●●	●○○ to ●●●	●○○	○○○ to ●●●	●○○ to ●●●
Decreased ADAMTS13 activity (< 10 %)	○○○ to ●○○	●●●	●○○	○○○	○○○	○○○
Treatment	Delivery of the infant	Plasmapheresis	Plasmapheresis and eculizumab	Delivery of the infant	Acetylsalicylic acid and anti-coagulation	Immunosuppres-sive therapy

[a] Proteinuria: > 300 mg/24 hours or urine/creatinine ratio of > 0.3 g/g

○○○: unlikely or not present; ●○○: mild or low likelihood; ●●○ moderate or moderate probability; ●●●: severe or high probability

with steroid pulse therapy and an additional immunosuppressive agent such as azathioprine or tacrolimus [64].

The patient should undergo anamnestic screening before a planned pregnancy and preeclampsia screening in the 1st trimester (between week 11 + 0 and week 13 + 6 of gestation) (see chapter on preeclampsia) to evaluate the risks [77, 78]. Until a few years ago, daily intake of 75–100 mg acetylsalicylic acid (ASA) to prevent preeclampsia and fetal growth retardation was recommended. More recent studies have shown a better outcome if this is increased to 150 mg ASA once daily, taken late at night [79–82].

Depending on the risk profile, patients with additional known antiphospholipid syndrome or who have already experienced complications (e.g., thrombosis, pulmonary artery embolism) should be administered low-molecular-weight heparin (e.g., enoxaparin) in addition to ASA for prophylactic or therapeutic anticoagulation [83–85]. Because of their teratogenic effect, coumarin derivates such as phenprocoumon or warfarin should be replaced by more suitable alternatives, whenever possible.

Thrombotic microangiopathies (TMA)

Preeclampsia/HELLP syndrome

With an incidence of 2–8 % (which is likely to increase), preeclampsia is one of the most common complications of pregnancy. It occurs predominantly in the 2nd and 3rd trimester of pregnancy, but in 5 % of cases it also occurs post partum [86–90].

Depending on the respective medical society, the leading symptoms of this entity are or were newly detected arterial hypertension (> 140/90 mmHg) and proteinuria of more than 300 mg/day after week 20 of gestation [91, 92]. More recent insights into pathogenesis, pathophysiology, and molecular and structural cellular processes and the use of new biomarkers have changed the understanding of this syndrome in recent years, leading to a revision of the classification and definition of preeclampsia (▶ **Table 4**) [93, 94]. The overriding importance of proteinuria, which for many years was considered a necessary diagnostic criterion, has been downgraded if other symptoms (e.g., thrombocytopenia, impaired liver function, new renal insufficiency, pulmonary edema or new-onset cerebral or visual disorders) are present.

It is generally assumed that the starting point for the pathophysiological development of preeclampsia and HELLP syndrome is disordered placental development (caused by immunological, genetic and environmental factors) and the ensuing chronic ischemia caused by atherosclerosis, vascular sclerosis, fibrin deposits and infarctions (▶ **Fig. 3**) [94, 99]. The consequences are persistent activation of thrombocytes and vasoconstriction which increases the production of antiangiogenic factors such as sFlt-1 and soluble endoglin as well as reducing the release of proangiogenic factors such as PlGF and vascular endothelial growth factors. This leads to the development of either a primarily “fetal phenotype” (fetal growth restriction), a primarily “maternal phenotype” (hypertension and organ complications) or a mixed form [100].

▶ **Table 3** Possible immunosuppressive drugs which can be used during pregnancy and lactation.

Drugs (class of active ingredients)	Administration, dosage and characteristics during pregnancy	Administration, dosage and characteristics during lactation
Azathioprine (purine analog)	▪ Current studies have provided no evidence for any increased risk of malformation (lower birth weight and preterm birth are most likely associated with the underlying disease or disease activity) ▪ The dose of 2 mg/kg/day should not be exceeded ▪ The mother should be offered a detailed ultrasound examination to monitor fetal growth ▪ If leukopenia occurs in the 3rd trimester, the dosage should be reduced and a complete blood count test carried out in the neonate	▪ No limitations, possibly carry out a complete blood count in the infant
Belimumab (monoclonal B-cell activating factor [BAFF] antibody)	▪ Current studies found no evidence of any increased risk of fetal malformations; however, alternative medication should be used because of the current lack of data	▪ Because of the current lack of data, breastfeeding mothers should either stop breastfeeding or switch to alternative medication.
Cyclophosphamide (alkylating agent)	▪ Because of its teratogenic effect, the patient should change here medication 3 months before a planned pregnancy ▪ Administration of the drug may be considered in life-threatening situations after organogenesis has been completed in the 2nd trimester of pregnancy (pancytopenia, lower birth weight and a possibly higher incidence of preterm births are possible)	▪ Mothers should not breastfeed when taking this drug because of its almost 100 % oral bioavailability and relevant passage to breast milk.
Hydroxychloroquine (antiprotozoal agent)	▪ Current studies found no evidence of any increased rate of malformations in the 1st trimester of pregnancy (increased rates were mostly due to underlying disease or increased disease activity) ▪ No fetotoxic risks in the 2nd and 3rd trimester	▪ Despite its passage to breast milk, no restrictions are necessary if the infant is regularly checked by a pediatrician.
Leflunomide (pyrimidine synthesis inhibitor)	▪ Teratogenic in animal studies, not enough data available about its impact in humans ▪ Before planning a pregnancy: either wait up to 2 years after discontinuing therapy or carry out 11-day washout treatment with cholestyramine or activated powdered charcoal	▪ Passage to breast milk is unlikely because leflunomide binds strongly to proteins (99 %); however, because of the lack of data, infants should not be breastfed.
Methotrexate (folic acid analog, antimetabolite)	▪ Teratogenic in humans with variable patterns of teratogenicity (CNS anomalies, ossification defects and skull anomalies, facial dysmorphias, defects of the extremities, pre- und postnatal growth retardation, developmental delay and intellectual defects, etc.) ▪ Must be discontinued 1–3 months before a planned pregnancy, followed by folic acid substitution (1–5 mg/days)	▪ Because there is not enough data, this medication should be avoided during lactation.
Mycophenolate mofetil (purine synthesis inhibitor)	▪ Teratogenic in humans (microtia and atresia of the external auditory meatus, craniofacial malformations of the oral cavity and tracheo-esophageal atresia, coloboma, cardiac malformations, etc.) ▪ Increased rates of preterm births and neonates with lower birth weights have been observed after intake in the 2nd and 3rd trimester ▪ Must be discontinued at least 6 weeks before a planned pregnancy	▪ Because there is not enough data, this medication should be avoided during lactation.
Prednisone, prednisolone (glucocorticoid)	▪ The medication of choice during pregnancy ▪ It should be noted that it is impossible to entirely preclude a slightly higher risk of cleft lip and palate (particularly if the drug is administered in the 8th to 11th week of gestation); it is assumed that these effects are dose-dependent, meaning that the lowest effective dose must be administered ▪ Depending on the duration of intake and dosages, there may be an increased risk of preterm birth and lower birth weight	▪ No restrictions
Rituximab (monoclonal CD20 antibody)	▪ Currently available data show no evidence of any increased risk of malformations in the 1st trimester; however, because of the lack of data, treatment should be changed before a planned pregnancy ▪ From week 20 of gestation, increased placental passage with B-cell depletion in the fetus, meaning that administration after week 20 of gestation should only occur in exceptional justifiable cases	▪ Despite the low oral bioavailability of rituximab, because of the lack of studies about its effects, alternative therapies should be attempted.

▶ **Table 4** Diagnostic criteria for preeclampsia published by various medical societies.

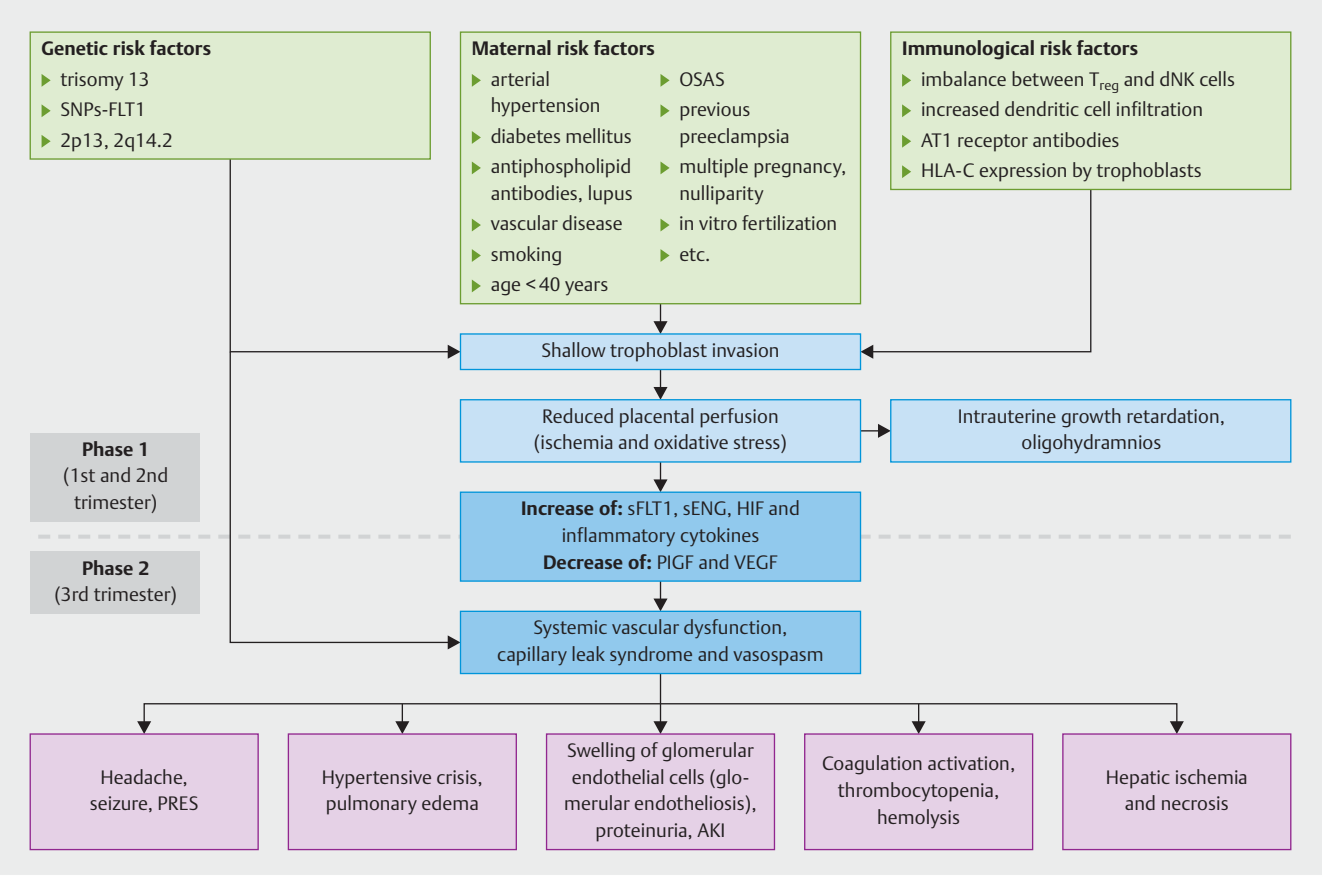
Medical society	Diagnostic criteria
American College of Obstetricians and Gynecologists (ACOG), 2013 [95]	▪ RR_{sys} ≥ 140 mmHg or RR_{dia} ≥ 90 mmHg (detected during 2 measurements carried out at an interval of at least 4 hours after week 20 of gestation in a previously normotensive patient), and ▪ first onset of one or more changes to the following clinical or laboratory values: 1. Proteinuria – ≥ 300 mg protein in 24-h urine collection, or – ≥ 0.3 g protein/g creatinine (≥ 30 mg/mmol) in spontaneous urine collection, or – ≥ 2+ on urine test strip (only if quantitative methods are not available) 2. Thrombocytes < 100 000/ml 3. Increase in serum creatinine to > 1.1 mg/dl (> 97.2 µmol/l) or doubling of creatinine level compared to previous value 4. Increase in transaminase level to 2 times the upper reference range 5. Pulmonary edema 6. Visual or neurological symptoms (headache not responsive to analgesics, blurred vision, photopsia, scotoma, etc.)
International Society for Study of Hypertension in Pregnancy (ISSHP), 2018 [96] **National Institute for Clinical Excellence (NICE)**, 2019 [97]	▪ Hypertension of pregnancy (RR_{sys} ≥ 140 mmHg or RR_{dia} ≥ 90 mmHg), and ▪ first onset of one or more changes to the following clinical or laboratory values after week 20 of gestation: 1. Proteinuria 2. Maternal organ function impairment: – AKI (serum creatinine ≥ 90 µmol/l (1.0 mg/dl) – Increased ALAT (GPT) or ASAT (GOT) to > 40 IU/L in the presence or absence of abdominal pain in the epigastric region or right upper abdomen – Visual or neurological symptoms (headache not responsive to analgesics, seizure, stroke, scotoma, etc.) – Hematological complications (thrombocytes < 150 000/ml, disseminated intravascular coagulation (DIC) or elevated hemolysis parameters) 3. Uteroplacental dysfunction (intrauterine growth restriction, abnormal uterine artery Doppler waveforms or intrauterine fetal death)
Society of Obstetric Medicine of Australia and New Zealand (SOMANZ), 2014 [98]	▪ RR_{sys} ≥ 140 mmHg or RR_{dia} ≥ 90 mmHg (detected during 2 measurements carried out at an interval of several hours after week 20 of gestation in a previously normotensive patient), and ▪ first onset of one or more changes to the following clinical or laboratory values: 1. Proteinuria (≥ 0.3 g protein/g creatinine (≥ 30 mg/mmol) in spontaneous urine collection or an increase in serum creatinine to > 90 µmol/l or oliguria (< 80 ml/4 h) 2. Thrombocytes < 100 000/ml or disseminated intravascular coagulation (DIC) 3. Elevated transaminase levels or strong abdominal pain in the epigastric region and/or right upper abdomen 4. Visual or neurological symptoms (headaches not responsive to analgesics, seizure, stroke, scotoma, etc.) 5. Pulmonary edema 6. Fetal growth retardation
German Society for Gynecology and Obstetrics (DGGG), 2019 **Austrian Society for Gynecology and Obstetrics (OEGGG)**, 2019 **Swiss Society for Gynecology and Obstetrics (SGGG)**, 2019	▪ Hypertension of pregnancy (RR_{sys} ≥ 140 mmHg or RR_{dia} ≥ 90 mmHg in a previously normotensive patient), and ▪ first onset of one or more changes to the following clinical or laboratory values: 1. Proteinuria – ≥ 300 mg protein in 24-h urine collection, or – ≥ 0.3 g protein/g creatinine (≥ 30 mg/mmol) in spontaneous urine collection 2. Organ function impairments (kidneys, liver, respiratory system, hematological system, placenta [intrauterine growth restriction], central nervous system) 3. Specific markers for preeclampsia (e.g., angiogenic factors)

RR_{sys}: systolic blood pressure; RR_{dia}: diastolic blood pressure; mmHg: millimeters of mercury; h: hours; g: grams; mg: milligrams; dl: deciliters; µmol: micromoles; l: liters; AKI: acute kidney injury; ALAT: alanine aminotransferase, previously GPT (glutamate pyruvate transaminase); ASAT: aspartate aminotransferase, previously GOT (glutamate oxaloacetate transaminase); IU: international unit

Risk factors which facilitate preeclampsia are: arterial hypertension, pregestational diabetes, age < 17 or > 40 years, multiple pregnancy, previous preeclampsia, systemic lupus erythematosus, antiphospholipid syndrome, nulliparity, premature placental separation, in vitro fertilization, etc. [101, 102].

Although preeclampsia is associated with a pathophysiological reduction in renal blood flow and glomerular filtration by 30–40 % compared to that of a healthy pregnant woman, Pr-AKI is a rare complication [103]. However, the risk of developing Pr-AKI increases to 7–36 % if preeclampsia is severe or is accompanied by HELLP syndrome [104 – 106].

Because of the clinical and laboratory similarities to other disease entities (lupus erythematosus, hemolytic uremic syndrome, etc.), the presence of arterial hypertension or proteinuria prior to pregnancy, the absence of characteristic symptoms (20 % of cases with HELLP syndrome do not present with prior hypertension or



▶ **Fig. 3** Pathogenesis of preeclampsia (image based on [94]).

proteinuria [104]) and the potential emergence of other disorders (e.g., acute fatty liver of pregnancy,) obtaining a differential diagnosis of preeclampsia is a challenge (▶ **Table 2**) [47].

Determination of the angiogenic factors sFlt-1 und PlGF may be done to differentiate preeclampsia from other clinical pictures (see above).

An sFlt-1/PlGF ratio ≤ 38 can almost entirely preclude the development of preeclampsia within the next week in a patient with clinical suspicion of preeclampsia. In contrast, an sFlt-1/PlGF ratio ≥ 85 in week < 34 + 0 of gestation or an sFlt-1/PlGF ratio ≥ 110 in week ≥ 34 of gestation are useful thresholds for the diagnosis of preeclampsia [107].

Because of the lack of treatment options, screening for preeclampsia in the 1st trimester (between week 11 + 0 and week 13 + 6 of gestation) is an important cornerstone of treatment. Using a combination of the patient's history, measurement of mean arterial pressure, bilateral measurement of the pulsatility index of the uterine arteries and the determination of PAPP-A and PlGF, the risk of developing preeclampsia can be detected with a probability of 75–92 % and a false-positive rate of just 10 % [77, 78]. If the findings are positive, it is recommended that patients take 150 mg ASA daily once per day every night to reduce the incidence of preeclampsia, as mentioned above [82].

More recent experimental therapeutic approaches are investigating the possibility of using apheresis to reduce sFlt-1 levels. A significant reduction in sFlt-1 serum concentrations has been achieved in small pilot studies which showed an alleviation of maternal symptoms including a reduction of maternal hypertension and proteinuria and increased fetal growth based on fetal percentile curves [108 – 110]. In addition, studies have shown that this delayed immediate delivery of the infant by 2–21 days.

Measures to influence the complement system are another potential treatment option. Depending on their location, single nucleotide polymorphisms within the complement C3 gene are a risk factor for severe preeclampsia [111], indicating that administration of the C5 complement inhibitor eculizumab could be a possible causal therapy in cases with overactivation of the complement system [112 – 115]. However, because the data is very limited, it is currently not possible to make any recommendations about this approach.

Thrombotic thrombocytopenic purpura (TTP)/ pregnancy-associated hemolytic uremic syndrome (HUS)

In addition to preeclampsia and HELLP syndrome, renal thrombotic microangiopathies also include clinical conditions such as hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

The characteristic common feature of the latter entities is a disseminated occlusion of arterioles and capillaries by fibrin and agglutinated platelets, leading to mechanical lysis of erythrocytes

and platelet aggregation [116]. The consequences are extracorpuscular hemolytic anemia and ischemia of affected organs. Although both clinical conditions occur very rarely in pregnancy, they are associated with high morbidity and mortality rates for both the mother and the fetus [117].

TTP is characterized by the appearance von Willebrand factor (vWF)-rich microthrombi in the arterioles and capillaries of different organ systems [118]. If endothelial cell injury occurs or there are high shear forces in the capillaries, vWF mediates the aggregation of endothelial cells and platelets and thus induces primary hemostasis. Under physiological conditions, excessive thrombus formation is inhibited by ADAMTS13 protease cleaving the large vWF multimers into smaller entities. As regards its pathophysiology, the underlying cause of TTP is a deficiency of this specific protease, which allows vWF-rich microthrombi to develop in arterioles and capillaries. Possible causes are an inherited autosomal recessive gene defect (hereditary form of TTP) with reduced or absent ADAMTS13 activity, the formation of inhibitory autoantibodies against ADAMTS13 protease (idiopathic form), or exogenous and endogenous factors (secondary forms of TTP, e.g., caused by medication, disease, surgical interventions, etc.) [119].

Pregnancy, particularly the second and third trimester, is a risk factor for developing TTP [120, 121]. It has been hypothesized that the physiological increase in vWF during pregnancy leads to decreased levels of ADAMTS13 protease. This could mean that ADAMTS13 activity in women with a genetic (previously asymptomatic) ADAMTS13 protease deficiency decreases so much that this results in clinical manifestation of a thrombotic microangiopathy [121].

If there is a suspicion of TTP, current standard therapy initially consists of plasmapheresis with fresh frozen plasma (FFP) to eliminate antibodies and restore enzymatic activity [122, 123].

In contrast to TTP, in **pregnancy-associated atypical hemolytic uremic syndrome**, unregulated activation of the alternative complement cascade pathway leads to chronic persistent, self-intensifying and uncontrolled complement activation. The cause is often gene mutations in regulatory complement proteins such as complement factor H, I, C3 and membrane cofactor protein [124]. Pregnancy is the triggering factor in around 20% of all women with aHUS (especially in the postpartum period).

Retrospective analyses of women who developed pregnancy-associated HUS show that more than half of cases had genetic mutations of the complement proteins [125]. It was also found that women with identifiable mutations had a significantly poorer clinical course: dialysis dependence at initial presentation (81 vs. 58%), progression to terminal dialysis-dependent renal failure (64 vs. 36%), a higher risk of recurrence (38 vs. 16%) and a higher risk of developing preeclampsia (8 vs. 0%) or fetal complications such as preterm birth or miscarriage (5 vs. 0%) [126]. As with TTP, plasma exchange to remove autoantibodies and replace defective gene products is an important cornerstone of the initial treatment of aHUS.

Repeated administration of eculizumab, a monoclonal anti-C5 antibody, which prevents the cleavage of C5 and thus terminal activation of the complement system, should be used for long-term therapy [127]. As eculizumab has not been detected either in the umbilical cord or in blood samples taken from neonates, it can also be administered during pregnancy [128, 129]. Because of the lack of clinical trials, it is currently not clear how long treatment with eculizumab should be continued. In a case series of 10 patients with aHUS who achieved stable remission when treated with eculizumab, 7 patients were able to successfully stop treatment while 3 patients suffered recurrence within 6 weeks of discontinuing therapy [130].

Another unanswered question is whether eculizumab should be administered prophylactically in the event of a second pregnancy of women with previous episodes of pregnancy-associated HUS. It is currently not possible to give a specific recommendation because of the lack of clinical data. Close monitoring is required throughout the course of the pregnancy and for up to 3 months after the birth, and eculizumab should be administered in the event of recurrence.

Because of the lack of data for pregnant women and breastfeeding mothers, the long-acting C5 inhibitor ravulizumab should only be prescribed after carefully weighing up the risks and benefits [131].

The monoclonal anti-CD20 antibody rituximab which is prescribed in specific cases should also only be used with great care in pregnancy because of the high risk (10% of cases) of thrombocytopenia, neutropenia and B-cell depletion for the fetus and neonate and the lack of long-term data [132].

Acute fatty liver of pregnancy (AFLP)

Acute fatty liver of pregnancy is a rare (1 : 20 000 pregnancies) but potentially life-threatening obstetric emergency with maternal and neonatal mortality rates of 2–10% [133]. It is caused by an inherited autosomal recessive mutation in maternal and fetal mitochondrial 3-hydroxyacyl-CoA dehydrogenase enzyme (LCHAD defect), which leads to an accumulation of hepatotoxic long-chain fatty acids and their metabolites in the maternal liver [134]. The clinical picture is very heterogeneous and can range from mild symptoms of disease with minimal biochemical anomalies to severe forms with fulminant hepatic failure and associated multiorgan failure. The consequences of severe hepatic dysfunction include elevated bilirubin and transaminase levels, coagulopathy, thrombocytopenia, lactic acidosis, hypoglycemia, ascites and encephalopathy [135].

Along with histologically confirmed microvesicular fatty deposits in hepatocytes, renal biopsy findings also include deposits of free fatty acids in the renal tubular cells, meaning that Pr-AKI (with a frequency of 50–75%) is a typical complication of AFLP [133, 136, 137].

Because of the temporal (occurrence is mainly in the 3rd trimester), laboratory and clinical similarities (nausea, vomiting, stomach pain, jaundice, hypertension and proteinuria), differentiating AFLP from preeclampsia or from HELLP syndrome is not always possible (▶ **Table 2**) [90]. An overview of the Swansea criteria for diagnosing AFLP is given in ▶ **Table 5** [133, 138, 139]. It should also be noted that in 20–40% of cases, patients with AFLP are given a concomitant diagnosis of preeclampsia/HELLP syndrome [137, 140].

As with preeclampsia, treatment for AFLP also focuses on immediately delivering the infant together with providing supportive, usually primary, intensive medical therapy. As in most cases

▶ **Table 5** Swansea criteria for the diagnosis of AFLP.

▪ Vomiting	▪ Serum ammonia (> 47 µmol/l)
▪ Abdominal pain	▪ Uric acid (> 5.7 mg/dl or > 340 µmol/l)
▪ Polydipsia/polyuria	▪ AKI or creatinine (1.7 mg/dl or > 150 µmol/l)
▪ Encephalopathy	▪ Coagulopathy (PTT > 14 s or aPTT > 34 s
▪ Bilirubin (> 0.8 mg/dl or > 14 µmol/l)	▪ Ascites or pale liver on ultrasound imaging
▪ Hypoglycemia (< 72 mg/dl or < 4 mmol/l)	▪ Microvesicular steatosis on hepatic biopsy
▪ Leukocytosis (> 11 000 cells/µl)	
▪ Elevated transaminase level (> 42 IU/l)	

At least 6 of the above criteria must be met to diagnose AFLP after other pathologies have been excluded.

AKI: acute kidney injury

with spontaneous liver regeneration after delivery, renal function usually normalizes again after the birth. In rare severe cases, however, plasmapheresis treatment or a liver transplant may be necessary [141, 142]. Because clinical studies are lacking, it is not possible to make any statement about the impact of AFLP on long-term renal function [141, 142].

The guidelines of the American College of Gastroenterology additionally recommend carrying out a genetic analysis of long-chain 3-hydroxyacyl-CoA dehydrogenase in both the mother and her children as well as regular screening of the children for symptoms of LCHAD defect (hypoketotic hypoglycemia, metabolic acidosis, hepatic function disorders, arrhythmias, cardiomyopathy) [143].

In the context of infections

Because of the physiological changes which occur during pregnancy (due to anatomical and functional changes in the urogenital tract, hormonal changes, the increased incidence of instrumental and surgical trauma and the occurrence of pregnancy-related complications such as preterm rupture of membranes without onset of contractions, intrauterine fetal death and complicated or septic miscarriage), pregnant women have an increased risk of infection. Recognizing infections or septicemia requires special attention to be paid to this particular patient cohort. On the one hand, many predictive scores only have a low positive predictive value; on the other hand, symptoms such as tachycardia, tachypnea or a drop in blood pressure can be misinterpreted as blood loss, a side effect of oxytocin administration or being pain-related [144].

An infection can cause both direct injury to the kidney and AKI due to hemodynamic changes occurring in the context of septic shock [145].

Urinary tract infections/pyelonephritis

The anatomical, functional, and hormonal changes which accompany pregnancy and the presence of a range of different risk factors (e.g., diabetes mellitus, HIV, sickle cell anemia, anomalies of the urinary tract or chlamydia trachomatis infections) promote urinary tract infections [146, 147].

Untreated or undiscovered infections (asymptomatic bacteriuria in 2–7% of cases) represent a risk factor for both the unborn child (preterm birth, fetal growth restriction) and the pregnant mother (risk of developing pyelonephritis, which in 20% of all affected pregnant women evolves into systemic inflammatory response syndrome [SIRS] or sepsis) [60, 148–154]. In addition to the risk of developing sepsis, 2% of all pregnant women with pyelonephritis go on to develop AKI [151].

Early aggressive therapy with suitable antibiotic agents and adequate fluid replacement are the most important measures which need to be carried out for the prophylaxis and treatment of Pr-AKI.

Administering fluids to patients with pyelonephritis, SIRS or sepsis aims to increase mean arterial and central venous pressure and increase urine volumes. It should be noted, however, that because of the already elevated plasma volume and the endotoxin-mediated damage to endothelial cells in the alveolar capillary membrane coupled with additional fluid volumes, both respiratory and cardiac complications (pulmonary edema, pleural effusion, increased mitral insufficiency) may develop. At the moment, it is not clear which type of fluid (balanced electrolyte solution, 0.9% NaCl, Ringer's lactate solution, etc.) benefits patients most. Studies carried out in recent years in critically ill and not-critically ill patient cohorts suggest that the use of sodium chloride-rich solutions is associated with an increased risk of developing AKI or an increased probability of kidney replacement therapy and mortality [155–157].

Typical pathogens causing urinary tract infections are Escherichia coli (75–80% of cases), various Klebsiella, Enterobacter and Proteus subspecies as well as Group B Streptococci (10% of cases) [151, 158, 159]. Antibiotic therapy should be administered according to the microbiological findings detected with resistogram typing. If the pathogenic bacteria spectrum is not known, then oral antibiotics, for example, nitrofurantoin or β-lactam antibiotics (penicillins or cephalosporins) are suitable to treat uncomplicated urinary tract and bladder infections. But it is important to be aware that nitrofurantoin must not be administered to patients with glucose-6-phosphate dehydrogenase deficiency or to any woman in the 3rd trimester of pregnancy because of the risk of fetal hemolytic anemia [160].

In contrast, the treatment of pyelonephritis should initially consist of intravenous antibiotic therapy, which can later be switched to oral administration. Treatment should be continued for a period of 10–14 days, and a repeat urine culture should be done one week after concluding antibiotic treatment as recurrence or failure of treatment can occur in up to 30% of cases [161].

An overview of possible antibiotics, their dosages and duration of administration is given in ▶ **Table 6**. It should be noted that when antibiotics are prescribed, the initial dose must be administered in full for 24–48 h irrespective of liver and kidney failure [82].

Postpartum infections

Cesarean section and miscarriage and early or premature rupture of membranes, endometritis, wound hematoma, cervical cer-

▶ **Table 6** Preferred antibiotics for the treatment of urinary tract infections und pyelonephritis during pregnancy and lactation.

Medication	Dosage and form of administration	Duration of administration	Specific features
Penicillin			
Amoxicillin	250–500 mg every 8 hours or 750–1000 mg every 12 hours (oral) In cases with severe infection 750–1000 mg every 8 hours (oral)	3–7 days	▪ efficacy limited for gram-negative pathogens ▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Amoxicillin/ clavulanic acid	875/125 mg every 8–12 hours (oral) 1000/500 mg very 6–8 hours (intravenous)	Not more than 14 days	▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Ampicillin	0.5–2 g every 8 hours (oral/intravenous) Dose can be increased to 15 g per day depending on the clinical picture	3–7 days (continue medication for at least 2–3 days after symptoms have resolved)	▪ poor oral absorption, intravenous administration is preferable ▪ during pregnancy: concentrations in plasma reduced by up to 50 % ▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Ampicillin/ sulbactam	750–3000 mg every 6–8 hours (intravenous)	5–14 days (continue taking medication for at least 2 days after symptoms have resolved)	▪ during pregnancy: concentrations in plasma reduced by up to 50 % ▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Sultamicillin	375–700 mg every 12 hours (oral)	5–14 days (continue taking medication for at least 2 days after symptoms have resolved)	▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Cephalosporins			
Cefaclor	500 mg every 8 hours (oral)	7–10 days (continue taking medication for at least 2 days after symptoms have resolved)	▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Cefalexin	500–1000 mg every 6–8 hours (oral)	7–10 days (continue taking medication for at least 2 days after symptoms have resolved)	▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Cefuroxime	250 mg every 12 hours (oral) 1.5 g every 8 hours (intravenous)	5–10 days (continue taking medication for at least 2 days after symptoms have resolved)	▪ oral bioavailability is between 30–50 %, parenteral administration should be preferred ▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea
Ceftriaxone	1–2 g every 24 hours (intravenous)	Duration of intake is based on the course of disease (continue taking medication for at least 2–3 days after symptoms have resolved)	▪ more suitable alternatives during pregnancy: penicillins, cefaclor, cefalexin, cefuroxime ▪ during lactation: small amounts pass into breast milk, in isolated cases the infant may present with fungal infection of mucous membranes, loose stools or diarrhea

clage, infection with Group B Streptococci, low socioeconomic status, obesity, age > 35 years and diabetes are all risk factors for postpartum infection [162]. The initial therapy should consist of treatment with a broad-spectrum antibiotic because of the polymicrobial bacterial spectrum (often Escherichia coli, Enterococcus, Staphylococcus and Streptococcus) [163].

Postrenal kidney damage

Obstruction-related kidney damage during pregnancy is a rare cause of Pr-AKI. Irrespective of the suspected etiology of AKI, ultrasound examination must always be carried out to exclude obstruction.

Hydronephrosis can be visualized on ultrasound examination in advanced stages of pregnancy and is caused by compression of the ureter at the pelvic brim by the gravid uterus and relaxation of the smooth ureteral muscles due to increased progesterone synthesis. Hydronephrosis is a normal physiological phenomenon which does not require treatment in an otherwise uncomplicated pregnancy [164, 165].

However, chronic urinary retention combined with pregnancy-related lithogenic factors (elevated calcium, oxalate, uric acid and sodium concentrations in urine) is a risk factor for the development of **renal calculi**, particularly in the 2nd and 3rd trimester of pregnancy [166 – 168]. Symptoms resemble those of non-pregnant women and include abdominal or flank pain, nausea, vomiting, hematuria, leukocyturia, and pyuria [169].

Unilateral renal calculi are risk factors for urinary tract infections; if they lead to urinary tract obstruction, this can lead to hypertension, premature labor or even preeclampsia [168, 170, 171]. **Bilateral stones** are a rare cause of Pr-AKI and almost always require invasive intervention (ureteroscopy, ureteral stents or nephrostomy catheter) [172, 173].

Iatrogenic **injuries/displacement of the efferent urinary tract** are also a rare cause of postrenal Pr-AKI, usually caused by surgical injuries incurred during emergency C-section, particularly in cases with preexisting anatomical anomalies (e.g., ectopic kidneys, duplications of the urinary tract, ectopic ureteral orifice, etc.) [174]. It should be noted that unilateral injury to the ureters does not usually lead to an increase in renal retention parameters or decreased diuresis. Hydronephrosis and the accumulation of urine outside the urinary tract can be detected on sonography or CT imaging.

The presence of a retroperitoneal mass or fibrosis can be a cause of obstruction even if the ultrasound scan of the kidney is unremarkable [175, 176]. MRI of the kidneys and the efferent urinary tract should be carried out.

Hyperemesis gravidarum

With an incidence of 0.2–2%, hyperemesis gravidarum (HG) is the most common cause of AKI in the first trimester of pregnancy [177 – 179]. In addition to persistent vomiting starting before week 12 of gestation, ketonuria, and weight loss of more than 5% of body weight without any other demonstrable cause, laboratory findings often include metabolic alkalosis (contraction alkalosis), hypokalemia and hypophosphatemia [180]. An increase in hematocrit levels together with slightly elevated aminotransferase levels, mild hyperthyroidism and thiamine (vitamin B_1) deficiency have been detected in rare cases [177, 178, 181].

The precise etiology of hyperemesis gravidarum is still not entirely clear. It has been suggested that it is triggered by hormonal changes during pregnancy. In addition to hyperthyroidism, molar pregnancy, diabetes mellitus, previous history of gastrointestinal disease, and asthma are all risk factors for developing hyperemesis gravidarum [182].

Hyperemesis gravidarum can induce hypovolemia, with activation of the sympathetic nervous system, renin angiotensin aldosterone system and increased release of ADH (antidiuretic hormone, vasopressin) leading to vasoconstriction of the renal vasculature, renal hypoperfusion, and a decreased glomerular filtration rate [183 – 185].

Antiemetic therapy and adequate fluid replacement are the most important therapeutic interventions for the prophylaxis and treatment of Pr-AKI induced by hyperemesis gravidarum. Depending on the severity of HG, vitamins and dietary supplements should also be administered to ensure adequate supplementation of the mother and fetus [186].

Peripartum bleeding

The prevalence of peripartum bleeding caused by miscarriage, uterine atony, placental disorders such as placenta previa and disorders of placental separation, obstetric trauma injuries such as tearing of the cervix or vagina, uterine rupture, or clotting disorders is between 0.5 and 5.0%. Peripartum bleeding is the most common but also the most dangerous obstetric emergency [187, 188]. In Germany, peripartum bleeding is usually defined as blood loss of more than 500 ml after vaginal delivery and of more than 1000 ml after cesarean section. Because of the increased uterine blood flow when giving birth of around 600–800 ml/min, persistent bleeding can quickly lead to hemorrhagic shock with decreased renal perfusion and decreased GFR [189].

Moreover, because of the physiological changes which occur in pregnant women, blood loss of 1000–1500 ml may occur without external signs of hemodynamic instability. Incipient hemorrhagic shock may be misinterpreted (e.g., as tachycardia caused by labor pains or as a side effect of oxytocin administration), which may divert attention away from the site of bleeding [189].

The clinical picture of persistent hypotension and associated disorders of renal microcirculation varies greatly and may include pronounced local reversible inflammatory reaction with subsequent tissue ischemia, tubulointerstitial edema, tubular cell necrosis (partly reversible, partly irreversible) and even irreversible renal cortical necrosis.

Early recognition of the cause and extent of the bleeding followed by rapid, aggressive treatment (early parenteral fluid replacement, surgical or medication-based intervention, transfusion, full coagulation workup, systemic vasoconstrictors, etc.) is therefore the most important procedure for the prophylaxis and treatment of Pr-AKI.

Rare causes of Pr-AKI

Peripartum cardiomyopathy, defined as severe, rapidly progressive cardiac insufficiency without any other identifiable causes, is a rare, severe complication of pregnancy which can occur in the last weeks of pregnancy and up to five months after giving birth; it has a mortality rate of 3–40% [190]. Its clinical symptoms resemble those of other forms of cardiac failure [191, 192]. Risk factors include ethnicity, advanced maternal age, socioeconomic factors, multiparity, multiple pregnancy, hypertension, and diabetes mellitus [193]. Its etiology is still not entirely clear but genetic, maternal and fetal hormonal factors as well as viral infections are assumed to play a role. The pathophysiological consequences for the kidney of undiscovered or untreated cardiac insufficiency during pregnancy are similar to those occurring in non-pregnant persons with acute or chronic cardiac insufficiency (cardiorenal syndrome) [185, 194].

Milk-alkali syndrome is another rare cause of Pr-AKI. Because of the pathophysiological changes which occur during pregnancy (increased gastrointestinal absorption of calcium due to higher levels of prolactin und placental lactogen to ensure fetal calcium supply) and preexisting hyperemesis (induces hypovolemia with contraction alkalosis leading to reduced calcium absorption in the renal tubules), pregnant women have an increased risk of developing hypercalcemia [36, 195, 196]. Taking additional vitamin D supplements or of alkaline or calcium-containing antacids (e.g., magaldrate, sucralfate) to treat reflux esophagitis can increase the risk of developing milk-alkali syndrome [197 – 199]. Clinical symptoms include loss of appetite, dry mouth, dizziness, headache as well as acute confusion and psychosis [200]. Laboratory tests show metabolic alkalosis, reduced parathyroid hormone levels, increased renal retention parameters and, usually, normal or lower phosphate levels [200]. Classic hypercalcemia may present with normal values during pregnancy because of the reduced level of serum albumin. The correct level of serum calcium ($calcium_{corrected}$ [mmol/l] = $calcium_{measured}$ [mmol/l] – 0.025 × albumin [g/l] + 1) or of ionized calcium should be determined [36].

In the kidneys, hypercalcemia initially leads to indirect inhibition of the Na-K-2Cl channels in the ascending branch of the Henle loop, inducing vasoconstriction and natriuresis which are associated with decreased renal blood flow and decreased GFR. The hypercalcemia-induced inhibition of ADH receptors in the collecting tubules of the kidney decreases water reabsorption, leading to decreased volumes which, in turn, increases the reabsorption of bicarbonate and thus increases metabolic alkalosis. Alkalosis then leads to increased reabsorption of calcium in the distal tubules of the nephron, resulting in a negative feedback loop [200].

Treatment consists of avoiding or discontinuing the intake of calcium or vitamin D-containing supplements and the administration of antiemetic drugs coupled with “aggressive” rehydration (some cases have volume deficits of 4–6 l).

In addition to peripartum cardiomyopathy and milk-alkali syndrome, other rare causes of Pr-AKI include fulminant viral hepatitis (herpes simplex virus and hepatitis E which is especially prevalent in developing countries), rhabdomyolysis caused by trauma or drug abuse (cocaine-induced hyperthermia, methamphetamines), sickle cell anemia, renal cortical necrosis (caused by hypoperfusion or disseminated intravascular coagulopathy due to premature placental separation, intrauterine fetal death or amniotic fluid embolism) and rupture of splenic artery aneurysm.

Summary

Pregnancy-related acute kidney injury is not a rare entity and its incidence is increasing. Pr-AKI significantly increases the risk of fetal or maternal complications, both during the entire pregnancy and postpartum. Early detection and treatment of Pr-AKI is therefore every important, but the range of different entities, the heterogeneity of symptoms, and the overlapping clinical and laboratory characteristics mean that diagnosing Pr-AKI may be a challenge for the treating physician.

As the timepoint when AKI occurs can already provide the first indications about the possible underlying etiology, renal values should already be monitored early in pregnancy because of the pathophysiological changes which occur during pregnancy and to better evaluate changes in renal function. In addition to determining the most common renal retention parameters, biomarkers may be used to obtain a differential diagnosis and investigate for lupus and lupus nephritis. The determination of angiogenic factors as sFlt-1 and PlGF can be used to diagnose preeclampsia and predict adverse pregnancy outcomes. Genetic analysis can be performed to diagnose other entities (e.g., AFLP, aHUS), to ensure that treatment during subsequent pregnancies is initiated at an early stage and to allow a risk assessment about the course of the pregnancy to be carried out with provision of the necessary resources. However, genetic analysis is expensive, time-consuming and not immediately available.

A better understanding of the range of different causes driving renal function deterioration during pregnancy and prompt appropriate treatment of Pr-AKI could significantly improve the prognosis for mother and child but this requires the involvement of an interdisciplinary team.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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