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Editorials

Women and kidney disease: reflections on World Kidney Day 2018

Kidney Health and Women's Health: a case for optimizing outcomes for present and future generations

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ABSTRACT

Chronic kidney disease (CKD) affects ~10% of the world's adult population: it is one of the top 20 causes of death worldwide and its impact on patients and their families can be devastating. World Kidney Day and International Women's Day coincide in 2018, 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 these learnings more broadly. Girls and women, who make up ~50% of the world's population, are important contributors to society and their families. Gender differences continue to exist around the world in access to education, medical care and participation in clinical studies. Pregnancy is a unique state for women, offering an opportunity for the diagnosis of kidney disease, and also a state where acute and chronic kidney diseases may manifest and that may impact future generations with respect to kidney health. There are

various autoimmune and other conditions that are more likely to impact women with profound consequences for childbearing and on the fetus. Women have different complications on dialysis than men and are more likely to be donors than recipients of kidney transplants. In this editorial we focus on what we do and do not know about women, kidney health and kidney disease and what we might learn in the future to improve outcomes worldwide.

Keywords: access to care, acute and chronic kidney disease, inequities, kidney health, women

INTRODUCTION

Chronic kidney disease (CKD) affects ~10% of the world's adult population: it is one of 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 coincide in 2018, 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 these learnings more broadly.

Girls and women, who make up ~50% of the world's population, are important contributors to society and their families. Besides childbearing, 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 endeavors, 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 underrepresented in many clinical research studies, thus limiting the evidence based 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 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. PE is a risk factor for the future development of CKD and end-stage renal disease (ESRD) in the mother [3] and is the principal cause of AKI and maternal death in developing countries [4]. Furthermore, PE is linked to 'small

babies', who are at risk for developing diabetes, metabolic syndrome, cardiovascular diseases (CVDs) and CKD in adulthood [5].

The presence of any degree of CKD has a negative effect on pregnancy, and given the increase in the risk of CKD progression postpartum, it raises challenging ethical issues around conception and the maintenance of pregnancies. Table 1 describes the various potential adverse effects of pregnancy on kidney health.

Autoimmune diseases

Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SS) preferentially affect women and are characterized by systemic inflammation leading to target organ dysfunction, including the kidneys. Sex differences in the incidence and severity of these diseases result from a complex interaction of hormonal, genetic and 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 [6–8].

Renal replacement therapies (RRTs)

The prevalence of CKD in women is always less than in men and they have slower progression to ESRD [9]. Women with CKD have a higher cardiovascular risk than women without CKD [10].

Access to RRT in general is inequitable around the world [11]. The equality of access to 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, but in multiple

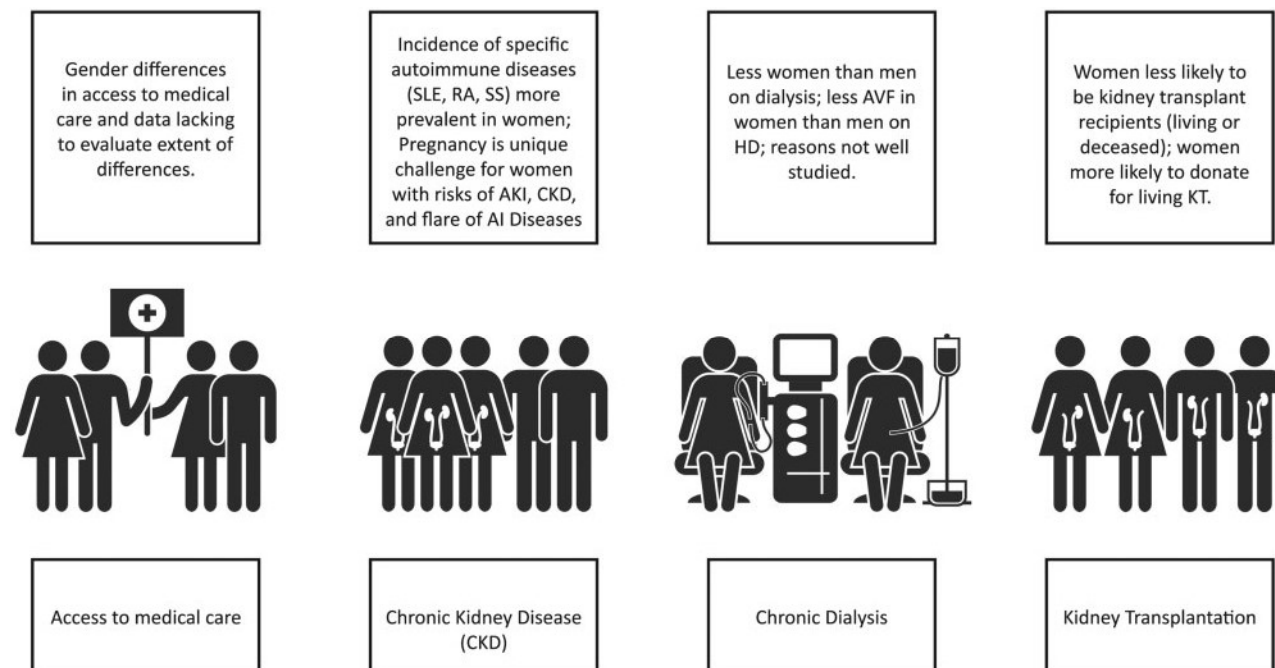


FIGURE 1: Sex differences throughout the continuum of CKD care. SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SS, systemic sclerosis; AKI, acute kidney injury; CKD, chronic kidney disease; AI, autoimmune; AVF, arteriovenous fistula; HD, hemodialysis; KT, kidney transplant.

Table 1. Adverse pregnancy outcomes in patients with CKD and in their offspring

Term	Definition	Main issues
Maternal death	Death in pregnancy or within 1 week–1 month postpartum	Too rare to be quantified, at least in high-resource settings, where cases are in the setting of severe flares of immunologic diseases (SLE in primis). Still an issue in AKI and in low-resource countries, Not quantified in low-resource countries, where it merges with dialysis need
CKD progression	Decrease in GFR, increase 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; 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 upon; in quiescent, well-controlled disease it 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 weeks	May be increased in CKD, but data are scarce. 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 weeks	Probably not increased in early CKD but may be an issue in dialysis patients. When not linked to extreme prematurity, may be specifically linked to SLE, immunologic diseases and diabetic nephropathy
Perinatal death	Death within 1 week–1 month from delivery	Usually a result of extreme prematurity, which bears a risk of respiratory distress, neonatal sepsis and cerebral hemorrhage
Small, very small baby	A baby weighing 1500–<2500 g at birth	Has to be analyzed with respect to gestational age
Preterm, early extremely preterm SGA (IUGR)	Delivery before 34–37 or 28 completed gestational weeks <5th or <10th centile for 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
Malformations	Any kind of malformation	Strictly and inversely related to preterm delivery; SGA and IUGR are probably related to the risk for hypertension, metabolic syndrome and CKD in adulthood
Hereditary kidney diseases	Any kind of CKD	Malformations are not increased in CKD patients not treated by teratogen drugs (MMF, mTor inhibitor, ACEi, ARB); the exception is diabetic nephropathy (attributed to diabetes). Hereditary diseases such as PKD, reflux nephropathy and CAKUT may be evident at birth
CKD–hypertension	Higher risk of hypertension and CKD in adulthood	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
Other long-term issues	Developmental disorders	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
		Mainly due to prematurity, cerebral hemorrhage or neonatal sepsis, and not specific of CKD, but are a threat in all preterm babies

GFR, glomerular filtration rate; SCr, serum creatinine; LLAC, lupus-like anticoagulant; PE-AKI, preeclampsia acute kidney injury; SGA, small for gestational age; IUGR, intrauterine growth restriction; MMF, mycophenolate mofetil; mTor, mechanistic target of rapamycin; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; PKD, polycystic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; IgA, immunoglobulin A.

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

Peak incidence	SLE, reproductive age	RA, perimenopausal	SS, >50–60 years of age
Female:male ratio	Peak 15:1 Total 9:1	Peak 4:1 After 60 years 1: 1	Peak 14:1 Total 3:1
Influence of estrogen	High levels Negative Low levels not clear	Positive Negative	not clear Negative

countries, men are reported to be more likely than women to receive dialysis [11, 12].

Women are more likely to donate kidneys for transplantation than to receive them, as reported from multiple countries. They are also less likely to be registered on transplant waiting lists and wait longer from dialysis initiation to listing.

Mothers are more likely to be donors, as are female spouses [13, 14].

PRESENT AND FUTURE: WHAT WE DO NOT KNOW

Pregnancy, AKI, autoimmune diseases, CKD, dialysis and transplantation present specific challenges for women for which many unanswered questions persist.

In high-income countries with increasing maternal age and assisted fertilization, there may be an increase in PE that 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 to PE, intrauterine growth restriction or both. It is unknown whether this will lead to an increase in CKD and CVD in women and impact their offspring in the future?

How should we define the preconception risks of pregnancy with respect to current proteinuria cutoffs? Indications on when to start dialysis in pregnancy are not well established, nor is there a specificity 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 in women with less than optimal kidney function [15]. How this will impact short- and long-term outcomes of mothers and their babies is unclear.

Teen pregnancies are very common in some parts of the world and are often associated with low income and education levels. The impact of uneven legal rules for assisted fertilization and the lack of systematic assessment of kidney function require more research.

Despite elegant demonstrations for the role of sex hormones in vascular health and immunoregulation, the striking predominance in females of SLE, RA and SS remains unexplained relative to other systemic diseases such as antineutrophil cytoplasmic antibody vasculitis and hemolytic-uremic syndrome. The incidence of kidney involvement in SLE during pregnancy and similarities/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.

Attention to similarities between conditions, 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 the risk for end-stage kidney disease: 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 living kidney donor?

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

SUMMARY

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. There is a

clear need for greater awareness, timely diagnosis and proper follow-up of CKD in pregnancy.

Focused studies on the unique contribution of sex hormones, and the interaction of sex hormones and other physiology, are important to improve our understanding of the progression of kidney diseases. 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, when better studied, may also lead to breakthroughs in understanding and care paradigms.

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 of kidney diseases for all women and girls around the world.

AUTHORS' CONTRIBUTIONS

All authors contributed to the conception, preparation and editing of the manuscript.

CONFLICT OF INTEREST STATEMENT

None declared. Full disclosures are listed in the individual author's conflict of interest forms.

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