

From the Cradle to the Grave: The Life Cycle of Gender Disparities in Kidney Care



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The global burden of chronic kidney disease (CKD) remains underappreciated and underrecognized—yet alarmingly, by 2040, CKD is projected to be the fifth leading cause of death.¹ Many patients with CKD are unaware of their diagnosis and are often asymptomatic during the early stages of their disease. Therefore, CKD is left to progress unchecked to the end point of kidney failure (KF), at which point there is a need for specialized and (for many of the world's population) prohibitively costly kidney replacement therapies (KRTs), such as dialysis and transplantation.² The theme of this year's World Kidney Day 2022 focuses on equity in access to kidney care for all—yet stark disparities persist in the risks of developing, diagnosing, and accessing appropriate kidney care for half of the world's population, women.

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At every life stage, from birth to old age, women have unique and specific vulnerabilities to CKD and its complications. It is only recently that we have begun to identify some of the complex biological, immunologic, and sociocultural factors that contribute to this inequity. Furthermore, it is important to acknowledge the differences in sex and gender when reading this article. “Sex” relates to biological, anatomic, and physiological differences, whereas “gender” refers to roles and attributes determined by cultural and societal influences. These terms are often (incorrectly) used interchangeably; however, they are distinct entities.³ The reader should note that most of the studies reviewed in this commentary refer to women as defined by their gender roles rather than by sex. We aim to highlight recent novel research on this important equity issue across different life points—birth, young adulthood, pregnancy, and older age—and offer possible strategies in an effort to reduce this disparity.

Birth

The fetal origins of adult disease suggest that even before birth, risk

factors are present which affect the likelihood of chronic disease for the future.⁴ Stratifying these risks based on sex, however, is a relatively novel concept. Lillås *et al.*⁵ recently published a study revealing total kidney volume measured using magnetic resonance imaging (as a proxy measurement for nephron mass) is directly related to measured glomerular filtration rate in otherwise healthy middle-aged cohort. The group used mediation analysis of gender to reveal that women (but not men) who were low birth weight had smaller adult kidney volumes (and thus, nephron mass).⁵ These results build on previously published data linking gestational age at birth to the risk of CKD in childhood to middle adult life.⁶ A Swedish national cohort study of more than 4 million singleton live births found that preterm (<37 weeks) and extremely preterm births (<28 weeks) had a 2- and 3-fold respective risk of developing CKD into middle adulthood.⁶ Nevertheless, when broken down by gender, only girls born prematurely had a statistically significant increased risk of developing CKD in middle adult life (20–43 years). This is an important finding given that the development of CKD during a woman's middle adult life directly coincides with her potential childbearing years.

Young Adulthood

Puberty and young adulthood are an important time for biological, hormonal, and developmental changes. Recent population linkage data between the Australian and New Zealand Dialysis Registry and the appropriate national death registers found that young women with KF (as compared with young

men) have the greatest disparity in “excess deaths” and the most numbers of “life years lost.”⁷ Young women (18–34 years) with KF had standardized mortality ratio of 53.6 (compared with the healthy population and a mortality of 16.7 for young men with KF) with excess deaths linked to cardiovascular disease and gastrointestinal disease.⁷ Importantly, kidney transplantation reduced (but did not completely negate) the sex differences observed in excess mortality.⁷

Of late, there is growing recognition of the role of sex hormones and how these affect all aspects of kidney disease, particularly kidney transplant survival. This is of particular relevance to women during young adulthood. Recent study of Maenosono *et al.*⁸ of more than 400,000 kidney transplant recipients found that graft outcomes differed in an age-dependent and sex hormone-specific fashion. Young women (15–24 years), regardless of kidney donor sex, experienced the highest rate of kidney transplant loss in the cohort.⁸ In contrast, postmenopausal women recipients had improved graft survival rates compared with men of a similar age.⁸ This is an important finding which highlights the role that sex hormones (estrogen and testosterone) may play in the regulation of the immune response and how it differs across the life course for women. It suggests that young women may benefit from a more targeted and individualized approach to their kidney transplant care.

Adverse Pregnancy Outcomes and the Risk of CKD

Childbirth itself remains to this day a life-threatening event for many women worldwide, particularly for those from low-income

countries; however, less is known on the long-term chronic kidney health implications for pregnancy complications. Updated systematic review and meta-analysis of Barrett *et al.*⁹ revealed that exposure to adverse pregnancy outcomes (such as hypertensive disorders of pregnancy, gestational diabetes, and preterm delivery) was associated with a higher risk of long-term maternal kidney disease. The risk of KF was 4.9 times higher in women with preeclampsia and 3.6 times higher in women with gestational hypertension (as compared with women with normotensive pregnancies).⁹ Women who had preterm deliveries had a 2.1 times higher risk of KF compared with women who delivered at term (notwithstanding the risk of CKD to the babies themselves, particularly preterm female babies, creating a self-perpetuating problem for the next generation).⁹

Perhaps more alarming, most women with the above-mentioned risk factors for long-term CKD are not routinely educated on this fact either during or after their pregnancy.⁹ This represents a significant lost opportunity for preventative health care particularly for women in low- and middle-income countries. This represents a departure from focusing on kidney disease care to a focus on preserving kidney health.

Older Age

There has been considerable debate on the rate of kidney function decline between the sexes, but recent results from the European EQUAL study revealed that 4 of 5 of older men with CKD progressed to KF faster than women (even after adjustment for potential mediators). Nevertheless, diabetes is an important determinant of kidney function

decline with a disproportionate negative effect specific to women.^{S1} This is an important finding, particularly given that women with type 2 diabetes have a 27% excess risk of stroke and 44% excess risk of coronary artery disease.^{S2}

Although historically it has been argued that women do not experience the same symptom burden than men with CKD, recent data reveal that women in fact suffer from a poorer quality of life with CKD (as compared with men). Moreover, they are less likely to know on their diagnosis^{S3} and consequently less likely to seek medical care. If they are able to seek care (noting that in many countries and cultures, women, particularly older women, are not “valued” members of society and are ascribed less worth than men^{S4}), they are 2 to 3 times more likely to choose conservative care instead of KRT or transplant,^{S5} influenced not only by familial, cultural, and financial limitations but also, sadly, it seems by our own profession’s conscious or unconscious bias.^{S4}

Here, finally, is the culmination of a lifetime of sex and gender disparity in both the overall risk of developing kidney disease and then having access to appropriate care.

A Call to Action

Considering the vast population located in diverse geographies and medical systems and economies, there is no single factor to instigate change to break the life cycle of CKD risk and prevent the unnecessary deaths of women from CKD in the coming decades.

Biological and immunologic differences between sexes cannot be modified—however, with a greater in-depth knowledge of how these affect the kidney health of women, we can potentially

tailor our care to improve health outcomes. There are also many potentially modifiable risk factors specifically related to gender differences, including the following: improving education and awareness of kidney disease in women, better screening practices for early diagnosis and treatment of disease to reduce the incidence of CKD before reaching the need of KRT, and, finally, recognizing and addressing bias toward women.

It is well recognized globally that girls, particularly those residing in low- and middle-income countries, generally do not receive the same educational and career opportunities as their male counterparts.^{S6} This creates a dichotomous society whereby half of the population (i.e., those most vulnerable to kidney diseases) are the least likely to be health literate enough to be aware of this risk (let alone know how best to mitigate it). Improving literacy and education levels for girls and women has been found to improve health outcomes and help to break the cycle of intergenerational poverty.^{S6} We support all global efforts to improve literacy levels for women.

Second, pregnancy should be used as an opportunity to screen for the risk of future CKD and more importantly to educate these women on their (and their children's) future risk. This is particularly important for women residing in lower income and middle-income countries who would otherwise be unable to afford expensive KRTs. Early

diagnosis and appropriate treatment of insidious chronic diseases, such as hypertension or type 2 diabetes, (hopefully) reduce the need for future KRT, which in many countries and health systems are not an option for any person, regardless of their sex or gender.

Third, we as nephrologists and physicians need to recognize our own biases with respect to sex disparities in kidney care and access to it. It is up to all of us, regardless of our sex or gender, to become ambassadors of positive change for humanity by championing and advocating for women. We have only begun to scratch the surface of this issue, and further research is required to deepen our understanding. Each country faces their own unique challenges specific to their peoples, culture, and health systems—alas, there is no “one solution fixes all”; however, there can be no equality in kidney care when one-half of the global population has so many additional barriers set in front of them.

SUPPLEMENTARY MATERIAL

[Supplementary File \(Word\)](#)

[Supplementary References.](#)

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