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Editorial

Women and kidney disease: reflections on World Kidney Day 2018☆

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1. Introduction

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 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 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 amongst men and women; women remain underrepresented 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.

2. What we know and do not know

2.1 Pregnancy

Pregnancy is a unique challenge and is a major cause of acute kidney injury (AKI) in women of childbearing age [2]; AKI and pre-eclampsia (PE) may lead to subsequent CKD, but quantification of this risk is not known [3] PE and hypertensive disorders of pregnancy occur in 3-10% of all pregnancies; PE is a risk factor for the future development of CKD and 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 two 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, reduced resilience after AKI episodes.

The long term effects of PE on both maternal and fetal health remains an area of active research with many unknowns. Despite the fact that PE increases the probability of hypertension and CKD in later years, but we have not evaluated a surveillance or reno-protective strategy to determine if 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.

2.2. Autoimmune diseases

Autoimmune diseases such as SLE, RA, and SS preferentially affect women and are characterized by systemic inflammation leading to target organ dysfunction, including 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

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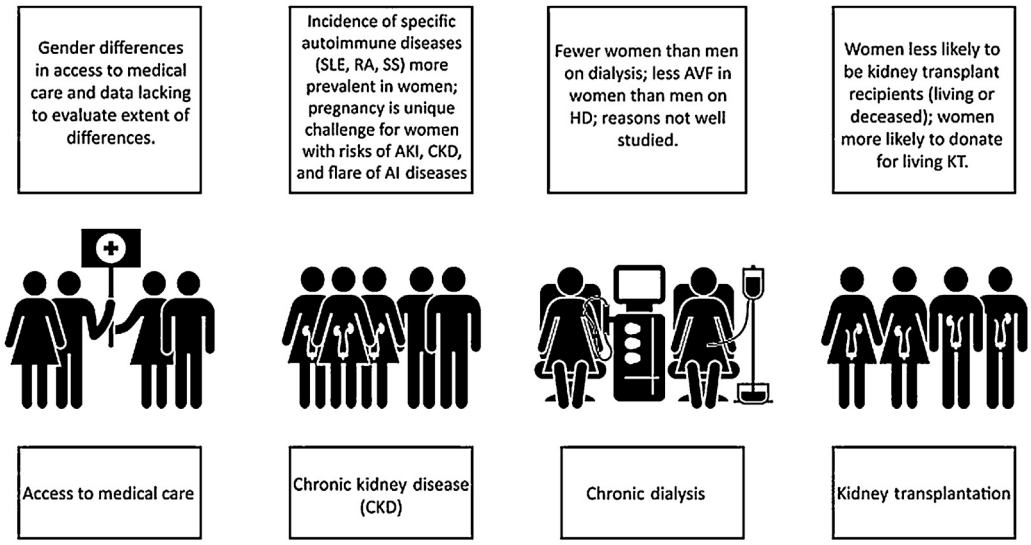

Figure 1. Sex differences throughout the continuum of CKD care. SSLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SS: systemic scleroderma; AKI: acute kidney injury; CKD: chronic kidney disease; AI: autoimmune; AVF: arteriovenous fistula; HD: hemodialysis; KT: kidney transplant.

Table 1
Adverse pregnancy outcomes in patients with chronic kidney disease 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 highly resourced settings, where cases are in the setting of severe flares of immunologic diseases (SLE in primis). 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; in quiescent, well controlled diseases do not appear to be increased with respect to non-pregnant, 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, in unstable patients.
Abortion	Fetal loss, before 21–24 gestational weeks	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 weeks	Probably not increased in early CKD, maybe 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 week–1 month form delivery	Usually a result of extreme prematurity, which bears a risk of respiratory distress, neonatal sepsis, cerebral hemorrhage
Small, very small baby	A baby weighting <2500–1500 g at birth	Has to be analyzed with respect to gestational age
Preterm, early extremely preterm	Delivery before 37–34 or 28 completed gestational weeks	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 pre-term 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, ARBS); exception: diabetic nephropathy (attributed to diabetes); hereditary diseases, such as PKD, reflux nephropathy, 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 pre-term babies adequate for gestational age.
Other long-term issues	Developmental disorders	Mainly due to prematurity, cerebral hemorrhage or neonatal sepsis, are not specific of CKD, but are a threat in all preterm babies

SLE: systemic lupus erythematosus; AKI: acute kidney injury; GFR: glomerular filtration rate; sCR: serum creatinine; CKD: chronic kidney disease; LLAC: lupus-like anticoagulant; PE-AK: 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; ARBS: angiotensin II receptor blockers; PKD: polycystic kidney disease; CAKUT: congenital anomalies of the kidney and urinary tract; IgA: immunoglobulin A.