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Women and kidney disease: reflections on World Kidney Day 2018



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Chronic kidney disease (CKD) affects approximately 10% of the world's adult population. It is within the top 20 causes of death worldwide,¹ and its impact on patients and their families can be devastating. World Kidney Day and International Women's Day in 2018 coincide, thus offering an opportunity to reflect on the importance of women's health and specifically their kidney health, on the community, and the next generations, as well as to strive to be more curious about the unique aspects of kidney disease in women, so that we may apply those learnings more broadly.

Girls and women, who make up approximately 50% of the world's population, are important contributors to society and their families. Besides bearing children, women are essential in childrearing and contribute to sustaining family and community health. Women in the 21st century continue to strive for equity in business, commerce, and professional endeavours, while recognizing that in many situations equity does not exist. In various locations around the world, access to education and medical care is not equitable among men and women; women remain under-represented in many clinical research studies, thus limiting the evidence base on which to make recommendations to ensure best outcomes (Figure 1).

In this editorial, we focus on what we do and do not know about women's kidney health and kidney disease, and what we might learn in the future to improve outcomes for all.

What we know and do not know

Pregnancy. Pregnancy is a unique challenge and is a major cause of acute kidney injury (AKI) in women of childbearing age²; AKI and preeclampsia (PE) may lead to subsequent CKD, but quantification of this risk is not known.³ PE and hypertensive disorders of pregnancy occur in 3% to 10% of all pregnancies; PE is a risk factor for the future development of CKD and end-stage renal disease (ESRD) in the mother, and is the principal cause of AKI and maternal death in developing countries.

The presence of any degree of CKD has a negative effect on pregnancy and, given the increase in risk of CKD progression post-partum, raises challenging ethical issues around conception and maintenance of pregnancies.⁴

Global differences in causes of AKI during pregnancy reflect socioeconomic and cultural issues: septic abortion after an illegal procedure is the leading cause of early AKI in countries where legal abortions are not available, while PE after assisted fertilization is becoming a leading cause in developed countries (see Table 1 for adverse effects of pregnancy and Figure 2 for relationship between pregnancy and kidney disease).

Besides maternal risks, PE is associated with intrauterine and perinatal death, preterm delivery, and restricted intrauterine growth; the latter 2 risks are linked to "small babies."³ In the long term, small-for-gestational age and preterm babies are at risk for developing diabetes, metabolic syndrome, cardiovascular diseases (CVDs), and CKD in adulthood⁵; the increased risk of CKD is probably due to low nephron number, leading to hyperfiltration, hypertension, and reduced resilience after AKI episodes.

The long-term effects of PE on both maternal and fetal health remain an area of active research with many unknowns. Despite the fact that PE increases the probability of hypertension and CKD in later years, we have not evaluated a surveillance or reno-protective strategy to determine whether progressive loss of kidney function can be attenuated.² Despite the risk for CKD in small-for-term children, there are no systematic screening programs for them either.

Autoimmune diseases. Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic scleroderma preferentially affect women and are characterized by systemic inflammation leading to target organ dysfunction, including of the kidneys. Sex differences in the incidence and severity of these diseases result from a complex interaction of hormonal, genetic, and

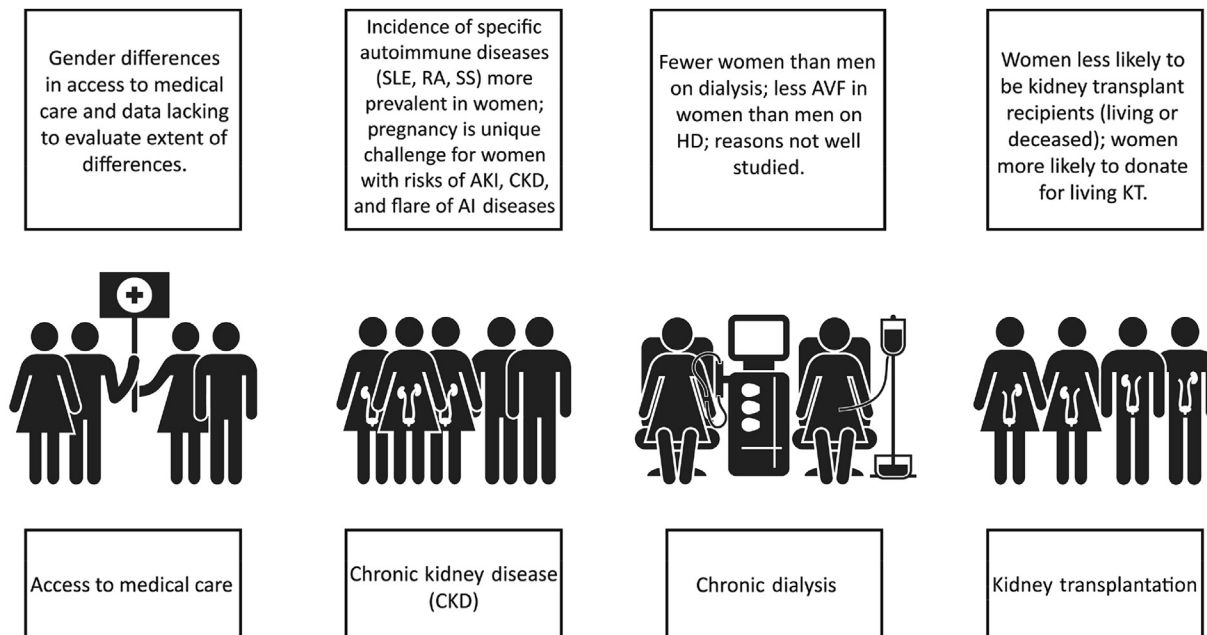


Figure 1 | Sex differences throughout the continuum of chronic kidney disease (CKD) care. AI, autoimmune; AKI, acute kidney injury; AVF, arteriovenous fistula; HD, hemodialysis; KT, kidney transplant; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic sclerosis.

epigenetic factors (Table 2). The public health burden of autoimmune diseases is substantial, as a leading cause of morbidity and mortality among women throughout adulthood.⁶

SLE is an autoimmune disease that affects approximately 5 million people worldwide, disproportionately women (9:1 female-to-male ratio) and individuals of non-European ancestry. The highest female predominance (up to 15:1) is in peak reproductive years. The biology of these differences has been explored extensively and include the number of X chromosomes and genetic variants on the X chromosome; the role of estrogen, whose primary effects are mediated by transcription activity of the intracellular estrogen receptors⁷; and the role of Cathepsin S protein as a potential cause of lupus, triggering the immune system to attack healthy cells.⁸ In addition, numerous non-HLA genetic markers may predispose individuals of European, Hispanic, and African American ancestry to lupus.

RA also preferentially affects women (4:1 ratio to men); peak incidence is at age 45 to 55, coincident with perimenopause. The possible association between estrogen deficiency and disease onset is further corroborated by noting the change in female-to-male incidence ratio after age 60 years (1:1); furthermore, RA symptom improvement or remission during pregnancy is well recognized.⁹ Renal

involvement in RA is relatively common, multifactorial, and a predictor of mortality in RA patients.

Systemic sclerosis predominantly affects women (female-to-male ratios range from 3:1 to 14:1); peak incidence is in the fifth and sixth decades. Estrogen may play a role in scleroderma pathogenesis through its stimulatory effect on transforming growth factor-β1 receptor and platelet-derived growth factor receptor.⁶

Renal replacement therapies. In CKD cohorts, the prevalence in women is always less than in men, and women experience slower progression to ESRD.¹⁰

The equality of access to renal replacement therapy (RRT) for women and girls is of concern because, in many societies, they are disadvantaged by discrimination rooted in sociocultural factors. There is a paucity of information about sex differences in RRT:¹¹ in Africa men were more likely to receive RRT than women; in Japan, the incidence of treated ESRD in women was less than half of that in men (3287 in men vs. 1764 in women per million ESRD); and in the USA, women have significantly higher likelihood of late initiation of dialysis compared with men. Awareness of previous kidney disease was much lower in women than in men, which may contribute to this later RRT start, higher hospitalization rates

Table 1 | Adverse pregnancy outcomes in patients with chronic kidney disease and in their offspring

Term	Definition	Main issues
Maternal death	Death in pregnancy or within 1 week to 1 month postpartum	Too rare to be quantified, at least in highly resourced settings, where cases are in the setting of severe flares of immunologic diseases (SLE <i>in primis</i>). Still an issue in AKI and in low-resourced countries; not quantified in low-resourced countries, where it merges with dialysis need.
CKD progression	Decrease in GFR, rise in sCr, shift to a higher CKD stage	Differently assessed and estimated; may be linked to obstetric policy (anticipating delivery in the case of worsening of the kidney function); between 20% and 80% in advanced CKD. Probably not increased in early CKD stages.
Immunologic flares and neonatal SLE	Flares of immunologic diseases in pregnancy	Once thought to be increased in pregnancy, in particular in SLE, are probably a risk in patients who start pregnancy with an active disease or with a recent flare-up. Definition of a “safe” zone is not uniformly agreed on; in quiescent, well-controlled diseases do not appear to be increased with respect to nonpregnant, carefully matched controls.
Transplant rejection	Acute rejection in pregnancy	Similar to SLE, rejection episodes are not increased with respect to matched controls; may be an issue in unplanned pregnancies and in unstable patients.
Abortion	Fetal loss, before 21–24 gestational wk	May be increased in CKD, but data are scant. An issue in immunologic diseases (eventually but not exclusively linked to the presence of LLAC) and in diabetic nephropathy.
Stillbirth	Delivery of a nonviable infant, after 21–24 gestational wk	Probably not increased in early CKD, may be an issue in dialysis patients; when not linked to extreme prematurity, may specifically linked to SLE, immunologic diseases, and diabetic nephropathy.
Perinatal death	Death within 1 wk to 1 mo from delivery	Usually a result of extreme prematurity, which bears a risk of respiratory distress, neonatal sepsis, and cerebral hemorrhage.
Small, very small baby Preterm, early or extremely preterm	A baby weighing <2500–1500 g at birth Delivery before 37–34 or 28 completed gestational wk	Has to be analyzed with respect to gestational age. Increase in risk of preterm and early preterm delivery across CKD stages; extremely preterm may be an important issue in undiagnosed or late referred CKD and PE-AKI.
SGA (IUGR)	<5th or <10th centile for gestational age	Strictly and inversely related to preterm delivery; SGA and IUGR are probably related to risk for hypertension, metabolic syndrome, and CKD in adulthood.
Malformations	Any kind of malformations	Malformations are not increased in CKD patients not treated by teratogen drugs (MMF, mTor inhibitors, ACEi, and ARBs); exception: diabetic nephropathy (attributed to diabetes); hereditary diseases, such as PKD, reflux nephropathy, and CAKUT may be evident at birth.
Hereditary kidney diseases	Any kind of CKD	Several forms of CKD recognize a hereditary pattern or predisposition; besides PKD, reflux and CAKUT, Alport’s disease, IgA, kidney tubular disorders, and mitochondrial diseases have a genetic background, usually evident in adulthood and not always clearly elucidated.
CKD-hypertension	Higher risk of hypertension and CKD in adulthood	Late maturation of nephrons results in a lower nephron number in preterm babies; the risks are probably higher in SGA-IUGR babies than in preterm babies adequate for gestational age.
Other long-term issues	Developmental disorders	Mainly due to prematurity, cerebral hemorrhage, or neonatal sepsis; are not specific to CKD, but are a threat in all preterm babies.

ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARBs, angiotensin II receptor blockers; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; GFR, glomerular filtration rate; IUGR, intrauterine growth restriction; LLAC, lupus-like anticoagulant; MMF, mycophenolate mofetil; mTor, mechanistic target of rapamycin; PE, preeclampsia; PKD, polycystic kidney disease; sCr, serum creatinine; SGA, small for gestational age; SLE, systemic lupus erythematosus.

in women on dialysis, and higher risk for 30-day readmissions than have been reported in men.

Women with CKD have a higher cardiovascular risk than women without CKD, but their risk is still lower than that of men with similar degrees of kidney impairment. In hemodialysis cohorts, there are differences in vascular access types in women versus men,¹² which may be due to biological or systemic factors. In some locations there is differential use of peritoneal and hemodialysis in women and men.

We do not know why and how much of this is due to differences in identification of kidney impairment, different access to care, or true difference in disease severity and prevalence. Women are more likely to donate kidneys for transplantation than to receive them. Data from different countries (USA, France, China, and India), confirm differential kidney transplant rates (lower in women than men), less likelihood of women being registered on transplant waiting lists, and longer time from dialysis initiation to listing. Mothers are more likely to be donors, as are female spouses.¹³

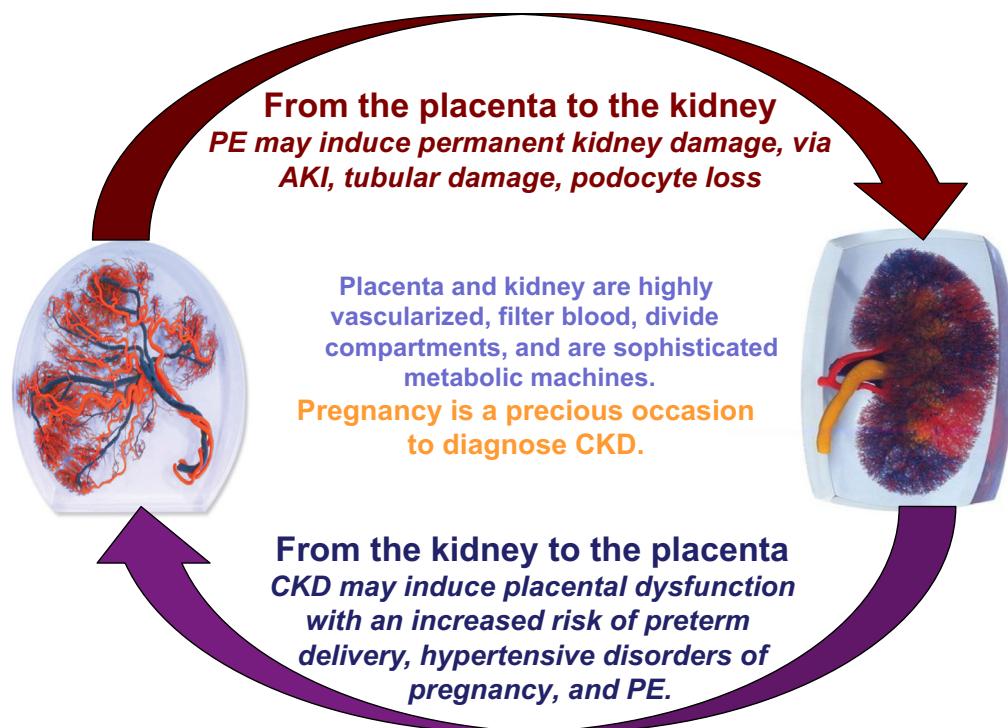


Figure 2 | Pregnancy and kidney function: complex interactions between 2 organs, the kidney and placenta. AKI, acute kidney injury; CKD, chronic kidney disease; PE, preeclampsia.

Psychosocial factors and education may also contribute to disparities. A number of reports find disparities in age and sex in access to kidney transplantation starting at the time of pre-referral discussions; irrespective of age, women were more likely not to have had discussions with medical professionals.¹⁴

There are sex differences in access to care in different regions of the world, and we do not have data to directly evaluate the extent of these differences, particularly in the poorest parts of the world.

Present and future: what we do not know

Given the data presented above with respect to pregnancy, AKI, autoimmune diseases, CKD, dialysis, and transplantation, there are many unanswered questions. In high-income countries with increasing maternal age and assisted

fertilization, there may be an increase in PE, which may impact future generations if associated with adverse fetal outcomes. The increase in *in vitro* fertilization techniques for those of advanced maternal age may lead to multiple pregnancies, which may predispose women to PE, intrauterine growth restriction, or both. Will this lead to an increase in CKD and CVD for women, and impact their offspring, in the future?

Due to the high heterogeneity of CKD, we do not know if and how pregnancy outcomes are modulated by the different nephropathies, due to scant evidence.

How should we define preconception risks of pregnancy with respect to current proteinuria cut-offs? Indications on when to start dialysis in pregnancy are not well established, nor is the specific role of frequency and duration. In those with kidney transplants, given the changing expanded donor policies, higher age at transplantation, and reduced fertility in older women, there may be changes in attitudes toward pregnancy with less than optimal kidney function.¹⁵ How this will impact short and long-term outcomes of mothers and their babies is not clear.

Teen pregnancies are very common in some parts of the world, and are often associated

Table 2 | Sex differences in the incidence and severity of autoimmune diseases

Distinctive characteristics		SLE	RA	SS
Peak incidence		Reproductive age	Perimenopausal	After 50–60 yr
Female-to-male ratio		Peak 15:1 Total 9:1	Peak 4:1 After 60 yr 1:1	Peak 14:1 Total 3:1
Influence of estrogen	High levels Low levels	Negative ?	Positive Negative	? Negative

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic scleroderma.

with low income and socioeconomic levels. The uneven legal rules for assisted fertilization and the lack of systematic assessment of kidney function point to the need for further research.

Despite elegant demonstrations for the role of sex hormones in vascular health and immunoregulation, the striking predominance in women of SLE, RA, and systemic sclerosis remains unexplained relative to other systemic diseases such as antineutrophil cytoplasmic autoantibody-associated vasculitis and hemolytic-uremic syndrome. The incidence of kidney involvement in SLE during pregnancy and similarities and/or differences in those with PE have not been well studied. The role of different medications and responses to medications for autoimmune diseases relative to sex has also not been well studied.

More attention to similarities between conditions and the importance of sex hormones in inflammation, immune modulation, and vascular health may lead to important insights and clinical breakthroughs over time. If women are more likely to be living donors, at differential ages, does this impact both CVD risk and risk for ESRD? Have we studied this well enough, in the current era, with modern diagnostic criteria for CKD and sophisticated tools to understand renal reserve? Are the additional exposures that women have after living donation compounded by hormonal changes on vasculature as they age? And are the risks of CKD and PE increased in the younger female kidney living donor?

In the context of specific therapies for the treatment or delaying of CKD progression, do we know whether there are sex differences in therapeutic responses to angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers? Should we look at dose finding and/or adjustments by sex? If vascular and immune biology is impacted by sex hormones, do we know the impact of various therapies by level or ratio of sex hormones? In low- to middle-income countries, how do changing economic and social circumstances impact women's health, and what is the nutritional impact on CKD of increasing predominance of obesity, diabetes, and hypertension?

In conclusion, women have unique risks for kidney diseases. Kidney diseases and issues related to access to care have a profound impact on both the current and next generations. Advocating for improved access to care for

women is critical to maintain the health of families, communities, and populations.

Focused studies on the unique contribution of sex hormones, or the interaction of sex hormones and other physiology, are important to improve our understanding of the progression of kidney diseases. Better scholarship on immunological conditions such as pregnancy (viewed as a state of tolerance to non-self) as well as SLE and other autoimmune and systemic conditions common in women may also lead to breakthroughs in understanding and care paradigms.

There is a clear need for higher awareness, timely diagnosis, and proper follow-up of CKD in pregnancy. In turn, pregnancy may also be a valuable occasion for early diagnosis of CKD, allowing for planning of therapeutic interventions.

World Kidney Day and International Women's Day 2018 are commemorated on the same day, an opportunity to highlight the importance of women's health and particularly their kidney health. On its 13th anniversary, World Kidney Day promotes affordable and equitable access to health education, health care, and prevention for all women and girls in the world.

The coinciding of World Kidney Day and International Women's Day offers an opportunity to develop and define best practices and future research agendas, and ultimately, to optimize outcomes of present and future generations living with or at risk for kidney disease.

DISCLOSURE

All the authors declared no competing interests.

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APPENDIX

World Kidney Day Steering Committee Members

Members of the World Kidney Day Steering Committee are Philip Kam Tao Li, Guillermo Garcia-Garcia, Mohammed Benghanem-Gharbi, Kamyar Kalantar-Zadeh, Charles Kernahan, Latha Kumar-aswami, Giorgina Barbara Piccoli, Gamal Saadi, Louise Fox, Elena Zakharova, and Sharon Andreoli.