

# Sex and Acute Kidney Injury

By Lisa M. Curtis

**E**nigmas abound in the clinical care and research related to acute kidney injury (AKI). Unfortunately, little conversion of research findings to changes in patient care has occurred.

The complexities associated with staging clinical AKI and identifying the timing of the insult, as well as the inability to identify characteristics that clearly define why and how certain patients recover while others progressively decline in renal function—some leading to chronic kidney disease (CKD)—all lead to an unsatisfying status of care for patients. Likewise, discordant findings in pre-clinical models of AKI have led to more questions than answers.

Sex remains a variable that has not often been examined specifically. Older studies, in both clinical and basic science investigations, have focused on male-only populations, owing to the lower incidence of AKI in females, or have been of mixed sex. Insufficient power in these latter studies to examine sex as a variable has resulted in an assumption of understanding without proper consideration that females may in fact exhibit different biology. With the advent of a focus on inclusion of women and females in research studies advocated by the National Institutes of Health NIH (1), a new awareness of the distinctions between women and men, and female and male subjects, is evolving.

Recent clinical studies are targeting female sex as a variable. At times, however, these studies are complicated by the inclusion of women across an age spectrum that

includes the menopausal shift. In addition, the reality of comorbidities in patients has made deciphering a sex-specific effect challenging. Studies in which the initiation of the insult can be identified in advance (e.g., cardiac procedures, renal transplantation) are few and have had conflicting outcomes, perhaps owing to the presence of preexisting kidney or vascular disease, which may mask a female sex-defined protection.

**The key is to remain persistent in our curiosity and perseverance to uncover the amazing physiology and pathophysiology of kidneys, male and female, so that robust changes can come to the care of patients with AKI.**

Basic science studies into the injury and reparative mechanisms in AKI allow for better precision in defining the insult and also allow for the absence of other comorbidities. A caveat to such studies of AKI is the lack of complete concordance between rodent models of AKI and the multiple manifestations of human AKI. As noted by ASN Past President Bruce Molitoris, MD, FASN, and colleagues a number of years ago, AKI models are “imperfect, but indispensable” (2).

Two primary rodent models of AKI are renal ischemia-reperfusion injury (IRI), which is induced by clamping the renal pedicle, or systemic administration of a toxin, principally cisplatin, heavy metals, or other

nephrotoxins. IRI is further complicated by variations in clamping of one kidney only, with or without contralateral nephrectomy, or bilateral pedicle clamping, often with varying durations of ischemia. Dosing schemes for administering a nephrotoxin may also vary, both in absolute amount as well as temporal administration differences, and a variety of agents may be used.

Notably, these studies rely on our basic understanding of renal physiology, much of which has been done in male rodents. Mechanistic studies of sex-specific differences in AKI are only beginning to be done, and clearly more research is needed. One overriding question worthy of investigation is deciphering why females, both humans and rodents in our models, exhibit a decreased susceptibility to AKI. In that distinction may lie novel and innovative treatments that can be applied to men and women, as well as new biomarkers to help stage and effectively treat preemptively in the course of injury.

As Albert Einstein said, “If we knew what it was we were doing, it would not be called research, would it?” The key is to remain persistent in our curiosity and perseverance to uncover the amazing physiology and pathophysiology of kidneys, male and female, so that robust changes can come to the care of patients with AKI. ■

## References

1. National Institutes of Health. Consideration of sex as a biological variable in NIH-funded research <https://grants.nih.gov/grants/guide/notice-files/NOTOD-15-102.html>.
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## Exposure to women's health issues in training, practice is topic of new survey

By Monica Reynolds, Keisha Gibson, Laura H. Mariani, and Michelle A. Hladunewich

**T**his year's World Kidney Day falls on International Women's Day, offering the nephrology community an excellent time to reflect on the theme, “Kidneys & Women's Health: Include, Value, Empower.”

What progress have we made in addressing women's kidney health? Why do so many unanswered questions remain? Most important, how do we as nephrologists currently care for women with chronic kidney disease (CKD)? How do we empower them?

For many of us, topics in women's health are fraught with anxiety owing to a poor knowledge base, uncertainties in the literature, or a lack of clinical experience. Yet our patients rely on us to provide the

most up-to-date knowledge on these topics in order to help them make informed decisions about the life-altering events associated with kidney diseases.

Although many nephrologists have a general sense of the risks and disparities that affect women with CKD, this information is not often at the forefront of the clinical visit because women of childbearing age still represent a minority of patients seen from day to day.

Preconception counseling takes dedicated time and can elicit a variety of emotions from both the patient and provider. Reviewing a detailed obstetrical history provides insight into a woman's risk for future proteinuria, hypertension, end stage renal disease (ESRD), and cardiovascular disease, but it is unclear if this is standard practice among nephrologists. Clinical training in women's health is also vague and likely largely dependent on a preceptor's personal experience. Without adequate exposure and structured didactics, discussions of safe contraception methods, fertility preservation options, optimal pregnancy timing, or appropriate anti-hypertensive and immunosuppressive agents for use while pregnant or breastfeeding may simply fall short.

CureGN is an observational prospective cohort study of biopsy-proven primary membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, and IgA nephropathy. With current enrollment including over 475 women aged 13 to 55, the study seeks to answer disease-specific questions about both pregnancy and women's health.

The women's health working group of CureGN is interested in your experience caring for women with CKD, and is conducting an international survey to better understand what limits your ability to provide reproductive counseling to women with CKD/ESRD, and what resources would be helpful to better serve this population.

We hope to improve the current state of clinical care for this growing population and help shape the future teaching of these clinically relevant and essential topics.

If you are an adult nephrologist, please visit <https://www.surveymonkey.com/r/womens-health-nephrology> to complete the survey, which is anonymous and should take less than 10 minutes to complete.

Results of the survey will allow us to compare adult nephrologists' exposure to women's health issues in training and current practice, their confidence in counseling and managing these issues, and ways to improve care in the future. We greatly appreciate your participation in this vital research. ■

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