

# Women with kidney diseases: Whatever we understand and lack of knowledge.

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### **ABSTRACT**

About 10% of adults worldwide suffer from chronic kidney disease, which is among the top 20 causes of death globally and can have a devastating effect on patients and their families. In 2018, World Kidney Day and International Women's Day fell on the same day, providing a chance to consider the significance of women's health, particularly their kidney health, on the community and the next generation. We should also endeavour to increase our curiosity about the particular features of kidney disease in women so that we can apply the knowledge we gain more broadly. Women and girls, who comprise over half of the global population, play significant roles in their families' and society's lives.

Gender disparities persist in global access to education, healthcare, and clinical research participation. Pregnancy is a special time for women to get screened for kidney illness, but it's also a time when acute and chronic kidney problems might appear, which can have an effect on the health of future generations' kidneys. Numerous autoimmune diseases and other illnesses have a higher propensity to affect women, having significant effects on both the foetus and the ability to carry children. In addition to being more likely to be kidney donors than recipients, women experience distinct consequences from dialysis than do males. This editorial focuses on the knowledge gaps regarding women, kidney health, and renal disease.

**Keywords :** *Women; Access to care; Kidney health; Acute and chronic kidney disease; inequities.*

### **INTRODUCTION**

About 10% of adults worldwide suffer from chronic kidney disease (CKD), which is among the top 20 causes of death globally<sup>1</sup>. The condition can have a catastrophic effect on patients and their families. 2018 marks both World Kidney Day and International Women's Day, providing a chance to consider the significance of women's health, particularly their kidney health, on the community and the coming generations. We should also endeavour to be more inquisitive about the particular features of kidney disease in women so that we can apply the knowledge we gain more broadly.

Women and girls, who comprise over half of the global population, play significant roles in their families' and society's lives. In addition to carrying children, women play a crucial role in raising them and helping to maintain. In the twenty-first century, women still aim for parity in business, trade, and other professional pursuits, even if they are aware that parity does not always exist. Men and women do not always have equal access to education and healthcare; women are still underrepresented in many clinical research studies, which reduces the amount of data that can be used to provide recommendations for the best possible outcomes (Figure 1). This editorial centres on the current state of knowledge on kidney health and illness in women, as well as potential future research directions to enhance overall results.

### **What Is and Is Not Known**

For women of childbearing age, pregnancy presents a special set of challenges. AKI and pre-eclampsia (PE) can result in future chronic kidney disease (CKD), but the extent of the risk is unknown. Pregnancy is negatively impacted by 2-5 CKD, especially in the earliest phases.<sup>6-7</sup> As CKD progresses, the dangers rise, raising potentially difficult ethical questions about getting pregnant and keeping a child.<sup>6-8</sup> We are aware that PE raises the risk of hypertension and chronic kidney disease (CKD) in later life, but we haven't looked into surveillance or renoprotective measures to see if renal function may be gradually reduced.<sup>9-12</sup>

Certain systemic diseases, such as rheumatoid arthritis (RA), systemic scleroderma (SS), and systemic lupus erythematosus (SLE), are more likely to impact women more than men. The proportionate impact of these acute and chronic diseases on the development of end-stage renal disease (ESRD) in females remains unknown. Women are always less common than men in CKD cohorts, and their progression to ESRD is slower.<sup>13–15</sup> We don't know why and to what extent this is caused by variations in the way kidney impairment is diagnosed, variations in patient access to care, or actual variations in the incidence and severity of the disease.

Though still lower than males with comparable levels of kidney impairment, women with CKD had a greater cardiovascular risk than women without the disease<sup>16</sup>. There are variations in the vascular access types between men and women in hemodialysis cohorts, which could be caused by biological. Donating kidneys for transplantation is more common among women than receiving them. We are unsure if this is due to other causes, cultural factors, or the difference incidence of CKD in men and women. In certain places of the world, particularly the poorest, there are still gender disparities in access to care, and the degree of these discrepancies cannot be clearly assessed due to a lack of data.

Pregnancy, preterm birth, hypertensive disorders associated with pregnancy, and foetal health. WOMEN'S HEALTH IS ESSENTIAL FOR BOTH CURRENT AND FUTURE KIDNEY HEALTH

### What is Acknowledged

The primary cause of AKI and maternal mortality, especially in underdeveloped nations, is PE.<sup>2,17</sup> The most frequent cause of AKI in women who are fertile is pregnancy.<sup>10, 18, 19</sup> Numerous illnesses and various regions have various causes. In nations without access to legal abortion services, septic abortion following an illicit operation is the primary cause of early AKI; in wealthy nations, on the other hand, PE following aided fertilisation is increasingly the predominant cause.<sup>12, 20–22</sup> Three to ten percent of pregnancies result in PE and hypertensive problems.<sup>2-3,18</sup>; in these conditions, an imbalanced pro- and anti-angiogenic dysregulation primarily targets the kidney, resulting in endothelial damage throughout the body, hypertension, and proteinuria. The incidence of PE rises at the extremes of reproductive age for the reasons previously indicated. It is higher in low-middle income nations

(perhaps reflecting undetected predisposing conditions). The kidney and placenta have an unambiguous link, and having chronic kidney disease (CKD) increases the risk of PE and hypertensive problems during pregnancy (Figure). In addition to CKD, additional illnesses mentioned as risk factors for PE include diabetes and immunologic CKD risk factors may include obesity, metabolic syndrome, illnesses, and baseline hypertension. Since many of these conditions exhibit even slight changes in renal function, the role of kidney function in the development of PE is recognised indirectly. Based on novel angiogenic-antiangiogenic markers, more recent classifications of PE distinguish between “placental” and “maternal” causes of PE, which may be crucial for care both during and after pregnancy.

PE has long-term repercussions on the health of both the mother and the foetus, but there are still many unanswered questions in this field of active research. PE increases the mother's risk of developing CKD and ESRD in the future. The causes are not entirely known, although podocyte loss—a defining feature of PE—suggests long-term glomerular injury.<sup>25</sup> Endotheliosis may signal glomerulosclerosis; tubular and vascular damage may coexist. Endotheliosis is linked to PE but is also seen in healthy pregnancies.<sup>26, 27</sup>

PE is linked to premature delivery, reduced intrauterine growth, intrauterine and perinatal death, and “small babies” in addition to maternal concerns.<sup>2, 3, 5</sup> Preterm and small babies are much more likely to experience neurological impairments and postnatal problems, including sepsis.<sup>28–32</sup> Since postnatal intensive care is necessary for both survival and deficit-free survival, the dangers might be larger in low-income nations.<sup>20, 21</sup> Over time, infants are vulnerable to adult onset diabetes, metabolic syndrome, cardiovascular diseases (CVDs), and chronic kidney disease (CKD). Since the kidneys finish developing in the latter stages of pregnancy, delayed or insufficient kidney growth leading to a low number of nephrons is most likely the cause of small for gestational age and preterm newborns' elevated risk of chronic kidney disease (CKD) and hypertension.<sup>33–37</sup>

### CHRONIC KIDNEY DISEASE PREGNANCY: DIALYSIS AND TRANSPLANTATION

#### What is Acknowledged

persistent renal illness From the beginning of the pregnancy,

CKD increases the chance of unfavourable outcomes (Table 1).<sup>6, 38, 39</sup> The risks may be increased in glomerular nephropathies, autoimmune disorders, and diabetic nephropathy, and they rise from CKD stage 1 to CKD stage 5.<sup>6, 7, 38–41</sup> Pregnancy outcomes following kidney donation indicate that a lower amount of renal parenchyma may be linked to an increased risk of PE and pregnancy-related hypertension problems.<sup>42, 43</sup>

Baseline hypertension and proteinuria are significant predictors of pregnancy-related risks. Among these, we know that malformations are not more common than in the general population (except in cases of inherited diseases like reflux nephropathy, polycystic kidney disease, or congenital kidney and urinary tract anomalies), maternal death is rare (except in highly resourced countries), and small for gestational age babies and preterm deliveries are intrinsically linked, more common in patients with stage 1 chronic kidney disease, and their frequency increases as kidney function deteriorates). Similar to this, the impact of pregnancy on the advancement of CKD remains incompletely recognised due to variations in research methodologies, obstetric practices, and follow-up periods. Overall, in early CKD, short- and long-term declines in kidney function are uncommon, but one possible reason for the first CKD diagnosis to occur is pregnancy. Pregnancy may be the only time advanced CKD is detected in nations with inadequate or unequal resources. When CKD is diagnosed in earlier stages, more rigorous therapy and surveillance may be required; in well resourced nations with well-established prenatal care, the implications of starting dialysis may raise significant clinical and ethical difficulties.<sup>49–51</sup>

### **Dialysis and organ replacement**

Reduced fertility is associated with end-stage renal disease (ESRD); data from Australia and Europe indicate a 1:10 ratio between the general population and transplantation, as well as a 1:1100 chance between transplantation and dialysis.<sup>52, 53</sup> The earliest reported instances of successful pregnancies while receiving dialysis were in the 1970s; nevertheless, in the new century, this was recognised as a legitimate therapeutic prospect. There have been over a thousand documented pregnancies among dialysis patients.<sup>55</sup> The most significant development has been the proof of a strong correlation between the frequency and duration of dialysis sessions and successful pregnancy outcomes; as a result, the current standard of care calls for strengthening dialysis up to daily.<sup>8, 54</sup>

Given the benefits of dialysis for women and their children, views towards counselling women with severe CKD may need to change. After receiving a kidney transplant, fertility is partially recovered.<sup>56–60</sup> But even in the best of circumstances (normal renal function, no Women who have kidney transplants are more likely to experience problems than women in the general population if they have hypertension or proteinuria at least two years following transplantation and have not experienced any recent bouts of rejection. On the other hand, if teratogen medications (mycophenolicThere is little experience with pregnancy among patients who have failed kidney transplants or diminished renal function, and therapy is still compelled to be based on anecdotal data or personal experience.<sup>61, 62</sup> Multiple pregnancies may have an increased risk in CKD patients, with both native and transplanted kidneys. Assisted fertilisation procedures are becoming more and more common in various settings, although there are few focused research in this population.

### **Women, kidney disease, and autoimmune diseases**

#### **What is Acknowledged**

Women are more likely to be affected by autoimmune illnesses including SLE, RA, and SS, which are characterised by systemic inflammation that damages target organs, including the kidneys. Hormonal, genetic, and epigenetic variables interact in a complicated way to cause disparities in the prevalence and severity of various diseases across the sexes (Table 2). The impact of autoimmune illnesses on public health, which five million people worldwide suffer from SLE, an autoimmune illness that affects various organs. Women and persons of non-European heritage are disproportionately affected, with a female to male ratio of nine to one. During the prime years of reproduction, there is the greatest female predominance (up to 15:1). The biology underlying these variations has been investigated; genetic variants on X chromosomes<sup>66–68</sup> and the number of X chromosomes provide one reason; the involvement of oestrogen in SLE is another significant etiological explanation. The transcription activity of intracellular oestrogen receptors, whose profile is changed in T-cells from female SLE patients, mediates the main effects of oestrogen.<sup>69, 70</sup> The protein known as cathepsin S has been implicated in the development of lupus by inciting the immune system to target healthy cells, especially in women. People of European, Hispanic, and Afro-American descent may be more susceptible to lupus due to a variety of non-HLA genetic markers.<sup>72</sup> Pregnancy-related

susceptibility to SLE is similarly complex, with increased IFN- $\alpha$  expression being one of the contributing factors. The placenta's expression of elevated IFN- $\alpha$  contributes to the harmful role of SLE by increasing vulnerability to the disease as well as placental reproduction success.<sup>73</sup> Due to their aberrant form and function, regulatory T-cells—which may be the key to cell regulating fetomaternal tolerance—may be more difficult to manage during pregnancy in women with SLE and may contribute to prenatal pathology in these cases.<sup>74</sup> About 50% of people with SLE have kidney problems, including vascular, interstitial, and glomerular abnormalities. Despite effective treatments, lupus nephritis remains a significant risk factor for total morbidity and mortality in SLE. In addition, women are more commonly affected by RA than males (4:1), with a peak incidence occurring between the perimenopausal years of 45 and 55. This implies a potential link between the start of disease and an oestrogen deficit. incidence of females to males ratio is roughly 1:1 after the age of 60, which may indicate that sex hormone changes play a role in the development of RA. It is also widely known that pregnant women often experience an improvement in or complete remission from RA symptoms.<sup>79–81</sup> In patients with RA, renal involvement is a complex and reasonably common predictor of mortality. Patients with RA have a much higher risk of developing CKD than those in general. The development of chronic kidney disease (CKD) can be caused by multiple continuing processes, such as interstitial nephritis and glomerulonephritis, which are conditions related to RA, chronic inflammation, combined with nephrotoxic anti-rheumatic medications. The primary cause of ESRD with RA and nephropathy is AA amyloidosis, which has a high correlation with RA activity. This correlation worsens morbidity. Crucially, a few of the long-term negative effects of combination RA medication can affect the kidneys.<sup>82–84</sup>

### **Females, Chronic Kidney Disease, and Renal Replacement Treatment Access**

#### **What is Acknowledged**

Not all patients obtain renal replacement therapy (RRT), despite the fact that it is a life-sustaining treatment that includes dialysis and transplantation. The rate of ESRD treated with RRT varies widely throughout nations and areas and is highly dependent on a nation's health care system and economy.<sup>90, 91</sup> Only 50% of patients in the world who need RRT receive it<sup>92</sup>; this number is significantly lower in low- and middle-income nations and regions; in certain Sub-Saharan African countries, fewer than

Disparities by sex in access to dialysis With treatment gaps

being greater in low-income countries, at least 2.284 million persons may have died before their time from not having access to RRT; conservative estimates in Asia and Africa put the number of those without RRT at 1.907 million and 432,000, respectively. With the greatest rise in Asia (0.968 million to a projected 2.162 million [1.71-3.14 million]), the expected number of RRT could more than quadruple to 5.439 million (3.899-7.640 million) by 2030.<sup>92</sup> These figures come from a thorough, comprehensive review.

There is insufficient data to compare treatment gaps by gender. Men were more likely than women to receive RRT, according to studies conducted in Africa. In Japan, the number of female patients treated for end-stage renal disease (3,287 in males vs. 1,764 women per million treated) was less than half that of male patients.<sup>91</sup> no justifications are provided in support of this discovery. According to a US study, women had a 1.70 odds ratio, which is much greater than men's, for starting dialysis later in life.<sup>98</sup> Women reported being far less aware of their past kidney disease than males did (2.9% $\pm$ 1.6% vs. 17.9% $\pm$ 5.9%), which could explain why RRT was started later in life in women.<sup>99</sup>

Men and women receiving dialysis have comparable mortality rates, although women experience greater incidence rates of some complications and morbidity related to the treatment. Women experience greater hospitalisation rates than males, according to a US survey on hospitalisations among 111,653 patients on maintenance hemodialysis. Additionally, compared to male hemodialysis patients, female patients are less likely to use arteriovenous fistulas, which are linked to decreased rates of death, complications, and expenses.<sup>101</sup> This could be caused by various variables such as differences in attitude, timing of referral, and anatomical/surgical problems with regard to vessel size. This hasn't been thoroughly investigated.

Given that the dialysis dose is determined by Kt/V, women with lower average urea distribution volumes or total body water than men may have underdialysis.<sup>102</sup> It has also been shown that clinical indices such as anaemia, nutrition, and quality of life (QoL) are worse in women undergoing dialysis.<sup>103</sup> There are ambiguous reasons.

#### **Disparities by sex in the availability of kidney transplants**

The most effective RRT for those without contraindications is transplantation. Global data indicates that while women are more likely than men to become living donors for kidney

transplantation, they are less likely to have kidney transplants themselves, whether from cadaveric or living donors.<sup>104</sup> Data from several nations, such as the US, France, China, and India, confirm that women have lower kidney transplant rates than men do, that women are less likely to be listed on national transplant waiting lists, and that it takes longer for women to start dialysis than for men to do so. Mothers and female spouses are the groups most likely to donate.<sup>91,105-108</sup> There is a gender gap in the paediatric population as well. A survey from 35 nations taking part in the European Dialysis and Transplant Association-European Renal Association-European Society for Paediatric Nephrology Registry was released.

### CONCLUSION

Women are particularly vulnerable to renal illnesses because these conditions have a significant effect on both the present and future generations, not to mention problems with access to care. Promoting better access to care for women is essential to preserving the health of populations, families, and communities. To enhance our comprehension of the development of kidney disorders, targeted research on the distinct role of sex hormones or the interplay between sex hormones and other physiology is crucial. Better research on immunological disorders like SLE and other autoimmune and systemic illnesses that are frequent in women, as well as pregnancy (which is thought of as a state of tolerance to non-self), could result in advances in knowledge and paradigms for treatment. Since the kidneys finish developing in the latter stages of pregnancy, delayed or insufficient kidney growth leading to a low number of nephrons is most likely the cause of small for gestational age and preterm newborns' elevated risk of chronic kidney disease (CKD) and hypertension.

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