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 age[2]; 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 postpartum, 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 adulthood[5]; 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

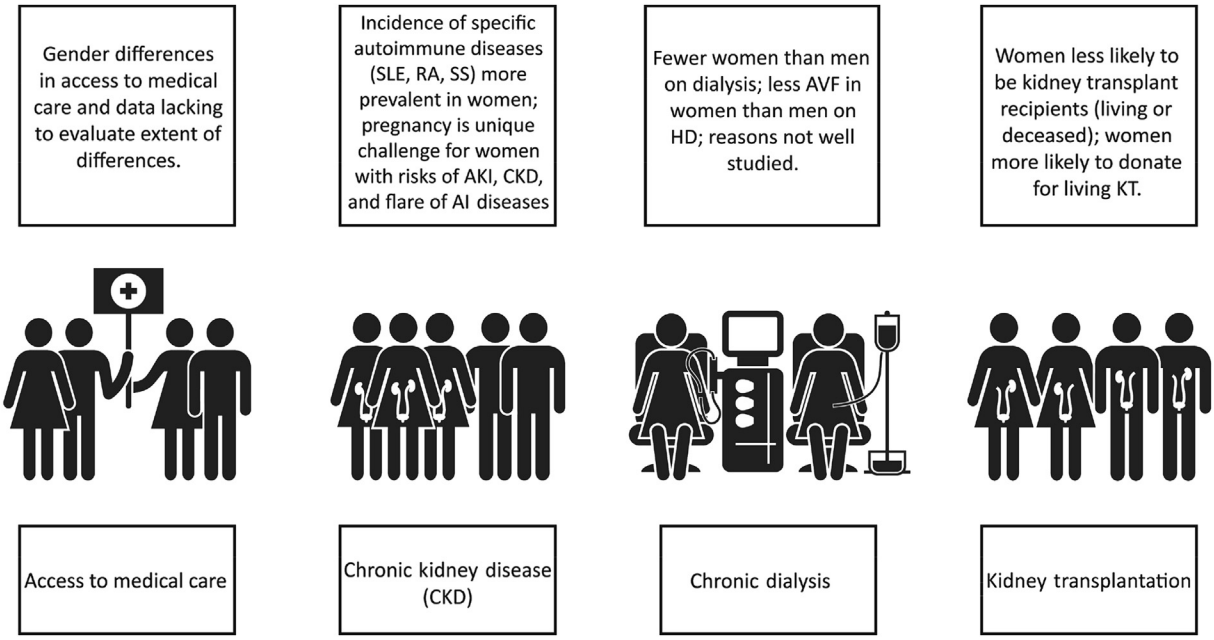

Figure 1 | Sex differences throughout the continuum of chronic kidney disease (CKD) care. AI, autoimmune; AKI, acute kidney injury; AVF, arteriovenous fistula; HD, hemodialysis; KT, kidney transplant; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic scleroderma.

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 receptors[7]; 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 scleroderma 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–beta 1 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

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