REVIEW ARTICLE

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Kidney diseases in women: difference in risks and opportunities

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INTRODUCTION

Gender differences in access to healthcare and education persist and negatively affect women in different regions of the world. This is also true in the context of chronic kidney disease (CKD), a condition that affects approximately 10% of the adult population worldwide[1].

In this article, we will address some of the kidney diseases that predominantly affect women, the peculiarities of renal involvement during pregnancy, as well as the differences between genders observed in treatment approaches, especially in renal replacement therapy (RRT). Knowledge about such features can contribute to better planning of health care for the general population.

CHRONIC KIDNEY DISEASE

Chronic kidney disease represents a heterogeneous and frequent group of kidney diseases associated with high morbidity and mortality. In women of reproductive age, the prevalence of CKD ranges from 0.1 to 4.0%, and although relatively low, the implications of pregnancy in this context are various and can be severe. Based on the glomerular filtration rate (GFR), CKD is divided into five stages[2], and the worse the kidney function, the greater the chances of an adverse outcome in the health of the pregnant woman and the newborn. The risk is greater for women on dialysis treatment.

The hemodynamic changes observed in normal pregnant women make it difficult to identify CKD during pregnancy. Increased blood volume, decreased systemic vascular resistance, and increased cardiac output determine glomerular hyperfiltration[3], expressed by a 50% increase in GFR (serum creatinine in the normal range: 0.4–0.6 mg/dL) and a slight increase in proteinuria (the threshold for elevated proteinuria in pregnancy has been set at a higher level of 300 mg/day). Considering that the estimated GFR (eGFR) is not validated in pregnancy, the current recommendation is to assess GFR through serum creatinine.

In the context of CKD and pregnancy, the adverse clinical impact may be of pregnancy on renal function and kidney disease in pregnancy. Pregnancy potentially accelerates GFR loss and shortens the time required for RRT. The risk of deterioration of renal function is greater if the CKD is more advanced in early pregnancy, the worse is the control of blood pressure (BP) and when proteinuria >1.0 g/day. On the contrary, compared to pregnancy in the absence of kidney disease, CKD can contribute to adverse outcomes for both the pregnant woman and her newborn, the most important being preeclampsia (PE), prematurity, low birth weight, and fetal or neonatal mortality[4].

Pregnant women with CKD should be accompanied by a team composed of an experienced obstetrician and nephrologist. Every woman with CKD should receive pre-pregnancy guidance on potential risks related to the progression of kidney disease, pregnancy complications, and adverse fetal outcomes. Planned pregnancy allows women to become pregnant at the right time, take the necessary medications to treat the different causes and complications of CKD, and permit pregnancy in better health conditions without adverse outcomes.

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GLOMERULAR AND OTHER RENAL DISEASES

In the context of kidney diseases that predominate in women, lupus nephritis certainly stands out, as systemic lupus erythematosus (SLE) presents across all ages, in a female-to-male ratio that ranges between 8:1 and 15:1, being higher in childbearing age[5]. Lupus nephritis occurs in up to 60% of patients with SLE and is one of the more severe manifestations of such disease, which is particularly associated with significant morbidity and mortality[6]. In fact, 10–20% of the affected patients will progress to end-stage kidney disease (ESKD) after 10–15 years[7].

Other autoimmune diseases with renal involvement like rheumatoid arthritis and Sjögren syndrome are also more frequent in women. Rheumatoid arthritis is associated with different renal lesions, such as glomerular diseases, secondary renal amyloidosis, and acute and chronic tubulointerstitial nephritis[8]. Renal involvement in Sjögren syndrome is not uncommon, corresponding predominantly to tubulointerstitial nephritis, which may lead to renal tubular acidosis and precede other complaints.

Additional conditions that favor the development of CKD and are frequent in females are recurrent urinary tract infection in childhood that can cause renal damage, as well as recurrent adult pyelonephritis[9].

HYPERTENSION AND CARDIOVASCULAR DISEASES

Hypertension (HTN) is the most common modifiable risk factor for cardiovascular disease (CVD) and the leading cause of morbidity and mortality in women worldwide. Biological differences in HTN and CVD between men and women, a consequence of genetic, epigenetic, and sex hormone-mediated factors, are multifaceted and incompletely understood[10]. There is limited evidence on specific sex differences in HTN and CVD, despite gender-related heterogeneity, which can be proven by the absence of any differentiation in managing HTN and CVD between males and females in the Brazilian and International Guidelines[11,12].

Young women are relatively safeguarded from developing HTN and CVD by the endogenous vascular protective effects of estrogen. As estrogen goes down in premature ovarian failure, premenopausal, and after menopausal period, women develop HTN and the associated organ damage. There is a twofold increase in the risk of HTN, with a prevalence of 75–80% in postmenopausal women in the USA, and HTN rates are higher in women aged >65 years than men[13].

Hypertensive women are older and have, besides the well-known risk factors for CVD, more nontraditional variables to be considered such as autoimmune diseases, breast cancer treatment, gestational diabetes, depression, and psychological stress. Women also have singular forms of HTN such as pregnancy-related disorders, polycystic ovarian syndrome, and the use of contraceptive agents during reproductive age[14,15].

Measuring BP correctly, in office, at home (HBPM), or ambulatory (ABPM), is recommended for diagnosis, control, and treatment. Considering ABPM, women are less likely to experience nondipping patterns at younger ages, but, as they age, white and masked HTN appear, and similar findings are compared to those of men in daytime and nighttime BP.

Despite the negative impact on cardiovascular outcomes in women, BP thresholds for diagnosis and treatment, BP targets, lifestyle modifications, and antihypertensive medications for women are the same as for men, with rare exceptions because of pregnancy and sex-specific adverse effects of some antihypertensive drug classes. Thereby, renin angiotensin system blockers and mineralocorticoid receptor antagonists are contraindicated in women of reproductive potential because of the risk of fetal abnormalities; there is a greater chance in women to develop an ACEI-related cough, and more commonly they experience calcium channel block side effects[15].

Hypertension and CVD must be managed with appropriate lifestyle modifications and a personalized pharmacotherapy approach that effectively lowers BP, prevents CVD, and minimizes adverse effects. There is a need for HTN and CVD studies designed for sex-specific analysis to understand the phenotype of women at increased risk (Table 1)[14,15].

PREECLAMPSIA

Functional and anatomical adaptations during pregnancy are even more pronounced when associated with PE. It is known that the relative risk for the development of ESKD could be increased with each PE experience and its severity[16].

Women with pregnancy-induced HTN syndrome (versus normal pregnancy) show a higher incidence of obesity, metabolic syndrome and HTN, earlier onset of HTN, higher estimated vascular (Framingham Risk Score), and lower eGFR. Therefore, the history of PE should be followed later in life to reduce risks and allow early detection of CKD[17].

Despite the importance of the known association between CKD and PE, not many scientific societies emphasize the need for renal evaluation after PE or at the beginning of prenatal care, which could allow diagnosis of a previous CKD or detection of its risk factors (Table 2)[18]. The prevalence of CKD not previously

known in patients experiencing PE is about 20%[19]. Women who had PE present a higher frequency of developing microalbuminuria 5 years postpartum or persistent proteinuria 3–6 months postpartum, thus increasing their risk for CKD and renal biopsy[20].

DIALYSIS

Even though CKD is more prevalent among women, about 60% of dialysis patients in Brazil and worldwide are men. Studies suggest that the reduction of renal function usually happens faster in men. Women seem to have a healthier lifestyle and adhere more easily to the dietary restrictions needed to control CKD progression when compared to men. Furthermore, some studies suggest an antifibrotic protective effect of estrogen in the kidneys, while testosterone seems to have an opposite pro-fibrotic, pro-inflammatory effect[21]. Another important factor that must be considered is the probable overdiagnosis arising from the use of some eGFR formulas in women.

Women start dialysis with a slightly lower GFR and are, on average, 1–2 years older than men. The choice of dialysis modality does not differ between men and women, with hemodialysis being the most commonly used method worldwide[21]. The percentage of women who start dialysis using catheters is slightly higher than that of men[22].

The adequacy of dialysis is another factor that should be carefully evaluated in women. Since urea distribution volume (V) is regarded as a constant for every individual, Kt/V overestimates dialysis adequacy among women, considering that V is a replacement for lean body mass[23]. For a similar reason, women are often overtreated for anemia. Despite a general acknowledgment that women have lower hemoglobin levels than men, the guidelines for anemia in CKD patients employ the same parameters of hemoglobin to define anemia in men and women, as well as recommend the same therapeutic target[24]. This situation certainly justifies a tendency of women needing higher doses of erythropoietin when compared to men.

Finally, women on dialysis have more frequent and severe symptoms and also need more time for post-dialysis recovery than men[25]. Men on RRT have greater family support than women—situation explained by socially determined gender roles; therefore, it is more frequent to find men cared for by their wives and relatives than the other way around[26].

Table 1. Women and cardiovascular disease.

Sex-specific risk factors under-recognized	Traditional risk factors poorly considered	Lifestyle modification early on: Life's simple 7 must be done!
Prematurity	Hypertension	Blood pressure management
Age at menarche (≤10 years)	Hypercholesterolemia	Lipids control
Polycystic ovarian syndrome	Metabolic syndrome	Control weight (normal body mass index)
Contraceptive use (type, duration)	Diabetes	Reduce blood sugar
Gestational diabetes	Smoke	Stop smoking
Premature ovarian failure/menopause		Become and remaining active. Exercise 150 min/day
Gestational hypertension, especially pre-eclampsia		Healthy diet
Delivery small for gestational age infant	**Key points** • Cardiovascular disease is poorly diagnosed • False perception that women are at low-risk population: reduced awareness and there is a need for reconsideration this bias of recognition • Knowledge barriers: lack of specific evidenced-based data • Risk calculation maybe different for men and women in a more personalized way • Consider lifestyle modifications and treatment early on when sex-specific risk factors are present	
Pre-term delivery (<37 weeks)		
Recurrent miscarriage		
Breast cancer treatment		
Inflammatory diseases		
Depression and stress		

Table 2. Key points in the relationship between chronic kidney disease and pre-eclampsia.

- PE can increase the risk of CKD and CVD later in life.
- PE is an early stress test for CKD diagnosis.
- The history of PE should be an early detection indicator of CKD.
- PE is associated with long-term microalbuminuria and persistent proteinuria.
- Women who had PE have higher incidence of obesity, metabolic syndrome, and hypertension later in life.
- Renal evaluation at the beginning of prenatal care could diagnose previously CKD.

PE: pre-eclampsia; CKD: chronic kidney disease; CVD: cardiovascular disease.

KIDNEY TRANSPLANTATION

As for the whole population, kidney transplantation (KT) is considered the best RRT for women. Compared to the other RRTs, KT promotes increased survival, a better quality of life, and lower costs[27]. However, there are some disparity issues to be highlighted. Women are more frequently living donors than men, for parents or husbands. The potential explanations are the higher level of empathy or the economic dependence because fathers and husbands are often family providers[28]. Conversely, men account for more deceased donors because traumatic death is more frequent in this group[29].

Women have less access to the waiting list and are less transplanted after being listed[29]. Factors reported as potential causes are the lower probability of KT offered as RRT, difficulties in completing the pre-KT evaluation, and more frequent concerns about KT. Due to previous pregnancies, women are more prone to develop antibodies against the human leukocyte antigens and subsequently against the potential donors, limiting to find a compatible graft. Some effects have also been attributed to the hormonal profile, with women producing more vigorous immune reactions because of the immune-stimulating effect of estrogen and the diminished immune-suppressing effect of testosterone[30].

After KT, graft survival is lower in women, even after adjusting for other factors. Recently, more robust evidence showed that these results are seen when women received a graft from male donors. An exacerbated immune response in female recipients against the HY antigen (present in all male tissues) may explain these outcomes[31].

Infertility is common among women in dialysis therapy, which is associated with the effects of uremia on the hypothalamic-pituitary-gonadal axis. However, a restoration to normal hormone levels occurs around 6 months after KT, and fertility increases. Pregnancy counseling after KT is crucial because of the risk of immunosuppression on the fetus, the risk of worsening kidney allograft function, and other maternal or fetus complications, such as pre-eclampsia, premature delivery, small for gestational age, and intrauterine growth restriction[32].

CONCLUSION

As described, women have unique risks for kidney diseases that should be recognized to increase the opportunities for timely diagnosis and equitable access to health education, health care, and prevention. We also highlight that pregnancy may be a special opportunity for an early diagnosis of CKD. The deleterious effects of PE may result in cardiometabolic and renal overload that may be associated with the development of CVD and CKD later in life. Finally, it is still necessary to evaluate several aspects of RRT for better treating women (dialysis adequacy, treatment of anemia, opportunities in transplantation, and others).

AUTHORS' CONTRIBUTIONS

GMK: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **AFM:** Writing – original draft, Writing – review & editing. **CISR:** Writing – original draft, Writing – review & editing. **HSP:** Writing – original draft, Writing – review & editing. **JAMN:** Conceptualization, Writing – original draft, Writing – review & editing. **JM:** Writing – original draft, Writing – review & editing. **LRRM:** Conceptualization, Writing – original draft, Writing – review & editing. **MGB:** Writing – original draft, Writing – review & editing. **TAF:** Writing – original draft, Writing – review & editing. **APS:** Writing – original draft, Writing – review & editing.

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