

# A new millennium for women and kidney disease

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## INTRODUCTION

Taking advantage of this year's synergy, as World Kidney Day (WKD) and International Women's Day fall on the same day, the theme chosen for WKD 2018 was "Kidneys and Women's health", drawing the attention of the nephrology community to the special features of diseases of the kidney as they affect women. When focusing on this subject, we come to see the major gaps in this area of knowledge. On one hand, it is now comprehensively accepted that there are unique biological and behavioral differences resulting in sex/gender variances, albeit mostly in favour of women. However, on the other, despite mounting evidence in multiple medical disciplines, these disparities have not been so well explored in nephrology, and so we try, in this editorial, to review current knowledge in this field.

## EPIDEMIOLOGY

Acknowledgment of chronic kidney disease (CKD) and its dimension as a public health problem has gained greater importance in the last two decades, due to the recognition of CKD's high morbimortality and high prevalence, ranging from 10-13%<sup>1</sup>. As for gender differences in CKD epidemiology, it seems that the proportion of women with CKD is higher than that of men, resulting in a 60:40 ratio, whereas in some countries including Portugal, it becomes even more unbalanced with a twofold higher ratio of CKD in women than in men<sup>2</sup>. This disparity may not accurately denote a higher CKD burden, as it most likely results from a longer life expectancy of women and possibly from a CKD overdiagnosis due to inherent limitations of estimated glomerular filtration rate equations, including lack of correction for body surface area. Hence, when considering CKD progression, most data from population-based

studies show that men have a faster function decline than women. Many theories based on biological differences such as the protective effects of estrogens versus the detrimental effects of testosterone or socio-cultural lifestyle disparities have been postulated; however, clinical evidence to support these is rather weak.

Regarding end-stage renal disease (ESRD) and starting renal replacement therapy (RRT), we observe a male predominance<sup>1</sup>, in a proportion of 60:40. Although surprisingly consistent globally, data comparing the gender difference for the treatment gaps remain scarce. Although when considering faster CKD progression in men, one must recognize non-biological factors, such as access to medical care and personal preference such as greater choice for conservative care among elderly women. Nevertheless, mortality is higher among men at all levels of predialysis CKD, and, even so, they reach ESRD in a higher proportion than women. Whereas mortality among individuals on RRT is similar for men and women<sup>1</sup>.

Another unique to women event, pregnancy poses unparalleled obstacles for women as a cause of acute kidney injury in women of childbearing age. Ranging, in developed countries, from hypertensive complications (such as preeclampsia) or other thrombotic microangiopathies to other obstetric complications (including septic abortions, placental abruption, and intravascular disseminated coagulation) more common in developing countries. All of which may lead to subsequent CKD, but quantification of this risk is not known.

Turning to access to transplantation, the perception that this is lower for women than for men dates back more than three decades. This may be due to patient preference, gender selection bias by health-care personnel, or socioeconomic reasons. However recent studies based on developed countries evidenced declining disparities, after adjusting the analysis of transplantation

rates in men and women for the preformed antibodies. Since pregnancy is a sensitizing event, women will have more preformed antibodies, which justifies 14% fewer deceased kidney allocation in women<sup>1</sup>. In terms of living donation, apart from the predictable disadvantage of preformed antibodies, particularly in spousal donations, the differences remain mostly speculative.

### ■ WOMEN'S SPECIFICITIES: PREGNANCY IN CKD, DIALYSIS AND TRANSPLANTATION

Where do women with CKD stand in terms of pregnancy? CKD affects up to 6% of women of childbearing age in high-income countries, and is estimated to affect 3% of pregnant women<sup>3</sup>. The complex alterations of the hypothalamic-pituitary-ovarian axis together with the effects of inflammatory disease are the major reasons for compromised fertility in women with CKD. Nevertheless, the chance of pregnancy is high enough so that in daily practice one needs to prevent it if it is not desired or approach it in a multidisciplinary manner if it does occur. The perception of the intimate association between kidney disease and pregnancy reflects the adverse outcomes from early stages of CKD until later stages of kidney function during pregnancy and postpartum. Lindheimer *et al* demonstrated that women presenting pre-pregnancy serum creatinine  $\geq 2.8$ mg/dL were associated to pregnancy problems in about 86% and only 76% had successful obstetric outcomes. Forty percent of these women progressed to ESDR within 1 year<sup>3</sup>. Notably, baseline hypertension and proteinuria are the most important modulators of pregnancy-related risks. While not all causes of kidney disease are major determinants of worsening of kidney disease during pregnancy, diabetic nephropathy and lupus nephritis have been linked to more adverse outcomes. Equally so, the negative effect of kidney disease on pregnancy can be shown by extremely high rates of caesarean section (70%), preterm delivery  $<37$  (89%) and  $<34$  (44%) weeks, small gestational age  $<10\%$  (50%) and  $<5\%$  (25%) percentiles as well as increased needs for neonatal intensive care unit (70%)<sup>4</sup>. Pregnancy *per se* is a potential timeframe for the initial diagnosis of CKD and kidney biopsy seems no longer frightening when prompt diagnosis is required, as long as it is performed with controlled blood pressure, normal coagulation and under 30 to 32 weeks' pregnancy<sup>4</sup>. Fortunately, CKD and pregnancy are no longer enemies for women who desire to conceive. While we believe that small impairments of kidney function are linked to successful pregnancies, we agree that baby

steps should be taken when counseling a pregnant woman with a more advanced CKD, in terms of managing determined health issues (Table I).

For countless years, being on dialysis and getting pregnant was considered unthinkable among medical community. However, in the last few decades, great progress

**Table I**

Management of health issues in pregnant women with CKD

<p><b>Chronic Kidney Disease</b></p>	<p><b>Pre pregnancy</b></p> <ul style="list-style-type: none"> <li>• Recommend fertility preservation if cyclophosphamide needed</li> <li>• Use progesterone-only contraception methods</li> <li>• Provide folic acid supplementation (5mg/day)</li> <li>• Remove teratogens before conception (including statins)</li> <li>• Use ACE inhibitors and ARB until conception</li> <li>• Retinopathy assessment and target HbA1c% <math>&lt;6,5\%</math> in diabetic nephropathy</li> </ul> <p><b>Lupus nephritis</b></p> <ul style="list-style-type: none"> <li>• Recommend lupus inactivity for 6 months</li> <li>• Low-molecular-weight-heparin in proteinuric, lupus flare and antiphospholipid antibodies</li> <li>• Hydroxychloroquine to reduce the risk of congenital heart block</li> </ul> <p><b>Diabetes Mellitus</b></p> <ul style="list-style-type: none"> <li>• Screening of gestational DM when using steroids and/or calcineurin inhibitors</li> <li>• Switch to insulin if type 2 diabetes</li> </ul> <p><b>Hypertension</b></p> <ul style="list-style-type: none"> <li>• Target BP <math>&lt;140-90</math>mmHg</li> <li>• Use labetalol, nifedipine and methyldopa</li> </ul> <p><b>Preeclampsia</b></p> <ul style="list-style-type: none"> <li>• Low dose aspirin 75-100mg/day</li> </ul> <p><b>Postpartum</b></p> <ul style="list-style-type: none"> <li>• Restart RAAS blockage as soon as renal function is stable (enalapril, captopril safe to use in breastfeeding)</li> </ul>
<p><b>Hemodialysis</b></p>	<ul style="list-style-type: none"> <li>• Target diastolic BP 80-90mmHg</li> <li>• Avoid diuretics, ACE inhibitors and ARB</li> <li>• Intensify dialysis: 5-7 per week; <math>&gt;20</math> hours/week; urea <math>&lt;107</math>mg/dL; increase dry weight 0.45-1kg/week in first trimester; 0.3-0,5kg/week in the second and third trimester</li> <li>• Minimum heparin use</li> <li>• Improvement of calcium/phosphorus metabolism</li> <li>• Anaemia: Hb target 10-11g/dL; serum ferritin 200-300 <math>\mu</math>g/mL. Iron supplementation 10-15mg/day + 50-100% increase EPO</li> <li>• Nutrition: calories intake of 25-35Kcal/Kg/day</li> </ul>
<p><b>Peritoneal Dialysis</b></p>	<ul style="list-style-type: none"> <li>• Increase exchanges</li> <li>• No indication to switch to HD, if dialysis dose achieved.</li> </ul>
<p><b>Kidney Transplantation</b></p>	<ul style="list-style-type: none"> <li>• Conceive at least 1 year post-transplantation and ideally with:</li> <li>• No rejection in previous year</li> <li>• Stable renal function</li> <li>• Minimal proteinuria</li> <li>• Stable non teratogenic medication: tacrolimus, azathioprine and steroids; Avoid mycophenolate and cyclosporine</li> </ul>

has been made in the care of pregnant dialysis patients (and even in pre-pregnancy stages). These results have been linked to increased dialysis intensity during pregnancy and expanded multidisciplinary care. In fact, since the first successful pregnancy in a patient on hemodialysis (HD) in 1971, the number of successful pregnancies have been increasing over time with a fetal survival gain of ~25% per decade, reaching over 90% in recent years<sup>5</sup>. Presently, women who desire to get pregnant are no longer dissuaded from conceiving while on dialysis if there is no forthcoming option for transplantation. Still, awareness of the potential risks must be a mainstay, as even intensively dialyzed women present high rates of preeclampsia (18%) and cervical incompetence (18%), higher than those expected for the general population. Considering the use of the abdominal cavity in peritoneal dialysis (PD) patients, it would seem unreasonable to maintain the pregnant patients in PD. Surprisingly, PD can be continued during pregnancy as long as an increase in the number of exchanges is performed. It should be noted however that a total dialysis dose may not be achieved and this may be linked to decreased overall surface of exchange due to a gravid uterus. As far as fetal outcomes are concerned, a higher rate of low-weight newborns can be expected (67% in PD versus 31% in HD)<sup>6</sup>.

Renal transplantation is the desire of most ESRD patients. It has advantages, particularly for women who desire to conceive, as fertility is usually restored in women following transplantation. The first successful pregnancy in a renal transplant recipient occurred in 1958, with an exponential rise in the number of pregnancies over the subsequent decades. Nonetheless, an inferior rate exists when compared to the general population<sup>3</sup>. As far as optimal post-transplantation pregnancy timing goes, there are various unanswered questions. The first concerns optimal pre-pregnancy kidney function and the second the interplay of the effects of immunosuppressive therapy on both pregnancy and allograft outcomes. When assessing reduced pregnancy rates in transplanted women, a significant bias may exist concerning improved contraception counseling in this population as well as the employment of teratogenic medication such as first-line agent mycophenolate mofetil.

## ■ WOMEN: KIDNEY AND AUTOIMMUNE DISEASES

When it comes to autoimmune diseases and their known predominance in females, isn't it time to reform diagnostic and treatment options in this specific

population? Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SS) play a leading role in public health issues as important causes of morbidity and mortality among women. SLE predominantly affects women of childbearing age (9:1 female-to-male ratio with up to 15:1 in peak reproductive years), and lupus nephritis in particular occurs in ~40% of cases<sup>6</sup>. Unfortunately, even today, in the context of preserved kidney function, the risk of adverse pregnancy outcomes is increased in women with active lupus nephritis. While black and Hispanic ethnicity are non-modifiable risk factors for poor pregnancy outcomes (mostly preterm delivery), proteinuria, hypertension and active disease are all factors that can be managed from a medical perspective through effective preconception management. Fortunately, the new millennium has brought us new strategies. Tacrolimus is now seen as a new hope when lupus flare develops<sup>3</sup>, avoiding premature rupture of membranes, preterm delivery, maternal sepsis, and gestational diabetes related to steroid therapy. Similarly, RA also affects predominantly women (4:1 female-to-male ratio with a peak incidence between 45 and 55 years old), though, unlike SLE, pregnancy leads to a surprising improvement of the disease. Although SS is reported in a not so pronounced female to male ratio (3:1 to 14:1 with a peak incidence in the fifth and sixth decades) it is additionally linked to the female population. An equal denominator, estrogens<sup>7</sup> are part of the pathophysiology of all these 3 diseases previously described, affecting either positively or negatively the disease. With this in mind, where are we heading to in the new paradigm of estrogen therapies?

## ■ CONCLUSION

Women have unique risks for kidney diseases. As in many other areas of scientific knowledge, particular aspects of female kidney disease remain uncharted territory. There are notable signs of improved management in this field but further efforts should be made in order to achieve full potential outcomes. The Lancet opinion of 1975 states: "*Children of women with renal disease used to be born dangerously or not at all – not at all if their doctors had their way*"<sup>8</sup>. In the new millennium, we urge the need of fully changing this paradigm, as children of women with renal disease should be well born whilst their mothers are assisted by new millennium doctors aiming for new millennium outcomes.

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