

Recommendations on Pregnancy-associated Acute Kidney Injury - modified Delphi consensus statements

Cathy Nelson-Piercy¹, Nattachai Srisawat², Kianoush Kashani³, Nuttha Lumlertgul², Raghavan Murugan⁴, Harin Rhee⁵, Raj Chakravarthi⁶, Tarakeswari Surapaneni⁷, Anjali Acharya⁸, Ghada Ankawi⁹, Kate Bramham¹⁰, Jorge Cerda¹¹, Katherine Clark¹², Rolando Claure-Del Granado¹³, Swarnalata Gowrishankar¹⁴, Valerie Luyckx¹⁵, Shina Menon¹⁶, Carlos E Poli-de-Figueiredo¹⁷, Raja Ramachandran¹⁸, Manisha Sahay¹⁹, Srinivas Samavedam²⁰, Rasha Shemies²¹, Manjunath Shetty²², Kate Wiles²³, Lizemarie Wium²⁴, Vin-Cent Wu²⁵, Manjusha Yadla²⁶, Claudio Ronco²⁷, Ravindra Mehta²⁸, Marlies Ostermann²⁹

Affiliations

¹ Department of Obstetric Medicine, Guy's & St Thomas' Foundation Trust, London, UK

² Excellence Centre for Critical Care Nephrology, Division of Nephrology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Bangkok, Thailand

³ Division of Nephrology and Hypertension, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

⁴ Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

⁵ Department of Medicine, Pusan National University School of Medicine, Busan, Republic of Korea

⁶ Department of Nephrology, Yasodha Hospitals, Hyderabad, India

⁷ Department of Obstetric Medicine, Fernandez Hospitals, Hyderguda, Telangana, Hyderabad, India

⁸ Division of Nephrology, Jacobi Medical Center, New York City Health and Hospital Corporation/NYCHHC, Albert Einstein College of Medicine, Bronx, NY, USA

⁹ Division of Nephrology, Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

¹⁰ Department of Nephrology, King's College London, London, UK

¹¹ Division of Nephrology, Departments of Medicine, Albany Medical College, Albany, New York, USA

¹² Department of Women & Children's Health, School of Life Course & Population Sciences, King's College London, London, UK

¹³ Division of Nephrology, Department of Medicine, Hospital Obrero No 2 - Caja Nacional de Salud, Cochabamba, Bolivia

¹⁴ Department of Pathology, Apollo Health City, Hyderabad, Telangana, India

¹⁵ Department of Nephrology, University Children's Hospital, University of Zurich, Zurich, Switzerland

33 ¹⁶ Division of Nephrology, Department of Pediatrics, Lucile Packard Children's Hospital and Stanford
34 University School of Medicine, Palo Alto, CA, USA

35 ¹⁷ Division of Nephrology, School of Medicine, Pontifical Catholic University of Rio Grande do Sul
36 (PUCRS), Porto Alegre, Brazil

37 ¹⁸ Department of Nephrology, Post Graduate Institute of Medical Education and Research, Chandigarh,
38 India

39 ¹⁹ Department of Nephrology, Osmania Medical College and General hospital, Hyderabad, Telangana,
40 India

41 ²⁰ Ramdev Rao Hospital, Hyderabad, India

42 ²¹ Mansoura Nephrology and Dialysis Unit, Mansoura University, Egypt

43 ²² Department of Nephrology, JSS Medical College, JSSAHER, Mysuru, India

44 ²³ Department of Women's Health, Barts Health NHS Trust, London, United Kingdom.

45 ²⁴ Department of Obstetric Medicine, King's College Hospital NHS Trust, London, UK

46 ²⁵ Department of Nephrology, National Taiwan University Hospital, Taipei, Taiwan

47 ²⁶ Department of Nephrology, Gandhi Medical College, Hyderabad, India

48 ²⁷ Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, International Renal
49 Research Institute of Vicenza, Vicenza, Italy

50 ²⁸ Department of Medicine, University of California San Diego, San Diego, California, USA

51 ²⁹ Department of Critical Care, King's College London, Guy's & St Thomas' Hospital, London, UK

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54 **Corresponding Author:**

55 Marlies Ostermann

56 Department of Critical Care, King's College London, Guy's & St Thomas' Hospital,

57 Westminster Bridge Road, London, SE1 7EH, UK

58 Email: Marlies.Ostermann@gstt.nhs.uk

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Abstract

Acute kidney injury (AKI) during pregnancy and the postpartum period, collectively known as Pregnancy-associated AKI (PrAKI), remains a significant health concern worldwide, particularly in low-and middle-income countries where it accounts for a substantial proportion of maternal mortality and morbidity and may adversely affect the fetus. In January 2024, the 32nd Acute Disease Quality Initiative meeting was conducted to develop expert-derived pregnancy-specific recommendations on the causes, diagnosis, and management of PrAKI, and to highlight questions for future research. The panel of 30 multi-professional international experts in obstetrics, midwifery, obstetric medicine, pediatrics, internal medicine, anaesthesiology, nephrology, and critical care used an established modified Delphi process to develop consensus recommendations for PrAKI based on data up to December 2023. The panel developed 17 consensus statements / suggestions related to epidemiology, pathophysiology, diagnosis, management, long-term renal and non-renal complications, and the impact on the infant/neonate. Key suggestions were to identify pregnant and postpartum women at high risk for PrAKI to enable prevention, surveillance and timely diagnosis, and direct multidisciplinary management based on the principles of treating the causes to optimize short and long-term neonatal and maternal outcomes. Future observational and interventional studies should address existing gaps in knowledge and organizational healthcare, as PrAKI remains a substantial driver of health inequity in women, their families and communities worldwide.

INTRODUCTION

Globally, pregnancy-associated acute kidney injury (PrAKI) is an established risk factor for maternal and fetal mortality and morbidity, and occurs more frequently in lower-resource settings.¹ Hard data to support advocacy and action for change is however lacking. The 32nd Acute Disease Quality Initiative (ADQI) meeting was convened in January 2024 in Hyderabad, India, to evaluate the global burden of acute kidney injury (AKI) during pregnancy and the post-partum period, focussing on epidemiology, risk factors, aetiology, diagnosis, management and follow-up. Participants were selected to mirror the global multi-disciplinary workforce caring for patients with or at risk of PrAKI, including representatives from obstetrics, midwifery, obstetric medicine, pediatrics, internal medicine, critical care, nephrology and anaesthesiology. The primary aim was to develop evidence-based consensus statements to educate and guide healthcare practitioners regarding PrAKI and to improve the care and outcomes of pregnant women and their children. In addition, priority areas for further research were identified.

METHODS

Prior to the in-person meeting, the working groups met virtually to identify the key questions for discussion and consensus and to review the literature up to December 2023. During the meeting, a modified Delphi method was applied.² Working groups presented key questions to the entire panel for feedback. During break-out sessions, the groups refined the questions and formulated answers, supported by evidence when available and by expert opinion when no clear evidence was available. Statements were presented to the panel several times and re-revised iteratively in response to feedback until consensus was achieved.

Certainty of evidence was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.³ Where evidence was lacking and consensus could not be reached, the group made recommendations for future research. A priori, it was decided that agreement by 85% of votes would be necessary for consensus. The final anonymous voting round took place electronically after the meeting.

The panel resolved that the term 'PrAKI' included AKI due to both, pregnancy-specific pathologies, e.g. pre-eclampsia / hyperemesis / post-partum haemorrhage / chorioamnionitis, as well as AKI that develops during pregnancy due to causes that are coincidental. Abortion (an induced termination of

pregnancy) was distinguished from miscarriage (a spontaneous pregnancy loss) but the panel acknowledged that both, septic miscarriage and septic abortion may cause AKI.

Within this document, the terms “woman” and “women’s health” are used. However, it is important to acknowledge that kidney and obstetric services and care delivery must therefore be appropriate, inclusive, and sensitive to the needs of individuals whose gender identity does not align with the sex they were assigned at birth.

1. SPECTRUM OF PRAKI

Q1. What is known about the epidemiology of PrAKI?

Consensus statement: PrAKI is a significant global public health problem associated with maternal and perinatal morbidity and mortality, which varies in incidence, severity, and outcome according to socioeconomics, healthcare expenditure, and access to antenatal care. Pre-eclampsia, sepsis, and hemorrhage are common causes.

Rationale: The overall incidence of PrAKI as reported in the literature is variable, ranging between 40-100 cases per 10,000 pregnancies.^{1,4-9} Postpartum PrAKI occurs in 16-40 per 10,000 pregnancies, accounting for 20-50% of PrAKI.^{1,9-12} PrAKI incidence has been reported to increase over the past 20 years but heterogeneity is observed across regions, partly due to geographic and income differences.^{4,13-15} An inverse relationship appears to exist between national total health expenditure as a percentage of a country’s gross domestic product (GDP) and PrAKI incidence. High-income countries (HIC) report the lowest incidence of PrAKI,^{14,15} with higher incidences observed in low and middle-income countries (LMIC).¹⁶ The incidence of severe PrAKI meeting Kidney Disease Improving Global Outcomes (KDIGO) AKI stage 3 criteria, is highest in Africa, with incidences from 77 to 233 per 10,000 pregnancies.^{12,17}

Approximately 6-12% of PrAKI is associated with maternal mortality,^{11,12} and 16-37% of women with PrAKI require hemodialysis.^{1,13} Compared to pregnancies without AKI, PrAKI also increases the odds of adverse pregnancy outcomes, including miscarriage, preterm birth, stillbirth, and perinatal death by 3.5-fold (95% CI 1.9-6.5).¹⁵⁻¹⁹ Fetal death or miscarriage has been reported in 22-36% of PrAKI cases.^{11,16,19} Pre-eclampsia/eclampsia is the most common aetiology of PrAKI, followed by haemorrhage and sepsis.^{8,11,13,16,17,19}

Q2. What are the risk factors for PrAKI?

Consensus statement: Risk factors for PrAKI include underlying comorbidities, maternal health during pregnancy, access to prenatal care and other socio-demographic factors.

Rationale: Given the discrepancies in incidence and outcomes of PrAKI between higher and lower resource settings, it is clear that factors beyond pregnancy impact the risk and PrAKI risk factors likely overlap with those contributing to maternal mortality. For instance, hypertensive disorders of pregnancy have increased in HIC (perhaps due to older age and obesity), while they appear to have decreased in LMIC as maternal care improved. Even within HICs, PrAKI is more common among minoritized and vulnerable populations.²⁰ Dramatic differences in risk of PrAKI suggest that underlying inequities and social determinants of health related to where a woman grew up and what opportunities she had as a child, teenager and young woman are important contributors via structural, cultural and socioeconomic mechanisms. A mother's birth history or prior pregnancy history, medical comorbidities, and access to healthcare will impact her biomedical health and susceptibility to pre-eclampsia, chronic kidney disease (CKD) and PrAKI.²¹ Outcomes in PrAKI are associated with individual physical and clinical risk factors but are also significantly impacted by the timeliness with which a woman seeks care, and the quality of the care she receives.²²

Q3. How can high-risk persons be identified for primary prevention of PrAKI?

Consensus statement: Risk profile assessments before and during pregnancy can identify women at increased risk of PrAKI and inform strategies for primary prevention. These include optimizing an individual's medical, pregnancy, and kidney health and addressing social determinants of health.

Rationale: Early identification of high-risk pregnant individuals allows increased surveillance for PrAKI and provides opportunities for early interventions. PrAKI risk profiles encompass social determinants of health, clinical characteristics, medical comorbidities, and pregnancy- and kidney-specific risk factors (Table 1). Primary prevention of PrAKI should be provided at the population, health care system, and patient level.^{23,24} The assessment of environmental, socioeconomic and/or cultural factors, as well as processes of care is of particular importance in resource-limited regions where these dimensions are major contributors to overall PrAKI risk. To prevent PrAKI, modifiable risk exposures must be identified and remedied. The provision of regular and quality antenatal and peripartum care and equity of access

are key interventions. Antenatal and peripartum care must include measures to reduce the risk of sepsis and haemorrhage, as well as the prevention, early diagnosis, and management of pre-eclampsia.

2. PATHOPHYSIOLOGY AND RISK FACTORS

Q4. How does pregnancy physiology influence the pathophysiology of AKI?

Consensus statement: Physiological changes in pregnancy may alter the susceptibility for PrAKI. The presence of the fetal-placenta unit (FPU) is unique to pregnancy, resulting in hemodynamic, neurohumoral, immunological, vascular and structural changes that are additionally influenced by pre-existing comorbidities.

Rationale: Pregnancy induces lower peripheral vascular resistance, higher heart rate, lower arterial blood pressure, and increased cardiac output. An increase in plasma flow rate due to circulatory vasodilation leads to an increase in glomerular filtration rate (GFR). These circulatory alterations may mask volume depletion or exaggerate organ hypoperfusion as a consequence of other exposures, e.g., sepsis or hypovolemia.^{25,26} At the microvascular level, the glomerular endothelial cells may become mildly swollen and vacuolated²⁷, and some pregnancy-associated physiological changes can predispose to PrAKI. (Figure 1) For instance, humoral and cellular changes in the maternal immune system enhance tolerance to the FPU but also increase the risk of infection, autoimmune disorders and PrAKI. Mechanical pressure from the gravid uterus and pregnancy-associated hormonal changes can lead to physiologic dilatation of the urinary collecting system with reduced peristalsis.²⁸ These structural changes increase the risk of ascending urinary tract infection, potentially leading to acute pyelonephritis and PrAKI.^{29,30} Patients with pre-existing structural renal abnormalities, such as autosomal-dominant polycystic kidney disease, nephrolithiasis, and previous upper urinary tract infections, are particularly at risk.

A normal pregnancy is an immune-tolerant state. The FPU is a physical interface between the mother and the fetus, with paternal antigens expressed by the fetus. As paternal antigens are foreign to the mother, a successful pregnancy depends on immune adaptation, including suppression of the adaptive maternal immune system but only minimal changes in the innate immune system.³¹ Trophoblast cells form a specific placental cell layer that has a number of immune protective mechanisms and protects the embryo from the maternal immune system dedicated to destroying foreign tissues. The main mechanisms of immune escape at the maternal–fetal interface are a reduction in the expression

of major histocompatibility complex (HLA) molecules by trophoblast cells, the presence of complement regulators, activation of regulatory T cells, and an increase in immune checkpoints.³² The major HLA Class II is not expressed, and Class I only has few alleles in the first trimester (HLA-E, HLA-F, HLA-G). Several factors, such as chemokines, growth factors, cytokines, and angiogenic factors, such as the Placental Growth Factor (PlGF) and Vascular Endothelial Growth Factor (VEGF), are produced. In addition, complement regulatory proteins are secreted by the placenta (MCP-CD46, DAF-CD55, and MIRL-CD59), avoiding complement activation during pregnancy.³³ The presence of a healthy FPU protects the mother and the fetus but any alteration in the immune balance or the crosstalk between trophoblasts and maternal cells can lead to adverse outcomes in pregnancy, including AKI.³⁴

Pre-eclampsia, eclampsia, and 'Haemolysis, Elevated Liver enzymes, Low Platelets' (HELLP) are pregnancy-specific syndromes resulting from placental dysfunction. (Figure 1) Placental ischemia leads to the production of antiangiogenic factors [e.g., soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin], inflammation, and immune responses that induce a maternal angiogenic imbalance and an inflammatory state resulting in maternal endothelial and multi-system dysfunction characteristic of pre-eclampsia.³⁵ These changes can cause hypertension, proteinuria, and sometimes AKI. Maternal predispositions include pre-existing chronic hypertension, CKD, diabetes, previous AKI and autoimmune disorders. Acute cortical necrosis (ACN) is more common during pregnancy, and may occur as a consequence of pre-eclampsia, abruptio placenta, postpartum hemorrhage, puerperal sepsis, or rarely thrombotic microangiopathy (TMA).³⁶

Pregnancy-associated immunological changes may also lead to flares in certain autoimmune conditions. Women with systemic lupus erythematosus (SLE) and antiphospholipid antibodies are at increased risk of adverse outcomes in pregnancy.³⁷ Pregnancy can result in a lupus flare or even a primary manifestation of the disease with the attendant risk of lupus nephritis as well as pre-eclampsia and PrAKI.³⁸⁻⁴⁰ In general, primary TMA's are rare but pregnancy is a predisposing factor. While complement regulatory proteins of the placenta provide protection during the first and second trimester, AKI due to complement-mediated thrombotic microangiopathy (CM-TMA) may occur in the late stages of pregnancy or postpartum.

Q5. How does pregnancy affect the AKI course and its recovery?

Consensus statement: Compared with other AKI syndromes, the presence of the FPU alters recovery of AKI and maternal morbidity and mortality.

Rationale: During pregnancy, hyperfiltration, increased renal blood flow, and a decrease in renal functional reserve are well-described.^{41,42} These changes not only increase the risk of PrAKI but may also lead to slower recovery of renal function or more maladaptive repair.^{41,43} ACN is often associated with a poor prognosis and progression to end-stage kidney disease (ESKD).

Women with PrAKI have a higher likelihood of inpatient mortality compared to women admitted without PrAKI (OR 13.50; 95% CI 10.47–17.42).²⁴ In the long-term, they also have an increased risk of cardiovascular events (OR 9.74; 95% CI 9.08–10.46), development of CKD and ESKD, and kidney related hospitalization.

Q6. What is the effect of PrAKI on the fetus?

Consensus statement: The underlying etiology of PrAKI and other predisposing factors may result in preterm birth, small for gestational age (SGA), and intra-uterine growth restriction by direct and indirect mechanisms.

Rationale: PrAKI can lead to fetotoxicity by increased maternal serum concentrations of uremic toxins, potassium, or acids.^{44,45} There are also other potential effects on the fetus, including 1) placenta hypoperfusion (e.g., volume depletion, sepsis or hemorrhage) or vascular occlusion (e.g., TMA, malaria); 2) placental dysfunction due to systemic diseases [e.g., sepsis, lupus nephritis, acute fatty liver of pregnancy (AFLP)]; or 3) abnormal placentation due to pre-eclampsia. The fetal effects of placental dysfunction include fetal growth restriction, still-birth and preterm delivery.

3. DIAGNOSIS OF PRAKI

Q7. What is the role of kidney health assessment in pregnancy?

Consensus statements:

- i) **We recommend that a kidney health assessment (KHA) be performed at the first encounter in all pregnant women. In high-risk women and those with ongoing insults, we recommend ongoing KHA. (Best practice statement)**
- ii) **We suggest, at a minimum, serum creatinine (SCr) (using a standardized assay) and blood pressure measurement, urinalysis, urine dipstick, or quantitative proteinuria assessment where feasible, be used for KHA. (Weak recommendation, grade B)**
- iii) **We recommend against using estimated glomerular filtration rate (eGFR) to assess kidney function in pregnancy. (Strong recommendation, grade B)**

Rationale: A systematic KHA in pregnancy is essential. The components of KHA include a comprehensive evaluation of PrAKI risk factors, SCr and blood pressure measurement, urine dipstick or quantitative proteinuria, and a review of medications.⁴⁶ SCr is suggested for kidney function monitoring during pregnancy but several challenges exist, including the availability and standardization of assays and potential confounding factors.^{47,48} Published reference ranges for SCr during pregnancy are 0.53-0.87 mg/dL (47-77 μ mol/L) but vary by gestational age and SCr assay methods.⁴⁹ Values above reference SCr warrant serial monitoring, and can indicate gestational changes, AKI, AKD, or pre-existing CKD.

Standard eGFR formulae are not validated in pregnancy. The Modification of Diet in Renal Disease (MDRD) equation underestimates and the Cockcroft-Gault equation overestimates the actual GFR depending on the stage of pregnancy.⁵⁰ The measurement of timed creatinine clearance is cumbersome but might be used for drug dosing.⁵¹ The current evidence does not support the use of salivary urea nitrogen or cystatin C during pregnancy.^{52,53}

Urinalysis might reveal proteinuria and/or hematuria. Hematuria may indicate glomerular or structural kidney diseases. Proteinuria may represent physiologic changes (if <300mg/d), preeclampsia, glomerular or tubular disease or pre-existing CKD.⁵⁴ Ideally, quantitative proteinuria assessment is recommended but point-of-care urine dipstick might be the sole available tool, especially in limited-resource settings. The presence of microalbuminuria ($\geq 2+$) should prompt an assessment for kidney dysfunction.⁵⁵

Pre-existing comorbidities (such as hypertension and diabetes) require optimization during pregnancy. High-risk women or those experiencing new health challenges should undergo ongoing KHA at each clinical encounter.

Q8. When is PrAKI suspected?

Consensus statements:

- i) We suggest that PrAKI be suspected in high-risk women with associated exposures/risk factors, and in those with specific signs and symptoms. (Best practice statement)**
- ii) We recommend documenting each episode and distinguishing specific causes to guide treatment and determine future risks. (Best practice statement)**

Rationale: The initial step towards early recognition of PrAKI begins with identifying high-risk individuals. Healthcare providers and pregnant women should be educated on how to recognize signs and symptoms of PrAKI throughout pregnancy. Appreciating clinical scenarios associated with PrAKI, such as hypertensive disorders of pregnancy, HELLP syndrome, AFLP, various causes of antepartum, intrapartum and postpartum hemorrhage, infections, TMA, medications, and obstetric complications, is crucial and informs further investigations.

Multiple episodes of PrAKI can complicate pregnancy. It is important to recognize each episode, differentiate its causes and plan for prevention, treatment and follow-up accordingly.

Q9. How is PrAKI diagnosed?

Consensus statements:

- i. We recommend that SCr from a previous baseline (preconception or at the first antenatal visit), when available, be used to diagnose PrAKI. (Strong recommendation, grade B)**
- ii. In the absence of a baseline SCr, the published reference ranges in pregnancy may be used as a reference SCr. (Weak recommendation, grade B)**
- iii. We recommend serial monitoring in patients with SCr above the reference concentrations and in those with an increase in SCr above baseline to diagnose Pr AKI, acute kidney disease (AKD), or CKD. (Strong recommendation, grade B)**
- iv. We suggest that PrAKI be considered if there is:**
 - Any increase in SCr from baseline concentrations associated with a new insult**
 - Prolonged oliguria or anuria in the antenatal or postpartum period**

(Weak recommendation, grade B)

- v. **We suggest the KDIGO consensus criteria be used for AKI staging and prognostication. KDIGO stage 1 needs to be interpreted within the clinical context.** *(Weak recommendation, grade B)*
- vi. **We suggest that complete recovery from AKI be defined as a return of SCr to preconception baseline or reference SCr.** *(Weak recommendation, grade B)*

Rationale: There is no standardized definition of PrAKI. The KDIGO consensus criteria for AKI are based on a rise in SCr and/or fall in urine output but are less studied in pregnancy.⁵⁶ Published reference ranges for SCr during pregnancy vary. Notably, the availability and standardization of urine testing and creatinine assays may be limited in some settings.

Oliguria may be a peripartum physiologic response.⁵⁷ However, prolonged oliguria (≥ 6 hours in the antenatal and postpartum period or ≥ 12 hours in the peripartum period) should be considered abnormal. About 20% of patients with PrAKI stage 1, no apparent cause could be identified, and the episodes were not associated with worse outcomes.²⁰ KDIGO AKI stages 2 and 3 during pregnancy are linked to poor maternal and fetal outcomes.^{58,59} Complete recovery should be defined as a return of SCr to its baseline or reference value.

Q10. How can PrAKI be investigated?

Consensus statements:

- i. **We recommend investigating PrAKI using a combination of blood/urine tests, kidney imaging, and kidney biopsy based on etiology, and available resources.** *(Strong recommendation, grade B)*
- ii. **We suggest that selected pregnancy-specific biomarkers be incorporated into clinical assessment to differentiate pre-eclampsia from other causes of PrAKI or an underlying CKD. There is insufficient data to recommend the use of kidney-specific biomarkers to diagnose and stage PrAKI.** *(Weak recommendation, grade C)*

Rationale: The causes of PrAKI involve functional alterations and/or structural damage, with functional causes being most prevalent during the first trimester. The timing of PrAKI provides valuable insights into potential causes. (Figure 2) The PrAKI work-up can be tailored based on the suspected etiology and available resources.⁶⁰⁻⁶² (Supplementary Table S1) Data on alternative biomarkers for PrAKI diagnosis and

risk assessment are limited and inconclusive.^{63,64} However, the measurement of serum concentrations of antiangiogenic factors [e.g., soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF)] may aid the diagnosis of pre-eclampsia.⁶⁵

The decision to perform a kidney biopsy in pregnancy is complex and should include a multidisciplinary discussion with the patient. A kidney biopsy can be justified when the results will guide treatment and will help to prolong the course of the pregnancy and improve fetal outcomes, for instance in patients with unexplained rapidly declining kidney function, *de novo* nephrotic-range proteinuria in the absence of pre-eclampsia, active urine sediment, suspected lupus flare or PrAKI in kidney transplant patients. The risk of kidney biopsy complications (ranging from small hematomas to major bleeding requiring blood transfusion) during pregnancy is higher (7%) than in the postpartum period (1%).⁶⁶ The biopsy should ideally be performed before 23 weeks of gestation. It may inform treatment and help prolong pregnancy in a carefully selected subgroup of pregnant women.^{66,67} A systematic review demonstrated that 66% of kidney biopsies performed in pregnancy resulted in therapeutic changes.⁶⁶

4. MANAGEMENT OF PRAKI

Q11. How can risk assessment inform the prevention and management of PrAKI to improve maternal and neonatal outcomes?

Consensus statement: Individualized risk assessment incorporating pre-existing and current risk factors for PrAKI, as well as ongoing surveillance and monitoring, may enable the implementation of care plans to prevent PrAKI or facilitate accurate and timely diagnosis and management for the mother-baby dyad.

Rationale: PrAKI is often asymptomatic, and kidney function testing pre- or post-partum is rarely performed or is not possible, particularly in low-resource settings.^{22,67} Approaches to promote early diagnosis and intervention, such as e-alerts and point-of-care testing, have not been studied or validated in pregnancy. Therefore, risk assessment for PrAKI is a cornerstone of primary prevention and management.⁶⁸ Ongoing iterative risk assessments for PrAKI throughout pregnancy and the peripartum period should include: 1) situational risk (*e.g.*, access to antenatal and intrapartum care, nutritional health); 2) pre-existing individual risk (*e.g.*, diabetes, hypertension, CKD); and 3) identification of trigger events for PrAKI (*e.g.*, hyperemesis gravidarum, sepsis, obstetric hemorrhage, nephrotoxins). Timely

recognition of PrAKI trigger events and appropriate treatment of the underlying trigger is imperative to prevent AKI progression and improve outcomes. (Table 2) Where immediate treatment of the cause of PrAKI is not possible, for example, when the decision is made to prolong the pregnancy in a woman with pre-eclampsia to optimize fetal condition, close observation and optimization of haemodynamics and fluid status are crucial. Continuity of care and multi-disciplinary joint decision-making are essential to improve maternal and neonatal outcomes.⁶⁹

Q12 What interventions for PrAKI can be used to improve maternal and neonatal outcomes?

Consensus statement: Determining the specific cause of AKI, and medication management, informs the treatment of PrAKI. Fluid balance and volume status assessment must also consider the unique physiological and pathophysiological changes in pregnancy.

Rationale: A fundamental principle in PrAKI management is that treatment must be directed toward the specific cause.⁷⁰ (Table 2) Fluid resuscitation is critical when AKI is related to a decrease in effective blood volume and should be directed to maintain renal and uteroplacental perfusion.^{71,72} However, fluid administration should be performed with caution in women with pre-eclampsia or cardiomyopathy owing to the increased risk of pulmonary edema. If oliguria persists despite adequate fluid resuscitation, further fluid infusion should be minimized.

A careful medication review must be undertaken, and any drugs with the potential to cause further renal injury should be stopped, if possible (*e.g.*, non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics).⁷³ Prescription of any medication during PrAKI should balance the risks and benefits to the mother with any potential perceived harm to the fetus.⁷⁰ Renally cleared medications need dose adjustment according to the degree of renal impairment.⁷⁴ Given the increase in the volume of distribution in pregnancy and the risk of AKI, therapeutic drug monitoring, if available, may aid in monitoring and dosing of nephrotoxic medications (*e.g.*, vancomycin, tacrolimus).

A challenge is to differentiate between conditions where delivery of the fetus is central to stopping the disease process and diseases that are not affected by delivery. In cases of pre-eclampsia, placental abruption, HELLP syndrome, and AFLP, prompt delivery of the fetus must be considered to reverse maternal organ dysfunction.⁷⁵ To control bleeding or to remove the source of sepsis (*e.g.*, septic abortion, chorioamnionitis), delivery may also be needed.^{76,77} (Table 2) Intrinsic pathologies, such as

glomerulonephritides, do not necessarily warrant delivery. Thrombotic thrombocytopenic purpura (TTP) should be treated with plasma exchange, and improved outcomes have been demonstrated with complement inhibitors, e.g., eculizumab or ravulizumab in CM-TMA.^{78,79} Glomerulonephritis flares are often treated with steroids and other pregnancy-compatible immunosuppressants.^{73,80,81} Management of biopsy-proven acute tubular necrosis is supportive, with restoration of intravascular volume, avoidance of nephrotoxins, and support with kidney replacement therapy (KRT). In cases of post-renal AKI, relieving the obstruction is urgent. This may require ureteric stenting or placement of percutaneous nephrostomies, as appropriate with minimization / avoidance of radiation exposure or delivery of the fetus if the obstruction is due to the gravid uterus.

Q13. How can KRT be applied in PrAKI to improve maternal and neonatal outcomes?

Consensus statement: The maternal indications for KRT do not differ from those of non-pregnant individuals.

Rationale: KRT may be necessary in case of progressive AKI and complications of AKI, including fluid overload, refractory hyperkalaemia, uraemic symptoms and severe metabolic acidosis.^{82,83} Based on the obstetrics literature among patients with CKD, KRT should be considered when plasma urea is >17-20 mmol/L to prevent fetal uremic toxicity and when the risks of pre-term delivery outweigh those of KRT initiation.⁸⁴ For women receiving hemodialysis during pregnancy, we suggest a dialysis dose prescription aiming for a pre-dialysis urea concentration <12.5 mmol/L,⁸⁴ or blood urea nitrogen concentration <50 mg/dL.⁸⁵⁻⁸⁷ A dialysis dose that targets these urea concentrations should be the standard of care in pregnancy as it is associated with improved fetal outcomes, likely due to reduced uremia and a consequent lower risk of polyhydramnios and prematurity.^{86,88}

The choice of modality must be based on patient preferences, stage of pregnancy, availability of various modalities, and the expected efficiency of the modality for that individual.⁸⁹ Intermittent hemodialysis is used for most patients. For critically ill pregnant patients with PrAKI requiring continuous renal replacement therapy, based on evidence from the non-pregnant populations, the dose prescription should be at least an effluent flow of 20-25 mL/kg/h of pre-pregnancy body weight.⁸⁹

Q14. What is the role of breastfeeding and contraception in PrAKI?

Consensus statement: PrAKI management includes informed discussion of feeding choices and timely contraceptive counseling.

Rationale: The World Health Organization recommends exclusive breastfeeding for six months, with supplemental breastfeeding continuing for two years based on substantial evidence for the mother and infant's nutritional, immunological, and other broader benefits.⁹⁰ The benefits of breastfeeding are greater for premature infants. Feeding choices should be implemented in the care of postpartum women, irrespective of the level of care and independent of PrAKI. Medications compatible with breastfeeding should be prescribed where possible although safety data informing prescribing practices in lactation are sparse.

Facilitating access to contraceptive choices is imperative for health promotion, and to support choice in childbearing and pregnancy spacing, as unintended pregnancy is associated with increased risk to the mother and the fetus.⁹¹

5. LONG-TERM RENAL AND NON-RENAL COMPLICATIONS OF PRAKI FOR MOTHER AND FETUS

Q15: What is the role of a risk profile assessment post-PrAKI?

Consensus statement: We suggest all women and children should have a post-PRAKI risk profile assessment documented before discharge from the index PrAKI healthcare encounter. Given the risk of renal and non-renal complications after PrAKI, a comprehensive health review facilitates tailored follow-up. (Best practice statement)

Rationale: Data on the long-term outcomes after PrAKI is limited with some studies describing an association between ongoing proteinuria / albuminuria and the development of CKD.^{10,92-104} (Supplementary Table S2) However, most studies do not test for resolution of PrAKI or differentiate between women with pre-eclampsia and PrAKI.^{9,105} Given the increased risk of CKD, cardiovascular morbidity and mortality in patients with other causes of AKI, it is likely that these outcomes are also pertinent to women with PrAKI.¹⁰⁶ It is also anticipated that the underlying causes of PrAKI influence long-term outcomes. For instance, conditions such as pre-eclampsia are associated with different long-term outcomes compared to atypical haemolytic uraemic syndrome (aHUS).¹⁰⁷⁻¹¹⁰

In light of these risks, all women should undergo an individual post-PrAKI risk profile assessment after the index healthcare encounter, including those who have experienced pregnancy loss or termination. (Figure 3) The assessment involves consideration of pre-pregnancy risk factors, obstetric-related aspects and renal and non-renal post-partum factors. (Supplementary Table S3)

While a significant number of patients diagnosed with PrAKI receive their diagnosis within a hospital setting, individuals with milder cases of AKI, those following abortion or stillbirth, or those residing in resource-limited environments may be identified in the community. Therefore, the optimal time for conducting risk stratification is upon discharge from the healthcare encounter, regardless of the setting.

PrAKI is also associated with adverse fetal / obstetric consequences, including fetal growth restriction, and preterm birth.^{6,92,95,105,111-117} Despite the current absence of long-term follow-up data for children born to mothers with PrAKI, a growing body of evidence suggests a potential association with adverse long-term outcomes, particularly after pre-eclampsia. Therefore, these neonates must have a comprehensive health check-up, including consideration of maternal, PrAKI-related, and paediatric risk factors tailored to resource availability. (Figure 4)

Q16: What is the suggested management of women after PrAKI?

Consensus statement: Management and follow-up of women after PrAKI is tailored based on their individual risk profile and healthcare setting and includes consideration of medical and psychological needs, customized education, and subsequent pregnancy planning.

Rationale: Long-term follow-up of women after PrAKI is informed by their risk profile. This follow-up should include monitoring of renal health and overall well-being using a comprehensive multi-disciplinary approach dependent on resource setting. Until data to inform specific follow-up for women with PrAKI is available, a modified approach based on a previous ADQI framework is recommended.⁴⁶ (Figure 3). Access to testing of SCr and urine dipstick should be universal for all women at primary care level. The frequency should be determined by the severity of PrAKI and resolution, as well as comorbidities and other health-care needs. Similar to follow-up after other types of AKI, the key components include assessment of Kidney function, Advocacy, Medications, Pressure, and Sick day management, as well as Pregnancy planning (KAMPPS). (Table 3) Persistent kidney abnormalities may

necessitate further investigations, such as renal imaging or biopsy, to identify any structural damage due to acute kidney disease or pre-existing CKD, with consideration of conditions that may be more common in pregnancy, e.g., ACN or aHUS. Medication stewardship needs to include contraception, breast feeding status, and future pregnancy planning.¹¹⁸

Psychosocial support is an often overlooked but essential component of long-term follow-up. Women who have experienced PrAKI may have undergone a traumatic pregnancy and birth experience requiring emotional and mental health support.¹¹⁹

Q17. What is the suggested management of children born to mothers with PrAKI?

Consensus statement: Prematurity and fetal growth restriction are more common with PrAKI and are associated with long-term complications. Follow-up management tailored to the individual risk profile is essential.

Rationale: PrAKI can be associated with hemodynamic instability, a pro-inflammatory uremic milieu, and potentially harmful medications, all of which may impact fetal development.^{92,95,103,105,111-117} No data exist specifically on the long-term outcomes of children born to mothers with PrAKI, in particular for those born at term or without any perinatal complications. However, infants born premature and/or SGA are at risk for long-term sequelae, including cardiovascular, renal and respiratory disease, and adverse neurodevelopmental outcomes.^{115,117} Therefore, it is imperative that neonates born to mothers with PrAKI have a comprehensive health check-up, including consideration of maternal, PrAKI-related, and paediatric risk factors tailored to resource availability. A post-PrAKI Pediatric Risk Profile Assessment which includes risk factors in the birthing mother, details of PrAKI, and post-natal course, performed at discharge from the birth encounter can help individualize follow-up and management (Figure 4 and Supplementary Table S4). When deciding on kidney follow-up, the balance between the availability of resources and the risk of medicalizing infants who have a relatively normal postnatal course and development needs to be recognised.

Children born premature and/or SGA may benefit from a comprehensive KHA performed at 2 years corrected age, including assessment of Blood pressure, Urine for protein, Child's growth and development, Kidney function, and Sonography for baseline kidney size and appearance (where

feasible). (BUCKS, Figure 4) Components of BUCKS may be re-assessed every 1-2 years during childhood based on the initial abnormality.

Regular collaboration between obstetricians, nephrologists, paediatricians and primary care providers ensures a comprehensive and holistic approach to long-term follow-up to promote health and quality of life.¹²⁰ Education on the importance of adherence to medical recommendations, regular monitoring, and teaching of signs of progressive disease empowers women and their advocates (partner / family / friends / community) to actively participate in their ongoing care.

DISCUSSION

Globally, PrAKI as a pregnancy complication is more frequently seen during pre-eclampsia, sepsis, and hemorrhage. Defining and diagnosing PrAKI presents multiple challenges because of pathophysiological changes in pregnancy and socioeconomic and cultural differences, leading to potentially late identification of the condition and delay of necessary interventions. Efforts to improve prevention, recognition and management of PrAKI by treating the underlying cause (when known) while optimizing maternal and neonatal outcomes require multi-faceted interventions, including enhanced antenatal care, early identification of high-risk patients, timely diagnosis, and swift initiation of treatment, including dialysis in severe cases, and timely delivery of the fetus.

The potential for future research to improve PrAKI outcomes is vast. (Supplemental Table S5) Long-term studies are also needed to understand the impact of PrAKI on maternal health, particularly the risk of CKD. Research into novel interventions for early detection and management of PrAKI, including exploring the potential for targeted therapies based on molecular and genetic findings, could have the potential to revolutionize care for pregnant women worldwide.

CONCLUSIONS

PrAKI is a significant public health concern requiring urgent attention. Improved antenatal care and education of healthcare practitioners in the recognition and management of PrAKI will undoubtedly improve outcomes for both mothers and newborns, and alleviate the burden of PrAKI worldwide.

FIGURE LEGENDS

Figure 1 Pathophysiology of PrAKI

Pregnancy-associated acute kidney injury has multiple different aetiologies. Some pregnancy-specific physiological changes can lead to pregnancy-specific AKI and some other risk factors increase the susceptibility of kidneys to other AKI mechanisms.

Figure 2. Risk factors and pregnancy specific aetiologies of PrAKI according to gestational age

The potential causes of pregnancy-associated acute kidney injury differ according to gestational age.

Figure 3. Schematic for PrAKI follow-up

The figure displays a potential paradigm for the follow-up care of patients who experience PrAKI. The degree of nephrology-based follow-up increases as the number of comorbidities, severity of AKI, and the degree of adverse pregnancy outcome increases. The timing and nature of follow-up are suggestions as there is limited data to inform this process. The items in each bucket follow the “OR” rule; therefore, each patient should follow the most severe bucket if they even meet one criteria of that bucket.

Modified from Acute disease quality initiative 22⁴⁶, with permission.

Abbreviations: HT, hypertension; KAMPPS, Kidney function, Advocacy, KRT, kidney replacement therapy; Medications, Pressure; PrAKI, pregnancy-associated acute kidney injury; SCr, serum creatinine;

Figure 4. Post PrAKI Pediatric Risk Assessment

Schematic for follow-up of infants born to mothers with pregnancy-associated acute kidney injury (PrAKI). The figure displays a potential paradigm for the care of children whose mothers experienced PrAKI based on their risk assessment. The timing and nature of follow up are suggestions as there are limited data to inform this process.

*high risk newborns includes sick newborns, and those requiring neonatal intensive care. There are limited data on their long-term kidney health and their follow-up may be tailored based on their neonatal course.

^ the timing of repeat check may depend on the degree of abnormality at discharge, and on feasibility of follow up including resources and maternal health

Abbreviations: BP, blood pressure; PrAKI, pregnancy-associated acute kidney injury; SCr, serum creatinine; upc, urinary protein creatinine ratio; WHO, World Health Organisation

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887 **Table 1. Risk Factors for Pregnancy associated AKI**

	Individual risk profiles
Demographic	Advanced maternal age, minority ethnicities High / low BMI
Medical comorbidities	Type 1 and 2 diabetes prior to pregnancy Chronic hypertension or high early pregnancy blood pressure CKD Systemic Lupus Erythematosus Antiphospholipid Antibody syndrome Any cause of volume depletion Acute infection: HIV, malaria, dengue, tropical infectious disease Heart failure Illicit drug use, alternative medicine
Pregnancy-specific	Any considered as high-risk by obstetric assessment Previous or current pre-eclampsia / HELLP Assisted reproductive techniques / IVF Multiple pregnancy Septic miscarriage/abortion Antepartum or postpartum hemorrhage Intrauterine death Sepsis Acute Fatty Liver of Pregnancy Hyperemesis gravidarum

Kidney-specific	Previous AKI Nephrotoxins Decreased renal reserve (low birth weight) Proteinuria CKD Urinary tract infection
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889 **Abbreviations:** AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease;
890 HELLP, hemolysis, elevated liver enzymes, low platelets; HIV, human immunodeficiency virus; IVF,
891 in-vitro fertilisation; PrAKI, pregnancy-associated acute kidney injury

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Table 2. Management of Pregnancy-associated Acute Kidney Injury

Pregnancy-specific syndromes		Not specific to pregnancy	
Condition	Treatment / Management	Condition	Treatment / Management
Hyperemesis	- Correct volume deficit - Correct electrolyte imbalance - Antiemetics	Heart failure	- Treatment of cause - Diuretics - Inotropes - Mechanical circulatory support
OHSS	- Fluid and electrolyte management - Consideration of termination of pregnancy (if refractory)	Gastrointestinal fluid loss	- Fluid and electrolyte management - Treatment of cause
Hemorrhage	- Isotonic crystalloids - Blood and blood products - Hemostatic agents - Embolization of bleeding vessel - Mechanical tamponade devices - Surgery / hysterectomy		
Sepsis	- Fluid resuscitation - Early Antibiotics - Vasopressors - Source control - Consideration of delivery of fetus for source control		
Pre-eclampsia / HELLP syndrome	- Blood pressure control - Seizure prophylaxis - Fluid balance - Delivery of fetus depending on gestational age	Nephrotoxin exposure	- Stop nephrotoxic medication(s) - Switch to an alternative medication - TDM
AFLP	- Delivery of fetus - Management of hypoglycemia - Correction of coagulopathy - Encephalopathy treatment - Management of diabetes insipidus - Management of acute liver failure	Glomerulonephritis	- Immunosuppression with pregnancy-compatible medications
TTP / aHUS	- Plasma exchange - Fresh frozen plasma - Rituximab - Corticosteroids - Eculizumab	Rhabdomyolysis	- Treatment of underlying cause - Fluid therapy - Correction of metabolic acidosis
Ureteral obstruction due to gravid uterus	- Ureteric stent placement - Percutaneous nephrostomy - Delivery of fetus	Obstruction	- Treatment of cause - Stent placement - Urological management

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898 **Abbreviation:** AFLP, acute fatty liver of pregnancy; OHSS, ovarian hyperstimulation syndrome; HELLP,
899 hemolysis, elevated liver enzymes, low platelets; aHUS, atypical hemolytic uremic syndrome; TDM,
900 therapeutic drug monitoring; TTP, thrombotic thrombocytopenic purpura

901 **Table 3. Post-PrAKI management - KAMPPS**

PrAKI KAMPPS Accessible, culturally sensitive care of pregnant women aligned with paediatric care when possible	
Kidney function	<i>Resource limited setting:</i> • Urine dipstick (with consideration with presence of lochia) • Kidney function measurement by SCr or eGFR <i>Resource sufficient setting:</i> • Kidney function measurement by SCr or cystatin C, measured GFR, or eGFR • Evaluation of proteinuria / albuminuria (with consideration of resolution of pre-eclampsia) • When available, consideration of biomarkers, imaging, and other tests including renal biopsy, as feasible and indicated • Optimisation of current kidney and other health status
Advocacy	• Education of women, advocates (partner/family/friends/community) and caregivers about AKI and CKD and importance of follow-up • Communication with other care providers
Medications	• Reconciliation, review (including breast-feeding status), and adjustment • Specifically discuss risk benefits of ACEI, ARB, MRA, SGLT-2 inhibitor, and diuretics if available • Review contraception • Review KENDs and over-the-counter medications
Pressure	• Education about BP goals and targets • Informed discussion about fluid status (with consideration of pregnancy and postpartum changes in volume status), ideal weight, role of diuretics with consideration of breastfeeding status
Pregnancy Planning	• Review of current contraception and fertility status • Discussion about future pregnancy plans and potential outcomes according to risk assessment • Review of medications, advice about safety in future pregnancy and timing of any pre-pregnancy / at conception changes, role of folic acid and aspirin according to the risk profile • Education of women about risk of recurrent PrAKI and prevention • Communication with health care providers for future pregnancy where possible

Sick day protocols	• Education of women on medications that need monitoring during acute illnesses • Consideration of protocols to withhold Kidney Eliminated and Nephrotoxic Drugs (KENDs)
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903 **Abbreviations:** BP, blood pressure; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BP,
904 blood pressure; KAMPPS, Kidney function, Advocacy, Medications, Pressure, Pregnancy, Sick day; KEND, kidney eliminated / nephrotoxic drugs;
905 ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; SCr, serum
906 creatinine; SGLT-2, sodium glucose co-transporter-2; PrAKI, pregnancy-associated acute kidney injury

Maternal Susceptibility
Pre-existing conditions (Hypertension, DM, CKD, HIV, obesity, etc)
Multiple pregnancies
Structural abnormalities

Pregnancy

Feto-Placental Unit

	Hemodynamic		Immunological			Structural
Pathological	Microvascular	Macrovascular	Humoral	Cellular	Antibodies	Obstruction
Physiological	Implantation	Reduced BP	Fetal tolerance	Neonatal immunity		Renal tract dilatation

PrAKI

Nephrotoxic drugs	Sepsis
Auto-immune disease/GN	TTP
UTI	HUS

AKI due to pregnancy specific pathologies

Hyperemesis Gravidarum	Pre-eclampsia
Septic Miscarriage / Abortion	HELLP
Molar pregnancy spectrum	APH / PPH with shock
OHSS	Puerperal Sepsis
	AFLP
	PPCM

Gestational Age (WK)

AFLP	Acute Fatty Liver of Pregnancy	DM	Diabetes Mellitus	HUS	Hemolytic Uremic Syndrome	PPH	Postpartum Hemorrhage
AKI	Acute Kidney Injury	GN	Glomerulonephritis	OHSS	Ovarian Hyperstimulation Syndrome	PrAKI	Pregnancy-Associated Acute Kidney Injury
APH	Antepartum Hemorrhage	HELLP	Hemolysis, Elevated Liver Enzyme Levels, and Low Platelet Levels	BP	Peripartum Cardiomyopathy	TTP	Thrombotic Thrombocytopenic Purpura
CKD	Chronic Kidney Disease	HIV	Human Immunodeficiency Virus	WK	Week	UTI	Urinary Tract Infection

Figure 2. Risk factors and pregnancy specific aetiologies of PrAKI according to gestational age

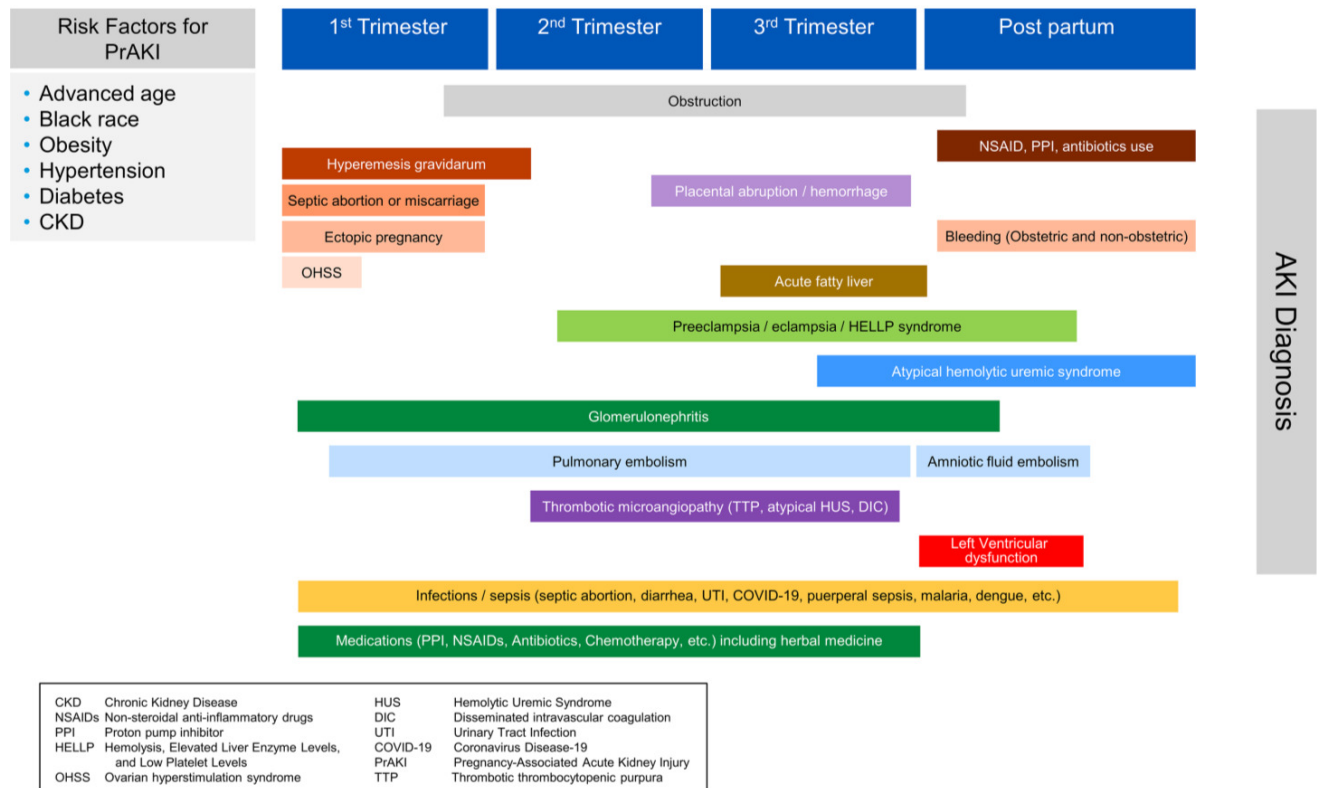


Figure 3 Schematic for PrAKI follow-up

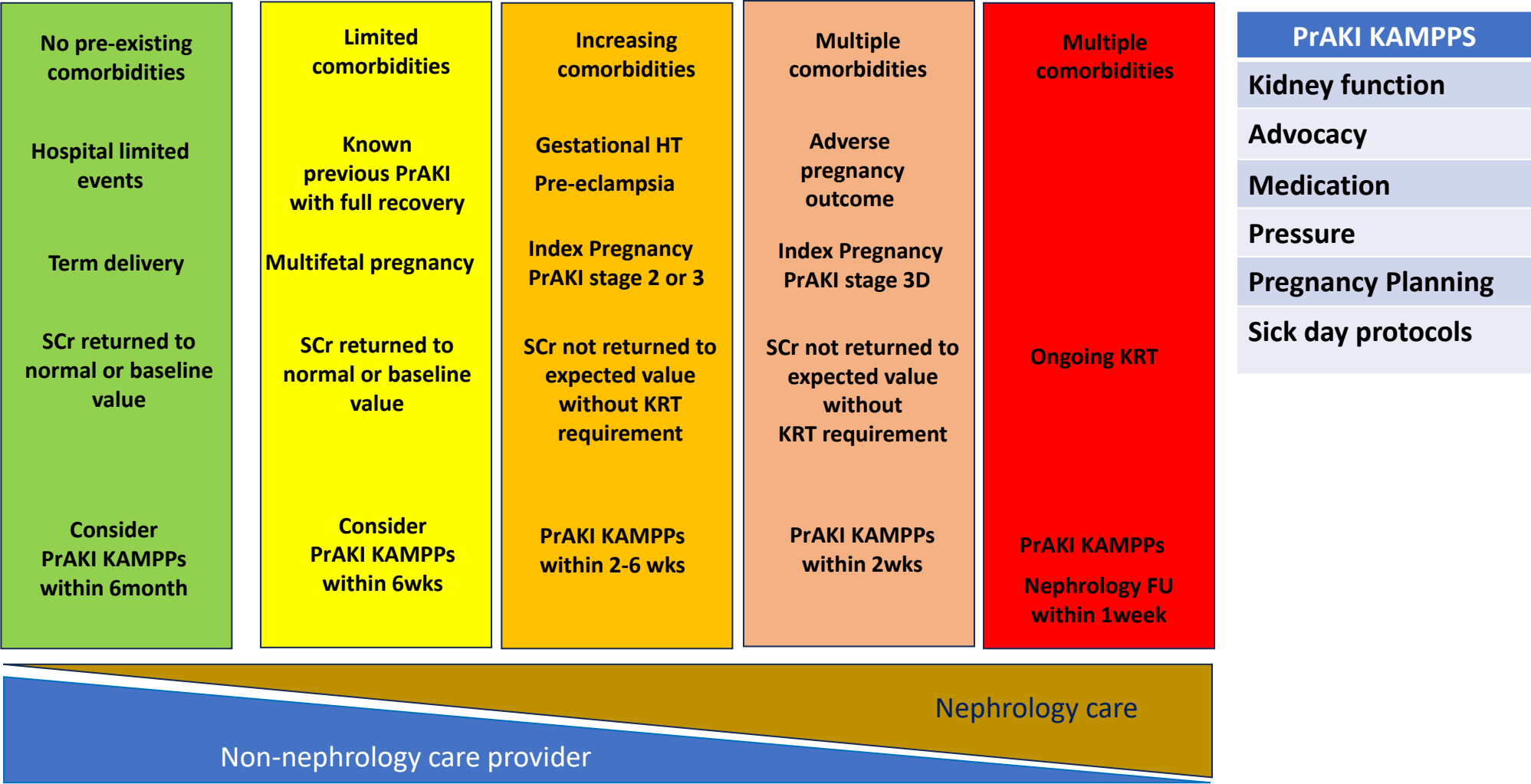


Figure 4. Post PrAKI Pediatric Risk Assessment

Child born at term after Stage 1 PRAKI and otherwise uncomplicated pregnancy	Child born at term after severe, persistent PrAKI or pre-eclampsia	Prematurity Small for gestational age Other high risk newborns*	Prematurity Small for gestational age Other high risk newborns*	BUCKS
		Age appropriate creatinine and blood pressure at discharge	Elevated creatinine and/or hypertension at discharge	Blood Pressure
Follow-up per WHO Nurturing Care Framework		WHO Recommendations for preterm, LBW infants plus additional national guidelines where available		Urine dipstick for protein, urinalysis or Upc if available
	Consider annual BP check Promotion of healthy lifestyle • Low salt diet • Physical activity promotion • Avoidance of rapid weight gain in infancy and early childhood	BP check at each healthcare visit Promotion of healthy lifestyle BUCKS at age 2	Creatinine, BP check in 2-6 weeks^ Subsequent follow up based on above Referral to nephrologist if persistent abnormal BUCKS at age 2	Check growth, development
Tailored education for all families and caregivers, and advocacy for resources to support follow up				
				Kidney function (SCr; consider cystatin C if available)
				Size of kidney on ultrasound