ASN American Society of Nephrology

Kidney News

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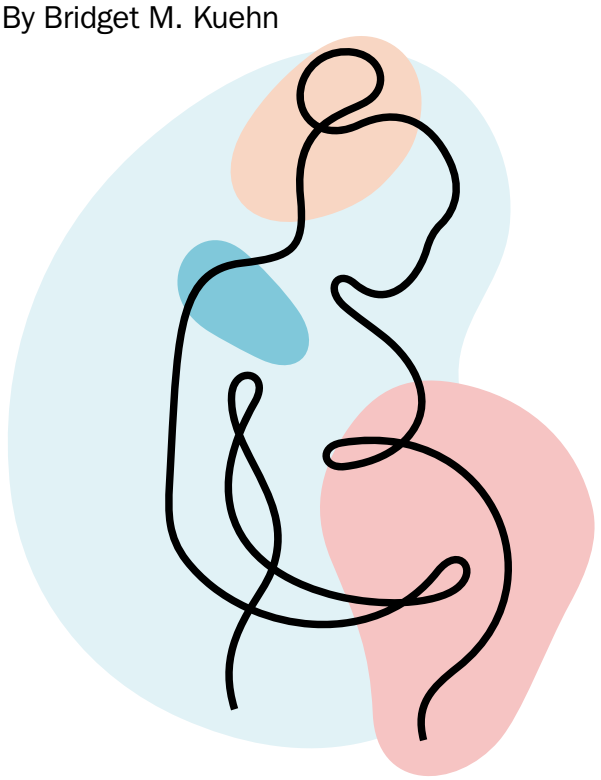
Pregnancy with Kidney Diseases Brings Joy and Challenges

By Bridget M. Kuehn



Pregnancy can pose unique challenges for patients with kidney diseases and their clinicians (1). Growing numbers of women are undergoing pregnancies while on dialysis, and their outcomes are improving (2). New tactics for managing kidney diseases during pregnancy, such as high-intensity dialysis (3) and home dialysis (4), may improve the odds of successful outcomes. Each patient's experience with pregnancy and kidney diseases is unique. Several patients with kidney diseases in Tennessee and North Carolina recently shared their pregnancy experiences and insights with *Kidney News*.

Unexpected diagnosis

Charlotte Hartawan, of Sparta, Tennessee, did not know she had kidney disease until she unexpectedly became pregnant with her third child. Elevated blood pressure during her first few prenatal appointments in March, April, and May 2022 led her obstetrician to order blood and urine tests, which revealed she had kidney disease. "That's when everything kind of blindsided me," she said. "It has been kind of a roller coaster for the past year."

A nephrologist with Nephrology Associates in Nashville, Tennessee, Dr. Christin Giordano, joined her care team along with her original obstetrician and a high-risk obstetrician. But Hartawan felt the high-risk obstetrician did not know much about kidney diseases. "I felt like I was being dismissed," she said. "Like we don't know what to do, so we are just going to wait and see."

In August 2022, she transferred her obstetric care to a team at Vanderbilt University, and at that time, the team, along with Giordano, decided that she should start dialysis. "It was scary because I did not know what to expect," Hartawan said. The worst part was having a catheter implanted, she said. She explained that lying on her back during pregnancy left her breathless, and having the procedure with only local anesthetic felt overwhelming.

Starting in August 2022, Hartawan traveled approximately 1¼ hours from Sparta to Murfreesboro, Tennessee, 5 days a week for 5-hour dialysis sessions. To help ease the burden, she began training to perform home hemodialysis. But before she could graduate, she was hospitalized and remained

Continued on page 2

Collaboration Yields 3D Kidney Atlas, Insights on Stone Disease

By Bridget M. Kuehn

A recently published, three-dimensional (3D) molecular atlas of the human kidney in healthy and disease states may help accelerate research to provide more personalized approaches to kidney disease care.

The results were published July 19, 2023, in *Nature* (1) and provide a detailed account of the atlas. The work is the result of a close collaboration between two large consortia: the Kidney Precision Medicine Project (KPMP) (2), which focuses on mapping kidney diseases and progression, and The Human BioMolecular Atlas Program (HuBMAP) (3), which focuses on mapping healthy human tissue, explained Sanjay Jain, MD, PhD, professor of medicine, pathology, and pediatrics and director of the Kidney Translational Research Center at Washington University School of Medicine in St. Louis, MO, and one of the study's principal investigators.

"The goal of the KPMP is to transform kidney health for people with kidney disease[s]," said Michael Eadon, MD, associate professor of medicine and medical molecular genetics at Indiana University School of Medicine in Indianapolis and another of the study's principal investigators. "We want to bring novel molecular insights into well-known chronic kidney disease and acute kidney injury syndromes."

Investigators from 55 sites participated in the KPMP. Some focused on recruiting participants and collecting biopsy tissue. Others used specialized techniques to conduct

Continued on page 4

Inside

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Pregnancy with Kidney Diseases Brings Joy and Challenges

More on this topic in the special section

Continued from cover

in the hospital for approximately 2 weeks to be carefully monitored until her delivery in September 2022. Her elevated blood pressure made it challenging for her clinicians to distinguish whether the cause was kidney disease or preeclampsia. During her hospitalization, she received 6 hours of dialysis, 6 days a week.

She said Giordano went above and beyond throughout her care. Giordano reached out to other nephrologists with expertise in kidney diseases and even waited with Hartawan and brought her snacks until Hartawan's husband arrived when she went into labor. "You could [recognize] it in her words and just simple things she would do," Hartawan said.

Hartawan's son was born at 31 weeks' gestation and spent 6 weeks in the neonatal intensive care unit. She had to travel to Nashville, approximately 1½ hours away from her residence, to visit her newborn son. "He's doing great," Hartawan said. She continues to undergo home hemodialysis 4 days a week and had surgery in February of this year to create an arteriovenous fistula, which provides more permanent dialysis access.

She said that during her pregnancy, figuring out how to juggle her medical care, caring for her 9- and 15-year-old children, and being without a job—she chose to quit her job in May 2022—were all challenging. "I had to listen to my body," she said. "If I went back to work, I feel I would not have been able to carry this pregnancy as long as I did."

Hartawan said, in addition to the joy her son has brought to her family, she believes his unexpected entry into their lives may have saved hers. "I feel as if he [was] a miracle to bring attention to the health issues I have," she said. "I probably wouldn't have had anything done [about my kidney disease] until it was too late."

Uplifting care

Danielle Parker of La Vergne, Tennessee, was diagnosed with lupus and kidney disease in 2015 while in college. Taking mycophenolate and changing her lifestyle helped Parker experience remission quickly. "I decided to start meditating and doing yoga; I completely changed my diet from that point," Parker said. "Over the years, I did not have a lot of flare-ups. I was very much a stickler about my medicine."

At age 30, she and her partner began talking about having a child, and she consulted with her nephrologist, Dr. Christie A. Green, with Nephrology Associates in Murfreesboro, who agreed it was a good time, given how stable Parker was. Green referred Parker to a nephrologist in her practice who specialized in caring for pregnant women with kidney diseases and talked with Parker about what to expect, including potential flares during pregnancy. The physician advised she would have to change her lupus medication to azathioprine because it is safer during pregnancy. Parker was hesitant to make the change initially but made the switch as soon as she found out she was pregnant.

"I was told it could be a little harder to get pregnant," she said. "It was not hard at all. It happened way faster than I thought." By September 2022, she was pregnant. Parker said she had a little more joint pain than usual during the pregnancy. "My biggest fear during my pregnancy was my kidneys," she said. "That was my family's biggest fear."

She developed cholestasis, a condition that causes a build-up of bile during pregnancy. She also had protein in her urine during pregnancy. Additionally, Parker had to stop receiving regular intravenous iron transfusions to treat severe anemia, caused by a sickle cell trait, to reduce the risk of infection. As a result, her hematocrit and hemoglobin levels dropped. She also tested positive for anti-Ro antibodies, which can affect the fetus's heart. As a precaution, her doctors did a weekly echocardiogram of the fetus's heart.

At approximately 35 weeks of pregnancy, Parker's blood pressure began to rise. She was very concerned about developing preeclampsia, a life-threatening rise in blood pressure, which her sister developed during pregnancy. "I was terrified," she said. She did not develop preeclampsia but did acquire gestational hypertension and thus, delivered her son at 37 weeks. Her son is now 5 weeks old and is doing well. Parker chose to continue treatment with azathioprine because she had fewer side effects, and her kidney health improved. She plans to undergo another pregnancy after giving her body at least 18 months to recover, as her physician recommended.

The excellent care she received from her team, which included a nephrologist, rheumatologist, cardiologist, and hematologist, and from the obstetricians at Vanderbilt University Medical Center provided her reassurance through some of the challenges she experienced. "I enjoyed going to the doctor because it was good news every time," she said. "It made me feel so good because everybody, even Dr. Green, was excited for me."

Parker stopped working during her pregnancy to focus on her health and to study for a master's degree she was pursuing. She warmly remembers the time she spent "nesting" in preparation for her baby's delivery. "I had a lot of time to focus on me, more meditation, and just uplifting myself," she said. "I wholeheartedly feel like that contributed to me having a better pregnancy."

Under pressure

When Atisha Carrillo, of Seagrove, North Carolina, was diagnosed with kidney failure, she asked her physician if she should use contraception. Her physician advised that she had a <1% chance of becoming pregnant because of her medical condition but was recommended to still consider contraception. But shortly after having a catheter implanted to begin peritoneal dialysis, she discovered she was 4 weeks pregnant.

"I was terrified and kept thinking about the movie 'Steel Magnolias,'" Carrillo said. Carrillo, like the main character, had diabetes from a young age, resulting in lost kidney function. In the movie, the main character dies from kidney failure-related complications following a pregnancy.

Carrillo felt pressure from the high-risk obstetrician she consulted to have her pregnancy aborted. But seeing the image of her fetus on the ultrasound made Carrillo determined to continue the pregnancy. "I was willing to risk myself," she said. "It was a stressful time."

With the help of a trained partner, she underwent home hemodialysis 7 days a week, early in the morning, to avoid disrupting her husband's and two children's routines. Her intensive hemodialysis regimen was developed by her nephrologist, Dr. Jennifer Klenzak-Stoddard, with Pinehurst Nephrology Associates in Pinehurst, North Carolina. "I'm very strong-willed," Carrillo said. "I focused on what I had to do day-to-day."

She was hospitalized at 30 weeks' gestation and gave birth to her son via cesarean delivery at 33 weeks' gestation. After the delivery, the obstetrician who had pressured her apologized. "She thought I was too young and didn't have it in me to do what needed to be done to keep the baby healthy," Carrillo said. Her son was able to go home after 2 weeks of care in the neonatal intensive care unit.

Carrillo and her care team worked and learned together throughout the pregnancy. Support from her husband and mother helped her endure the challenges she encountered. She believes the early and intensive dialysis she received during her pregnancy may have helped preserve her kidney function until she received a kidney transplant from a living donor. Her son is now a healthy 7-year-old. "It's important for patients [who] are on dialysis, who may already feel defeated in a lot of ways, to understand pregnancy is possible," Carrillo said. "With the right guidance and resources, it can be done."

Uneventful pregnancy

Dana Colliflower of Manchester, Tennessee, had given up on getting pregnant after unsuccessful fertility treatments. Then, she was diagnosed with immunoglobulin A (IgA) nephropathy, approximately 2 years ago, after a routine examination detected high blood pressure and protein in her urine. "My original nephrologist thought I probably had IgA nephropathy since I was 18 or 19 years old, but it is something that doesn't get caught until you have enough symptoms," she said.

Colliflower's kidney function dropped to approximately 35% at its lowest. But gastric surgery in 2021 helped improve her kidney function. Giordano, the nephrologist who cared for her during pregnancy, advised that she may want to avoid taking certain medications if she was considering getting pregnant when she began treatment. While Colliflower thought pregnancy was impossible at the time, having that information up front enabled her to quickly stop the medication when she found herself unexpectedly pregnant in 2022. One of the most helpful things her nephrologist did for her was discuss the risks associated with kidney diseases during pregnancy early on, she said. "Having those risk factors presented to me right away gave me time to wrap my head around all of it and made me feel like I was prepared if something happened," Colliflower said.

Her physicians' primary concerns were keeping her blood pressure in the normal range and monitoring for signs of preeclampsia. She met every 2 weeks with one of the members of her clinical care team, including her nephrologist, obstetrician, and high-risk obstetrician. "I'm very thankful for the doctors that I had," she said. "They kept us informed and at ease through everything that popped up during my pregnancy."

Colliflower had a very uneventful pregnancy. The temporary pregnancy-associated immune suppression provided a respite from some of her symptoms. Her physicians carefully monitored the fetus's growth during the pregnancy because chronic kidney disease can affect the placenta, leading to intrauterine growth restriction. Ultimately, her son was delivered 5 days early because the monitoring showed that his growth had slowed, and he weighed 5 pounds, 3 ounces.

"He was going to get more nutrition outside of the womb," Colliflower explained. She was not quite prepared for how small her son would be. She only had a few premature-sized outfits and no premature-sized diapers. She also did not know that premature infants can have difficulties maintaining their temperature until their first pediatrician visit. "It was just little things like that it would have helped to know," she said. Her son is now a happy, healthy 5-month-old baby. "He's growing too fast," she continued.

Colliflower thinks it would be helpful for physicians caring for pregnant women with kidney diseases to help them prepare for the possibility of having a premature or a smaller, full-term infant. She also wishes she had been advised that her son would have an elevated risk of developing an autoimmune disease during childhood. Her pediatrician informed her about the risk and carefully monitors her son for potential symptoms. That information would not have changed anything, Colliflower said, but it would have provided helpful information. "We were just so blessed to have the pregnancy in the first place," she said. ■

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Collaboration Yields 3D Kidney Atlas

Continued from cover

in-depth, multi-omic analyses on more than 400,000 kidney cells or their nuclei. Benjamin Humphreys, professor of medicine and chief of the Division of Nephrology, who was not involved in the KPMP project, called the *Nature* paper a "landmark" and "team science at its finest." "These technologies are so powerful and so cutting edge that it's really beyond the capacity of any single group to master," Humphreys said. "That is why the KPMP has brought all of these labs together to leverage their expertise and put it together in this tremendous effort."

Patient-driven

Approximately 200 patients with kidney diseases have volunteered to participate in the KPMP and have altruistically donated kidney biopsies to the project. "Patients are at the center of this consortium," Jain said. Patient-led community engagement work groups have shaped the project by helping set priorities, writing informed consent procedures, and lobbying for the project to provide participants with insurance to help cover the costs of any complications associated with the biopsy, Eadon noted.

"The Central Hub has closely worked with the community engagement group and the recruitment sites to establish procedures to obtain biopsies in an ethical and safe manner with no financial burden to the study participants," Jain said. "Patients have given us great input and kept us focused on what truly matters within the KPMP to translate the findings as quickly as possible to clinical care," Eadon added.

ASN President Michelle Josephson, MD, FASN, professor of medicine and surgery at The University of Chicago Pritzker School of Medicine, IL, who was not involved in the KPMP project, said the willingness of project participants to undergo a non-clinical biopsy demonstrates their interest in partnering with scientists. Josephson remarked that the project's results so far show how powerful partnerships can be. "It's a message to the whole kidney community how interested, engaged, and committed our patients are in this field and getting answers," she said.

The biopsies are incredibly valuable, said Eadon. He explained that most kidney biopsies available to researchers are typically collected during clinical care, often at an advanced stage of disease. But many of the biopsies used in the study were taken at an earlier stage of illness or after an acute kidney injury when biopsies typically would not be taken. "It allows us to capture the disease and understand it at a much earlier timepoint," Eadon commented, "at a point where we can come up with therapies to prevent the progression of that disease or aid in the recovery of acute kidney injury."

Investigators from the 55 participating sites, which include some recruiting sites and other sites that study the biopsy tissue using specialized techniques, have identified more than 100 cell types in the kidney and changes that occur as kidney diseases progress.

"Our hope is that by understanding what each individual cell undergoes as it transitions from health to disease, we can interrupt that process and prevent it from happening," Eadon said. For example, the team has identified an injury process where a portion of kidney cells undergoes adaptive repair and returns to its initial phenotype, while a subset changes or dies off, contributing to failed tubulogenesis and fibrosis in the kidney. The next step for the team will be turning to collaborators who can work with mouse models to tease out the mechanisms of repair and cell death and identify a "point of no return for a cell to repair or die," Eadon said.

The project also maps cellular "neighborhoods" or communities of cells, assessing how they differ between healthy cells and various disease states. Investigators are probing the genes and signaling pathways that these cellular communities use to communicate.

"If one cell is perturbed, the entire community is perturbed," Jain explained. "The atlas effort would not be possible without the critical team efforts of meticulous procedures for collecting clinical data and high-quality biospecimens implemented by the recruitment sites, the infrastructure developed by the Central Hub, tissue assessment by KPMP pathologists, and all the Tissue Interrogation Sites [that] generate high-quality data," he continued.

Jennie Lin, MD, a physician-scientist and assistant professor of medicine at the Northwestern University Feinberg School of Medicine in Chicago, who was not involved in the KPMP project, said the KPMP atlas will provide an invaluable resource to help scientists identify all of the relevant cell types involved in kidney disease pathways of interest and help them refine their hypotheses. The meticulous mapping work performed by the KPMP group will save other scientists much time and money in exploratory work that can be redirected toward testing these refined hypotheses.

She noted that a lot of "omics" data from mouse kidney samples are available for scientists to study. However, there are limitations to the data they can provide. For example, specific DNA variants in the apolipoprotein L1 (*APOL1*) gene cause kidney diseases in humans, but mice do not naturally express *ApoL1*, limiting their physiologic relevance to the disease. "Getting human samples is critical because mice are not tiny humans," Lin said. "They are important models for kidney disease[s], but there are certain human-specific insights [that] we can only obtain from looking at human kidney tissue at this level."

Stone disease

KPMP investigator Tarek M. Ashkar (El-Achkar), MD, the Terence P. Kahn Professor of Nephrology and adjunct professor of anatomy, cell biology, and physiology at Indiana University School of Medicine and affiliated with the Richard L. Roudebush VA Medical Center in Indianapolis, has been focusing on the role of specialized kidney cells in a region called the papilla and how their interactions in special neighborhoods could play a role in stone disease. Patient volunteers in this part of the project underwent a surgical procedure rather than a biopsy to collect the necessary tissue, Eadon noted.

The samples allowed the team to create an atlas for this specific region, which was published in a study in *Nature Communications* (4); Ashkar and his coauthors have identified changes in patients with stone disease. They identified new types of cells in the area, confirmed the existence of a hotly debated cell type, and identified injured cells near the mineral deposit sites, Eadon said.

"We learned [that] there is a very impressive signature of inflammation in the papilla of patients with stone disease," Ashkar said. These results urge researchers to conduct more studies on the role of inflammation in stone disease because they may suggest that therapies targeting inflammation might be helpful to treat patients with

stone disease or prevent recurrence, he continued.

The study's authors also identified two molecules, matrix metalloproteinase (MMP)7 and MMP9, produced in elevated amounts in patients with stone disease, which might be helpful clinical markers. The hope is that if the results are replicated in larger studies, they will provide clinicians with a new tool for monitoring patients with stone disease. "The goal of the KPMP is to deliver the right therapy for the right patient at the right time," Ashkar said. "Identifying these different cell states [in different forms of kidney diseases] and their spatial relationships will enable us to reach that goal in the future."

Lin said that the stone disease study provides an example of how the KPMP's work can be translated into clinical medicine. If the biomarkers are validated in future studies, it could give nephrologists an early warning of stone disease. "It could potentially provide a new approach to taking care of patients with stone disease," she said. "It could help [nephrologists] detect complications early and tailor their treatments to individual patients."

Next phase

The two publications mark the end of phase one of the KPMP project, which began in 2017. The project will continue in phase two to recruit approximately 200 patients each year, with the ultimate goal of reaching 1000 patients, Ashkar said. The additional data will allow the team to identify more cell types and add greater detail to the atlas, remarked Jain. It will also help the researchers explore the connection between the molecular-level changes and patient outcomes, Eadon said.

Data from the project are posted on the KPMP website (www.kpmp.org) faster than they are published (2). In addition to rigorously validating their methods to ensure the integrity of the data, the team is also creating interactive tools that will make the data accessible to individuals, ranging from clinicians and researchers to high school students working on science fair projects, Jain said. "Some of the tools we will create will pave the way for attracting future generations into the field of kidney science," Jain added.

Ashveena Dighe, MS, MPH, the KPMP Central Hub Administrative Core co-director and clinical research project manager at the Kidney Research Institute at the University of Washington in Seattle, said in an e-mail that there had been more than 20,000 data downloads from the website. Ultimately, the goal is to enable clinicians to identify specific cell states in their patients' kidneys and match the therapy to the condition, for example, an immune state-related injury or hypoxic injury. "We are essentially taking a page from what oncologists have been doing for many years when they look at tumor tissue and select therapies," Eadon observed.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded phase one of the project and has committed to provide nearly $15 million each year over the 5 years of phase two (5). Josephson said it was very exciting to see the NIDDK invest in such a large-scale project in the field of nephrology and that the resources being created by the KPMP would help advance research on all aspects of kidney diseases. "It's really a turning point in our ability to move the entire field forward," Josephson concluded. ■

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Groundbreaking Advance from the Kidney Precision Medicine Project Reveals an Atlas of Kidney Cells in Health and Disease

By James F. George and Anupam Agarwal

Advancements in single cell and spatial transcriptomics, advanced imaging, and proteomics are revolutionizing our understanding of the biology of the kidney in health and disease. An exemplar of such pioneering work is the product of a collaboration between the Kidney Precision Medicine Project (KPMP) and The Human BioMolecular Atlas Program (HuBMAP), resulting in a detailed atlas of cell states and niches in both healthy and injured human kidneys. Supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health, KPMP is a multi-site collaboration among clinicians and investigators and more importantly, patients, from across the United States.

A cornerstone study recently published in *Nature* (1) goes beyond detailed categorizations of kidney cell types by providing context for kidney cell interactions in the transcriptomic, epigenetic, spatial (local and global), and functional domains using a variety of sophisticated technologies and bioinformatic tools. Learning the niches in which the various cell types reside, the cell types that are contiguous within these niches, and how they change as a function of disease is key for understanding how the variety of cell types within the kidney communicates and forms a functional network.

Using 58 reference tissues from 35 donors and 52 diseased tissues from 36 patients, the authors discovered, through unsupervised clustering, 100 distinct cell populations classified into 77 subclasses of epithelial, endothelial, stromal, immune, and neural cell types, encompassing the array of cell types in normal kidneys as well as in kidneys with a spectrum of acute and chronic diseases. The classifications also include a variety of cell states defined at a molecular level. These data were used to predict the locations of these cells in Slide-seq and Visium spatial data sets, permitting their spatial localization and association with functional units and in situ cellular niches. Key biological pathways among tubules, interstitium, and immune cells that are altered in the injured state were identified. An intriguing role for the thick, ascending limb segment of the loop of Henle was also uncovered, specifically with molecular changes similar to that observed in proximal tubules after injury. The data, which are being made publicly available through interactive visualization and data repositories, constitute this landmark study and will provide new insights into the pathobiology of kidney homeostasis and disease at the cellular level (some visualizations can be found at https://atlas.kpmp.org/explorer/ and https://hubmap-consortium.org/hubmap-data/).

A related study in *Nature Communications* (2) describes a molecular atlas for changes in the human kidney papilla in patients with kidney stone disease from calcium oxalate. Using papillary kidney biopsies obtained during clinical-indicated, elective percutaneous nephrolithotomy for stone removal, the investigators defined the spatial localization and niches within the papilla and discovered immune active zones co-located with mineral deposition. Notably, within the papilla, they found enhanced inflammatory stress signaling and macrophage activation in stone formers. Within these areas, they also noted upregulation of matrix metalloproteinase (MMP)7 and MMP9 gene expression. Using this information, they found significantly higher levels of MMP7 and MMP9 protein in the urine of patients with inactive stones and even higher levels in formers of active stones, indicating a correlation between the concentration of these proteins in the urine and disease activity. Therefore, it is possible that MMP7 and MMP9 in the urine could be used as a non-invasive biomarker of stone disease. These findings provide new insights into the complex organization of the human kidney papilla and its role in immune activation and altered mineral metabolism.

For the field of nephrology, this seminal work showcasing a human kidney atlas represents a major advance and will transform our approach to diagnosis and treatment of kidney diseases in an era of precision-guided, personalized care. The leadership team of the Division of Kidney, Urologic, and Hematologic Diseases of the NIDDK should be commended for their support of this creative and innovative work and for paving the path toward improving kidney health. ■

James F. George, PhD, is with the Department of Surgery, and Anupam Agarwal, MD, is with the Department of Medicine at The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.

The authors report no conflicts of interest.

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ASN President's Update

Affirming Action, Demanding Fairness, and Maintaining Unity

By Michelle A. Josephson

Last month, I wrote about how divided the United States has become, and the editorial was immediately prescient (1). Responses to the Supreme Court of the United States' (SCOTUS') decision in the Students for Fair Admissions, Inc. (SFFA) v. President and Fellows of Harvard College highlight this polarization. In a six to three decision, the SCOTUS ruled that race should not be used as a consideration in college admissions, essentially eliminating 62 years of affirmative action (2).

In 1961, U.S. President John F. Kennedy signed Executive Order 10925, requiring government contractors to "take affirmative action to ensure that applicants are employed, and that employees are treated during employment, without regard to their race, creed, color, or national origin" (3). The executive order also established a commission "to consider and recommend additional affirmative steps which should be taken by executive departments and agencies to realize more fully the national policy of nondiscrimination within the executive branch of the Government."

The SCOTUS' decision has major implications for individuals applying to U.S. universities, colleges, and medical schools, as well as for health care in the United States. Diversity in nephrology is critical because it strengthens the specialty and results in better care for the more than 37 million Americans with kidney diseases, a disproportionate number of whom are Black or African American. As history has proven, diversity will not happen without our being intentional about achieving it.

The American Society of Nephrology (ASN) issued a statement disagreeing with the SCOTUS' decision on Thursday, June 29, 2023 (4). In its statement, ASN asserted:

- Diverse organizations "are more innovative, more empathetic, more inclusive, and perform at a higher level," as well as "experience less turnover, are considered more satisfying workplaces, are financially more profitable, and impact the business sector more positively."
- "[R]ace concordance between patients and their physicians results in higher levels of communication, trust, and adherence to medical advice."
- "Unfortunately, [long-standing] inequities within the educational system in the United States disproportionately disadvantage minoritized groups, especially Black Americans."
- The decision "will hamper long-standing efforts to diversify the health care workforce, including physicians, in the United States"; "make it even more difficult for applicants from minoritized and historically disadvantaged racial groups to enter undergraduate programs from which candidates are accepted into US medical schools"; and "have wide ranging effects across undergraduate and graduate medical education as well as science, medicine, and health care."

SFFA is an outgrowth of the Project on Fair Representation, established in 2005 as "a not-for-profit legal defense foundation that is designed to support litigation that challenges racial and ethnic classifications and preferences in state and federal courts" (5). Established in 2014, SFFA "is a nonprofit membership group of more than 20,000 students, parents, and others who believe that racial classifications and preferences in college admissions are unfair, unnecessary, and unconstitutional" (6). SFFA supports and participates in "litigation that will restore the original principles of our nation's civil rights movement: A student's race and ethnicity should not be factors that either harm or help that student to gain admission to a competitive university." Both organizations are led by Edward Blum, a legal strategist who is also a visiting fellow at the American Enterprise Institute, a think tank based in Washington, D.C.

In 2014, SFFA filed a petition against Harvard College, claiming that the university discriminates against Asian Americans by holding them to higher admissions standards than any other racial or ethnic group, including White individuals. While this petition may have appeared to be a case advocating for more fair admissions standards for Asian Americans, Blum actually built a case against affirmative action. By addressing the issue of discrimination of Asian Americans and removing race considerations to "level the playing field," he pitted Asian Americans against Black Americans, one minoritized group against another.

Colleges and universities consider other applicant characteristics, such as athletic abilities and musical talent, students attending high schools with a track record of high acceptance rates at certain colleges or universities, geography, and family members having attended the school (legacy). Forty-three percent of White undergraduates admitted to Harvard are legacy, athletes, or related to donors or staff compared with less than 16% of African American, Hispanic and Latinx, and Asian American undergraduates (7). A few days after the SCOTUS decision, three groups in Boston, MA, requested that the U.S. Department of Education review "Harvard's special admissions treatment for students whose parents are alumni, or whose relatives donated money," claiming that the practice discriminates against Black, Hispanic and Latinx, and Asian applicants (8).

As most applicants who receive admissions priority from being legacy, from a specific geographical area, from a specific high school, or for being musically talented are White Americans (7), removing race will not level the playing field. In athletics, the "travel sports culture" in the United States is creating a pipeline for wealthy Americans (most of whom are White) to help their children pursue scholarships (or admissions or both) in "non-revenue sports" at the most competitive colleges (9). This is an effective strategy, as acceptance rates can be very high. At Harvard, for example, nearly 90% of recruited athletes are ultimately admitted (7).

Even if racism is less overt than it once was, it continues 160 years after the Emancipation Proclamation. I suspect that if we each think about our lives, we can recall personal experiences of how society treats people differently along racial lines or how admissions decisions are fraught. I would like to share a few personal experiences that provided me with insights into some of the issues raised by SFFA v. Harvard. These perspectives left me thinking that there is no equity without race as an admissions consideration.

When my brother and his wife worked in northern Kenya, they met and provided medical care for a sister and brother who were Ethiopian refugees. Before my brother and sister-in-law had biological children, they reared the two orphaned siblings as international foster children in the United States. While the children were visiting New York City, my parents took them to see a Broadway play. Waiting outside the theater to see their first show, the children were standing next to my mother. A police officer approached the 14-year-old boy and started questioning him as to why he was standing there. The officer did not ask other people waiting outside the theater, only the refugee from Ethiopia.

By contrast, I did not face biases based on the color of my skin. Growing up in Brooklyn, I attended public school until after the New York City teacher's strike in 1968, which prompted my parents to reassess educational opportunities for their children. In 1969, I started attending a private school. The small class size enabled more personalized attention. Our headmaster met with college admissions officers and advocated for us. When I applied to college, I may not have been a legacy candidate, an athlete, or a musician, but I had some advantage over students with similar test scores who did not attend private schools with faculty who advocated for their students.

Even though Columbia University is fewer than 20 miles from my childhood home in Brooklyn, I could not apply for admission because it did not allow women as students until 1983 (10). Had I been a bit older, even more colleges would have been unavailable to me. Luckily, I had plenty of options, a headmaster who was advocating for me, and a family who could, along with a few loans, support the cost of my higher education.

When I applied to medical school, every school was available to me. Jefferson Medical College in Philadelphia was the last U.S. medical school to admit women, in 1961, the same year that President Kennedy advocated for affirmative action (11). Most medical schools did not increase their class sizes when women were admitted. As such, men who would have previously been admitted to these schools were not admitted because there were not sufficient spots for them with the admission of women. A limited resource, which college or medical school spots are, creates a zero-sum game, and those individuals who benefit are going to vary over time, like my being accepted to medical school as a woman.

I understand that other perspectives on this issue exist. Asian Americans are understandably concerned that they may be held to a higher standard for college admissions. I cannot disagree with this perspective, their feelings about it, or that Asian Americans have faced discrimination in the United States. They have.

Too often, people are lumped together, although they

are distinct from different regions and with different cultures. The diversity among Asian Americans is extensive: Chinese Americans, Filipino Americans, Indian Americans, Japanese Americans, Korean Americans, and Vietnamese Americans, to name a few. It is not surprising, therefore, that a wide range of opinions about affirmative action exist, as do perspectives about whether race should be considered in college admissions across Asian demographic subgroups (12).

My sister-in-law is of Chinese descent, and thus my nieces and nephew are one-half Asian. Over the years, my brother mentioned that he was glad they carried his last name, as he thought it would help them not be discriminated against based on their names. Also disagreeing with the SCOTUS decision, my brother supports the inclusion of race in admissions considerations because he believes that diversity in higher education is a worthwhile goal. "Highly competitive colleges and universities are gateways to leadership positions in society, and we need to make a commitment to diversity in education to ensure that there is diversity in leadership," he told me. "Furthermore, all students benefit from exposure to people with different perspectives [who] have been shaped by a variety of life experiences."

My brother also believes that Asian American applicants to college should not be held to a higher standard than applicants who are White Americans. That is the problem, and it extends beyond the correlation of acceptance rates with standardized test scores and high school grade-point averages. Why did Harvard's admission committee members consistently rate Asian American applicants lower than other applicants on subjective personal qualities, such as "likeability," "courage," and "kindness" (13)? This reality speaks to a more troubling issue of implicit bias that the SCOTUS decision does not address.

The SCOTUS decision also fails to account for the fact that the United States is increasingly multiracial. Between 2010 and 2020, the number of Americans who identified as "multiracial" increased by 276%, making it the fastest growing racial category (14).

Black Americans also hold a wide spectrum of opinions regarding affirmative action. For example, some have voiced concerns that these efforts have unintended consequences of lower expectations and standards. Speaking to this point, John H. McWhorter, PhD, a linguistics scholar at Columbia University, wrote, "an unintended byproduct of what we could call academia's racial preference culture: that it is somehow ungracious to expect as much of Black students—and future teachers—as we do of others. That kind of assumption has been institutionalized within academic culture for a long time. It is, in my view, improper. It may have been a necessary compromise for a time, but it was never truly proper in terms of justice, stability or general social acceptance" (15).

As nephrologists, we are no strangers to the difficult and unintended consequences of dealing with limited and scarce resources. In the 1960s, "death panels" decided who would receive lifesaving dialysis and who would not. Although dialysis is no longer as scarce a resource in the United States, nearly 90,000 patients are now on the kidney transplant waitlist. Black patients do not fare as well as non-Black patients in this system. They are less likely to receive a preemptive transplant referral, complete the transplant evaluation, or have a living donor. They are also more likely to receive lower-quality kidneys.

Because the inclusion of race in the estimated glomerular filtration rate (eGFR) previously delayed the eligibility of Black Americans to being on the transplant waitlist, the removal of race from the eGFR means they will become eligible for kidney transplantation sooner. To address this historical inequity, transplant programs are retroactively providing the additional time lost, precipitating some Black Americans to move up the list. There are not sufficient organs for everyone who needs one, however, so providing equity to Black patients will likely decrease offers for others on the list.

To respond to this challenge, the transplant community, including ASN, is working on several fronts to increase the number of available kidneys for transplant and taking steps to increase equity in access to transplantation. These measures help, but they will not fully undo the shortage. That can only be achieved when there are sufficient organs. For that to happen, we will likely have to wait until xenografts are a reality.

As history has proven, diversity will not happen without our being intentional about achieving it.

In his closing statement of the SCOTUS decision, Chief Justice John G. Roberts, Jr., wrote, "At the same time, nothing prohibits universities from considering an applicant's discussion of how race affected the applicant's life, so long as that discussion is concretely tied to a quality of character or unique ability that the applicant can contribute to the university" (2). For the past decade, the University of California, Davis, School of Medicine has "become one of the most diverse medical schools in the country" by following the approach suggested by Chief Justice Roberts (16). Using a "socioeconomic disadvantage scale, or S.E.D." to rate "every applicant from zero to 99, taking into account their life circumstances, such as family income and parental education," UC Davis makes decisions on admissions based on S.E.D. "combined with the usual portfolio of grades, test scores, recommendations, essays and interviews." Other medical schools are adopting this sort of approach, which addresses many of the concerns about the SCOTUS decision that I have raised here.

Finally, it is striking that the SCOTUS justices who concurred with the decision included a footnote that "[n]o military academy is a party to these cases, however, and none of the courts below addressed the propriety of race-based admissions systems in that context" (2). Why is affirmative action appropriate for the military but not for the rest of society? As Associate Justice Ketanji Brown Jackson wrote: "The Court has come to rest on the bottom-line conclusion that racial diversity in higher education is only worth potentially preserving insofar as it might be needed to prepare Black Americans and other underrepresented minorities for success in the bunker, not the boardroom" (2, 17). ■

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ASN Advocates Urge Congress to Improve the U.S. Transplant System

By the ASN Staff, with special thanks to Lindsey Duquette

More than 37 million Americans are living with kidney diseases, including more than 800,000 people with kidney failure, a life-threatening condition without a cure. Transplantation is the optimal therapy to manage kidney failure for most people, yet a kidney transplant is not accessible to all who might benefit: more than 12 Americans who make it on to the kidney transplant waitlist die every day while waiting for a kidney.

In July, ASN members headed to Capitol Hill to urge members of Congress to support the swift enactment of S. 1668/H.R. 2544, the Securing the U.S. Organ Procurement and Transplantation Network (SUS OPTN) Act. This legislation, aimed at improving the nation's transplant system, is a top legislative priority for ASN. ASN members educated their congressional delegation about how this vital legislation empowers the Health Resources and Services Administration (HRSA), the federal agency that oversees transplant care, and the kidney and transplant community to continue improving and modernizing the transplant ecosystem.

ASN's Policy and Advocacy Committee and its Quality Committee members offered their clinical expertise to congressional leaders and their staff, highlighting the following:

1) Kidney transplant care is an essential tool to manage kidney failure.
2) Access to transplant care must be maximized at every opportunity.
3) The SUS OPTN Act will help kidney and transplant professionals in supporting their patients seeking a kidney transplant by allowing the HRSA the statutory flexibility to increase investment in and make important, new improvements to the nation's transplant system.

Additionally, ASN advocates met with their congressional delegations and key leaders on the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor, and Pensions, which have legislative jurisdiction over the bill.

Congressional Kidney Caucus Co-chairs Representatives Larry Bucshon, MD (R-IN), and Robin Kelly (D-IL) introduced the SUS OPTN Act in the House,

which rapidly and unanimously advanced the legislation out of the House Committee on Energy and Commerce on a bipartisan basis. A powerful group of bipartisan Senate leaders, including Senators Ron Wyden (D-OR), Chuck Grassley (R-IA), Ben Cardin (D-MD), Todd Young (R-IN), Bill Cassidy (R-LA), Elizabeth Warren (D-MA), Jerry Moran (R-KS), and Cory Booker (D-NJ), jointly introduced the SUS OPTN Act in the Senate. The legislation has been referred to the Senate Committee on Health, Education, Labor, and Pensions for review.

This bipartisan, bicameral legislation includes statutory revisions requested by the Biden administration to support the instrumental HRSA OPTN Modernization Initiative. Led by HRSA Administrator Carole Johnson, this important initiative focuses on "putting patients first, prioritizing information flow to clinicians, promoting innovation through continuous competition, and enhancing transparency and accountability" and reflects numerous ASN advocacy priorities raised over years of advocacy by ASN members to improve transplant care.

Table 1 outlines the key opportunities for improvement in the transplant system and depicts how the provisions of the SUS OPTN Act allow HRSA the flexibility to pursue them, in partnership and under advisement of patients, health professionals, and other stakeholders in the kidney and transplant community.

The structural changes included in the SUS OPTN Act will enable further improvements to the transplant system requested by ASN and the kidney advocacy community. ASN is joined in advocating for this legislation by nearly 30 other patient and health professional organizations and other stakeholders. The society has met with HRSA numerous times to share its perspectives on opportunities for improvement to the U.S. transplant system that would ensure it optimally serves patients by increasing accountability, transparency, and efficiency. ASN also participated in a July "OPTN Industry Day," which the HRSA organized, with a wide array of stakeholders to discuss and seek input on its plans to modernize the U.S. transplant system.

ASN will continue to work with Congress and the HRSA to achieve these crucial changes to ensure that all people who would benefit from a kidney transplant have access to this life-saving therapy.

Read ASN's statement on the introduction of the legislation on the ASN Advocacy and Public Policy homepage (www.asn-online.org/policy), and contact your congressional delegation to encourage them to support this important legislation through ASN's Legislative Action Center (www.asn-online.org/policy/lac.aspx). ■

Table 1. U.S. Organ Procurement and Transplantation Network Opportunities

Opportunity for improvement	Securing the U.S. OPTN Act
Enabling competition and new ways of thinking about improving the nation's transplant system for the first time in 40 years	Eliminates the rule that the contractor be a not-for-profit organization with prior expertise in the OPTN contract scope of work
Allowing new bidders with expertise in one, but not all, of the many important functions of the OPTN to bid, bringing fresh ideas and potentially new expertise	Allows the Secretary of the U.S. Department of Health and Human Services to award multiple grants, contracts, or cooperative agreements to carry out the work of the OPTN
Investing appropriately in our nation's transplant system, including modernizing the dated information technology system on which it relies	Strikes the 2000s' era statutory cap on the OPTN contract amount
Ensuring accountability and good governance by having separate boards for the OPTN and any OPTN contractor(s)	Specifies that OPTN awardees must be distinct from the entity tasked with supporting the board of directors

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This special section of *Kidney News* focuses on reproductive health and kidney diseases. *Kidney News* thanks Christin Giordano McAuliffe, MD, FACP, and Matthew A. Sparks, MD, FASN, for selecting and co-editing these articles, which span topics from fertility issues and strategies to hemodialysis in pregnant patients to patient support following adverse pregnancy outcomes. This special section is the second of two parts, with additional articles appearing in the July issue of *Kidney News*.

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The section co-editors report no conflicts of interest.

Chronic Kidney Disease, Female Infertility, and Fertility Preservation

By Lauren Weissmann

Female infertility is defined as the inability to conceive while timing intercourse in a 12-month period under the age of 35 and in a 6-month period at the age of 35 or older (1). It affects 10%–15% of individuals or couples. An immediate evaluation is warranted before attempting to conceive in patients with significant gynecological risk factors, such as irregular menstrual cycles, uterine fibroids, and endometriosis, as well as a history of and treatment for any medical conditions that may predispose a woman to have diminished ovarian reserve, such as chronic kidney disease (CKD).

Ovarian reserve reflects the quantity of oocytes that are in a woman's ovaries. Oocyte quantity is finite and depletes naturally throughout a woman's life, starting before birth and continuing until menopause, when no viable oocytes remain (2). This natural and continuous process of atresia cannot be slowed or reversed. Furthermore, some women may have genetic predispositions, such as a family history of early menopause or a fragile X messenger ribonucleoprotein 1 (FMR1) mutation, which would cause their ovarian reserve to be lower and potentially diminish at a more rapid pace than others. In addition, iatrogenic causes include treatment with chemotherapeutic agents or radiation to the pelvis.

In particular, certain classes of chemotherapeutic drugs, such as alkylating agents, are known to be highly gonadotoxic. Cyclophosphamide is the most common of these drugs used to treat some forms of kidney diseases. It acts via its phosphoramide, metabolite-forming, permanent DNA strand cross-linkages, which lead to cell apoptosis (3). With non-regenerative cell lines, such as primordial follicles/oocytes, this toxicity is not considered reversible. Therefore, strong consideration should be given to refer patients to reproductive endocrinology and infertility subspecialists to consider fertility preservation before use of such therapies that may render a woman infertile (4).

With the advancement in in vitro reproductive sciences of the technique of oocyte vitrification, success rates using frozen-thawed oocytes are now more similar to use of fresh oocytes in in vitro fertilization. The high water content in an egg cell makes it susceptible to forming ice crystals in the freezing process and less likely to survive the thaw. Vitrification is the technique of extremely rapid cooling so there is no chance of ice crystal formation. In 2012, the experimental label of oocyte cryopreservation or "egg freezing" was removed, allowing egg freezing to be more widely offered and used (5). It is successfully performed at most reputable reproductive endocrinology and infertility centers nationwide. In addition, if a sperm source is available, in vitro fertilization and embryo cryopreservation for future use are recommended. The live birth rate with use of frozen-thawed oocytes is highly dependent on the woman's age at the time of oocyte cryopreservation, her ovarian reserve, and—similarly using frozen embryos—her maternal age when the embryos were created. The process of stimulating follicular growth using injectable gonadotropins and culminating in the minor invasive procedure of the egg retrieval usually occurs over a 2-week period that can be initiated at any point during the menstrual cycle and generally tolerated well (6). Therefore, the process should not interfere with timely initiation of treatment for her underlying disease. Insurance coverage can vary widely depending on particular plans. Unfortunately, many insurance plans may not cover oocyte cryopreservation because regardless of a potential medical indication, it is widely considered elective. Out-of-pocket costs vary widely depending on clinic and region and can generally range from $5000 to $10,000.

In addition to diminishing egg number with advancing age, egg quality also declines more rapidly at the age of 35 or older. In addition, an individual egg and resulting embryo become more likely to be aneuploid, or have an abnormal number of chromosomes, with advancing maternal age. Therefore, the concept of fertility preservation should also be considered in any patient who may need to delay childbearing for treatment of underlying health conditions, such as CKD or the time and recovery it takes a woman to successfully undergo a kidney transplant. Oocyte or embryo cryopreservation can also allow the flexibility in the future of attempting to have a genetically related child with the use of a gestational carrier, if carrying a pregnancy itself is deemed too much of a health risk to allow. ■

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Chronic Kidney Disease and Male Factor Infertility

By Engy Habashy

Infertility is defined as the inability to conceive after 12 months of timed intercourse. Infertility is a common problem, affecting approximately 10%–15% of couples trying to conceive. Male factor infertility accounts for up to 50% of all cases (1). In a well-conducted study of 346 couples attempting to conceive, cumulative pregnancy rates were 38%, 68%, 81%, and 92% at 1, 3, 6, and 12 months, respectively (2). Therefore, it is reasonable to initiate an evaluation after 6–12 months of an inability to conceive. The successful production and expulsion of male gametes require the intricate function of multiple organ systems. Thus, it is unsurprising that many disease processes can negatively impact male reproductive health. Although much attention has been focused on the impact of chronic kidney disease (CKD) on female reproductive health, male reproductive health can also be negatively impacted.

The correlation between CKD and subfertility has been well-established in the literature. Males with CKD have higher incidence of sexual dysfunction, loss of libido, arteriosclerosis, endocrinopathies, impaired spermatogenesis, neuropathy, hypertension, and polypharmacy (Figure 1). A study of 66 males with different stages of kidney diseases revealed a significant decrease in testosterone correlating with the degree of kidney function loss. Luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin also showed a tendency to increase. The same study also revealed negative linear correlation between CKD stage and sperm concentration, motility, tail morphology defects, and total motile sperm counts (3), each of which contributes to infertility. Worsening kidney function is thought to impact male reproductive health by causing accumulation of uremic metabolites in the testes, thereby negatively affecting Sertoli and Leydig cells' function and contributing to inflammation and fibrosis of the seminiferous tubules (4).

Diabetes mellitus and medication side effects are additional elements that exist to a greater extent in the CKD population than in the general population and have adverse effects on male reproductive health. The negative impact of antihypertensive agents on erectile function is well established. The impact of these agents on male reproductive potential is less clear. Investigators proposed that calcium channel blockers can impair fertilization, whereas angiotensin-converting enzyme inhibitors appear to improve sperm motility (5).

In patients with kidney failure, studies demonstrated a correlation between the duration of hemodialysis and the decline in sperm quality and testicular volume. Kidney transplantation has been shown to restore spermatogenesis and the reproductive hormonal axis in some but not all patients with kidney transplants (6). In parallel, with improvement in semen and hormonal parameters, kidney transplantation may also contribute to improvement in erectile function (7). Xu et al. (8) assessed spontaneous pregnancy rates after kidney transplant and noted an increase in birth weight and a decrease in prematurity rate, 24 months after the male partner's kidney transplant. In patients who continue to suffer from poor semen parameters after transplant, studies show moderate success rates with assisted reproductive technology/intracytoplasmic sperm injection (9).

In summary, males with CKD are at an increased risk of subfertility. Nephrologists and urologists often collaborate in caring for patients with various urinary pathologies (stones, congenital kidney disease, or anatomic abnormalities). Male factor infertility in men with CKD is another opportunity where the close collaboration between nephrologists and reproductive urologists can greatly impact the quality of patients' lives. As one would expect, with couples facing infertility challenges, the evaluation of the female partner by a reproductive specialist is paramount. ■

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The author reports no conflicts of interest.

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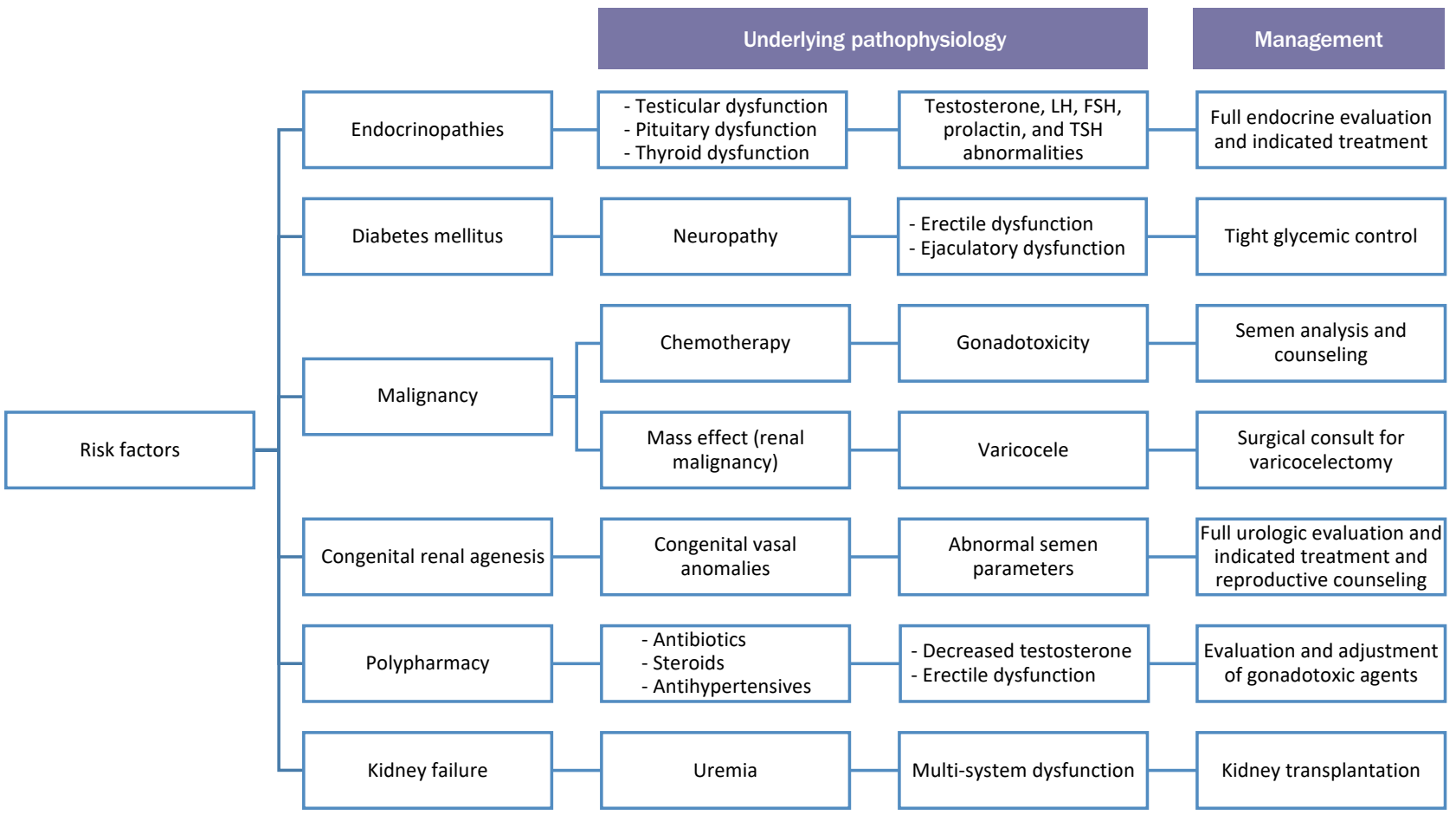
Figure 1. Infertility risk factors and considerations in males with CKD



TSH, thyroid-stimulating hormone.

Pregnancy and Kidney Transplantation

By Swee-Ling L. Levea

Women of childbearing age with kidney failure have significantly reduced fertility rates due to disruption of the hypothalamic-pituitary-gonadal (HPG) axis, leading to infertility and anovulation. However, within a few months of kidney transplant, both the HPG axis and sex hormone levels can return to a normal level with restoration of fertility (1). The first successful pregnancy occurred in March 1958 when Edith Helm, a 23-year-old kidney transplant recipient, delivered her son by cesarean section. Since then, more than 14,000 pregnancies in kidney transplant recipients have been reported worldwide (2).

Ideal time to become pregnant after kidney transplant

In women who desire pregnancy after transplant, the ideal time to conceive is 1 to 2 years after kidney transplant, according to the American Society of Transplantation (3) and the European Best Practice Guideline group (4) (outlined in Table 1). Women of childbearing age who are contemplating conception should be counseled on the teratogenic effects of immunosuppressants and the impact of pregnancy on allograft function and of allograft function on pregnancy outcomes.

Maternal and fetal complications

Pregnant kidney transplant recipients have a higher risk of preeclampsia, with incidence rates ranging between 22% and 38% compared with the general U.S. population (3.8%) (5–7). Low-dose aspirin should be prescribed to all pregnant kidney transplant recipients because it reduces the risk of preeclampsia. There is also a higher risk of gestational diabetes (3%–8%), pregnancy-induced hypertension (24%–54%), and cesarean delivery (43%–63%) (5–7). Urinary tract infection is the most common infection, with incidence rates ranging between 15% and 42% (8). Monthly surveillance with prompt treatment, if infection is identified, is recommended. Allograft dysfunction can occur, with acute rejection rates between 4% and 9% (5, 7). Risk factors for poor outcomes include higher pre-pregnancy creatinine (>1.5 mg/dL), hypertension, and proteinuria >500 mg/24 hours. There is a higher rate of preterm delivery (<37 weeks) at 40%–60%, low birth weight (<2500 g) at 42%–46%, and intrauterine growth restrictions at 30%–50% (5, 7).

Table 1. Criteria for pregnancy after kidney transplant

- 1–2 Years after transplant
- Stable allograft function, creatinine <1.5 mg/dL
- No recent episode of acute rejection or ongoing rejection
- Absence of or minimal proteinuria, ≤500 mg/24 hours
- Normal or controlled blood pressure
- Maintenance immunosuppression at stable dosing
- Discontinuation of mycophenolate mofetil and sirolimus 6 weeks before conception

Immunosuppression management before, during, and after pregnancy

Careful management of immunosuppression before, during, and after pregnancy is critical due to risks of teratogenicity and adverse effects, such as allograft rejection. The safety data for these agents are limited to animal studies and data from transplant pregnancy registries and case reports due to exclusion of pregnant females from immunosuppression trials (2, 3, 7, 9). Breastfeeding is not contraindicated, and the safety of breastfeeding while using maintenance immunosuppression drugs has been reported (9). An overview of the medication safety is outlined in Table 2 (7–9). Prednisone, tacrolimus, cyclosporine, and azathioprine are generally considered safe during pregnancy and lactation. Mycophenolate mofetil and mycophenolic acid are teratogenic and should be stopped at least 6–12 weeks before pregnancy and not recommended during lactation. This is often replaced with azathioprine before pregnancy. Due to increased

Continued on page 16 >

Table 2. Immunosuppressive agents used in pregnant women with kidney transplant

Drug	FDA category	Fetal effects	Recommendations in pregnancy	Recommendations in breastfeeding
Immunosuppression recommended to be stopped before pregnancy				
Mycophenolate mofetil/ mycophenolic acid	D	Congenital abnormalities, cleft lip and palate, limb abnormalities, microtia, atrial septal defect, and trachea-esophageal atresia	No; stop 6–12 weeks before conception	No
Sirolimus	C	Toxicity in animal studies but not teratogenicity	No; stop 6–12 weeks before conception	Unknown
Everolimus	C	Toxicity in animal studies but not teratogenicity	No; stop 6–12 weeks before conception	Unknown
Belatacept	Unknown	Limited data	Do not administer in pregnancy.	Unknown
Immunosuppression commonly used during pregnancy				
Prednisone	C	Rare, except at large doses (cataract, adrenal insufficiency, and infection); possible ↑ in oral clefts	Yes	Yes; not encouraged if prednisone dose is >60 mg daily
Azathioprine	D	Sporadic congenital abnormalities and transient immune alteration	Yes	Yes
Tacrolimus	C	Rare; reversible hyperkalemia and renal impairment	Yes; ↑ doses to achieve pre-pregnancy target levels	Yes
Cyclosporine	C	Rare; reversible hyperkalemia and renal impairment	Yes; ↑ doses to achieve pre-pregnancy target levels	Yes
Immunosuppression used for treatment of rejection				
Methylprednisolone	C	Rare; cataract, adrenal insufficiency, and infection	Yes	Yes
Anti-thymocyte globulin	C	Unknown	Do not administer in pregnancy.	Unknown; possible transfer into milk
Intravenous immunoglobulin	C	None reported	Yes	Yes
Rituximab	C	Reversible B cell deficiency and infection	Avoid pregnancy for 6 months after exposure; do not administer in pregnancy.	Unknown

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C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

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Pregnancy and Kidney Transplantation

Continued from page 13

activity in P450 3A and maternal blood volume during pregnancy, dose adjustments (an increase of 25%–50%) are necessary to achieve target goals (10).

Conclusion

Successful pregnancy in kidney transplant recipients is feasible, and the care from a multidisciplinary team—including obstetricians with expertise in high-risk pregnancies, transplant nephrologists, and primary care physicians—is critical. Pre-transplant and pre-pregnancy counseling are crucial for women of childbearing age given the potential maternal and fetal risk. ■

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The author reports no conflicts of interest.

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Home Hemodialysis for Pregnant Patients: A Short Review and Case Report

By Jennifer Klenzak-Stoddard and Janet Thrower

Pregnancy has a profound effect on total body volume, intravascular volume, hemodynamics, and metabolism. The dramatic changes in volume, body weight, and clearance requirements pose challenging clinical decisions for the nephrologist. In addition to the physiological demands of pregnancy, the nephrologist must consider the economic, psychosocial, and pragmatic obstacles facing each patient. For example, patients may not have transportation or access to daily in-center dialysis, or they may have older children to care for or work responsibilities that may make daily dialysis difficult to access. Home hemodialysis (HHD) has undergone a revolution in technological advances with the creation of machines that are easier to use and more portable and use less dialysate than traditional in-center machines. These innovations have allowed more patients access to HHD.

The NxStage system may be used for short, daily or nocturnal HHD, and its innovation is the frequent, low dialysate-volume approach to clearance (1). The clearance prescription using the NxStage system is related to volume of dialysate and filtration fraction, and the time of treatment is determined secondarily. The physiological benefits of frequent dialysis, including improved blood pressure control and regression of left ventricular hypertrophy, are well-established (2).

There are limited data on the use of the NxStage dialysis modality in pregnancy. Three previous cases of successful pregnancies in patients using the NxStage system have been reported (3). As the use of frequent, low dialysate-volume approach modalities continues to expand, we proposed that this is a safe and recommended modality for the management of end stage kidney disease in pregnancy.

Here, we add another case to the literature of pregnancies resulting in live birth in patients using the NxStage machine for home dialysis.

A.C., a 29-year-old woman with kidney failure due to IgA nephropathy, became pregnant shortly after initiating dialysis. She was undergoing thrice-weekly in-center dialysis via fistula and had a peritoneal dialysis (PD) catheter placed in anticipation of transitioning to PD. Residual urine volume was 1200 mL/day. At the time of pregnancy, the initial prescription for in-center HD was 24 hours weekly (4-hour treatments, 6 days/week), which continued until transition to HHD at week 14 of gestation. In determining the NxStage dialysis prescription, we focused on maintaining a pre-HD blood urea nitrogen (BUN) under 50 mg/dL using daily dialysis treatments, based on the guidelines available at that time (in 2016) (4). Ultrafiltration was limited to 1 L/treatment to avoid hypotension. We allowed the estimated dry weight to rise liberally to avoid hypotension. The initial prescription was a filtration fraction of 33% with 30 L dialysate, which correlated to 4 hours/day, 7 days/week. At 25 weeks' gestation, the dialysate volume was increased to 35 L to maintain clearance goals, but due to pre-HD BUN levels remaining over 50 mg/dL, at 26 weeks' gestation, the volume of dialysate was increased to 50 L, and the patient started a nocturnal daily prescription with a time of 6.5 hours of treatment/night.

Secondary to the frequent and prolonged nature of dialysis treatments, the buttonhole cannulation technique was used. Weekly complete blood count and metabolic panels were monitored. Epogen and heparin were limited to single-dose vials, as recommended by the manufacturer to avoid exposure to benzyl alcohol. (Benzyl alcohol is a preservative in multi-dose vials.) Non-pregnancy-related complications included: 1) a fistulagram at 13 weeks' gestation, for which the patient was covered with three lead aprons to reduce radiation exposure and 2) a PD catheter exit site infection during the second trimester. There was a clinical decision to defer PD catheter removal until the pregnancy had completed. The PD catheter was removed at the time of delivery.

Pregnancy-related complications included: 1) hospitalization for uncontrolled diabetes at 25 weeks' gestation and 2) admission for uncontrolled hypertension and contractions at 31 weeks' gestation. The patient was readmitted at 32 weeks' gestation and remained confined to the hospital until her cesarean delivery at 33 weeks' gestation. The infant's weight was 5 pounds, 4 ounces, and his length was 17.75 inches. At the time of this report, he is a healthy, 7-year-old child.

Most nephrology practices have varied experience with successful pregnancies among patients receiving dialysis. Pinehurst Nephrology Associates in North Carolina has had four pregnancies resulting in live births in the last 25 years. Three of the newborns survived past infancy. Unfortunately, one of the pregnancies resulted in a neonate with multiple birth defects and maternal complications that led to the deaths of both the infant and the mother within 1 year of delivery. A.C. is the only patient who was dialyzed using the NxStage system during pregnancy; the remaining three individuals who were pregnant were all treated in-center with 4-hour treatments, 6 days/week. ■

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Dr. Klenzak-Stoddard reports being a paid consultant and investigator for Medtronic, a medical director for DaVita, and a shareholder with Johnson & Johnson. Ms. Thrower reports no conflicts of interest.

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Hemodialysis Prescription in Pregnant Women

By Nishanta Tangirala and Michelle A. Hladunewich

Pregnancy in women receiving dialysis is an uncommon occurrence but a growing reality in recent years (1). With improved therapeutic advancements, the literature suggests a 3- to 6-fold increase in dialysis pregnancy rates from 1996–2000 to 2001–2013 (1–3). Despite significant improvements in live birth rates, these pregnancies remain high risk with significant adverse maternal fetal complications, including preeclampsia and preterm birth (3). Preterm babies of mothers receiving dialysis have twice the odds of serious adverse events, including higher resuscitation needs and neonatal intensive care admissions (3).

The management of hemodialysis in pregnancy is subject to variability internationally. Hemodialysis prescriptions often reflect influencing factors, including patient health status, lifestyle, and geography. Hemodialysis accessibility is also dependent on jurisdictional availability of infrastructure and resources. There are numerous challenges to consider when prescribing hemodialysis in pregnancy, including dialysis regimens, ultrafiltration (UF), and nutritional requirements. To date, there are no randomized controlled studies evaluating regimens in pregnancy, with optimal management left to consensus opinion supported by limited case series and cohort studies. Our recommendations for dialysis prescriptions are outlined in Table 1.

Both fertility and pregnancy outcomes are improved with intensive hemodialysis (>36 hours) compared with conventional hemodialysis (<20 hours), with a demonstrated dose response relationship (4). It is hypothesized that the increase of uremic clearance is the underlying driver of improved pregnancy outcomes, including live birth rates, advanced gestational age, and a trend toward larger newborns (4). Amplified dialysis from the first trimester works to maintain maternal circulating volume, blood pressure, and interdialytic weight gain and in turn, reduces use of antihypertensive agents (4). Given the burden of intensive regimens, it is important to adjust the regimen based on residual kidney function with a goal to maintain urea <35 mg/dL(5, 6).

The UF prescription in pregnancy is challenging and needs to be individualized (5). Maternal weight gain and blood volume expansion throughout pregnancy should be balanced against the severe hemodynamic changes and rapid volume depletion that can occur with hemodialysis and, in turn, cause detrimental placental flow disruptions affecting the fetus. For this reason, cautious UF is recommended with the goal of minimizing hemodynamic instability and hypotension (5).

Adequate nutrition is critical to maternal and fetal well-being. It is estimated that pregnant women receiving dialysis require increased caloric support (approximately 35 kcal/kg) in addition to standard pregnancy caloric increments for each trimester (6). Protein intake of 1.2–1.8 g/kg/day of pregestational weight is also required to support fetal development (6). Additionally, folic acid, zinc, and water-soluble vitamins are recommended from the first trimester. Electrolyte imbalances are common, and supplementation of potassium, calcium, and even phosphate may be required with intensive dialysis. Typically, a 3K potassium bath is prescribed.

Anemia is more common in pregnant women receiving hemodialysis, and iron deficiency is linked to worse perinatal outcomes. All women should receive oral or parenteral iron supplementation. Pregnancy is postulated to be a state of relative erythropoietin (Epo) resistance, requiring an average 50% increase in supplemental Epo to achieve the target hemoglobin 10–11 g/dL with no documented teratogenic or hypertensive risks (5).

Hemodialysis during pregnancy is complex. Preconception counseling and multidisciplinary team management are paramount. The trifactor of dialysis intensification, judicious UF, and maternal nutritional support remains the cornerstone of supporting these high-risk pregnancies. ■

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Table 1. Dialysis prescription recommendations during pregnancy

Dialysis intensification	
• Increase dialysis duration to approximately 36 hours/week (5–7 sessions/week). • Less dialysis is typically required in women with residual kidney function. • Aim predialysis urea at <35 mg/dL. • New, unrecycled, high biocompatible membranes are recommended. • Lower blood flow (300 mL/min) and dialysate flow rates (500 mL/min) maintain hemodynamic stability. • Heparin anticoagulation is safe.	
Dialysate composition	
Sodium	137–140 mmol/L
Potassium	2–3 mmol/L
Calcium	Increase to 1.5–1.75 mmol/L
Bicarbonate	25 mmol/L
Blood pressure and ultrafiltration	
• Ultrafiltration should be cautiously individualized to avoid hemodynamic instability. Dry weight may increase 300–500 mg/week in second and third trimesters. • Aim target blood pressure at 120/70–140/90 mm Hg. • Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists should be discontinued. Diuretics should also be prescribed with caution due to risk of placental hypoperfusion. • Assessment for superimposed preeclampsia should be considered with new or progressive hypertension >140/90 mm Hg or further organ involvement. • The sFlt-1/PlGF ratio, where available, can assist with the diagnosis of preeclampsia between 26 and 36 weeks' gestation. • Prescribe low-dose aspirin from 10 to 12 weeks' gestation. • Magnesium to prevent eclampsia must be used cautiously. Lower doses with close monitoring are recommended.	
Calcium and phosphate	
• Encourage increased dietary phosphate, given increased frequency of dialysis. Phosphate supplementation may be required. • Monitor calcium and phosphate closely. • Noncalcium-based phosphate binders should be discontinued. • 1,25-Dihydroxyvitamin D (calcitriol) is recommended if vitamin deficiency or primary hyperparathyroidism is present.	
Anemia	
• Aim for hemoglobin target of 10–11 g/dL. Increase Epo dose accordingly. An increase of 50% of the usual Epo dose is typically required. • Maintain transferrin saturation above 20%. (Parenteral iron is typically required.)	

PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase 1. Table created based on Hladunewich et al. (4), Cabiddu et al. (5), and Wiles et al. (6).

Obstetric Perspective on Hypertensive Disorders of Pregnancy

By Andrea Johnson

Hypertensive disorders of pregnancy, which include gestational hypertension; preeclampsia; eclampsia; and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, are the leading contributors to maternal and perinatal morbidity and mortality worldwide (1). Women with underlying kidney diseases have an increased probability of developing preeclampsia during their pregnancy. Once diagnosed, delivery timing is a delicate balance between the risks of prematurity for the newborn and risks of worsening disease for the mother.

In most cases of preeclampsia, women will develop proteinuria due to a capillary leak and decreased colloid oncotic pressure. However, there are recent publications that support widening the definition of preeclampsia to include cases that manifest as hypertension without proteinuria and vice versa (2). Current practice guidelines state that once proteinuria meets diagnostic criteria for preeclampsia, repeated quantifications of proteinuria are not necessary, as the change in proteinuria (massive, marked, modest, or none) does not correlate with differences in maternal or fetal outcome (1, 3, 4). Thus, urine protein levels are not routinely followed once the diagnosis of preeclampsia is made. The diagnosis of preeclampsia in women with preexisting proteinuria due to underlying kidney diseases is particularly challenging, as there are not well-established clinical criteria to differentiate preeclampsia from worsening kidney diseases using proteinuria alone. Instead, the clinician must rely on other laboratory evaluations and symptoms.

Due to the physiology of preeclampsia, women affected with preeclampsia lack the hypervolemia associated with normal pregnancy. During the delivery admission, a clinician should use caution with fluid management to correct the intravascular depletion and oliguria. For example, vigorous intravenous fluid therapy can lead to increased pulmonary wedge pressure, causing pulmonary edema and subsequent respiratory compromise, especially in the setting of preeclampsia with severe features (5). Additionally, with severe disease, intense vasospasm leads to further contraction of the intravascular space as kidney blood flow and the glomerular filtration rate decrease. These intrarenal changes often manifest as oliguria during labor and the first 24 hours postpartum (1).

Women who are diagnosed with a hypertensive disorder of pregnancy are closely surveilled for signs of uteroplacental insufficiency with fetal growth and amniotic fluid assessments on ultrasound and at least weekly antenatal testing to assess fetal well-being. Fetal growth restriction, oligohydramnios (low amniotic fluid), and/or non-reassuring fetal status may necessitate preterm delivery. However, most preterm deliveries occur due to worsening maternal disease prior to 37 weeks, usually due to severe-range blood pressures (>160 mm Hg systolic or >110 mm Hg diastolic) and/or significant serum laboratory changes (platelets <100 x 10^9 L, liver enzymes more than twice the upper limit of normal concentrations, or creatinine >1.1 mg/dL or doubling). Serum uric acid levels are not used clinically to make the diagnosis of preeclampsia or to determine disease severity (1).

Collaboration and communication between maternal fetal medicine specialists and nephrologists will ensure the best outcomes for both the mother and newborn.

The current standard of care is to offer delivery at 37 weeks (full term) to those patients with mild hypertensive disease (gestational hypertension or preeclampsia without severe features). This recommendation is based largely on the results of the Induction of Labour Versus Expectant Monitoring for Gestational Hypertension or Mild Pre-eclampsia After 36 Weeks' Gestation (HYPITAT) trial, which showed a significant reduction in a composite of adverse maternal outcome, including new-onset severe preeclampsia, HELLP syndrome, eclampsia, pulmonary edema, or placental abruption in women who underwent induction of labor after 36 weeks compared with expectant management (6). For those women with severe hypertensive disease (HELLP, eclampsia, or preeclampsia with severe features), delivery is typically recommended at 34 weeks or at the time of diagnosis if after 34 weeks. However, delivery timing often requires individualization for these patients. For those patients with pre-existing kidney diseases or cases that fall outside of prescribed guidelines, collaboration and communication between maternal fetal medicine specialists and nephrologists will ensure the best outcomes for both the mother and newborn. ■

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The author reports no conflicts of interest.

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How to Talk with Patients Experiencing Pregnancy or Perinatal Loss: A Primer for Nephrologists

By Emma Grabinski

People with chronic kidney disease (CKD) are more likely to experience adverse pregnancy outcomes resulting in pregnancy or neonatal loss. This includes spontaneous abortion, preeclampsia, preterm birth, fetal growth restriction, and stillbirth (1). CKD affects up to 3% of pregnant people in the United States (1), so nephrologists should be prepared for how to approach this.

Pregnancy and neonatal loss are experienced in different ways, but common themes seem to be stigma, shame, and guilt. Loss is associated with worsening chronic disease, decreased quality-of-life indicators, and higher rates of mental health disorders, including anxiety, depression, and even suicidality (2). How physicians react to the loss can significantly impact how the patient grieves and copes.

1 Use simple language, not medical language.

a. Use *baby* instead of *fetus* or *neonate*. Ask if the patient named the baby, and if so, use the baby's name.

2 Acknowledge the loss and the grief the patient is experiencing and show empathy. Avoid trying to be positive.

a. Express, "I am so sorry for your loss; this must be so hard for you. Please let me know if I can provide support in any way."
b. Do not make statements, such as "The baby is in a better place." or "At least you know you can get pregnant."
c. Ask if the patient has received information for behavioral health support. If not, Postpartum Support International has links for support groups and specialized therapists throughout the United States, Canada, and internationally (4).

3 Help reduce self-blame and guilt.

a. Even if compliance was potentially a contributing factor, placing blame is unhelpful and may damage the physician-patient relationship and potentially impact the ability to improve disease states for the future.
b. Reassure the patient he or she did not cause the loss.
c. Offer to discuss ways to optimize the patient's CKD to improve his or her physical health when the patient is ready.

4 Do not forget other family members.

a. Frequently the birthing partner is the focus of support. Providing acknowledgment and empathy to the non-birthing partner reinforces that loss affects the whole family.

Perinatal loss can also impact caregivers' psychosocial well-being, especially if physicians have personally experienced loss. This may lead to physicians attempting to distance themselves to cope with their own feelings. Physicians can reduce their risk of negative emotions and improve their sense of satisfaction by providing empathetic care to patients (5). If a physician has experienced a loss, sharing this (but not focusing on this) with the patient can lead to a better connection and may result in the patient feeling more comfortable with the physician. Acknowledging our own emotions and using peer support—even just debriefing with a trusted colleague—have been shown to be protective of physicians' mental health and burnout (6). Feeling prepared to discuss bad news may also reduce the impact on the physician's sense of well-being. Using a standard model or protocol may reduce this stress (7).

Pregnancy and neonatal loss are difficult for all involved, and patients often receive inadequate emotional support. Providing care that is socially and culturally relevant, respectful, and dignified is as important as clinical competence. Physicians can improve their own mental well-being by being prepared and experiencing an empathetic connection with their patients. ■

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The author reports no conflicts of interest.

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LETTERS TO THE EDITOR

The following Letters to the Editor are in response to the article "We Do Not Need to Rethink Our Approach to Overcorrection of Hyponatremia" by Helbert Rondon-Berrios and Richard H. Sterns published in the May 2023 issue of ASN *Kidney News*. The authors' response appears on page 23.

We Should Continually Think About Our Approach to Hyponatremia

By Joel M. Topf, Michael Fralick, and Thomas E. MacMillan

We read with interest Drs. Rondon-Berrios and Sterns' editorial regarding the treatment of hyponatremia in the May issue of ASN *Kidney News* (1) on the original investigation published in March 2023 in *NEJM Evidence* (2). This is a 10-year retrospective examination of hyponatremia at five hospitals in Toronto, Ontario, Canada. We found 22,858 medicine admissions with a serum sodium <130 mmol/L with only 12 cases of osmotic demyelination syndrome (ODS) despite exceeding sodium correction of 8 mmol/L in 24 hours in 18% of admissions. The patients with an initial sodium of <110 mmol/L had a markedly higher proportion of ODS.

The authors criticized our inclusion of a low-risk population. They claimed that patients with an initial sodium over 120 mmol/L are known to be at low risk for ODS, but do not support this assertion with any references. Most of the largest prior case series on patients with hyponatremia excluded patients with initial sodium over 125 mmol/L (3–8). We included patients in this group to empirically evaluate the risk of ODS. More than one patient in our ODS cohort came from this purportedly "low risk" group. While our study indeed confirms that the risk of ODS is low in patients with an initial sodium between 120 and 129 mmol/L, ODS did occur, and the risk may not be as "vanishingly low" as the authors suggested. Additionally, in the authors' own review of case reports of ODS with slow correction of hyponatremia, one-quarter of their cases came from patients with initial sodium levels over 120 mmol/L (9).

The editorialists state that patients with acute water intoxication should have been excluded from the study and claim that this group is at very low risk of ODS, although they do not provide support references. Determining the acuity of hyponatremia is not possible in a cohort study, as patients rarely have sodium measurements on the days preceding admission. Current guidelines recognize this and recommend that when the acuity of hyponatremia is uncertain, it should be treated as chronic, which is the approach we took in our study and the approach the authors used in their own publications (2, 9). Additionally, in a systematic review of patients with hyponatremia due to excessive water intake, 39% of symptomatic patients had symptoms for more than 48 hours (10). The meta-analysis also found a 3% rate of ODS, questioning the assertion that this population is low risk.

The authors also question how we determined the rate of sodium correction. We defined overcorrection as any change in sodium of >8 mmol/L occurring within any period of 24 hours or less, until the sodium reached 130 mmol/L, or the patient was discharged; this approach has been used previously (8). While there are many ways of measuring sodium overcorrection, there is no consensus on the optimal method, and others have used maximum correction rates (11). There is no evidence that defining overcorrection using fixed time points is more closely linked to the risk of ODS than using maximum correction rates (11). Most patients do not have sodium measurements at exactly 24 and 48 hours, which is partly why we did not use these to define overcorrection in our study.

The authors state that ODS is a clinical diagnosis and that only the most severe cases show up on brain imaging. They do not provide any references to support this claim. In Lohr's review of ODS, only 12 of the 74 cases were a "clinical diagnosis" (12). In the study by George et al. on the rapid correction of hyponatremia, they found nine cases of ODS; all of them were diagnosed by MRI-based brain imaging (5). In the authors' recent review, 20 of the 21 cases of ODS had MRI findings consistent with the diagnosis (9).

The authors conclude by saying the current approach to severe hyponatremia of using DDAVP [desmopressin] should not be relaxed and that we should ask ourselves what percentage risk of ODS would we be willing to accept for our patients or family members so that they can be discharged from the hospital 1 day or 2 days earlier. They answer their own question as "none." In our opinion, the authors are too quick to dismiss the potential negative consequences to slowing the rate of sodium correction, especially in patients at lower risk of ODS. From a patient perspective, more frequent blood draws can be painful and uncomfortable, and many would value a shorter length of stay. From a health systems perspective, increasing length of stay can contribute to overcrowding, increased health care costs, and increased ICU mortality (13, 14). Most concerning is the recent finding that slower sodium correction is associated with increased mortality (15). This suggests that determining the ideal rate of correction may require prospective, interventional trials to determine and balance the harms and benefits of any strategy. ■

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Reevaluating Hyponatremia Treatment Guidelines: Rapid Correction of Severe Hyponatremia Is Associated with Improved Outcomes Without ODS

By Michael L. Moritz and Juan C. Ayus

Severe hyponatremia (sodium [Na] ≤ 120 mmol) can result in hyponatremic encephalopathy requiring emergent treatment with hypertonic saline to prevent death or permanent neurologic impairment (1). The relationship between the rapidity of correction and the development of osmotic demyelination syndrome (ODS) can be difficult to ascertain, as ODS is a rare, multifactorial condition associated with risk factors, including alcohol use disorder, hypokalemia, severe liver disease, malnutrition, hyperemesis, hypophosphatemia, and central nervous system hypoxia, with many reported cases occurring in the absence of hyponatremia or with slow correction (2–4). The optimal rate and limits for the correction of hyponatremia are uncertain. US and European clinical practice guidelines in 2013 and 2014, respectively, recommend limits of correction of between 8 and 10 mmol/L/24 hours, with re-lowering of the serum Na with free water or desmopressin if these limits are exceeded, for the prevention of ODS (5, 6). A recent *NEJM Evidence* report found ODS to be rare and unrelated to rapid correction (7), prompting us to suggest in an accompanying editorial that more liberal treatment guidelines are warranted (8). Since then, a report in the *Journal of Critical Care* found more rapid correction to be associated with improved patient outcomes, without increased development of ODS, in patients with severe hyponatremia in the intensive care unit (ICU) (9).

Evidence published after the treatment guidelines supports more liberal rates of correction. Eleven studies involving 7695 patients with severe hyponatremia (120 mmol/L or lower) reported 26 cases (0.34%) of ODS, and approximately 80% of these had alcohol use (Table 1) (7, 9–18). Rapid correction of hyponatremia (>8 mmol/L/24 hours) was common, occurring in approximately 40% of patients, and was not associated with ODS in the absence of alcohol use. The *NEJM Evidence* study found 12 suspected cases of ODS (0.05%) in 23,445 patients presenting to the emergency department with hyponatremia (Na < 130 mmol/L) (7). ODS was unrelated to rate of correction, with rates of correction at 24 and 48 hours being ≤4 and 8 mmol/L in three patients (25%) and ≤9 and 14 mmol/L in nine patients (75%). Two recent case series involving 60 patients with ODS found two-thirds with alcohol use disorder or liver disease, only 20% with severe hyponatremia, and 25% with rapid correction (>8 mmol/L/day) (2, 3). These studies suggest that ODS is related to underlying risk factors rather than rapid correction of hyponatremia.

The report in the *Journal of Critical Care* was a large, retrospective, multi-center study across 208 US hospitals that included 1024 patients with severe hyponatremia (≤120 mmol/L) in the ICU (9). Rapid correction (>8 mmol/L/day) occurred in 44% of patients and was associated with decreases in adjusted mortality (4.37%) and length of hospital (1.8 days) and ICU (1.16 days) stays. A subanalysis found rates of correction of 8–12 and >12 mmol/L/day to be associated with a decreased length of stay when compared with <8 mmol/L/day and rates between 10 and 20 mmol/L/day to be associated with the shortest length of stay. A further analysis of 376 patients with high-risk factors for ODS (Na ≤ 105 mmol/L, potassium ≤ 3.5, or a history of liver failure) found no cases of ODS, despite 52% receiving rapid correction.

One of the premises of the hyponatremia treatment guidelines was lack of evidence that rapid treatment of hyponatremia improves outcomes (5). Evidence now demonstrates that rapid correction is associated with improved patient outcomes and that ODS is rare and related to risk factors—in particular, alcohol use—and not to rapid correction. The current treatment guidelines are overly restrictive and could be contributing to worse patient outcomes with increased mortality and length of stay. Hyponatremia treatment guidelines should be revised in favor of a single, 48-hour limit of 15–20 mmol/L (19, 20), which would simplify treatment, allow for more active treatment with rapid intermittent bolus with hypertonic saline, and decrease the use of desmopressin to control correction, all without producing ODS. ■

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Continued on page 22 >

LETTERS TO THE EDITOR

Reevaluating Hyponatremia Treatment Guidelines

Continued from page 21

Table 1. Rates of correction and outcomes in patients with severe hyponatremia

Reference (year); study type; setting	PNa	n	ODS			Rates of correction, PNa mmol/L (%)	Rapid correction[a] Yes vs No	
			n (%)	PNa (max Δ/24 hours), mmol/L	Risk factors		Mortality, %	Length of stay, days
Geoghegan et al. (10) (2015); retrospective; single center	<120	412	1 (0.24)	Na, 97 (21)		>10/24 Hours[a] (27.9); 6–10/24 hours[b] (51.2); and <5/24 hours[c] (21.1)	5[a] vs 5[b] vs 12[c]	In hospital, 4[a] vs 5[b] vs 5[c]; ICU, 2[a] vs 2[b] vs 2[c]
Krummel et al. (11) (2016); retrospective; single center	≤120	147	0	—		≥12/24 Hours or ≥18/48 hours[a] (18.1)	In hospital, 19.2[a] vs 24.6; long term, 38.5[a] vs 52.5	NA
Winzeler et al. (12) (2016); prospective; two centers	≤120	155	0	—		>12/24 Hours or >18/48 hours (11.6)	NA	NA
George et al. (13) (2018); retrospective; seven hospitals	<120	1490	9 (0.6)	98 (11) 107 (22) 110 (12) 112 (15) 113 (16) 115 (9) 117 (13) 118 (7) 118 (7)	78% Alcohol; 63% hypokalemia	>8/24 Hours[a] (41); >10/24 hours (26); and >18/48 hours (12)	8[a] vs 19	NA
Woodfine et al. (14) (2019); retrospective; single-center emergency department patients	≤116	623	2 (0.3)	Na, <104 (16, 24)	100% Alcohol	Composite criteria for rapid correction (25)	NA	NA
Turkmen et al. (15) (2022); retrospective; single center	≤115	145	0	—		>10/24 Hours[a] (40); 6–10/24 hours[b] (37); and <6/24 hours[c] (23)	7[a] vs 9.4[b] vs 26.5[c]	9.5[a] vs 11[b] vs 10[c]
Mustajoki (16) (2023); retrospective; single-center emergency department	<116	363	5 (1.4)	104 (14) 107 (11) 108 (11) 108 (12) 112 (14)	100% Alcohol; 80% hypokalemia	>8/24 Hours (27) and >10/24 hours (13)	NA	NA
Nagase et al. (17) (2023); retrospective; single center	≤120	221	0	—		>10/24 Hours or >18/48 hours[a] (7); 4–10/24 hours[b] (60); and <4/24 hours[c] (33)	19[a] vs 8[b] vs 19[c]	21[a] vs 25[b] vs 31[c]
Massop et al. (18) (2023); retrospective; single-center prescription with 3% NaCl	≤120	130	0	—		>10/24 Hours (20.7)	NA	NA
MacMillan et al. (7) (2023); retrospective; five centers	<120	2985	9 (0.3)	NA	Alcohol hypokalemia	>8/24 Hours (48)	NA	NA
Kinoshito et al. (9) (2023); retrospective; 208 hospital ICUs	≤120	1024	0	—		>8/24 Hours[a] (44)	8.4[a] vs 13.4	9.2[a] vs 10.1

NA, not available; PNa, plasma sodium.
[a]Rapid correction.
[b]Intermediate correction.
[c]Slow correction.

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Authors' Response to Letters to the Editor

By Helbert Rondon-Berrios and Richard H. Sterns

We thank the *Kidney News* editors for the opportunity to respond to the Letters to the Editor (1, 2) regarding our invited commentary on hyponatremia correction (3). With a reference limit, our commentary could not provide the evidence demanded by the letter writers. Readers interested in that evidence can find it in our recent comprehensive review just published in *CJASN* (4). The review was authored by 24 hyponatremia experts from nine countries. All of the authors share our concern that the conclusions drawn from the study by MacMillan et al. (5) and the accompanying editorial by Ayus and Moritz (6) were unwarranted.

A major flaw in the study by MacMillan et al. (5) was that most of the patients studied were at extremely low risk of developing osmotic demyelination syndrome (ODS). In their letter, Topf et al. (1) ask for references. They need look no further than reviews written by Drs. Ayus and Moritz (7). Topf et al. (1) argue that ODS was found among patients whose initial serum sodium was between 120 and 129 mmol/L; the argument reveals another flaw: the study erroneously equated central pontine myelinolysis (CPM) with ODS. CPM has many causes—not just rapid correction of hyponatremia. The term "ODS" was introduced in 1986 (8) at a time when Ayus and others were recommending correction of severe hyponatremia by as much as 25 mmol/L within 12 hours (9). The purpose of the new term was to refocus attention away from the many causes of CPM to something that was occurring much too often in that era.

ODS describes a potentially crippling clinical syndrome of delayed neurological deterioration following rapid correction of severe, chronic hyponatremia. Patients with ODS do not always have CPM documented by imaging or autopsy (8), and patients with CPM do not always have ODS (10–12). The study by MacMillan et al. (5) looked for CPM in a population unlikely to have ODS; not surprisingly, the few cases found were unrelated to rapid correction of hyponatremia.

Citing a meta-analysis reporting a 3% ODS rate among patients with polydipsia (13), Topf et al. (1) also argue that their inclusion of patients with acute water intoxication did not minimize the true risk of ODS. However, all ODS cases in this meta-analysis either had chronic or unknown onset of hyponatremia. In contrast, a case series involving patients with psychosis and severe self-induced water intoxication (mean serum sodium of 110.9 ± 1.2 mmol/L) showed no neurological complications after correcting serum sodium by a mean of 21.6 ± 1.4 mmol/L per day (14).

Both letter writers (1, 2) cite evidence that slower correction of hyponatremia is associated with increased short-term mortality in critically ill patients (15). The association is unlikely to be causal. There is no evidence that hyponatremic fatalities were caused by inadequately treated cerebral edema (16). Series reporting deaths from herniation are based on litigation cases referred for an expert opinion (17). The true incidence of these catastrophes (which we all agree should be avoided) has been reported to be less common than CPM (18). It is implausible that a difference in correction rates of a few millimoles per liter was responsible for fatalities. It is far more likely that potentially fatal comorbidities affected correction rates (16). Rapid increases in the serum sodium concentration are usually caused by a spontaneous aquaresis in patients with easily reversible causes of hyponatremia who are free of an acute, life-threatening illness other than extremely low serum sodium concentrations. Hyponatremia corrects slowly in patients with shock, heart failure, acute kidney injury, advanced liver disease, and syndrome of inappropriate antidiuresis due to malignancies who cannot excrete dilute urine. In the study cited, the slow correction group consisted of nearly twice as many patients with heart and liver failure compared with the rapid correction group (15).

We do agree with the letter writers (1, 2) that a correction limit of 8 mmol/L per day is seldom necessary when the serum sodium concentration is higher than 120 mmol/L. At those levels, meticulous efforts to control the rate of correction are only needed in patients at heightened risk for ODS (e.g., alcohol use disorder, malnutrition, or advanced liver disease) and in patients with diabetes insipidus with desmopressin-induced hyponatremia who can rapidly become hypernatremic. We only wish that the study by MacMillan et al. (5) had limited its conclusion to that specific message.

Currently accepted therapeutic limits were proposed with the knowledge that limits are often inadvertently exceeded; they were meant to leave room for error (4). If adherence to those limits has made ODS much less common than it was when the disorder was first named (as demonstrated in some of the studies listed in the table provided in the letter by Moritz and Ayus [2]), that was the intent. ■

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Mycophenolate Mofetil for IgA Nephropathy: Yes or No?

By Sahibzadi Mahrukh Noor and Sayna Norouzi

The use of mycophenolate mofetil (MMF) in immunoglobulin A nephropathy (IgAN) remains controversial and is currently only suggested for Chinese patients as a steroid-sparing agent per Kidney Disease: Improving Global Outcomes (KDIGO) 2022 guidelines (1). The Effects of MMF on Renal Outcomes in Advanced IgAN Patients (MAIN) trial, recently published in *JAMA Network Open*, was a randomized clinical trial that compared MMF with supportive care in 170 Chinese adults with IgAN between September 2013 and December 2015, in addition to a post-trial follow-up period of 5 years (2). Inclusion criteria were patients aged 18–70 years having biopsy-proven IgAN, proteinuria >1.0 g/day, and an estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/1.73 m^2 or persistent hypertension (blood pressure [BP] >140/90 mm Hg or need of anti-hypertensive medication). Exclusion criteria included patients having secondary, familial, or crescentic IgAN; eGFR <30 mL/min/1.73 m^2; proteinuria >3.5 g/day; severe hypertension (systolic BP >180 mm Hg and/or diastolic BP >110 mm Hg); chronic kidney disease (CKD) due to other causes; and prior immunosuppressive therapy. Primary outcomes were a composite of doubling of serum creatinine (SCr), end stage kidney disease (ESKD)—dialysis, transplant, or kidney failure with an eGFR <15 and indication for kidney replacement therapy—death due to kidney or cardiovascular cause, and progression of CKD (≥30% reduction in eGFR if baseline eGFR was ≥60 or reduction of ≥50% if baseline eGFR was <60).

The run-in phase lasted 3 months in which 238 patients received optimized supportive care including maximally tolerated losartan and a low salt diet (<5 g/day, monitored via 24-hour urine sodium or chloride). Patients with proteinuria between 0.75 and 3.5 g/day after 3 months of optimized care (and without potassium >5.5 or an increase in creatinine of >30%) were enrolled into the trial for 3 years. Of the 238 patients, 68 (29%) were excluded during the run-in phase (49 with proteinuria <0.75 g/day, 6 with a creatinine increase >30%, 6 with hyperkalemia, and 7 declined to participate). Patients (170) were randomized in a 1:1 ratio of MMF plus supportive care vs supportive care alone. The MMF dose was 1.5 g/day for the first 12 months followed by a 0.75- to 1.0-g maintenance dose for at least 6 months. Of the 170 patients, 153 (90%) had a kidney biopsy performed within 1 year before randomization.

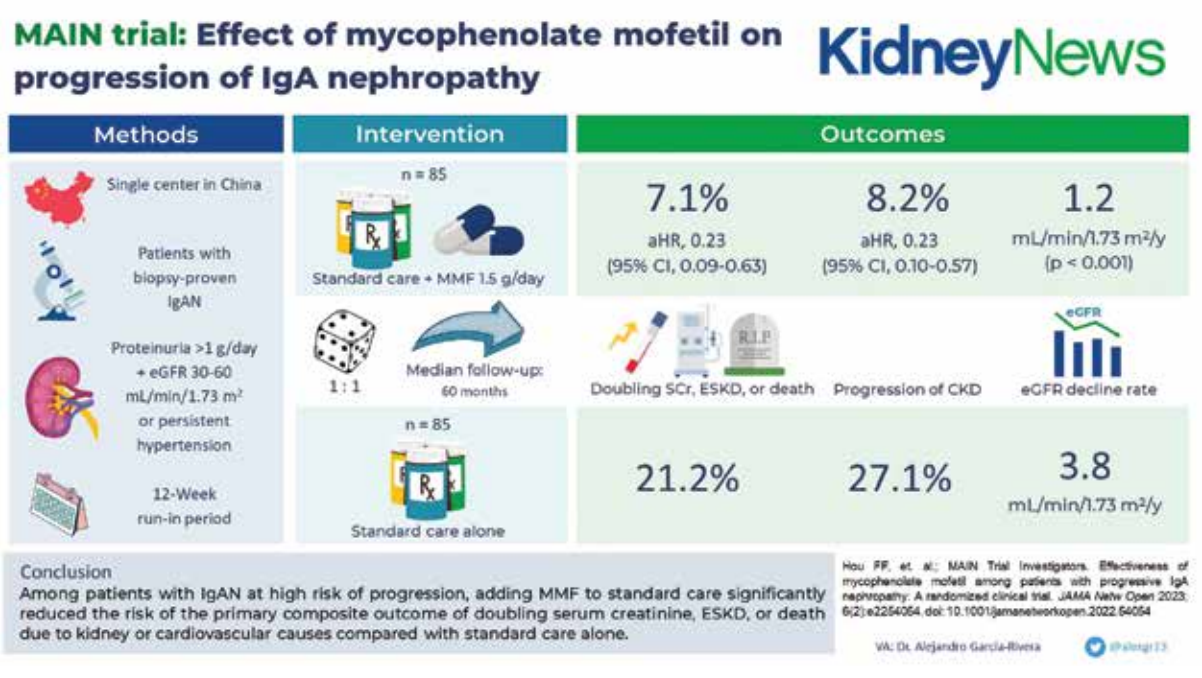
Of the 85 patients in each group, the primary composite outcome was observed in 6 patients (7.1%) in the MMF group vs 18 patients (21.2%) in the supportive care group (p = 0.008; adjusted hazard ratio [aHR], 0.23; 95% confidence interval [CI], 0.09–0.63). Progression of CKD occurred in 7 patients (8.2%) in the MMF group vs 23 patients (27.1%) in the supportive group (p = 0.001; aHR, 0.23; 95% CI, 0.10–0.57). The MMF group also had a higher reduction in proteinuria (57.1%) compared with the supportive care group (28.2%) (p < 0.001). The annual rate of eGFR loss was 1.2 vs 3.8 mL/min/1.73 m^2 in the MMF vs the supportive care groups, respectively (p < 0.001). During the post-trial follow-up of 157 patients, the mean annual eGFR loss was 7.1 in the supportive care group and 6.1 in patients who discontinued MMF after the trial vs 4.1 mL/min/1.73 m^2 in patients who continued MMF during the post-trial period.

Serious adverse events occurred more frequently in the MMF group; however, they were not statistically different (p = 0.37). Infections, especially pneumonia, and elevated liver enzymes were more common in the MMF group but also not statistically significant (p = 0.37 and p = 0.21, respectively). Gastrointestinal side effects were the only adverse effects that were statistically different between the two groups (p = 0.001).

The MAIN trial included Chinese patients only. This limited the generalizability of the study findings to non-Chinese patients. The study does not mention the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors (during the run-in or trial phase), which is now considered a major component of supportive care. The outcomes for the supportive care group could have potentially been different if SGLT2 inhibitors were included in the regimen. Since different grades of histologic disease respond differently to treatment, it would have been useful to stratify the results based on Oxford classification MEST-C (mesangial hypercellularity [M], endocapillary proliferation [E], segmental glomerulosclerosis [S], tubular atrophy/interstitial fibrosis [T], and cellular/fibrocellular crescents [C]) scores and the interval between biopsy and treatment initiation.

Previous trials studying MMF have had conflicting results. A randomized clinical trial conducted in China showed non-inferiority of MMF plus low-dose steroids vs standard dose steroids, along with significantly fewer side effects in the combination group (3). Another trial conducted in China that included 62 patients and a 1.5-year follow-up comparing MMF with steroids showed greater reduction in proteinuria in the MMF group (4). However, two other randomized clinical trials, conducted in Belgium (with 34 patients and 3 years of follow-up) (5) and the United States (with 32 patients and 2 years of follow-up) (6), showed no beneficial effects. A longer trial in Hong Kong (with 40 Chinese patients and 6 years of follow-up), which compared MMF for 6 months with supportive care, demonstrated a slower annual decline in eGFR: 1.1 mL/min/1.73 m^2/year in the MMF group vs 3.8 mL/min/1.73 m^2/year in the supportive care group (p = 0.012) (7). Reduction in proteinuria in the MMF group was also observed but only during the first 24 months. This corresponds with the finding in the MAIN trial in which discontinuing MMF vs continuing it during the post-trial period resulted in an accelerated eGFR decline, underscoring the importance of continuation of therapy. The trial conducted in Hong Kong did not include patients with advanced glomerulosclerosis, tubular atrophy, or interstitial fibrosis, whereas in the MAIN trial, 84% of patients had a MEST-C score of S1, and 54% had a score of T2, showing benefit in patients with advanced histological disease as well.

Since patients with an eGFR <50 mL/min/1.73 m^2 were excluded from most IgAN trials, KDIGO does not provide any standard treatment guidelines for such patients (1). The mean eGFR of patients in the Therapeutic Effects of Steroids in IgAN Global (TESTING) trial (8) was 62 compared with 50 mL/min/1.73 m^2 in the MAIN trial. The subgroup analyses showed equal benefits in patients with an eGFR >50 compared with an eGFR between 30 and 50 mL/min/1.73 m^2. The use of low-dose MMF compared with 2 or 3 g/day resulted in lower infectious complications: 17% vs 54% and 79%, when 2 g/day MMF dose was used in other trials (9, 10). Thus, as the authors mentioned, MMF could be considered a favorable option in patients with low eGFR and those at high risk of adverse effects with steroids. With the advent of SGLT2 inhibitors, budesonide, and sparsentan, the role of MMF in IgAN needs to be explored further using a multi-center trial with a large sample size and a long follow-up period. However, MMF could be a reasonable choice for Chinese patients. Despite the recent expansion in therapeutic options and multiple ongoing trials exploring novel treatments, the optimal treatment of IgAN continues to remain controversial. ■



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Dr. Noor reports no conflicts of interest. Dr. Norouzi reports being a member of the Speaker's Bureau of Calliditas Therapeutics.

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When Artificial Intelligence Is Incorporated into Science by Advanced Intelligent Humans: Refinement of the Banff Classification for Kidney Allografts

By Luis Eduardo Morales-Buenrostro and Josefina Alberú

The Banff Classification has provided a standardized approach to diagnosing and grading kidney allograft rejection for over 3 decades. This integration has improved the understanding of rejection mechanisms and provided additional tools for diagnosing and managing kidney allograft rejection. Its contributions have led to improved communication among pathologists and facilitated advancements in research and clinical practice in the field of kidney transplantation (1). However, its Achilles' heel is inter- and intra-observer variability, to which is added the constant evolution of the Banff Classification.

The development of an automated, histological classification system for kidney allografts is a major advance in precision diagnostics. Yoo et al. (2), in a manuscript published in *Nature Medicine*, demonstrate the effectiveness of this new system in accurately classifying different histological patterns in kidney allograft biopsies. Although the qualification made by the pathologists was used for each of the items of the Banff Classification, Yoo et al. (2) improved the precision by developing an innovative system that addresses their limitations by using deep learning algorithms.

The potential benefits of an automated system for histological classification of kidney allografts are immense. Automated systems and deep learning could allow for more accurate and consistent diagnoses and may improve patient outcomes by allowing proper treatment and follow-up. Indeed, the strength of this study is that graft prognosis was analyzed by comparing the pathologist interpretation with the automated system proposed, and it is evident that reclassification improved survival prediction.

Undoubtedly, it could evolve, as the authors propose, toward the use of artificial intelligence with digital image analysis, thus overcoming the limitations of inter- and intra-observer variability (3). Additionally, the system has the potential to reduce the workload of pathologists, allowing them to focus on more complex cases.

A potential limitation of this work is the elimination of graft pathologies characterized by inflammation not related to rejection. It would be interesting to see further research on the performance of this system on more diverse datasets. Overall, Yoo et al. (2) have made exciting progress in the field of precision diagnosis of allogeneic kidney allografts.

This study will be an invitation to replicate with a large number of kidney graft biopsies from other latitudes, using the tool elegantly described in the study. ■

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The authors report no conflicts of interest.

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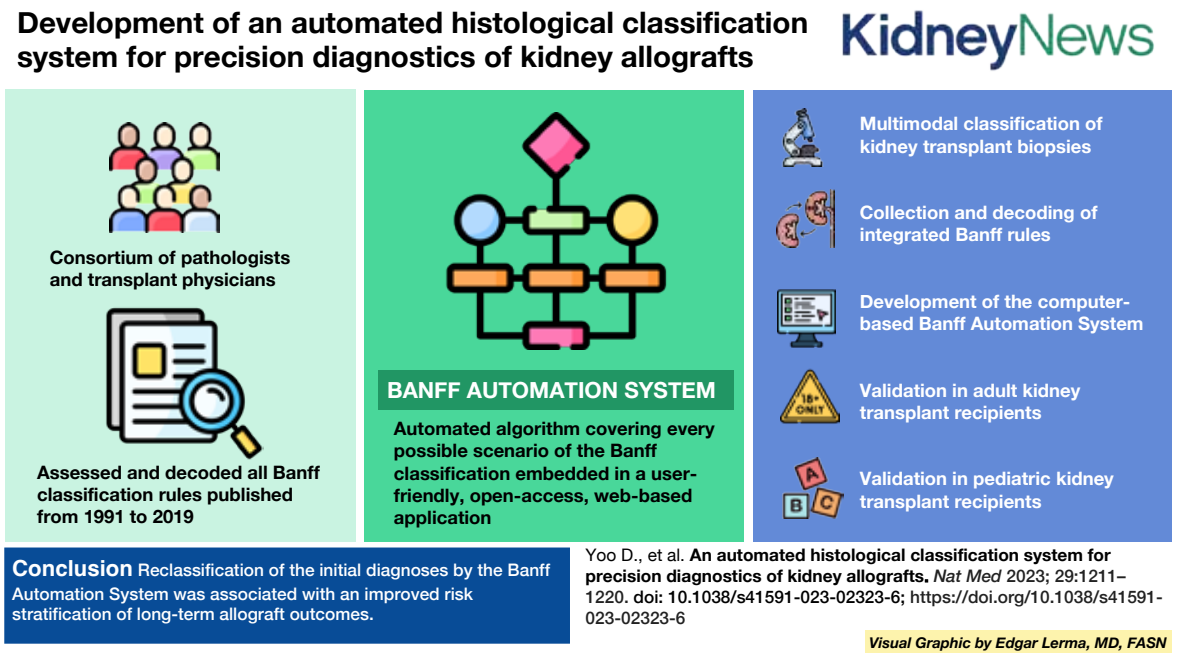

Findings

Modestly Reduced eGFR Associated with Adverse Outcomes in Young Adults

Modest reductions in kidney function in younger adults are associated with later increases in risk of cardiovascular disease, kidney failure, and death, reports a study in *BMJ*.

The population-based cohort study included linked Ontario, Canada, health care data on 8.7 million adults (aged 18–65 years; mean age, 41.3 years). All had at least one outpatient estimated glomerular filtration rate (eGFR) value with no history of kidney diseases. Modest reductions in kidney function were identified, based on age-specific eGFR reference levels: 100–110 mL/min/1.73 m^2 at aged 18–39 years, 90–100 mL/min/1.73 m^2 at aged 40–49 years, and 80–90 mL/min/1.73 m^2 at aged 50–65 years. Associations with all-cause mortality, any cardiovascular event, and kidney failure were assessed.

In the study sample, the mean index eGFR value was 104.2 mL/min/1.73 m^2, and the median follow-up was 9.2 years. Based on age-specific cutoffs, modest reductions in eGFR were found in 18.0% of patients aged 18–39 years, 18.8% of those aged 40–49 years, and 17.0% of those aged 50–65 years.

"Modest eGFR reductions were consistently associated with higher rates of adverse outcomes," the researchers write. At an eGFR between 70 and 80 mL/min/1.73 m^2, hazard ratios for adverse outcomes were 1.42 in participants aged 18–39 years, 1.13 for those aged 40–49 years, and 1.08 for those aged 50–65 years. Incidence rates were 4.39, 9.61, and 23.4 per 1000 person-years, respectively. Associations were significant for all three types of adverse events.

The effects of age on eGFR and the associated clinical risks are unclear, specifically at values above the 60 mL/min/1.73 m^2 cutoff for CKD. Thus, there is limited evidence to guide the management of younger adults with early reductions in eGFR.

The new analysis links modest age-specific reductions in eGFR to increased risks of adverse clinical outcomes. The risks appear more prominent in adults aged 18–39 years, beginning at index eGFR values under 80 mL/min/1.73 m^2. The researchers conclude: "These findings suggest a role for more frequent monitoring of kidney function in younger adults to identify individuals at risk to prevent chronic kidney disease and its complications" [Hussain J, et al. Associations between modest reductions in kidney function and adverse outcomes in young adults: Retrospective, population based cohort study. *BMJ* 2023; 381:e075062. doi: 10.1136/bmj-2023-075062].

Population Screening for CKD: Is It Cost-Effective Now?

In the era of sodium-glucose cotransporter-2 (SGLT2) inhibitor therapy, population-wide screening for albuminuria to identify chronic kidney disease (CKD) would be a cost-effective practice, suggests a study in the *Annals of Internal Medicine*.

The researchers designed a decision analytic Markov cohort model of CKD progression among U.S. adults aged 35 years or older. Cost-effectiveness analysis focused on the impact of screening for albuminuria from a health care sector perspective, with and without adding SGLT2 inhibitors to the standard of care for CKD. Data for the analysis came from the National Health and Nutrition Examination Survey, Centers for Medicare & Medicaid Services databases, and published studies including the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial.

One-time screening with the addition of SGLT2 inhibitors at aged 55 years increased costs from $249,000 to $259,000 and increased quality-adjusted life-years (QALYs) from 12.61 to 12.72, for an incremental cost-effectiveness ratio of $86,300 per QALY gained. This screening strategy reduced the incidence of kidney failure requiring dialysis or transplantation by 0.29 percentage points while increasing life expectancy from 17.29 to 17.45 years.

Other strategies were also cost-effective. One-time screening between aged 35 and 75 years avoided dialysis or transplantation in 380,000 people. For a strategy of screening every 10 years up to aged 75 years, cost per QALY gained was less than $100,000. In sensitivity analyses, costs per QALY were affected by the estimated effectiveness and costs of SGLT2 inhibitors.

Trials have demonstrated the efficacy of SGLT2 inhibitor therapy in patients with CKD, with and without diabetes. This new treatment appears capable of altering the natural history of CKD, suggesting that it should be included in cost-effectiveness analyses of CKD screening.

"Screening adults for albuminuria to identify CKD could be cost-effective in the United States," the researchers conclude. In contrast to studies performed before the availability of SGLT2 inhibitor therapy, "[B]oth one-time and periodic screening for CKD represent very good value in every age group when SGLT2 inhibitors are included in treatment [Cusick MM, et al. Population-wide screening for chronic kidney disease: A cost-effectiveness analysis. *Ann Intern Med* 2023; 176:788–797. doi: 10.7326/M22-3228].

Similar Outcomes with Different Glucose-Lowering Drugs in Type 2 Diabetes

In patients with type 2 diabetes, four different classes of glucose-lowering medications produce similar kidney outcomes at 5 years' follow-up, according to a clinical trial report in *JAMA Internal Medicine*.

The randomized "Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness" (GRADE) trial enrolled 5047 patients with type 2 diabetes at 36 U.S. centers. Approximately two-thirds of patients were men. The mean age was 57.2 years; hemoglobin A1c (HbA1c), 7.5; duration of diabetes, 4.2 years; and estimated glomerular filtration rate (eGFR), 94.9 mL/min/1.73 m^2.

Patients were assigned to receive insulin glargine, glimepiride, liraglutide, and sitagliptin, added to metformin. Treatment continued until HbA1c exceeded 7.5%, at which point insulin therapy was started. At 5 years, the chronic eGFR slope and a composite outcome of kidney disease progression were compared among treatment groups, along with secondary outcomes.

There was no significant difference in the mean chronic eGFR slope: –2.03 mL/min/1.73 m^2 per year with sitagliptin, –1.92 with glimepiride, –2.08 with liraglutide, and –2.02 with insulin glargine. Rates of the composite kidney disease outcome were 10.6%, 12.4%, 12.0%, and 11.9%, respectively. Albuminuria progression accounted for 98.4% of composite outcome events.

Secondary outcomes were also similar among treatments, including incident eGFR reductions to less than 60 mL/min/1.73 m^2. No treatment-related adverse kidney events occurred.

Among patients with type 2 diabetes, free of baseline kidney diseases, 5-year kidney outcomes are comparable with various classes of glucose-lowering medications. The authors discuss their findings in the context of randomized trials of the different types of drugs [Wexler DJ, et al. Comparative effects of glucose-lowering medications on kidney outcomes in type 2 diabetes: The GRADE randomized clinical trial. *JAMA Intern Med* 2023; 183:705–714. doi: 10.1001/jamainternmed.2023.1487].

How Does AKI Affect Risk of CKD Progression?

Once other characteristics are taken into account, patients with chronic kidney disease (CKD) who are hospitalized with mild to moderate acute kidney injury (AKI) have only a small, additional risk of CKD progression, reports a study in the *Annals of Internal Medicine*.

The analysis included 3150 patients with CKD, drawn from the Chronic Renal Insufficiency Cohort (CRIC) study. The occurrence of "hospitalized AKI" was assessed, defined as at least a 50% increase in inpatient serum creatinine (SCr). The main outcome of interest was kidney function trajectory, with the estimated glomerular filtration rate (eGFR) based on the SCr or cystatin C level.

Over a median of 3.9 years' follow-up, AKI episodes occurred in 433 patients: a rate of 13.7%. Severity was grade 1 or 2 in 92% of cases. Episodes of AKI were associated with reductions in eGFR: –2.30 based on SCr and –3.61 based on cystatin C.

However, after adjustment for other factors, including baseline eGFR and proteinuria, the associated declines in eGFR were much smaller: –0.38 based on SCr and –0.15 based on cystatin C, with overlapping confidence intervals. By both methods, there was a possibility of no effect on changes in the eGFR slope.

Studies have linked AKI to more rapid loss of kidney function, leading to trials of interventions to reduce AKI severity. However, studies of the association between AKI and subsequent changes in eGFR have had important limitations, including inadequate controls for differences between patients with and without AKI.

The new analysis of patients with CKD suggests that mild to moderate episodes of AKI have little or no effect on worsening subsequent kidney function, after adjustment for other variables. "Our results suggest that much of the kidney disease observed after AKI may already be present before AKI," the researchers write [Muiru AN, et al. Risk for chronic kidney disease progression after acute kidney injury: Findings from the Chronic Renal Insufficiency Cohort study. *Ann Intern Med*, published online ahead of print July 11, 2023. doi: 10.7326/M22-3617; https://www.acpjournals.org/doi/10.7326/M22-3617].

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