Women and kidney health: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Giorgina Barbara Piccoli[1], Sofia B. Ahmed[2], Fadi Fakhouri[3], Vesna D. Garovic[4], Michelle A. Hladunewich[5], Shilpanjali Jesudason[6], Jai Prakash[7], Angela C. Webster[8], Elena Zakharova[9], Michael Cheung[10], Jennifer M. King[10], Michel Jadoul[11], Wolfgang C. Winkelmayer[12] and Christina M. Wyatt[13]; for Conference Participants[14]

[1]Department of Internal Medicine, Centre Hospitalier Le Mans, Le Mans, France; [2]Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada; [3]Department of Nephrology, and Hypertension, Centre Hospitalier Universitaire Vaudois et Université de Lausanne, Lausanne, Switzerland; [4]Department of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; [5]Division of Nephrology, Department of Medicine, Sunnybrook Health Sciences Centre, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [6]Faculty of Health and Medical Sciences, University of Adelaide, Royal Adelaide Hospital, Adelaide, Australia; [7]Department of Nephrology, Banaras Hindu University, Varanasi, India; [8]Sydney School of Public Health, University of Sydney, New South Wales, Australia; [9]Department of Nephrology, Botkin Hospital, Moscow, Russian Federation; [10]KDIGO, Brussels, Belgium; [11]Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium; [12]Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; and [13]Department of Medicine, Division of Nephrology, Duke University Medical Center, Durham, North Carolina, USA

The KDIGO (Kidney Disease: Improving Global Outcomes) Controversies Conference on Women and Kidney Health was convened to identify key sex and gender issues in kidney care, practices for optimizing healthcare in women with kidney diseases, and priorities for future research. Participants emphasized the importance of addressing the influence of sex and gender in diagnosis, risk assessment, prognosis, and treatment of chronic kidney disease (CKD) and its complications, as well as considering issues across the lifespan (puberty, sexual and reproductive health, menopause). CKD is a risk factor for adverse pregnancy outcomes with every type of kidney disease and severity. All women of reproductive age known to have CKD should be counseled on contraception, the ideal timing of pregnancy, the risks and outcomes for mother and fetus, fertility treatments where these are available, medication management, and medical aspects of pregnancy termination. A successful pregnancy is possible across all severities of CKD, including in women living with dialysis or a kidney transplant. Pregnancy should be managed with a multidisciplinary care plan based upon the type of kidney disease and the presence and severity of kidney function impairment, hypertension, and proteinuria. Systematic assessment of blood pressure, proteinuria, and kidney function in all pregnancies would facilitate diagnosis of CKD and detection of acute kidney injury (AKI). Follow-up programs for women who experienced pregnancy-related AKI, preeclampsia, or other hypertensive disorders of pregnancy are important as these conditions may reflect undiagnosed CKD and have important implications for future cardiovascular health.

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Sex and gender influence the presentation, diagnosis, and management of kidney diseases and their complications.[1,2] Chronic kidney disease (CKD) can impact all aspects of reproductive health, including menstrual health, fertility, pregnancy outcomes, timing of menopause, body image, and sexual desire and satisfaction (Figure 1).[3–8] Over the last 2 decades, gender disparities and reproductive health have emerged as priority areas in kidney care, with advances in evidence-based clinical practice, education, and training. As a catalyst for further advances, KDIGO (Kidney Disease: Improving Global Outcomes) convened a Controversies Conference on Women and Kidney Health in February 2023. Supported by an in-depth review of the most relevant literature, the goal was to describe current best practices, identify areas of consensus and uncertainty, address ongoing controversies, and outline priorities for future research (Tables 1 and 2). The conference included individuals with multidisciplinary clinical and scientific expertise (i.e., adult and pediatric nephrology, obstetrics, reproductive health, neonatology,

Correspondence: *Giorgina Barbara Piccoli, Hospital Centre Hospitalier Le Mans, Nephrologie-dialyse-UIRAV Avenue Roubillard 196, Le Mans, 72000 France. E-mail: gbpiccoli@yahoo.it; or Christina M. Wyatt, Duke Clinical Research Institute, 300 W. Morgan Street, Durham, North Carolina 27701, USA. E-mail: christina.wyatt@duke.edu*

[14]Additional conference participants are listed in the Appendix.

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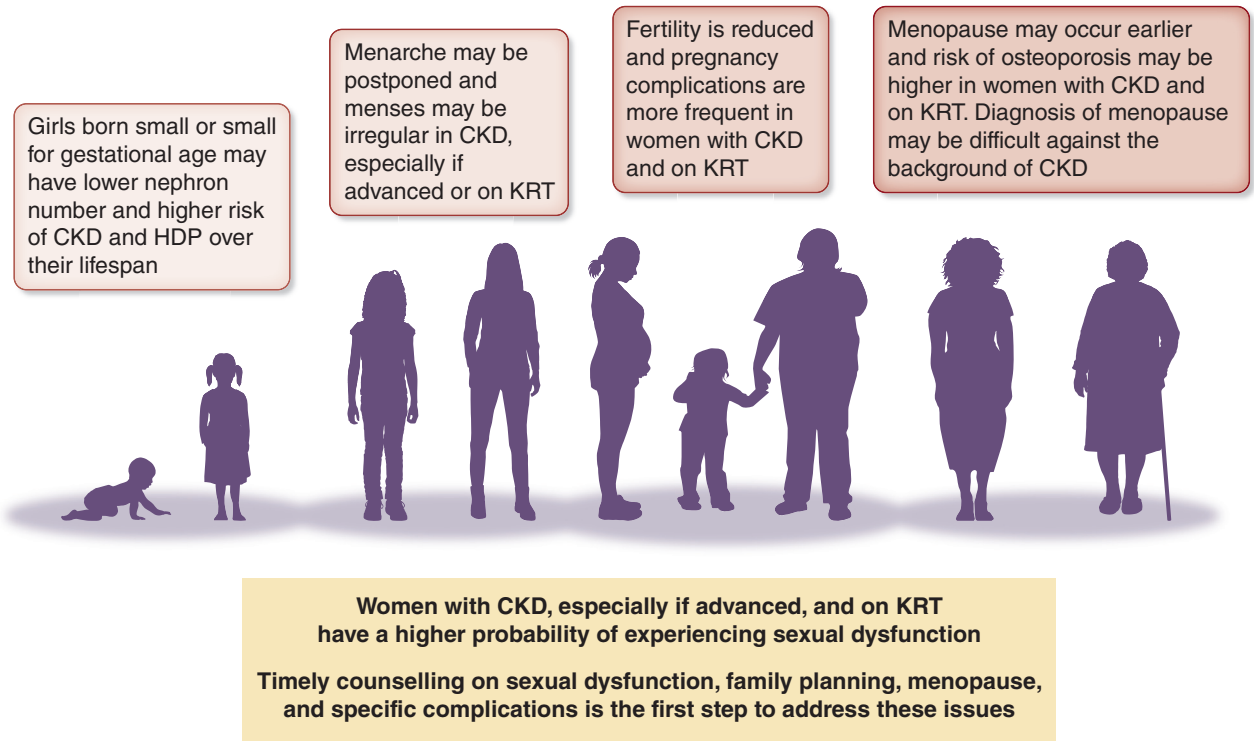

Figure 1 | Chronic kidney disease (CKD) and impact on women's health throughout the lifespan. HDP, hypertensive disorders of pregnancy; KRT, kidney replacement therapy.

midwifery, nutrition, bioethics, and epidemiology), as well as women with lived experience. Conference participants represented a broad range of healthcare and resource settings across the globe, as well as diverse cultural, social, and religious perspectives. Conference participants considered regional variation in the availability of resources, as well as opportunities to address disparities in reproductive and kidney health. Conference participants also considered issues related to gender identity and gender equity in kidney disease care and research. This report mainly focuses on kidney and reproductive health in individuals assigned female sex at birth, regardless of gender identity; the term "women" is used throughout for ease of translation across languages and cultural settings.

SEX AND GENDER DIFFERENCES IN CKD AND CKD COMPLICATIONS

Based on the current definitions of CKD, women have a higher prevalence compared with men, although it has been suggested that the estimated glomerular filtration rate (eGFR) threshold for diagnosis should perhaps be different in males and females.[1,15] Current equations for estimating GFR may not fully address potentially relevant factors such as age, sex, and gender.[16,17] Furthermore, the influence of a moderate reduction in eGFR on mortality and morbidity may differ according to sex.[18–22]

Men are more likely than women to start kidney replacement therapy (KRT),[1,23] which may reflect an overestimation of CKD in women,[22,24,25] faster CKD progression in men,[20,26] lower diagnosis and referral of women in the clinical setting,[27,28] or a higher likelihood of conservative care among women.[29,30]

Women undergoing dialysis report a higher symptom burden and greater symptom severity than men do.[31] At the same time, men with CKD or kidney failure generally show a larger health deficit, that is, an increased divergence from the health-related quality of life of age- and gender-matched counterparts in the general population.[32] Women with CKD have a higher odds ratio of mortality compared to the non-CKD population, even if their overall mortality rate is lower than for men with CKD.[20,33,34] Future studies should evaluate whether decisions regarding initiation and type of dialysis, conservative care, or withdrawal of dialysis vary by sex and gender and whether the effects of sex and gender are modulated by social, cultural, and economic contexts, including differences in shared decision-making, social support, and perceptions of frailty or quality of life.[35]

Women may have reduced access to deceased donor kidney transplantation compared with men,[36–40] in part owing to higher levels of preformed antibodies. Access to living donor kidney transplantation varies in different countries.[27] In many settings, women are more likely to serve as living donors.[41,42] According to a recent systematic review including 45 papers, the main reasons for sex and gender disparities in living kidney donation included socioeconomic (gendered division of roles within the families), biological (higher prevalence of

Table 1 | Areas of consensus related to reproductive health in women with kidney diseases

Clinical category	Consensus points
Sexual functioning and fertility in women with kidney diseases	• All women should have reproductive freedom. • Reproductive healthcare should be embedded in all parts of the healthcare pathway. • Family planning should be accessible, private, high-quality, nondiscriminatory, participatory, and based on informed decision-making. • Sexual functioning should be included as part of standard care and symptom assessment. • All women with CKD of childbearing age should be advised of the following: o Contraceptive choices, including reliability and safety o Ideal timing of pregnancy (age, CKD severity, KRT) o Potential outcomes of pregnancy for the mother and fetus based on clinical characteristics and risks • Women with CKD who are considering pregnancy should also be advised of the following: o Optimization of nonmedical care (exercise, healthy nutrition, attainment of healthy body weight) o Medication management in anticipation of pregnancy or at the start of pregnancy o Fertility and assisted reproductive technologies o Medical aspects of pregnancy termination
Pregnancy in women without known kidney diseases	• Populations of high priority for serum creatinine and proteinuria or albuminuria testing include patients with: o Diabetes o Autoimmune diseases o Previous history of PR-AKI, preeclampsia, or other HDP o Overweight or obesity o Preexisting hypertension o Personal history of low birth weight or prematurity o Assisted reproductive technologies
Pregnancy in women with CKD	A successful pregnancy is possible across all severities of CKD and on KRT within the individual and health system • Pregnant women with CKD should have access to multidisciplinary care and counseling from a team with expertise in management of the underlying disease and obstetrics skilled in pregnancies in the presence of maternal diseases. • Counseling and management should consider CKD severity (including need for KRT), type of disease, disease activity, hypertension, and proteinuria. • Control of the underlying disease and stabilizing kidney function in women with CKD and after kidney transplantation improves the likelihood of a good pregnancy outcome. • Aspirin prophylaxis should be offered to all pregnant women with CKD to lower the risk of preeclampsia. • In pregnant women with CKD, targeting home blood pressure to $<$130/80 mm Hg is a reasonable objective. • Serum creatinine, proteinuria, and other specific testing recommendations during pregnancy should be adapted to the local context and available resources.[a] • Antenatal kidney biopsy may be considered when it is expected to inform therapeutic management during pregnancy. • The presence of stable CKD does not change obstetrical or fetal indications for delivery. • Lactation should be supported if desired. • Women who experienced psychological trauma or a mental health disorder following their pregnancy[9,10] may need specific counseling or specialist referral.
Pregnancy in women on KRT	• Hemodialysis is the preferred modality for dialysis start in pregnancy, but peritoneal dialysis should be considered in selected cases • Intensive hemodialysis, adapted to local context and resources, allows for the best results. • Urea levels may be used to guide dialysis intensity. • Dialysis prescriptions should consider residual kidney function when titrating dialysis dose. • Strict monitoring of calcineurin inhibitor levels is indicated, under expert supervision, acknowledging the lack of evidence in this context.
Follow-up after pregnancy in patients with new diagnosis of a kidney disease or after HDP	• Patients with diagnosis or suspicion of a kidney disease during pregnancy should be offered follow-up, ideally with a nephrologist. • Postpartum visits with an obstetrician/gynecologist or other specialist after pregnancies complicated by preeclampsia or HDP should include cardiovascular, metabolic, and CKD risk assessments and diagnostic work-ups, if feasible. • Women who experienced psychological trauma or a mental health disorder following their pregnancy[9,10] may need specific counseling or specialist referral. • Women with CKD who experienced an HDP should undergo a preconception consultation if they plan a new pregnancy. o These women should be prescribed low-dose aspirin according to the current guidelines.[11–14]

CKD, chronic kidney disease; HDP, hypertensive disorders of pregnancy; KRT, kidney replacement therapy; PR-AKI, pregnancy-related acute kidney injury.
[a]Especially in middle- to lower-resource regions, which represent the highest prevalence of CKD and incidence of hypertensive disorders of pregnancy, or in settings where reimbursements are managed by private insurance providers, as in the USA.

Table 2 | Key knowledge gaps and research priorities and strategies to improve reproductive health in women with kidney disease

	Knowledge gaps	Research priorities and strategies
Epidemiology	Fertility rates and pregnancy outcomes in women across the severities and etiologies of CKD	• Capture pregnancy and parenthood data in all kidney disease registries • Harmonize core data sets for cohorts across the globe to allow aggregation of pregnancy outcomes in different kidney diseases • Promote data sharing to allow pregnancy and other reproductive health outcomes and interventions to be evaluated in high-, middle-, and low-resource regions
Reproductive issues in CKD and kidney failure	• **Fertility** o Assessment of ovarian reserve and impact of therapies potentially affecting it • **Contraception** o Impact of CKD on contraception efficacy; best approach for addressing contraception in amenorrhoeic women with CKD; timing of discontinuing contraception in CKD • **Menopause** o Distinguishing CKD-amenorrhea from natural menopause o Impact of menopause and menopausal therapies on kidney function	• **Fertility** o Develop studies to determine ovarian reserve in CKD also with respect to the impact of contemporary cyclophosphamide regimens • **Contraception** o Explore effectiveness of counseling delivered by nonnephrologists (such as nurses or pharmacists) in accordance with patient's values and preferences o Evaluate safety and efficacy of intrauterine devices in patients with kidney transplant or on peritoneal dialysis, as well as each contraceptive method in CKD, comparing type, dose, route of administration, duration of use, and severity of CKD • **Menopause** o Capture menopausal symptoms and diagnosis in women with CKD or kidney replacement therapy o Evaluate the timing and treatment of menopause and link to kidney and cardiovascular outcomes o Add menopause symptoms to research studies of symptom burden in CKD o Examine the impact of menopausal hormone therapy in the setting of CKD
Measuring kidney function in pregnancy	• How to interpret measures of eGFR in pregnancy given the normal changes in serum creatinine • Cost effectiveness of universal kidney function (e.g., eGFR, urine albumin) screening	• Evaluate the diagnostic and prognostic yield of testing kidney function in pregnancy, as well as the effect of identifying CKD on short- and long-term outcomes
Pregnancy outcomes and management	• Outcome data for different types of kidney diseases • Best drug management (timing for discontinuation of potentially toxic drugs; approach to anticoagulation and antiplatelet therapies; use of phosphate and potassium binders) • Best nutritional management • Best management of anticoagulation • Timing of kidney biopsy in pregnancy in native and transplanted kidneys • Optimal follow-up (timing, tests) for pregnant women with CKD	• Define a predictive score for maternal and fetal outcomes in women living with CKD • Define the best timing of drug management prior to or at the start of pregnancy (e.g., RAAS blockade, SGLT2 inhibitors, nonsteroidal mineralocorticoid receptor antagonists, or glucagon-like peptide-1 receptor agonists) • Assess the impact of the type and intensity of nephrology follow-up during at-risk pregnancies on maternal and fetal outcomes • Define the best timing for kidney biopsy in pregnancy and its role relative to biomarkers of different kidney diseases • Assess the risk of biopsy complications according to setting of care • Identify the prognostic role of changes in creatinine levels in pregnancy • Define the best nutritional assessment and advice for pregnant CKD patients • Assess the long-term effect of maternal diets on mothers and offspring • Develop and validate electronic health records–based algorithms to identify women at risk after pregnancies and evaluate clinical decision supports for risk stratification (e.g., flags for general practitioners, invitation to postpartum clinic) • Evaluate effectiveness of remote postpartum counseling for women after complicated pregnancies

(*Continued on following page*)

Table 2 | (Continued) **Key knowledge gaps and research priorities and strategies to improve reproductive health in women with kidney disease**

	Knowledge gaps	Research priorities and strategies
Timing of delivery in women with CKD	• The best timing for delivery in women with CKD • Information on risk factors for late complications	• Assess whether early delivery (32–34 weeks), in the absence of agreed fetal indications, offers greater kidney protection for the mother and whether delivery at 32–34 weeks has adverse effects for the fetus • Define the gains in the short- and long-term to prolonging pregnancy from 34 weeks and beyond 37 weeks • Analyze the delivery policies with respect to long-term maternal and offspring outcomes (kidney function, cardiovascular health, other) • Identify the frequency and the risk factors of sudden and unpredictable maternal and fetal deterioration • Validate biomarker use for diagnosis of preeclampsia in CKD
Kidney replacement therapy in pregnancy	• The best timing and the indications for dialysis start in pregnant women with CKD or with AKI • The potential advantages of hemodialysis versus peritoneal dialysis during pregnancy • Optimal drug management during pregnancy in kidney transplant patients • Whether pregnancy represents an added risk of cardiovascular impairment in women receiving kidney replacement therapy	• Identify optimal strategies with respect to dialysis start, frequency, and duration for improving maternal and fetal outcomes in CKD and in AKI • Compare outcomes in pregnant women who continue peritoneal dialysis and in those who switch to hemodialysis during pregnancy • Assess the advantages of dosing calcineurin inhibitors levels in pregnancy on graft function and hypertension • Assess pregnancy and graft outcomes of switching transplant immunosuppression before or during pregnancy • Explore whether pregnancy complications add to existing cardiovascular risks
PR-AKI and preeclampsia	• During pregnancy o A consensus definition of superimposed preeclampsia o The relationship among preeclampsia, AKI, and CKD o The best use of angiogenic markers to support diagnosis and decision-making and the advantage of longitudinal testing in high-risk pregnancies o Criteria for AKI diagnosis, in particular in the absence of baseline data • After pregnancy o The role of preeclampsia (causal factors, failed stress test, or marker of undiagnosed CKD) in the pathogenesis and diagnosis of CKD o The best criteria and cost-effectiveness for referral and follow-up of women after preeclampsia and related disorders to specialist care after an HDP o The best selection of patients who benefit from specialist follow-up	• Establish an evidence-based consensus on blood pressure diagnostic and treatment threshold targets, long-term cardiovascular disease risk assessment, and HDP terminology • Establish agreed criteria for diagnosing PR-AKI • Promote prospective studies of women after preeclampsia with or without identification of CKD, to quantify the benefit of early medical and lifestyle interventions after AKI or HDP • Develop and validate a cardiovascular and kidney health risk score that includes history of HDP • Identify specific phenotypes of HDP, integrating the use of different biomarkers and their risk factors • Investigate whether genetic and complement factors are correlated with specific phenotypes of HDP and predict long-term consequences • Investigate the association between preeclampsia and subsequent CKD in different populations and socioeconomic settings. • Evaluate diagnostic accuracy of novel diagnostic markers in PR-AKI • Conduct longitudinal studies or accurate data linkage to define the longer-term outcomes of women (and their offspring) with a history of PR-AKI • Define specific treatment strategies (e.g., magnesium prescriptions according to kidney function, and on dialysis)
Follow-up of children	• Strategies to prevent later CKD, cardiovascular disease, and metabolic abnormalities • Selection of children who would benefit from being followed-up with higher intensity	• Study the long-term outcome of children of women with CKD, on dialysis or living with a kidney transplant, according to severity of CKD and pregnancy outcomes

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Knowledge gaps	Research priorities and strategies
	• Evaluate the best strategies to prevent CKD, cardiovascular disease, and metabolic abnormalities in children born to mothers with CKD or who experienced PR-AKI or preeclampsia or other HDP • Compare data obtained in children of women with CKD according to severity of CKD • Compare data obtained in children of women with CKD, PR-AKI, or after preeclampsia or other HDP

AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDP, hypertensive disorders of pregnancy; PR-AKI, pregnancy-related acute kidney injury; RAAS, renin–angiotensin–aldosterone system; SGLT2, sodium glucose co-transporter-2.

male patients; higher risk of sensitization in women), and cognitive and emotional factors (more positive attitude toward donation in females).[43]

In the general population, the impact of cardiovascular disease varies by sex,[44] with stroke and heart failure causing more hospitalizations and deaths in women than in men,[45] and coronary heart disease causing more hospitalizations and deaths in men.[45] In people with CKD, sex differences in outcomes also vary between types of cardiovascular disease, and the magnitude of sex differences depends on severity of CKD.[33,46–49] When examining sex differences in cardiovascular outcomes or mortality in patients with CKD, future studies should systematically consider background sex differences in the general population and should carefully characterize both sex and gender.

Women are at increased risk of fractures due to osteoporosis, but fracture risk and concomitant CKD–mineral and bone disorders are not uniformly screened for, diagnosed, or treated in women with CKD.[50,51] Osteodensitometry measurement is not uniformly available, and parathyroid hormone, the most commonly used marker of CKD–mineral and bone disorders, is not a robust marker for fracture risk. Serum parathyroid hormone, calcium, and phosphate targets may differ by sex, but data are limited.[50]

Participation in clinical trials

Unequal sex and gender representation in clinical trials is an issue regardless of condition, study phase, location, or sponsor. A recent analysis of 1442 registered clinical trials published from 2015–2019 in 3 top medical journals found higher inclusion of males (56%) than females (44%).[52] Within 19 nephrology trials, participant distribution was 59% male and 41% female.[52] Gender inequalities in leadership and participation in randomized controlled trials in nephrology did not improve from 2011 to 2021.[53] Lower representation of females has been observed in recent trials of sodium glucose co-transporter-2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists, glucagon-like peptide-1 receptor agonists, and kidney transplant.[54] Likewise, in randomized controlled trials in patients on maintenance dialysis or with kidney failure, females are underrepresented in all regions and countries.[55,56] Differences may persist even after adjustment for sex distribution in the sampled dialysis populations.[55,56]

Sex and gender are not included in CONSORT (Consolidated Standards of Reporting Trials) guidelines. Recommendations from the SAGER (Sex and Gender Equity in Research) guidelines include procedures for the reporting of sex and gender information in study design, data analyses, results, and interpretation of findings,[57] but adoption is not widespread.[58]

REPRODUCTIVE HEALTH IN CKD

Comprehensive reproductive healthcare in women with CKD should seek to minimize unplanned pregnancies and support desired pregnancies.

Contraception in CKD

All women of childbearing age with CKD, including those living with dialysis or with a kidney transplant, should receive information regarding contraception in accordance with their values and preferences.[3,59–61] Family planning should be accessible, respectful of patient privacy, high quality, nondiscriminatory, informed, and based on shared decision-making. Contraception should be regularly revisited to ensure effective implementation and adherence.[62]

Available evidence suggests that oral contraceptives do not substantially impact kidney function.[3,63–65] Contraception is feasible in all patients with CKD, including those living with dialysis or with a kidney transplant, although particular care to avoid adverse effects is required.[59] An individualized approach is required, particularly in amenorrhoeic women with advanced CKD and on KRT, as well as those with high-grade proteinuria, hypertension, or underlying vascular disease. There is no absolute ban for any type of contraception, but progesterone-only contraception is associated with lower risks of adverse effects than combined hormonal contraception in older and younger age groups and in the presence of immunologic diseases or hypercoagulability states. Barrier methods and intrauterine devices are viable options, provided that infectious risks are managed, especially at the time of positioning them. These considerations hold also for kidney transplant patients.[56,59,66] The timing of the discontinuation must also be tailored to personal and medical

needs, balancing the risks of unplanned pregnancy with those of continued contraception.[66,67]

Appropriate contraceptive advice for adolescents with CKD and on KRT is critical during the transition from pediatric to adult kidney care, because teen pregnancies have a higher risk of preeclampsia and other pregnancy complications.[68–70]

Sexual dysfunction in CKD

Female sexual dysfunction is common, especially in advanced CKD and in patients on KRT.[71–73] This issue is minimally addressed by nephrologists, because of lack of training and uncertainty regarding treatments.[74,75] Consequently, self-administered treatments or approaches led by alternative practitioners are sometimes used. There was consensus among conference participants that sexual functioning should be included as part of general symptom assessment in women with CKD across all severities, addressing hormonal balance, drug side effects and interactions, nutritional status, and psychological and mental health, including changes in body image. Multidisciplinary work-up, including psychology and primary care, may identify individualized solutions.

Menopause and amenorrhea in CKD

Hormonal changes, most importantly hyperprolactinemia and hyperparathyroidism, as well as uremic toxicity and nutritional deficiencies in women with CKD may lead to anovulation, irregular bleeding, and amenorrhea.[76] Distinguishing CKD-related amenorrhea from natural menopause is important for reproductive counseling, fertility treatment, and diagnosis and management of menopause.[66] Irregular menses are common in advanced CKD and on dialysis, with improvement in menstrual abnormalities in up to 30% of women after kidney transplantation.[6] How to further improve menstrual health in women living with a kidney transplant needs to be further addressed.

Women with CKD-related amenorrhea can be misdiagnosed with menopause because the usual definitions of secondary amenorrhea (6 months or longer without menses in a woman who experienced menarche) from American College of Obstetricians and Gynecologists (ACOG)[77,78] and menopause (amenorrhea of 12 months, marking the end of the fertility life-phase) may overlap.[3,5,6,67,79] Determining menopausal status via hormonal levels (e.g., Women Ischemic Syndrome Evaluation classification[80]) is not reliable in women undergoing maintenance dialysis.[81] Kidney transplantation and adequate or high-efficiency dialysis have been associated with resumption of menses in up to one-half of the cases studied.[82]

The effect of menopause on kidney health is uncertain.[5] However, premenopausal women who undergo bilateral oophorectomy, particularly those ≤45 years old, are at higher risk of developing CKD.[83] Menopausal hormone therapy[84] has been associated with decreased odds of albuminuria,[85] while studies examining the effect of menopausal hormone therapy on eGFR have yielded conflicting results.[86,87] Studies examining the effects of menopausal hormone therapy on cardiovascular outcomes in women with CKD are very few.[88] Recently, a large observational study from South Korea, reporting on over 750,000 postmenopausal women with CKD, supported that those exposed to hormone replacement therapy had lower risks of major adverse cardiovascular events, progression to kidney failure, and all-cause mortality.[89] The results should, however, be considered with caution because of the observational nature of the investigation.

PREGNANCY IN CKD

Birth rates and fertility in CKD and with KRT

CKD affects about 3% of women of childbearing age, and the prevalence is likely higher in some regions.[90,91] Similar to the epidemiology of CKD in the general population, most of these cases are in early stages, and fertility is likely preserved; fertility rates decrease with kidney disease progression.[25,27] Overall, the prevalence of CKD in pregnancy may increase due to older age at pregnancy, wider use of medically assisted reproduction, and involvement of patients with CKD in reproductive choices.[92] Although a successful pregnancy is possible across all severities of CKD, fertility is lowest in women on dialysis and is only partially restored after kidney transplantation.[93] Fertility (live birth rates) and fecundity (conception) in women with CKD or on KRT are difficult to estimate given variability in reported measures (conception, live births, deliveries), underreporting of early pregnancy loss or termination, and lack of data in many regions. The most robust data have emerged from large registries or cohort studies in Australia, North America, and Italy.[94–98] Birth rates in women undergoing dialysis are rising, but remain substantially lower than in kidney transplanted cohorts, while pregnancy is 40%–50% rarer on peritoneal dialysis versus hemodialysis therapy.[93–95,97–99]

Preconception counseling in CKD

Conference participants agreed that reproductive freedom should be ensured to all women with CKD, including those on dialysis or after kidney transplantation.[100,101] Reproductive care should be embedded into all stages of nephrology care, including dialysis and pre- and posttransplant protocols.[102–104] All women of reproductive age with CKD should be offered balanced, personalized preconception counseling, considering local practices, resources, and culture.[105] Counseling should ideally be multidisciplinary, involving nephrologists and obstetricians along with experts in maternal-fetal and reproductive medicine, kidney transplantation, urology, and genetics, as indicated. Counseling should be offered from the initial nephrology visit and should cover maternal and fetal outcomes of pregnancy, fertility and assisted reproductive technologies where available, optimal timing of pregnancy (considering age, severity of CKD, and treatment), medication management in anticipation of pregnancy, and medical aspects of pregnancy termination (Table 3).[60,106,107]

Table 3 | Main counseling topics for pregnancy in CKD

Maternal outcomes of pregnancy in CKD	• A successful pregnancy is possible across all severities of CKD and with kidney replacement therapy. • Women with CKD have an increased risk of HDP and of preterm delivery (risk is increased in CKD G1 and increases with progressive impairment of kidney function).
Pregnancy and fetal outcomes of pregnancy in CKD	• Several complications are more common in women with CKD: IUGR, SGA, preterm birth, C-section delivery, admission to the intensive care unit (both for the mother and the infant), and neonatal mortality. • The likelihood of adverse pregnancy outcomes is related to type of disease, degree of disease progression, degree of proteinuria, and presence and control of hypertension. • Risk of congenital anomalies is not increased in women with nondiabetic CKD, with the exception of genetic diseases, provided no fetotoxic medication is used. Risk of fetal anomalies is increased in patients with diabetes, regardless of the presence of CKD. • Children born very preterm or SGA are at higher risk of developing hypertension, metabolic diseases, and CKD in adulthood.
Fertility and assisted reproduction in CKD	• Fertility is reduced in women with CKD, related to impairment of kidney function and type of disease (greater reduction in some immunologic diseases, particularly systemic lupus erythematosus). • Consider early referral for fertility assessment and assisted reproductive techniques. • Discuss the limited data available on efficacy and safety of IVF in women with CKD (evaluate single embryo transfer considering risk of complications with multiple pregnancies).
Timing of pregnancy in CKD	• Effects on maternal and fetal outcomes are related to type of disease, severity of CKD, degree of proteinuria, and presence and severity of hypertension. • Prior to pregnancy: o Optimize blood pressure (whenever possible <120/80 mm Hg pre-pregnancy). Elevated blood pressure at the start of pregnancy is associated with increased risk of pregnancy loss o Stabilize progression of CKD and albuminuria (when possible) o Stabilize and optimize underlying CKD treatment and control (i.e., diabetes mellitus, systemic lupus erythematosus) o Optimize immunosuppressive treatment in kidney transplant patients o Define an individualized "best timing" for pregnancy after KRT
Progression of CKD in pregnancy	• Pregnancy may accelerate progression of underlying CKD, in particular in advanced CKD. • Risk of CKD progression may be increased in women who develop HDP. • Individuals with advanced CKD should be offered counseling about the possibility of needing dialysis in pregnancy.

CKD, chronic kidney disease; HDP, hypertensive disorders of pregnancy; IUGR, intrauterine growth restriction; IVF, *in vitro* fertilization; KRT, kidney replacement therapy; SGA, small for gestational age.

Treatment of the underlying kidney disease should be optimized before pregnancy, with consideration of modifications that would be required before or shortly after conception. Optimizing blood pressure control before pregnancy is essential, and in patients with diabetes, optimal glycemic control reduces the risk of congenital malformations and improves pregnancy outcomes.[108,109]

Systemic immunologic diseases involving the kidney are associated with an increased risk of adverse pregnancy outcomes, regardless of disease severity. The risk decreases when the disease is in remission for at least 6 months. Changing potentially teratogenic treatments, such as mycophenolate acid analogues, to minimize risk of fetal harm may be associated with an increased risk of disease flares; therefore, confirmation of remission over a few months is recommended prior to pregnancy.[110] There is controversy about the use of cyclophosphamide in women of childbearing age with systemic lupus erythematosus, vasculitis, or glomerulonephritis, as withholding cyclophosphamide for fear of effects on fertility may risk undertreatment, and cyclophosphamide may be the only option in some settings. Clinical approaches varied among conference participants with respect to cyclophosphamide use in women of childbearing age, as well as use of gonadotropin-releasing hormone analogues for ovarian protection.[111]

In women with genetic kidney diseases, genetic counseling should address inheritance risk, prognosis, potential interventions in the patient and in her offspring, and the context-sensitive option of preimplantation genetic diagnosis.[112,113] The increased risk of adverse pregnancy outcomes linked to *in vitro* fertilization should be mentioned, as discussed below.[114] In women with congenital anomalies of the kidneys and urinary tract (CAKUT) or with autosomal dominant polycystic kidney disease and markedly enlarged kidneys, preconception counseling may benefit from involvement of a urologist.[113]

In women with advanced CKD or on KRT, assessment of fertility and assisted fertilization may be needed. *In vitro* fertilization is feasible in CKD, but relevant data are limited and mainly arise from kidney transplant recipients.[115] Anti-Müllerian hormone testing may be unreliable, because low levels are associated with vascular impairment, and high levels may occur when renal clearance is markedly reduced.[116,117] Conference participants emphasized that fertility assessment should not be based on anti-Müllerian hormone testing alone.

Basic approaches to infertility in women with CKD include optimization of nutritional status, detection of hormonal imbalances (including thyroid and parathyroid hormones and prolactin), and correction of anemia. Optimization of the dialysis dose is needed for women on dialysis; increasing hemodialysis frequency and duration may be advised. In women treated with peritoneal dialysis, especially if without residual kidney function, switching to hemodialysis may be considered to improve chances of conception. Evidence to support these strategies is limited, and approaches should be individualized.[102]

Measuring kidney function during pregnancy

Most women of childbearing age do not have GFR evaluation prior to or during pregnancy; therefore, when kidney impairment is identified for the first time in pregnancy, there are often no previous measures for comparison.

Kidney function changes throughout pregnancy, leading to an early decrease in serum creatinine, followed by a return to initial values peripartum (Figure 2).[118–122] The gold standard measurement during pregnancy is 24-hour creatinine clearance, because neither creatinine-based nor cystatin C-based GFR-estimating equations are validated in pregnancy.[123,124] However, 24-hour creatinine clearance is cumbersome and subject to preanalytical errors, leading to variable usage.[60,107]

Because women with CKD are at higher risk for adverse pregnancy outcomes, screening for undiagnosed CKD during pregnancy may guide management and improve outcomes; however, the advantages of systematic screening need to be demonstrated by dedicated long-term studies.[125–127] Testing serum creatinine, in addition to proteinuria, pre-, during, or postpregnancy may identify at least advanced CKD.[128]

The World Health Organization advises routine assessment for proteinuria during pregnancy.[129] Participants propose expanding the use of serum creatinine and albuminuria or proteinuria testing according to local policies and resources. While some nephrology societies recommend universal screening,[130] measurements of serum creatinine and albuminuria or proteinuria before or at the start of pregnancy should be advised at least in individuals with diabetes, autoimmune diseases, obesity, preexisting hypertension, or personal history of low birth weight or prematurity, AKI, preeclampsia or other hypertensive disorders of pregnancy (HDP), or assisted fertilization. It is important to consider pregnancy-related changes if the first assessment is done during pregnancy.[129]

Clinical considerations

Pregnancy in women with CKD not undergoing dialysis. Women with CKD have an increased risk of pregnancy-related complications, including preterm delivery, development of or increase in proteinuria, development or worsening control of hypertension, and preeclampsia and other HDP.[131–133] The main risks for infants, discussed in detail below, are linked to prematurity; there is no evidence of an increase in fetal malformations in the offspring of mothers with CKD, besides those related to genetic diseases (Supplementary Table S1), concomitant diseases such as diabetes mellitus, or drug-associated teratogenicity.

The main factors modulating maternal and fetal outcomes with CKD are preconception eGFR, proteinuria, especially if >1 g/d, and hypertension, especially if not optimally controlled. The baseline eGFR is probably the most important determinant of outcomes.[131–133] The trajectory of creatinine during pregnancy is important: in women with CKD G3–G5 or with a kidney transplant, a decrease of ≥10% of serum creatinine during early to mid-pregnancy (reflecting adaptation to physiological changes) has been associated with reduced maternal and fetal morbidity.[134,135] Other factors that affect outcomes include type of kidney disease, disease activity (remission or relapse), control of the underlying disease, and presence of antiphospholipid antibodies.[110] In unplanned pregnancies, the continuation of teratogenic or toxic drugs may contribute to adverse pregnancy outcomes. Development of a predictive score to estimate maternal and

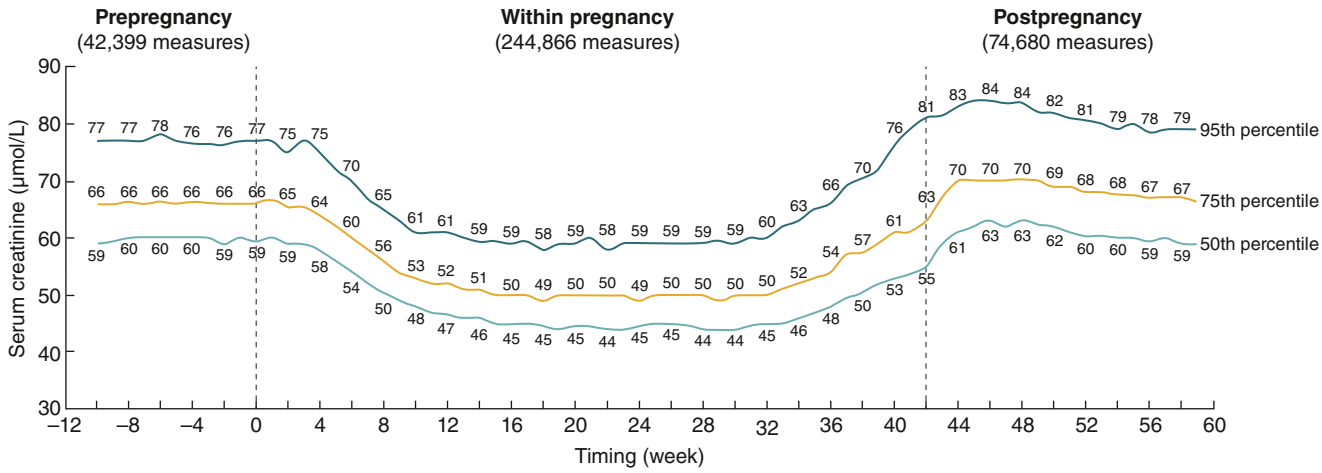

Figure 2 | Serum creatinine changes during pregnancy and postpartum. Reproduced from Harel *et al.* with permission.[120]

fetal morbidity, including as many of these potential effect modulators as possible, is identified as a research priority.

Specific issues related to glomerular diseases in pregnancy were recently addressed in a consensus paper.[110] Because immunologic diseases can flare in pregnancy, awareness and close monitoring are needed, even if the frequency of flares may not be increased compared with nonpregnant women.[110,136] A differential diagnosis including HDP is required, especially after 20 gestational weeks.[79]

Pregnancy in previously unknown kidney disease. Pregnancy may provide the first opportunity to diagnose CKD (Figure 3).[137,138] Kidney function is usually tested in the setting of complications, such as proteinuria, hypertension, kidney infection, or pain.

Kidney ultrasound is mandatory, because CAKUT or interstitial diseases are associated with a higher risk of pregnancy complications and may present with increased proteinuria or hypertension during pregnancy.[139,140]

The work-up when there is suspicion for glomerular diseases should be adapted to local resources and include complement fractions, IgA, IgG, IgM, antinuclear antibodies, extractable nuclear antibodies, anti-neutrophil cytoplasmic antibodies, antiphospholipid antibodies, glycated hemoglobin (A1c), and serologic testing for human immunodeficiency and hepatitis B and C viruses. In patients with heavy proteinuria, anti-PLA2R antibodies and serum and urine immunoelectrophoresis may be added.[110] Additional tests may be available in the future.[141] Microhematuria is present in up to 20% of healthy pregnancies, but urinary casts are unusual without active glomerular diseases.[142]

The differential diagnosis with HDP, discussed below, is often crucial.

Kidney biopsy

Kidney biopsy should be considered during pregnancy when it is likely to change management in the time frame of the pregnancy. A previous systematic review found that biopsy during pregnancy has increased risks of complications compared to postpartum biopsy, peaking around 25 weeks.[143] More recent reports indicate a lower, but still significant, risk of severe adverse events (Supplementary Table S2). The setting of care should be considered, and shared decision-making is essential. In some settings, performing the kidney biopsy during pregnancy versus immediately after pregnancy may allow otherwise uninsured women to have a definitive diagnosis and start treatment.[110,144] Conference participants recommend that the most experienced operator perform the kidney biopsy, and risks of pre- and postprocedure bleeding versus risks of the discontinuation of aspirin or heparin should be discussed on an individual basis.

Angiogenic markers for assessment of preeclampsia

If hypertension and proteinuria or an increase in serum creatinine are present after 20 gestational weeks in singleton spontaneous pregnancies, the differential diagnosis between CKD and preeclampsia should be considered. Preeclampsia and HDP may occur earlier in multiple pregnancies, pregnancies achieved by *in vitro* fertilization, or cases with severe fetal or placental malformations.[145–148] Women with CKD commonly experience worsening hypertension and proteinuria toward the end of pregnancy, which imposes a challenge in differential diagnosis from preeclampsia superimposed on CKD.

Pro-angiogenic and anti-angiogenic placental biomarkers, most commonly soluble fms-like tyrosine kinase-1 (sFlt-1) or the ratio between sFlt-1 and placental growth factor (PlGF), may support the differential diagnosis between CKD and preeclampsia. These tests, which are validated after 20 gestational weeks, have a high negative predictive value for the diagnosis of preeclampsia, and, in the setting of hypertension and proteinuria, normal levels may therefore suggest the presence of CKD.[110,149] Likewise, normal fetal growth, at least before 32–34 gestational weeks, supports CKD more than HDP.[149–153]

While useful for ruling out preeclampsia and identifying patients who could benefit from intensified surveillance,[149,154–156] these biomarkers should not be used in isolation or to prompt delivery. Of note, these biomarkers have not been validated in advanced CKD or in patients on dialysis and are not uniformly approved for clinical use. The diagnosis of preeclampsia superimposed on CKD may be particularly challenging; the few available studies suggest that the pattern of biomarkers may be different in these cases.[149,150]

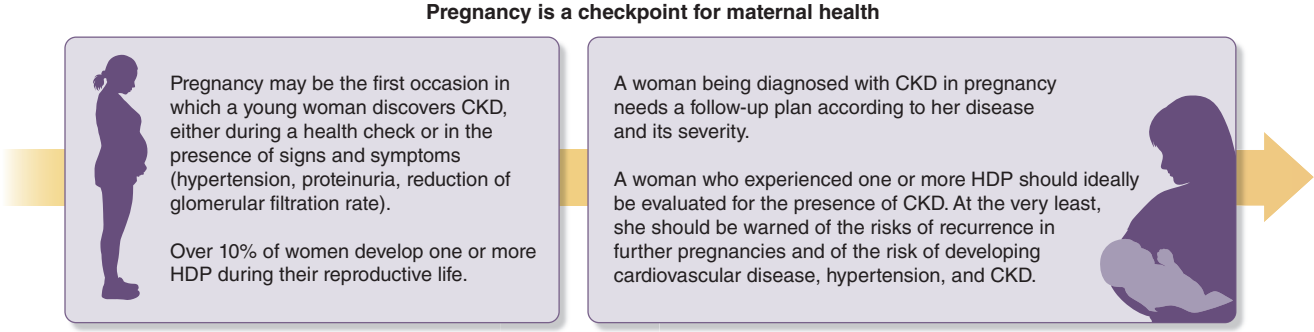

Figure 3 | Pregnancy as a checkpoint for maternal health. CKD, chronic kidney disease; HDP, hypertensive disorders of pregnancy.

Pregnancy in women receiving KRT. Patient and clinician perspectives and approaches are highly variable across countries and settings, and are important modulators of birth rates in women on KRT.[99,157] Residual kidney function in women on dialysis and better allograft function in transplant recipients confer improved fertility and outcomes.[157–159] Other factors impacting live birth rates in KRT include type of underlying kidney disease, comorbidities, years on dialysis, and dialysis intensity.[33,157–159] Patient expectations are changing toward wanting to achieve pregnancy, which creates broader ethical implications for clinicians and resource challenges for health services. Conference participants acknowledged that pregnancy while on dialysis may not be supported for all women, due to individual and local contexts. This pragmatic statement coexists with the strong support of conference participants for reproductive autonomy. Each setting should develop approaches to pregnancy in women receiving dialysis that balance individual autonomy with organizational, health system, and societal considerations.

Pregnancy-associated morbidity remains high in women receiving KRT.[157–160] High rates of preterm birth (>50%) and subsequent perinatal morbidity and mortality are driven by high rates of preeclampsia or placental dysfunction (>30%–50%).

Pregnancy outcomes in kidney transplant recipients are similar to those in women with CKD with similar kidney function[135,160] and are not always superior to those obtained with intensive hemodialysis.[159] Graft loss due to pregnancy is a clinical concern that is not borne out in recent data.[161–166]

Given the rare occurrence of pregnancy in women on chronic dialysis and the limited data from low- and middle-income countries (LMICs), the incidence of severe adverse outcomes, including maternal death, is unknown. Risk of maternal mortality is very low in high-resource settings; however, data are inconsistently captured, and long-term follow-up is rarely reported.[157,159,167]

Strategies for improving pregnancy outcomes in women receiving KRT include robust preconception counseling and management, optimization of lifestyle factors and pharmacologic therapy, and, whenever possible, management in a tertiary care facility with an expert multidisciplinary team (Figure 4).

Increasing dialysis intensity improves outcomes, especially in women without residual kidney function.[159] Unfortunately, availability of in-center extended-hour hemodialysis is limited, and strategies to facilitate intensive dialysis, including home dialysis and hospitalization, may not always be feasible.[137,168] Choice of dialysis modality in pregnancy will depend on individual choice, clinical context, and local availability. While fertility is lower on peritoneal dialysis, peritoneal dialysis remains an option particularly in patients with residual kidney function or where hemodialysis is less accessible.[169,170]

The management of immunosuppression in pregnant women with a kidney transplant varies regionally and across centers. Cyclosporine and tacrolimus are widely used, although interpretation of blood levels in pregnancy may be challenging[171] since target levels in pregnancy are not defined. Due to physiological hemodilution and changes in the unbound fraction, whole blood levels that are in the usual therapeutic range may be misleading, resulting in toxicity including graft dysfunction and hypertension in pregnancy.[170,172]

In advanced CKD, pregnancy may precipitate the need to start dialysis.[134] Although urea is considered directly fetotoxic and a marker of the biochemical milieu used to target dialysis efficiency in pregnancy, there is uncertainty around the urea threshold for starting dialysis.[159,173,174] Residual kidney function, catabolic states, and protein intake are the main

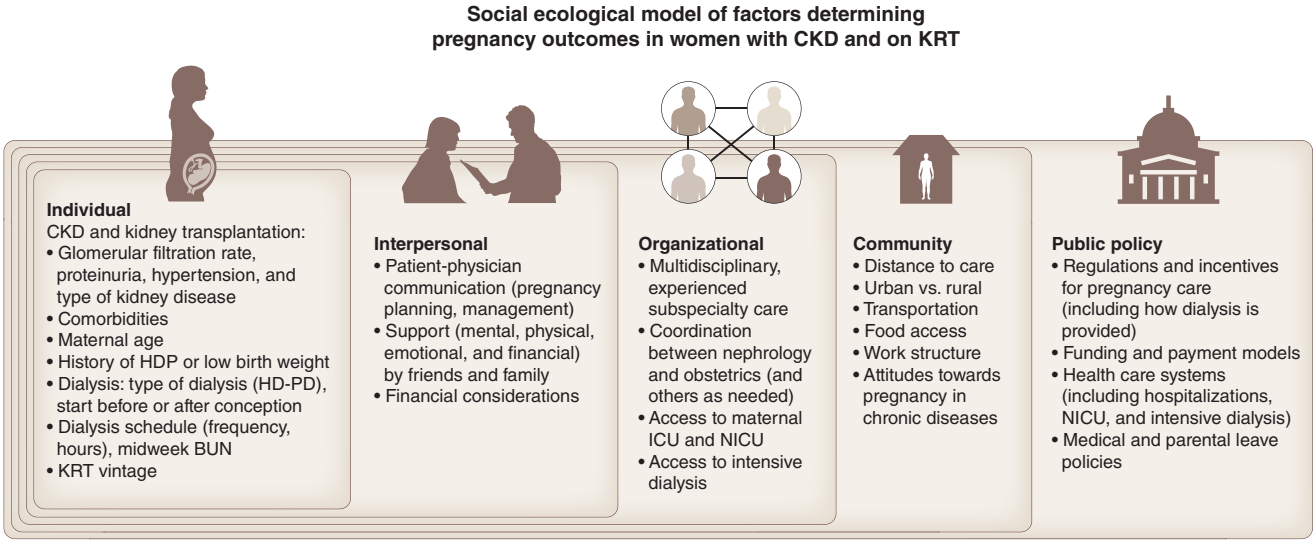

Figure 4| Social ecological model of factors determining pregnancy outcomes during kidney replacement therapy (KRT). BUN, blood urea nitrogen; CKD, chronic kidney disease; HDP, hypertensive disorders of pregnancy; HD-PD, hemodialysis, peritoneal dialysis; ICU, intensive care unit; NICU, neonatal intensive care unit.

factors affecting urea levels in advanced CKD.[175] Residual kidney function should be considered in determining the dialysis prescription in pregnancy. Twenty-four–hour creatinine and urea clearance are probably the best means by which to calculate residual kidney function.[176,177]

Although intensive dialysis improves perinatal outcomes, rapid loss of residual kidney function is a major risk of intensive dialysis schedules outside the context of pregnancy.[178,179] Women with good residual function may not require intensive dialysis to achieve low predialysis urea levels, reducing this risk and the burden on patients and dialysis services. Different targets have been proposed, including predialysis urea <12 mmol/l and predialysis blood urea nitrogen <50 or <35 mg/dl.[180,181] As discussed below, nutritional management may help stabilize urea levels in select patients.[182]

Follow-up during pregnancy in CKD

Key prognostic factors for maternal and fetal outcomes should be evaluated. In addition to kidney-related factors, these include age, parity, nonsingleton pregnancy, obesity, and obstetric and personal history, including patient birth weight and gestational age at birth.

Ideally, all women diagnosed with CKD before or during pregnancy should be offered dedicated follow-up during pregnancy,[60,106,107,125,183] recognizing that this may not be possible in all settings. Although all women with CKD have an increased risk of complications, extensive follow-up with specialized obstetric nephrology services may not be necessary if preconception parameters are favorable and no problem arises during follow-up.

The timing and types of tests to be performed in pregnant women with CKD are not established. Basic biochemistries include serum creatinine, urea, proteinuria (urine albumin-to-creatinine ratio, urine protein-to-creatinine ratio, or timed urine collection, considering local resources and patient preference), serum albumin, hemoglobin, and iron status, with additional testing as appropriate to the severity of CKD (Table 4). At a minimum, normotensive individuals with CKD without baseline proteinuria, normal prepregnancy eGFR, and without immunologic kidney diseases should undergo proteinuria and serum creatinine measurements in each trimester. The frequency should be increased in cases with decreased prepregnancy eGFR, proteinuria, or immunologic diseases.[60,106,107,125,183]

Likewise, frequency and type of fetal surveillance should be individualized based on risk assessment and resource availability. Serial assessments of fetal growth should be planned, referring to locally validated standards.[184] Fetal sonography and monitoring of uterine and umbilical Doppler flows are the gold standard; however, in settings where these imaging methods are not available, serial measurements of symphysis–fundal height is an inexpensive, easily performed alternative.[184]

Women with higher risk of complications should ideally be managed by a multidisciplinary team, with outpatient visits with a nephrologist or, when not available, a trained nurse together with an obstetrician or a midwife. In the absence of specialist care, at-home monitoring and remote telemedicine consultations may be an option. Implementation of telemedicine is a priority area for research, considering the barriers of start-up costs, lack of available specialists, limited internet access, and inconsistent reimbursement.

Postpartum follow-up should include measurements of blood pressure, eGFR, albuminuria or proteinuria; disease-specific tests; and resumption of medications contraindicated during pregnancy, such as angiotensin-converting enzyme inhibitors. Breastfeeding is discussed below.

Aspirin for preventing preeclampsia and indications for heparin

All pregnant women with CKD should receive prophylactic low-dose aspirin, started before 12 weeks gestation and up to term or to 34–36 weeks, unless contraindicated.[11,185] Although CKD is not explicitly mentioned, the current National Institute for Health and Care Excellence (NICE)[186] and ACOG[187] guidelines indicate low-dose aspirin for all patients at risk of preeclampsia. Timing of discontinuation should be discussed with an obstetrician, but recent data indicate earlier discontinuation can be safe in pregnancies at high risk for early delivery.[185] Different doses are prescribed (50–150 mg/d) in the absence of titration studies; outcome data in women with CKD are limited and monitoring for adverse events, mainly bleeding, is needed.[11–14,188]

In the presence of antiphospholipid antibodies, combination therapy of low-dose aspirin and heparin is the mainstay of prophylaxis; immunomodulation, especially with hydroxychloroquine, should be considered.[189] Heavy proteinuria is also a risk factor for venous thromboembolism; however, there is currently no established proteinuria or albumin threshold for starting heparin in pregnancy. In the absence of contraindications, conference members suggest that proteinuria and hypoalbuminemia are indications for a case-by-case discussion of heparin therapy, acknowledging that no threshold of hypoalbuminemia has been identified.

Blood pressure control and timing of discontinuation of proteinuria-lowering drugs

The optimal timing for discontinuation of proteinuria-reducing drugs (renin–angiotensin–aldosterone system blockers, SGLT2 inhibitors) in women with CKD is not clear. Conference participants consider imperative that women of reproductive age not be denied kidney-preserving therapies; to avoid long periods off anti-proteinuric drugs, participants recommend they be continued until conception, which should be monitored for, and stopped as soon as pregnancy is diagnosed.

Because blood pressure physiologically declines at the start of pregnancy,[190] an absence of lowering may be a marker of increased risk for pregnancy-related complications. Although data in pregnant women with CKD are limited, normotension is associated with lower risk of delivery before 34 weeks.[131,191]

Table 4 | Clinical and laboratory monitoring for kidney disease during pregnancy: comparison of the 4 available guidelines or best practice papers in Europe

Source, year	CKD G1–G2 monitoring frequency	CKD G3–G4 monitoring frequency	CKD G1–G2 type of monitoring tests	CKD G3–G4 type of monitoring tests	Other
The Italian Study Group on Kidney and Pregnancy, 2016[107]	4–6 weeks or more often, depending on hypertension and proteinuria	1–4 weeks, depending on hypertension and proteinuria	Glomerular filtration, proteinuria, electrolytes, vitamin D, iron status, blood cell counts, albumin, urinary culture. 24-hour urine collection may be added	Same as CKD G1-G2, but with monthly or more frequent 24-hour urine collections in case of severe proteinuria. Other tests as required	Urinary cultures every week if at high risk of urinary tract infection.
Wiles *et al.*, United Kingdom, 2019[60]	Frequency is not specified. Working in multidisciplinary teams is recommended	No different than CKD G1-G2	Standard obstetrical care and glomerular filtration (assessed by creatinine), proteinuria (uPCR), or albumin (uACR), vitamin D as per clinical practice	No different than CKD G1-G2	Clinical assessment for possible flares, including symptoms and urine testing, should be performed at all healthcare visits during pregnancy.
German Society for Gynecology and Obstetrics, German Society for Nephrology, Austrian Society for Gynecology and Obstetrics, 2022[183]	Frequency not specified	No different than CKD G1-G2	Glomerular filtration (assessed by creatinine), proteinuria (uPCR) or albumin (uACR) or urine dipstick.	No different than CKD G1-G2	Diabetes screening (if using steroids or calcineurin inhibitors) or oral glucose tolerance test.
The Netherlands, 2022[106]	Frequency not specified	No different than CKD G1-G2	Standard obstetrical care, urea level in 24-hour urine or a spot urine sample to estimate protein intake.	No different than CKD G1-G2	Frequent blood sugar checks with a glucose sensor for pregnant patients with diabetes mellitus and CKD G3b or higher.

CKD, chronic kidney disease; uACR, urinary albumin-to-creatinine ratio; uPCR, urinary protein-to-creatinine ratio.

Published guidelines have recommended different blood pressure target goals in pregnancies with CKD (Table 5).[60,106,107,183] Conference participants supported targeting blood pressure at least to <140/90 mm Hg, and whenever possible to <130/80 mm Hg, to be adapted based on individual circumstance, and monitoring for intrauterine growth restriction (IUGR).

Nutritional care

Nutritional management should include patient-centered and individualized care that integrates recommendations developed both for CKD and pregnancy, increasing energy intake during each trimester in nonobese women.[175,192] Both overweight or obesity and low body mass index or malnutrition are associated with increased risk of adverse pregnancy events.[193–196] Monitoring weight gain is important, as excessive weight gain is associated with increased risk of gestational diabetes and adverse pregnancy outcomes,[197] while edema could be a harbinger of preeclampsia or CKD progression.

Serum 25(OH) vitamin D should be monitored and supplemented if needed, as low levels are associated with a higher risk of preeclampsia.[198–200] Iron and vitamin D levels may be low in women on low-protein diets or with nephrotic syndrome.[110,198] If dietary intake is inadequate, calcium supplementation decreases risk of preeclampsia in the general population.[201] Due to the potential loss of nutrients in patients on intensive hemodialysis, water soluble vitamins, ions, and trace elements should be monitored and supplemented when needed.[202,203]

In the experimental animal, both low and high sodium intake are associated with impaired kidney growth in offspring.[204] In humans there is no convincing evidence showing that dietary salt reduction helps in the prevention and treatment of hypertension during pregnancy.[205] Hence, for the moment, it seems reasonable to follow the rules of healthy eating, including "normal" sodium intake (usually set at about 2–2.3 g of sodium, 5–6 g of sodium chloride), with the obvious exception of salt-losing nephropathies and contextualized to local climatic conditions.

In the general population, well-monitored vegan and plant-based diets, supplemented with iron and vitamins (B_{12}, D) when needed, are associated with lower incidence of gestational diabetes, better diabetes control, and lower weight gain during pregnancy.[206–208] Avoidance of ultraprocessed food is also advised on the basis of general population data.[209] Observational studies suggest that plant-based, moderately protein-restricted diets, with or without supplementation with essential amino acids and ketoacids, may help to delay the need for dialysis and control proteinuria in pregnant women with advanced CKD or significant proteinuria at the start of pregnancy. These diets were not associated with increased risk of infants born small for gestational age.[173,182,210] An identified research priority is to address the safety and benefits of moderately protein-restricted and plant-based diets in pregnant women with CKD.

OBSTETRIC CONSIDERATIONS

Timing of delivery

A multidisciplinary delivery plan should be developed and regularly reviewed. All available monitoring strategies should be used to allow the pregnancy to proceed as far in gestation as possible; these include basic maternal clinical assessments, as well as fetal growth, biometry, Doppler measurements, and, where needed, cardiotocography (a continuous recording of the fetal heart rate obtained via an ultrasound transducer placed on the mother's abdomen, now part of the routine monitoring of peripartum care, in particular in high-risk pregnancies[211]). Hospitalization should be considered when optimization of maternal conditions is required or when fetal condition is compromised.

Timing of delivery should be based on usual obstetrical guidelines with the added consideration of avoiding CKD progression. Current obstetric guidelines do not consider CKD and kidney function impairment in timing of delivery.[212] The only indications for delivery due to kidney

Table 5 | Recommended blood pressure targets during pregnancy

Italy 2015–2022[107,130]	United Kingdom 2019[186]	Germany 2022[183]	The Netherlands 2022[106]
In CKD and kidney transplant, ideal target is <130/80 mm Hg; <140/90 mm Hg is acceptable under careful clinical surveillance, in patients with good compliance. Hypertension occurring in pregnancy, with or without proteinuria, should be differentiated from preeclampsia, given the different prognoses for the 2 conditions in pregnancy.	135/85 mm Hg or less during pregnancy for women with CKD.	Between 110/70 and 135/85 mm Hg. Antihypertensive therapy must be continued during pregnancy, unless systolic blood pressure is constantly <110 mm Hg or diastolic is constantly <70 mm Hg or symptomatic hypotension is present.	Aim preconceptionally for <130/80 mm Hg. During pregnancy, initiate antihypertensive therapy if blood pressure is >140/90 mm Hg on repeated measurements. If on antihypertensives before conception, intensify if blood pressure is >140/90 mm Hg. Aim for systolic blood pressure between 130 and 140 mm Hg and diastolic blood pressure between 80 and 90 mm Hg. After birth, aim for <130/80 mm Hg.

CKD, chronic kidney disease.

function impairment refer to patients with preeclampsia, who may develop AKI. AKI is an indication for preterm delivery for all major obstetric guidelines (ACOG,[213] NICE,[214,215] International Society for the Study of Hypertension in Pregnancy[216]). The Dutch guidelines on CKD and pregnancy suggest inducing delivery at 39 weeks in patients with advanced CKD due to the increased risks of preeclampsia, loss of kidney function, and stillbirth, and considering earlier induction in case of preeclampsia or deterioration of the mother's condition or kidney function.[106]

Consistent with general principles for high-risk pregnancies, conference participants agree that before 34 weeks there is a presumption that prolonging pregnancy will benefit the fetus, even if kidney function and maternal clinical condition are worsening. After 34 weeks, recent data suggest that delivery may be safer for both mother and neonate than prolonging high-risk pregnancies with preeclampsia, even in medium- and low-resource settings.[217] A similar strategy may be considered in the case of other complications, including worsening of preexisting CKD. In all circumstances, decisions for preterm delivery should be made by a multidisciplinary team involving obstetricians, nephrologists, and neonatologists, balancing fetal risks versus short- and long-term risks of deterioration in maternal health.[186,212,216,218–220]

Lactation

Breastfeeding is associated with short- and long-term health benefits for the mother and the infant.[221] Breastfeeding is possible across all severities of CKD, including in women on KRT or with an immunological disease, provided that no medication contraindicated in breastfeeding is used.[221–224] For instance, some angiotensin-converting enzyme inhibitors are compatible with breastfeeding and are preferred to angiotensin receptor blockers, which lack safety data. No data are available for SGLT2 inhibitors. Because medication safety in pregnancy and breastfeeding is continuously updated, please refer to reference sites (e.g., www.ncbi.nlm.nih.gov/books/NBK501922 or www.lecrat.fr). Data on quality of milk from breastfeeding women with CKD or undergoing KRT are scarce but overall reassuring.[225,226]

PREGNANCY-RELATED AKI

Pregnancy-related AKI (PR-AKI) is a leading cause of AKI in young women.[227,228] In 1 large, worldwide study, PR-AKI accounted for 1% of all AKI, 0.3% in high-income and 3.6% in low- and middle-income settings.[229–231] Uncertainties about PR-AKI incidence reflect different definitions, lack of diagnosis or reporting in earlier stages, overlap with CKD, and lack of universal access to dialysis, which is often used to define severe AKI.[167,227,228,232] Definitions of AKI have not been established in the context of pregnancy, mainly because of the dynamic changes of serum creatinine throughout gestation.

The diagnosis of AKI outside of pregnancy is currently based on an increase in serum creatinine and a decrease in urine output.[233] Standard definitions as proposed by RIFLE (Risk, Injury, Failure, Loss, and End-stage renal failure), AKIN (Acute Kidney Injury Network), or KDIGO[233,234] may not apply in pregnancy, as they can underestimate creatinine increases if the expected physiological decrease in pregnancy is not taken into account.[232] Despite limitations, higher RIFLE stages, as well as need for dialysis during pregnancy or shortly after delivery, have been associated with a higher risk of incident CKD, chronic dialysis dependence, maternal death, and perinatal mortality. In obstetric patients admitted to intensive care units, the RIFLE score is an independent predictor of mortality.[235–237] Limited data suggest that the AKIN stage may also be useful in pregnancy.[232,238,239] Biomarkers useful in the diagnosis of AKI outside of pregnancy (Supplementary Table S3)[240] are not validated in pregnancy. Where available, PlGF and sFlt-1 may be helpful in ruling out preeclampsia as a cause of serum creatinine increase.

PR-AKI is commonly classified as prerenal, renal, and postrenal injury. In PR-AKI, an approach addressing obstetric complications and pregnancy-specific disorders of gestational periods (Figure 5) may be more informative.[227]

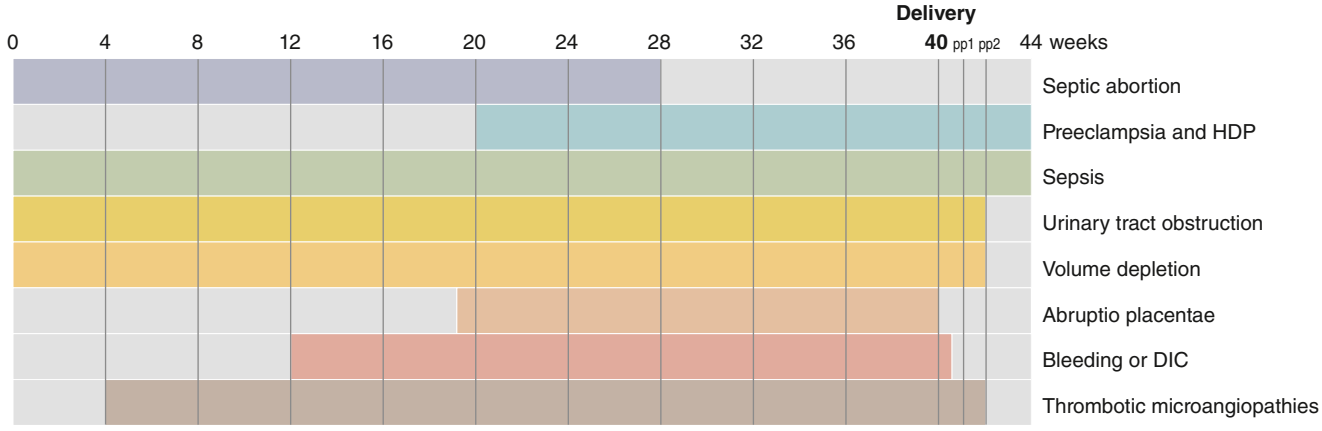

Figure 5 | Gestational periods of pregnancy-specific disorders. DIC, disseminated intravascular coagulation; HDP, hypertensive disorders of pregnancy; pp1 or 2, postpartum 1 or 2 weeks.

In high-resource settings, the most frequent cause of AKI in late pregnancy is preeclampsia, followed by rare conditions, including thrombotic microangiopathies.[241] Sepsis, septic abortion, and intrapartum hemorrhage are more common in LMICs. In women with high serum creatinine levels at referral, distinguishing AKI from CKD can be problematic. In fact, in the absence of systematic screening before pregnancy, CKD is often first diagnosed in pregnancy. Especially in LMICs, where prepregnancy access to care is severely limited, many women initially diagnosed as having PR-AKI actually have undiagnosed CKD and remain dialysis-dependent after delivery.[167,227,228]

Lack of obstetric nephrology training is a barrier to optimal management of PR-AKI. Other barriers vary by setting and may include limited access to dialysis, insufficient coverage of pregnancy complications, and separation of maternity and general hospitals. Overcoming these barriers is a healthcare priority.

Key aspects of PR-AKI management are summarized in Figure 6.[242] The criteria for urgent initiation of dialysis are the same as in nonpregnant patients. No specific data are available on timing of dialysis initiation in PR-AKI, and controversy exists even in the nonpregnant population.[243,244] Dialysis may be considered earlier in the presence of high urea levels, especially when PR-AKI is superimposed on CKD, because a late start of dialysis is associated with poor maternal and fetal prognosis.[137,168]

Several antihypertensive medications can be safely used during pregnancy (Supplementary Table S4). Loop diuretics can be used to control volume overload and to reduce the burden of antihypertensive medications in PR-AKI.[245–250] Severe AKI is an acknowledged indication for considering delivery or pregnancy interruption, on the basis of the maternal and fetal status and the period of pregnancy.

HYPERTENSIVE DISORDERS OF PREGNANCY

HDP comprise different clinical manifestations, from isolated hypertension or proteinuria to preeclampsia and hemolysis, elevated liver enzymes and low platelets syndrome; some classifications also include IUGR.[251,252] These conditions overall affect up to 10%–15% of pregnancies.[169] It remains controversial whether these disorders represent a continuum or are separate entities.[168,252,253]

The incidence of preeclampsia is usually reported as 3%–5% per pregnancy; this figure is lower in such populations as healthy kidney donors prior to donation (1%–2%).[254] The incidence per woman is cumulative and may be as high as 7.5%, although precise estimation is difficult as most studies report only the incidence per pregnancy.[255] The risk for recurrence of preeclampsia or other HDP is higher, but estimates vary broadly, from 15% to over 70%.[256–258] The risk of recurrent HDP rises with the number of previous complicated pregnancies and after early-onset preeclampsia or IUGR.[257,258]

Preeclampsia is associated with the presence of underlying, often undiagnosed, CKD and with an increased lifetime risk of developing kidney failure, as discussed below.[127,259–261] PR-AKI and preeclampsia share several risk factors, including CKD, diabetes mellitus, systemic immunologic diseases, hypertension, and obesity.[259] Incidence of both preeclampsia and PR-AKI is higher at the extremes of reproductive age.[252] Preeclampsia increases the risk of AKI, and a history of AKI increases the risk of developing preeclampsia.[262,263] It is plausible that AKI in the context of preeclampsia may be a risk factor for future CKD, in a manner similar to AKI being a

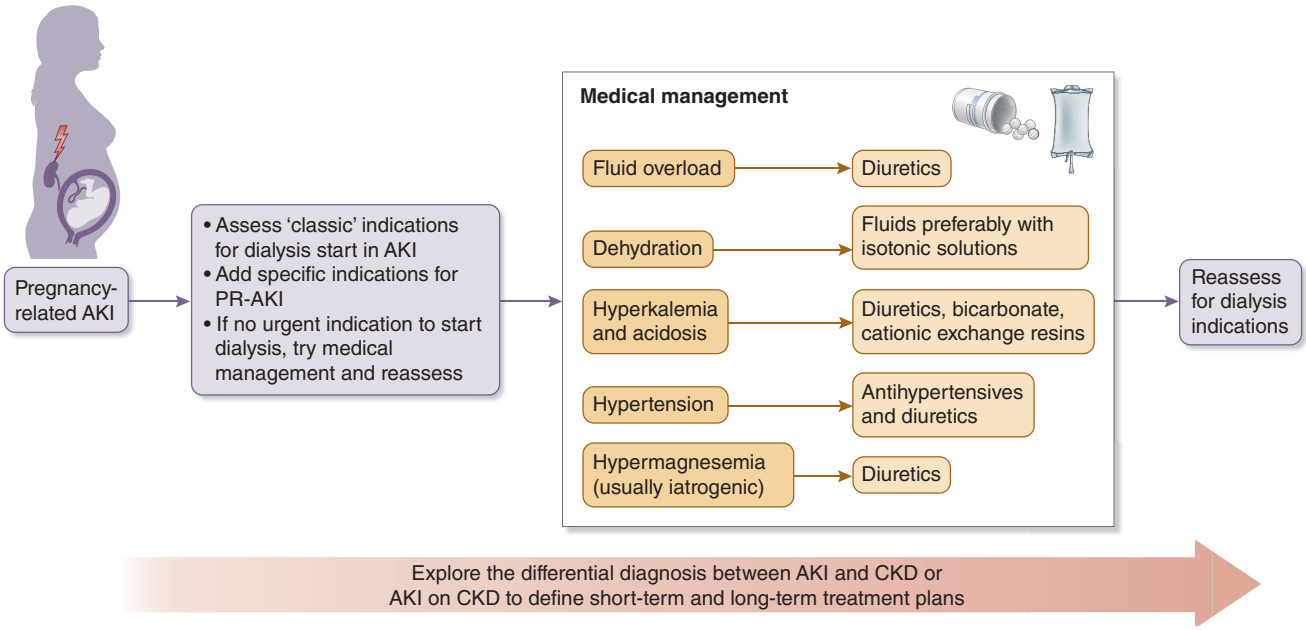

Figure 6 | Management of pregnancy-related acute kidney injury (PR-AKI). CKD, chronic kidney disease.

well-recognized risk factor for kidney disease in the general population.

Mode of delivery is modulated by preeclampsia and PR-AKI; early delivery is usually by Caesarean section. Some drugs used for delivery complications, including antibiotics or tranexamic acid, can cause AKI or cortical necrosis.[264,265]

FOLLOW-UP AFTER PREGNANCY

Follow-up after preeclampsia and PR-AKI

Up to 20% of pregnancies complicated by preeclampsia occur on the background of an underlying, undiagnosed, CKD.[127,259,266] Preeclampsia and other HDP significantly increase the risk for long-term CKD or kidney failure,[127,236,259–261,266–273] hypertension, cardiovascular and metabolic diseases,[235,274–276] and AKI.[263,277] Preeclampsia and other HDP also may reflect latent autoimmune diseases that become evident months or years after delivery.[236,269,273,278,279] Risk of kidney failure increases with the number of pregnancies complicated by preeclampsia and other HDP, including delivering an infant either preterm or with low birth weight.[260]

Although preeclampsia is consistently associated with higher risk of kidney failure,[261] the reasons why are not fully clear,[252] because the link between preeclampsia and CKD is confounded by shared risk factors and by the frequent presence of underlying CKD.[259] Because preeclampsia and other HDP are usually managed in an obstetrical setting, unless they cause PR-AKI or are suspected to reflect underlying CKD, the role of nephrologists is mainly in guiding follow-up after preeclampsia.

Preeclampsia, by definition, should resolve 4–12 weeks postpartum. If proteinuria or hypertension persist, it is commonly agreed that the patient should be referred for further investigations, including consideration of kidney biopsy.[218] The absence of proteinuria and hypertension at 3–6 months from delivery does not exclude the presence of underlying CKD, particularly in the case of tubulointerstitial disorders, CAKUT, or autosomal dominant polycystic kidney disease; hence, a more comprehensive diagnostic pathway is advocated by some experts, including kidney ultrasound, serum creatinine, and blood and urinary electrolytes.[127,130,259,266] After an episode of PR-AKI, patients should undergo regular follow-up due to the risk of developing CKD. A further suggested strategy for improving early CKD diagnosis is adding PR-AKI, preeclampsia, and other HDP as risk factors for CKD and kidney failure in future KDIGO guidelines.

According to the most recent obstetric guidelines, postpartum visits after complicated pregnancies should include cardiovascular risk assessment and diagnostic workup.[186,237,280] However, CKD is not specifically included in these recommendations, and, even in high-resource settings, only a minority of women with previous HDP have a specialist follow-up (as indicated in some obstetric and cardiology guidelines) at 6 months.[281] Conference participants advised annual medical reviews for at least 5–10 years postpartum. A healthy diet, exercise, targeting ideal body weight, smoking cessation, and optimal blood pressure control (<120/80 mm Hg) should be advised to improve long-term cardiovascular and kidney health.[61] Women may experience psychological trauma or mental health disorders following their experience[9,10] and may need specific counseling or referral.

The increased health risks, both for recurring episodes with future pregnancies and for cardiovascular and kidney disease later in life, should be explained to women who have experienced preeclampsia. In women with a history of preeclampsia or an HDP who are planning a new pregnancy, conference participants recommend preconception consultation, ideally with a nephrologist, prescription of low-dose aspirin from the start of pregnancy, counseling regarding calcium and vitamin D and healthy nutrition; and follow-up by a multidisciplinary team during pregnancy, where available.[130]

Postpartum follow-up in women with CKD

Pregnancy provides a unique opportunity to diagnose CKD and establish long-term follow-up. All women with CKD should be seen within 4–8 weeks of delivery. Frequency and timing of outpatient visits should be based on individual risk assessment, taking into account eGFR, presence of proteinuria or hypertension, cause of CKD, pregnancy-related complications (PR-AKI, preeclampsia, and other HDP), and whether CKD was known before pregnancy.[60,106,107,125,183] Postpregnancy follow-up should include breastfeeding support, advice about contraception and future pregnancies, and psychological follow-up, if needed. It is advisable that nephrologists and obstetricians/gynecologists are involved in the early postpartum period (up to 6–8 weeks), and nephrologists and general practitioners thereafter. Medication choices and dosages should be revised based on need, severity of CKD, and lactation choices. Human leukocyte antigen sensitization should be evaluated 3 months postpartum. In women on dialysis, revising the dialysis schedule is a priority. Education will be needed for women newly started on dialysis, with planning of transplant listing and discussion of treatment options. In women living with kidney transplantation, drug treatment should be reviewed.

Follow-up of children

The current recommendations for all neonates include 1 visit within 48 to 72 hours of discharge; at 6, 10, and 14 weeks; every 3 months from 3 months to 2 years; and every 6 months between years 2 and 6 (Supplementary Table S5).[282,283] Need for short- and long-term follow-up increases in the event of prematurity, IUGR, low birth weight, or congenital malformations, including CAKUT.[284] However, these indications are not uniformly followed, in particular in LMICs and underresourced settings in high-income countries.[285–287]

Compared with children of normal birth weight, children of low birth weight (usually defined as <2500 g[288]) and small for gestational age have a higher prevalence of reduced kidney

function, obesity, metabolic syndrome, diabetes, and hypertension in adulthood.[289–293] A reduced nephron number is probably the central factor in the development of CKD and early-onset hypertension.[294–296] The impact of being born small, small for gestational age, and with a low nephron number is carried through subsequent generations, and women born small and small for gestational age have a significantly increased risk of developing preeclampsia in their pregnancies.[267,297] These findings support the need to implement early nephroprotective measures and establish long-term follow-up for children with low birth weight.

Key research questions relate to the possibility that more intensive follow-up of babies with low birth weight or growth restriction prevents development or allows for early detection of CKD, cardiovascular disease, and metabolic abnormalities. More studies are needed for elucidating the impact on future health, and in particular on cardiovascular and kidney health, of being born to a mother living with a kidney transplant or undergoing dialysis or being exposed to preeclampsia or PR-AKI. Collaborations with neonatologists and pediatricians are fundamental to inform research agendas.

SUMMARY AND CONCLUSIONS

CKD impacts many aspects of health throughout the lifespan, but data on the effects of sex and gender on kidney disease epidemiology and outcomes, as well as optimal management of reproductive health in women with CKD, are limited. More data are needed on the cost-effectiveness of systematic screening for CKD in all pregnant women and the safety of newer drugs, such as SGLT2 inhibitors or glucagon-like peptide-1 agonists, during pregnancy or breastfeeding. Multidisciplinary consensus is needed on the management of pregnancy in women with CKD. Sex- and gender-specific recommendations should be considered in developing guidelines. Data sets with harmonized core measures should be available to develop a global atlas of maternal and fetal outcomes and facilitate global improvements in pregnancy outcomes in women with CKD. In addition, we hope to see evidence-based consensus on risk stratification, terminology, and treatment for HDP, with focus on short- and long-term kidney and cardiovascular health. Funding entities, ethics boards, and clinical trialists, among others, have a responsibility for championing sex and gender research.

APPENDIX

Additional Conference Participants

Ghada Ankawi, Saudi Arabia; Rossella Attini, Italy; Divya Bajpai, India; Pazit Beckerman, Israel; Kate Bramham, United Kingdom; Edwina A. Brown, United Kingdom; Céline Camilleri, France; David Collister, Canada; Iara da Silva Santos, Spain; Nicole L. De La Mata, Australia; Irene de Lourdes Noronha, Brazil; Sandra M. Dumanski, Canada; Abduzhappar Gaipov, Kazakhstan; Lynn A. Gomez, Philippines; María Carlota González-Bedat, Uruguay; Abril Gutiérrez, Mexico; Morgan E. Grams, USA; Carinna Hockham, United Kingdom; S. Ananth Karumanchi, USA; Andrea G. Kattah, USA; Natalia L. Kozlovskaya, Russia; Holly J. Kramer, USA; Christoph C. Lees, United Kingdom; Jennifer S. Lees, United Kingdom; A. Titia Lely, Netherlands; Adeera Levin, Canada; Liz Lightstone, United Kingdom; Anika Lucas, USA; Claudio Luders, Brazil; Valerie A. Luyckx, Switzerland; Magdalena Madero, Mexico; Angela Makris, Australia; Jolanta Małyszko, Poland; Dominique E. Martin, Australia; Amy Metcalfe, Canada; Gabriella Moroni, Italy; Andrea L. Oliverio, USA; Alejandra Orozco Guillen, Mexico; Marlies Ostermann, United Kingdom; Dimitrios Petras, Greece; Aarti Pillai, India and Italy; Milan Radović, Serbia; Guilherme Ramires de Jesus, Brazil; Lynne Roberts, Australia; Mauro H. Schenone, USA; Alina Seman, Italy; Silvi Shah, USA; Tarik Sqalli, Morocco; Sylvia Stracke, Germany; Irma Tchokhonelidze, Georgia; Massimo Torreggiani, France; Daniele Trevisanuto, Italy; Yusuke Tsukamoto, Japan; Ifeoma I. Ulasi, Nigeria; Viraraghavan Vadakkencherry Ramaswamy, India; Enrico Vidal, Italy; Amanda J. Vinson, Canada; Jack F. M. Wetzels, Netherlands; Kate Wiles, United Kingdom; Germaine Wong, Australia; Melanie Wyld, Australia.

DISCLOSURES

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Supplementary material is available online at www.kidney-international.org.

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