ASN American Society of Nephrology

KidneyNews

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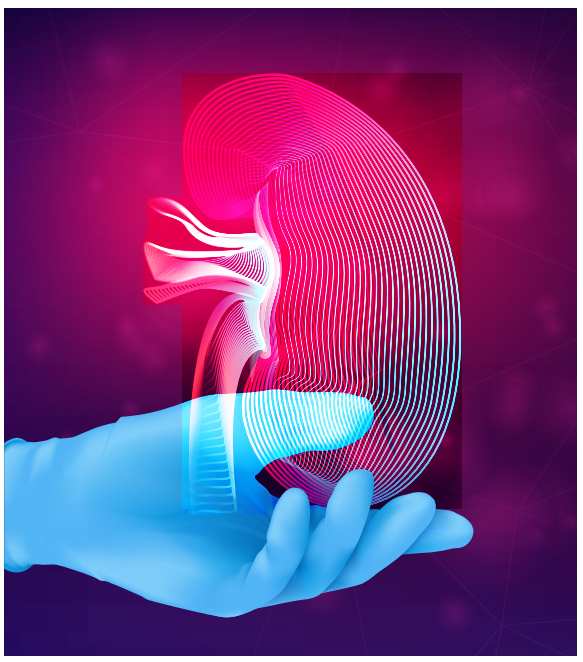
KidneyX Summit Highlights Innovative Approaches to Kidney Care

By Melanie Padgett Powers



Every day, 13 people die in the United States while waiting for a kidney transplant, and those experiencing dialysis face a 50% mortality rate during the first 5 years of treatment. Communities of color are disproportionately affected, with increased incidence, fewer organs available for transplant, and poorer outcomes overall (1). The successful creation of an artificial kidney would revolutionize kidney care in the United States, likely saving lives with more transplants, shorter transplant wait times, alternatives to transplants, and less need for dialysis.

More than $9 million was awarded to eight research teams working on innovative approaches to developing a bioartificial kidney at the 2023 Kidney Innovation Accelerator (KidneyX) Summit on June 12, 2023, in Washington, DC. The KidneyX prize competition—now in its fifth year—is a public-private partnership between ASN and the U.S. Department of Health and Human Services. The program has held six competitions, awarding approximately $17 million to 75 winners in 26 U.S. states (2). Supporters in Congress are now calling for a funding increase to $25 million for KidneyX in the 2024 federal fiscal year.

"KidneyX is engaging community researchers and investors to bring breakthrough therapies to Americans with kidney disease[s]," said Admiral Rachel L. Levine, MD, U.S. Assistant Secretary for Health, in her closing keynote at the KidneyX Summit. "Through the power of prize competitions, we have the opportunity to transform lives and generate new solutions for kidney care. Prize challenges are different from science grants because they expand the solution space beyond just academia and researchers. Prizes are an open innovation tool to bring nonprofits, researchers, and governments together while stimulating niche markets and neglected markets like kidney care was before KidneyX."

The 2023 winners fell into two tracks: 1) accelerating the prototype of a bioartificial kidney and 2) components and tools that enable the development of an artificial

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Generative AI, Like ChatGPT, Shows Great Promise and Risks

By Melanie Padgett Powers

In January 2023, ChatGPT seemed to pop up overnight. In staff meetings, casual conversations, and conference sessions, the artificial intelligence (AI) chatbot—a software application that mimics human conversation through text or voice interactions—was the hot, new topic in seemingly every industry. Although ChatGPT was actually released as a free prototype in November 2022 by the AI laboratory OpenAI, which created it, it took a few months to hit the mainstream. Reaction ranged from fascination and high hopes to fear that the "robots" were taking over.

ChatGPT is only one example of a generative AI tool, a type of AI that generates content, including images and text. ChatGPT is a type of large language model, which is a model trained on large quantities of text, and it can perform a variety of tasks. The November release last year was based on Generative Pre-trained Transformer (GPT)-3.5. In March 2023, OpenAI released GPT-4 as a paid version.

Generative AI tools carry a lot of promise in health care, potentially increasing efficiency and improving patient communication, but experts caution that these are very early days. ChatGPT and similar tools come with risks and warnings about inaccuracy and bias, among other areas. In addition, clinicians must be sure tools they are using adhere to the Health Insurance Portability and Accountability Act (HIPAA).

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KidneyX Summit Highlights Innovative Approaches

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kidney. Before the winners explained their approaches at the summit, KidneyX Steering Committee member and patient David Rush, in his morning keynote address, encouraged researchers and physicians to remember why they are doing this. "It's not just me going through kidney disease; it's my kids, it's my wife, it's my family, it's my support system," said Rush, who is undergoing home dialysis after his transplanted kidney failed in 2017 after 7 years. "When you're doing these things, you're not just doing it for me. You're doing it for future generations.… Remember your why. Remember why you wanted to become a doctor, remember why you wanted to be a nurse.… Don't lose that vision."

Transplanting pig kidneys into humans

Two of the prize winners are trying to make it possible to transplant genetically modified pig kidneys into humans. Xenotransplantation researcher David K.C. Cooper, MD, PhD, FRCS, of Harvard University, believes this is the solution to increasing the supply of available kidneys for transplant. His team has successfully transplanted pig kidneys into primates, with the kidneys functioning for more than 1 year in several of the animals and one kidney functioning for 4 years. But the results are not consistent enough yet for the U.S. Food and Drug Administration to allow human trials, he explained. To improve success, his team needs to develop a better immunosuppressant regimen, Cooper said. He is hopeful they will see success in a couple of years, which would open the door for human trials.

Cooper pointed out that 45% of patients receiving dialysis are taken off the transplant waiting list because they have died or have developed co-morbidities that make them unsuitable for transplant. He believes those patients should be the first to be offered a pig kidney. "One day, organ transplantation from deceased human donors, I think, will be of historic interest only," Cooper said. "People at a meeting like this in 30 years' time will say, 'Once upon a time, they actually transplanted kidneys from dead people—can you believe that?'"

Like Cooper, Matt Tector, PhD, chief scientific officer at Makana Therapeutics, is also working on using pig kidneys for humans. Tector's team is trying to solve the challenging fact that every human has antibodies to every pig, which would cause the human body to destroy a transplanted pig kidney in minutes or hours. His team selected 44 patients on the kidney transplant waitlist to evaluate how their antibodies bind to the cells in genetically modified pigs. They discovered that knocking out one or two genes was not enough. But by knocking out three genes, the human anti-pig antibodies fell to an acceptable level. Next, they tested the three-gene-knockout pigs on 822 patients and found that 40% of the patients fell into the detectable but manageable level, whereas 30% of patients had no detectable anti-pig antibodies. "We're very excited that these triple-knockout pigs can be useful for 70% of patients in need of an organ transplant," Tector said, "and we're hoping to move forward with clinical trials in the near future."

Tools to develop artificial kidneys

Nephrologist William Chang, MD, PhD, of Yale University, proposes improving care of patients with end stage kidney disease (ESKD) by combining innovations in stem cell technology and tissue engineering with the established clinical practice of peritoneal dialysis. "Kidney organoids can now be generated from patient-derived stem cells," Chang explained. But the question is how to use them therapeutically. "I believe you can implant these in the abdomen as an augmentation of peritoneal dialysis," Chang said. "You can then drain fluid and allow filtration to occur." Advantages include that the stem cells are derived from the patients, reducing infection risk, and that peritoneal dialysis is well-established and is the preferred form of dialysis by many patients with ESKD, Chang noted.

Bioengineer Shuvo Roy, PhD, of the University of California, San Francisco, is aiming to provide patients with a small, implanted, bioartificial kidney. Roy's team has developed a bioartificial kidney that uses a mechanical hemofiltration unit and a bioreactor with engineered renal tubule cells. Importantly, patients with the device would not need treatment of immunosuppressive drugs, he said. The team has successfully implanted and operated the device in pigs for 7 days without immunosuppression. Roy estimated his team needs approximately $20 million and 3–4 years to get through the first clinical human trials. "If we do that, we're able to get to something that will provide patients a better quality of life and save costs and allow us to change how end stage renal disease is treated," he said.

Vascular biologist and tissue engineer Ben Shepherd, PhD, is co-founder and chief executive officer of Trestle Biotherapeutics. His team focuses on regenerative medicine. They aim to develop implantable therapeutic tissue that would replace the kidney, using a patient's own stem cells to grow more cells and then a new kidney in the laboratory. This would be a solution "that restores renal function, that provides freedom of mobility, that doesn't come with an increased risk of infection, [and] that doesn't come with an increased risk of cancer," he said.

Shepherd explained that all of the technology his team needs already exists; the challenge is putting it all together. "[At Trestle, we are] taking newly formed stem cells and creating cells that will become the kidney, organizing those into miniature organs that contain blood-filtering units that are essential to renal function. And we're now using 3D bioprinting techniques to make larger tissue with interconnected, fluid-filled channels so that we can mature that tissue and get it ready for transplantation. But to be clear, there's a long way to go," Shepherd continued. "Some of these things are more advanced than others. Some simply require more capital and research and development. And some, we must understand much better before we could ever safely administer them to a patient."

As the KidneyX Summit came to a close, Rush reiterated the importance of developing technology that would realistically work with patients' lives and their needs. "With all the exciting things on the horizon—it's great to see all the technical stuff and scientific things, [but we need to marry] the two between the patient and the technology, making sure that the technology equals some of the patients' needs and some of the needs of the people involved in the patients' lives," Rush said. "We need both of them to co-exist." ■

2023 KidneyX winners

Track 1 participants each received $1.6 million, and Track 2 participants each received $1 million.

Track 1: Accelerating the prototype of a bioartificial kidney

David K.C. Cooper, MD, PhD, FRCS
Alemtuzumab induction therapy in monkeys with life-supporting pig kidney transplants

Matt Tector, PhD
Renal xenograft phase 2: Solving the donor kidney shortage

Track 2: Components and tools that enable the development of an artificial kidney

Anthony Atala, MD
3D Vascularized biomimetic renal construct platform for accelerated vascular integration

William Chang, MD, PhD
Engineering bioartificial kidneys: Combining kidney organoids and peritoneal dialysis

Nils Olof Lindström, PhD
Draining artificial kidneys by connecting synchronized nephrons to synthetic organizers

Harald C. Ott, MD
Manufacturing and system dynamics tools enabling autonomous blood purification implants

Shuvo Roy, PhD
Immunoprotective bioreactor for kidney cell encapsulation

Ben Shepherd, PhD
Bioengineered therapies for patients with kidney failure

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Generative AI

Continued from cover

"There's a lot of promise for artificial intelligence and machine learning," said nephrologist Girish N. Nadkarni, MD, MPH, director of The Charles Bronfman Institute for Personalized Medicine and system chief of the Division of Data-Driven and Digital Medicine (D3M) at the Icahn School of Medicine at Mount Sinai in New York. "One is the significant promise in helping to cut down the drudgery of medicine…. More specific to nephrology, if you think about patients on dialysis, there's a lot of documentation burden there."

Generative AI use cases

Telehealth use and virtual communication with patients skyrocketed during the COVID-19 pandemic, a convenience and patient expectation that is not going away, said nephrologist Karandeep Singh, MD, MMSc, associate chief medical information officer of artificial intelligence at the University of Michigan Medical School. But the increased administrative burden can contribute to clinician burnout, he said. Could chatbots increase productivity, lessening that burden?

ChatGPT and similar tools are good at creating boilerplate text that is tailored to the circumstance or context, Singh said. "Maybe I can reply to double the number of messages if all I need to do is to say the short version of what I want to say and then have this tool turn that short version into something that's coherent and more palatable as a letter to a patient," he suggested.

Chatbots will likely be integrated as part of electronic health record (EHR) systems. They could be instructed to listen in on an ambient conversation between a patient and clinician and write up a summary of the discussion. Or, a chatbot could draft a letter or follow-up instructions to a patient based on the information in their EHR. In fact, Epic and Microsoft are already piloting a program to draft responses to patients at three sites: University of California San Diego Health, Stanford Health Care in California, and University of Wisconsin Health, Madison (1). It is part of a larger partnership between the two companies to implement AI tools into Epic's EHR system.

Singh also envisions a nephrologist using an AI chatbot for diet management for a variety of patients. For example, if a clinician wants to create a meal plan for a patient who speaks Punjabi, incorporating Indian food that is low in phosphorus and potassium, it could take a lot of research time. But a generative AI tool, such as ChatGPT, could quickly create a sample meal plan based on the parameters that a clinician inputs. The clinician would then fact-check the results. "I think that's the sort of thing where you don't put patient information in there, but you can tailor something to that person in a way that would have been much harder before," Singh said.

It could also be prompted to translate the text into another language and at a specific reading level, said Daniel Rizk, an MD/MS dual-degree student and mentee of Singh's in his machine learning lab. "I've tested [ChatGPT] with Spanish, and its translation is quite good, but further, you can say, 'Write this at a sixth-grade level,'" Rizk explained. "You can tailor the language so that it can match the patient even a little bit better, which, I think, is just another component of saving time and meeting the patient where they are."

In the area of practice management, these tools can be used to create physician schedules. "You can put in your set of constraints—like this person can't work on this day; this person can't work on that day—and come up with a schedule that works for everyone. You can get a reasonable first draft of the schedule," Singh said. He also believes as the tools advance, software will be consolidated, which can save practices money. "Small practices that are used to paying for a lot of these tools separately are going to be thinking more of 'What tools am I using that are specific to one task?' and 'Could I instead use something more general like a large language model to actually accomplish that task?'"

The use of AI is only going to increase, and it is critical that clinicians keep updated.

Other potential use cases include chatbots taking patients through a series of questions to help them schedule an appointment or generating summaries of an existing EHR for a clinician to review, said Lili Chan, MD, associate professor in the Division of Nephrology and D3M at the Icahn School of Medicine at Mount Sinai. As part of a research project, Chan is using AI—not specifically generative AI—to see if it can identify novel risk factors, such as social determinants of health (SDOH), from EHRs of dialysis patients. "The goal is to develop some way of increasing the recognition of these factors to the overall practice," she said. "So maybe we could pull them from the EHR and do some form of a flag of the patient or reporting to the physician." Her team is in the early stages, surveying patients about their SDOH, before testing the AI system.

Generative AI concerns

GPT-3.5 is free and open for anyone to try; however, Chan cautioned that many use cases in health care are "still quite a bit away" because there have been no firm validation studies. In particular, there needs to be research on the safety and efficacy of these tools for patient communication, she said. In addition, clinicians must not input any patient information into ChatGPT or similar tools, as they are not HIPAA compliant. Experts agree that clinicians should always fact-check any answers from generative AI. ChatGPT, in particular, is prone to "hallucinations," in which it does not have the answer and can respond with false information. The answers can often sound and look accurate, such as fabricated journal citations or book titles and authors.

"The current crop of models is prone to something called hallucinations. So, they only know what's in their training set," Nadkarni said. "They obviously can extrapolate a lot, but if there's not something in their training set and you ask [them] a question, because they want to generate a response, they make up stuff…. That might be fine in creative writing… but in medicine, that might be dangerous because [they] can make up a diagnosis."

Another concern is bias. Generative AI is pulling information from the data sets it was given. It does not know how to discern truth. Instead, it is "predicting" which words come after one another based on the context. "A lot of these models can potentially be generated from data that [are] inherently biased," Chan said. "And so, when they generate this information, it will also result in data that [are] biased. I think that is quite a large concern."

Chan pointed to previous research that examined stigmatizing language in the EHR, showing that words such as "noncompliant" and "nonadherent" were used more often for Black patients. "If we're now using an existing EHR to describe a patient, then those biases or stigmatizing language in those notes are going to be perpetuated within that generated text from AI," she explained.

Regulation needed

Despite all of the attention on AI, there are no federal regulations for the technology. At a Senate committee hearing in May 2023, some Democrats and Republicans said they support creating a federal agency to regulate AI. Even Samuel Altman, chief executive officer of OpenAI, told the committee that he supports regulations, according to news reports (2, 3). For now, Nadkarni said, "Health care [practitioners] and health systems need to have some sort of oversight, ethics, and governance to ensure they are being used safely and efficaciously and appropriately."

Experts also agreed that health care clinicians need to become educated on how AI works, along with the benefits and risks. Even if clinicians do not seek out AI, it will be incorporated into future tools that they frequently use. Microsoft, for example, announced in March 2023 that it is incorporating its new AI tool, Copilot, into its 365 suite of programs (4). Furthermore, patients will be using AI and bringing information to their doctors, much like they use Google, Singh said.

The use of AI is only going to increase, and it is critical that clinicians keep updated, Rizk added. "There's this kind of wave of AI that's coming for the majority of professions in America and more globally," he said, "and I think it's really important that doctors are stakeholders in this conversation and deployment." ■

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ASN President's Update

Finding Ways to Take Sides but Remain United

By Michelle A. Josephson

ASN Kidney Week will return to Philadelphia, PA, in 2023, from November 1st (Early Programs) through November 5th (Annual Meeting). Philadelphia is known as the City of Brotherly Love because its name combines two Greek words: *phileo*, which means love, and *adelphos*, which means brother (1). William Penn, the city's founder, wanted to establish a place of religious tolerance where people would not be persecuted for their beliefs. He also hoped to live in peace with the region's indigenous population.

In medicine, no matter our affiliations or titles, we all benefit from a shared, common goal: the health of the patient.

In thinking about the City of Brotherly Love, I'm struck that we are living through a divisive time, failing to agree on much of anything and demonizing differing views. Everywhere you look, one group or position is pitted against another, particularly in politics. People dig in their heels and will not even listen to other approaches. We have really hit an all-time high—or, from my perspective, an all-time low—with what can only be described as tribalism.

As ASN returns to Philadelphia and (in many ways) the birthplace of the United States of America, I must ask: Are we still united? I am not so sure. That may sound like an unpatriotic opinion, especially in July when the country celebrates its 247th birthday. However, our current state of politics has me feeling that way.

Stubbornly taking sides is an age-old phenomenon. As a transplant nephrologist, I am well aware of people taking sides, healthy debates about care and ethics, and identity politics. Is a transplant nephrologist a transplanter or a nephrologist? My answer to that question is "Yes!" I like having a clear identity, and I'm fundamentally a consensus builder. As a transplant nephrologist, however, I have gotten used to living with multiple perspectives and simultaneous identities. Through this experience, I have become comfortable hearing different perspectives and, when possible, finding common ground.

Not everyone feels this way. Some colleges and universities try to shield students from hearing ideas that differ from their own and that they may find discomforting. Although a frequent practice, not all academic institutions approach differences of perspective this way. Robert Zimmer, president of the University of Chicago from 2006 to 2021, passed away in May. During his tenure, he put into place "Chicago Principles," guidelines for upholding the idea that "concerns about civility and mutual respect can never be used as a justification for closing off discussion of ideas" (2). Perhaps my years at the University of Chicago have helped me get used to hearing different perspectives, as much as I may disagree with some of them.

In medicine, no matter our affiliations or titles, we all benefit from a shared, common goal: the health of the patient. That is a huge advantage in having us consider different approaches and being able to reach agreement or accept a plan. And in nephrology—whether private practitioner, academic clinician, researcher, educator, general nephrologist, transplant nephrologist, or other kind of nephrology subspecialist—we too have a common, shared goal. This reality was nicely articulated in the We're United 4 Kidney Health campaign that used surveys, focus groups, and a consensus-building process to identify four priorities: intervene earlier, transform transplant, accelerate innovation, and achieve equity (3).

Working toward such a shared goal is one way to unite. Another approach is to unite in opposition to a shared enemy. David M. Oshinsky won the 2006 Pulitzer Prize in History for his book, *Polio: An American Story. The Crusade That Mobilized the Nation Against the 20th Century's Most Feared Disease* (4). He tells the story of how the public, led by a patient organization that became the March of Dimes; politicians, especially former President Franklin D. Roosevelt, who was diagnosed with polio in 1921; and scientists, most notably Jonas E. Salk, MD; Albert B. Sabin, MD; and Isabel M. Morgan, PhD, worked together to find a cure.

To take it a step further, an old proverb states, "amicus meus, inimicus inimici mei" ("my friend, the enemy of my enemy"). Although the origin of this proverb is debated, I'm struck by how many cultures have used it (or a close variation) throughout history.

With the story of polio and this proverb in mind, you may be thinking that is exactly what we did during the COVID-19 pandemic. Didn't we stick together against a shared enemy—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—particularly for the first year of the pandemic? I believe we reverted to opposing camps during the second year of the pandemic due to the difficulty in balancing personal freedoms and public health. Too many people unnecessarily lost their lives because they did not accept the science behind the vaccine.

Balancing personal freedoms and public health is nothing new. We have speed limits, seat belt laws, and motorcycle helmet laws, to name a few. However, the pandemic helped fuel this division between personal freedoms and public health, causing it to take on other dimensions and reach a crisis point, especially when we consider the current debate over reproductive health in the United States.

In Roe v. Wade, a 1973 case before the U.S. Supreme Court, Roe argued that the Texas antiabortion law violated an individual's right to liberty under the 14th Amendment to the U.S. Constitution. Roe further argued that the Texas law infringed on rights to marital, familial, and sexual privacy guaranteed by the Bill of Rights and that the right to an abortion is absolute. Roe sided with personal freedoms.

By contrast, Wade argued that states have an interest in safeguarding health, maintaining medical standards, and protecting prenatal life. According to Wade, a fetus is a person protected by the 14th Amendment, and protecting prenatal life from the time of conception is a compelling state interest. Wade argued for the public health of the unborn fetus.

In the Supreme Court's decision on Roe v. Wade, Justice Harry Blackmun, who drafted the majority opinion, wrote that the court held a woman's right to an abortion was implicit in the right to privacy protected under the 14th Amendment. Nearly 50 years later in 2022, the Supreme Court reversed itself in Dobbs v. Jackson Women's Health Organization, stating that the Constitution does not confer a right to abortion and returned to individual states the power to regulate any aspect of abortion not protected by federal law.

Since the Dobbs v. Jackson ruling, we have witnessed turmoil, unrest, and chaos, as well as even more divisiveness. Some states are upholding the right to abortions, whereas others are restricting access after 6–22 weeks of pregnancy. A few states may be considering bans for women to travel to a different state for an abortion, and Idaho is the first state to make it illegal to help a minor cross state lines to get an abortion without parental consent. In May 2023, the only five women in the 46-member South Carolina Senate formed a coalition that fought unsuccessfully against the 6-week ban on abortions in that state (5). The five senators include three Republicans, one Democrat, and one Independent, which gives me hope—despite the ultimate result in this case—that we can work together across political divides to address important challenges. For now, the law is on hold, however, until the state Supreme Court can review the case.

The issue of reproductive health has become even more complicated with conflicting rulings over the abortion drug mifepristone. In April 2023, U.S. District Court Judge Matthew J. Kacsmaryk, a federal judge in Texas, ruled in Alliance for Hippocratic Medicine et al v. the U.S. Food and Drug Administration (FDA) et al to suspend the FDA's 23-year-old approval of mifepristone. On the same day as Judge Kacsmaryk's ruling—illustrating how divided the United States is—Judge Thomas O. Rice of the U.S. District Court of Eastern Washington state ordered U.S. authorities not to make any changes that would restrict ac-

cess to mifepristone.

As a member of the Council of Medical Specialty Societies (CMSS), ASN condemned Judge Kacsmaryk's ruling and raised concerns over how it undermines the FDA (Table 1). A "coalition of 50 specialty societies representing more than 800,000 physicians across the house of medicine," CMSS "works to catalyze improvement through convening, collaborating, and collective action" (6). In addition to ASN, CMSS includes the American College of Physicians, American College of Surgeons, and American College of Obstetricians and Gynecologists.

The Biden Administration took Judge Kacsmaryk's ruling to the Fifth Circuit Court, which blocked the part of the ruling that overturned the 2000 FDA approval but also restricted mifepristone's use from 10 weeks to 7 weeks of pregnancy. The administration then appealed the ruling to the Supreme Court, which blocked the lower court's ruling but has returned the case to the Fifth Circuit Court. The future of access to mifepristone is unclear. The only matter that is clear is that this situation is very fluid. Whatever recent rulings apply to mifepristone are unlikely to be the end of this story, and the Supreme Court's decision in Dobbs last year raises the possibility that each state will have the ability to regulate mifepristone individually in the future.

In addition to concerns over how Judge Kacsmaryk's ruling undermines FDA's authority, sets a terrible precedent for the future of patient-physician relationships, and increases the likelihood of further divisiveness, nephrologists have a personal stake in the outcome of access to reproductive care, including mifepristone. Full access to reproductive health services in nephrology is often a matter of kidney health and sometimes a matter of life and death (7). This is also an equity issue, with individuals who are socially disadvantaged and minoritized having both an increased risk of kidney diseases as well as reduced access to reproductive care (8).

For our patients with reduced kidney function, pregnancy can further diminish their kidney health as well as be associated with pre-term deliveries. Furthermore, for all women, even healthy women who do not have access to reproductive services, illegal abortions performed by individuals who are not medically trained have been associated with acute kidney failure, septicemia, and death (9).

As nephrologists, we have a vested interest in full reproductive health services, including but not limited to pre-pregnancy counseling, contraception, and prenatal care, as well as surgical and medical abortions. For our patients with kidney diseases—no matter what state in which they live—there is no choice between personal freedoms or public health. This issue is a matter of both kidney health and survival. Can we at least agree upon that?

Supporting FDA's role in safeguarding patients, I urge the Supreme Court to act swiftly to reverse Judge Kacsmaryk's decision. I also recognize that we live in divisive times. In my book group comprised of female pediatric pulmonologists, general pediatricians, psychiatrists, a pediatric ER physician, a primary care physician, a pediatric intensivist, a nurse, an ethicist, and me—a nephrologist—we differ on assessments and interpretations of the books we read as well as many of the most controversial issues of the day. We all agree, however, on the need to reverse Judge Kacsmaryk's decision.

The ASN membership is much larger and more diverse—with many opinions on this issue—than is my book group. Do you all agree with my perspective on this case? I think you should, but whether you do or not, I am always open to dialogue. ■

Michelle A. Josephson, MD, FASN, is Professor of Medicine and Surgery, University of Chicago, IL, and is ASN President. To comment on Dr. Josephson's editorial, please contact email@asn-online.org.

Table 1. CMSS response to Judge Kacsmaryk's ruling

The Council of Medical Specialty Societies (CMSS), a coalition of 50 specialty societies across medicine, strongly condemns Judge Kacsmaryk's decision which threatens to restrict access to a Food and Drug Administration (FDA)-approved medication and other treatments. We stand with patient groups who have recently warned of the threat that could result from this misguided Mifepristone ruling. We remain concerned that the recent order from the Fifth Circuit Court of Appeals will generate further confusion among the public as to the availability of mifepristone, a drug conclusively proven to be safe and effective, and undermine the scientific rigor of FDA review and approval.
The case of *Alliance for Hippocratic Medicine et al v FDA et al* sets a dangerous precedent that erodes an institution critical to Americans having access to the care they need. This decision is in direct conflict with CMSS's policy opposing government interference into the practice of medicine. As stated, "CMSS opposes any governmental efforts that interfere with the practice of medicine and undermine the integrity of the patient-physician relationship."
Physicians of all specialties depend on FDA for the rigorous assessment of the safety of drugs and devices. It is critical that physicians and other scientific experts determine the safety and efficacy of drugs and treatments. This ruling sets in motion a process to block access to mifepristone, which is used in the treatment of several diseases. This judicial decision on mifepristone could lead other courts to inappropriately block access to other safe and efficacious FDA-approved drugs and treatments.
Physicians and the patients we serve trust the expertise of FDA. If this judge's ruling is allowed to stand, physicians and patients can no longer assume that determinations about drug safety are made by experts.
We support the FDA's role in safeguarding patients and urge the United States Supreme Court to act swiftly to reverse Judge Kacsmaryk's decision.

See Council of Medical Specialty Societies (10).

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C3 Glomerulopathy with Concurrent Thrombotic Microangiopathy: Clinical and Immunological Features

By David Vadala and Jeffrey H. William

C3 glomerulopathy (C3G) and complement-mediated thrombotic microangiopathy (TMA) are both rare kidney diseases, with an incidence rate ranging from 0.2 to 1 case/million/year (1). Although they both occur due to dysregulation and overactivation of the alternative complement pathway with common pathophysiological mechanisms, they are two distinct disorders with significant clinical and pathologic heterogeneity (2). The presence of concomitant C3G with TMA is extremely rare, with sparse data in the existing literature (3). Furthermore, the prior descriptions of such cases do not provide as detailed an explanation of the unique clinical features, histological characteristics, immunological assays, and clinical outcomes with treatment.

Chabannes et al. (4) set out to elucidate these uncertainties with the largest retrospective case series, to date, identifying 16 patients with concurrent C3G and TMA, selected from 278 patients with biopsy-proven C3G in the French National Registry from 2009 to 2019. The median age at diagnosis was 39 years, 63% were female patients, 81% had hypertension, and 88% had an estimated glomerular filtration rate of <30 mL/min (median, 13 mL/min). Almost all patients (88%) had significant proteinuria, with a median of 3.5 g/g. Monoclonal gammopathy was identified in 25% of patients. Histological data from the 16 biopsies showed mesangial hypercellularity and endocapillary proliferation in the majority of cases, with crescents present in 38% of patients, along with interstitial fibrosis and tubular atrophy in 69% of patients. Immunofluorescence showed C3 predominant deposits in all cases.

Genetic analysis showed rare, heterogenous, pathogenic variants in 6 of 14 screened patients (43%). The most frequent acquired anomaly in the absence of a pathogenic variant in complement pathway genes was monoclonal gammopathy. It has been hypothesized that monoclonal immunoglobulins may play an immunologic role in alternative pathway dysregulation (5). Given the lack of standard-of-care treatments, the case series study (4) showed that therapeutic management was variable and included an array of immunosuppressive therapies, including corticosteroids, cyclophosphamide, eculizumab, rituximab, and clone-directed therapy. Patients treated with eculizumab (63%) had significantly improved kidney outcomes with a median survival of 21 months compared with 1.5 months in those who did not receive it ($p < 0.015$). Over a 90-month period, mixed C3G-TMA was associated with a poor kidney prognosis, and 39% of patients reached end stage kidney disease within 1 year of diagnosis and had a lower median renal survival compared with patients with isolated C3G (4) (Table 1).

Several important questions remain about these two rare kidney diseases. For example, does their coexistence in this subset of C3G patients indicate a shared pathophysiology, or is it just coincidence? Although alterations in the alternative complement pathway may lead to either disease process, the specific mutations that result in these distinct phenotypes are still being elucidated. We already know that different mutations within the complement factor H (*CFH*) gene itself can alter the factor H protein in distinct ways, leading to pathologic changes of either TMA (C-terminus) or C3G (N-terminus) (6). However, it is not clear if there are specific genetic mutations or acquired factor deficiencies or inhibitors that may specifically predispose to a mixed C3G-TMA phenotype. Although they have a different pathophysiology, the coexistence of anti-neutrophil cytoplasmic antibody and anti-glomerular basement membrane antibodies in "double-positive" vasculitis has been described as a hybrid-like disease process, with different rates of relapses and kidney survival than either diagnosis alone (7). A comparison of mixed C3G-TMA

phenotypes versus either of these individual disease processes may be instructive in approaching future treatment strategies. Another significant limitation in this study was that there was no histological consensus on the definitions differentiating TMA versus membranoproliferative glomerulonephritis lesions, leading us to be cautious in suggesting an association at all. Perhaps the most important reported outcome of this study is the expanding role of eculizumab in the treatment of these disease entities, with drastically improved kidney survival in this C3G-TMA cohort.

The ultra-rarity and heterogeneity of these disease processes and their even rarer coexistence will make it virtually impossible to conduct larger randomized studies. With publications such as these, we are further expanding the literature exploring the morphological, genetic, autoimmune, and functional assays in these patients with the hope of developing more targeted therapies to improve clinical outcomes in the future (8). ■

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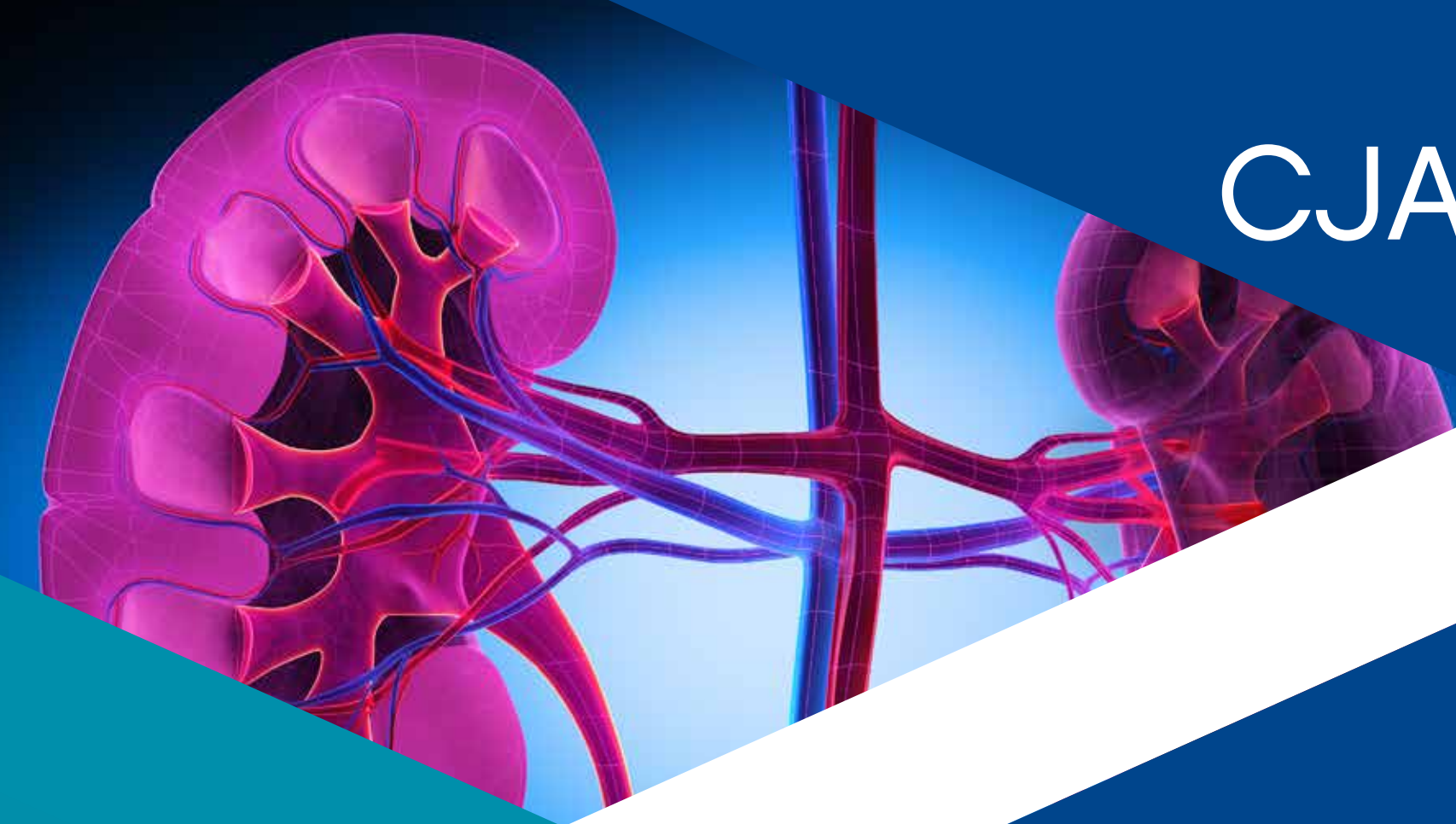
Table 1. Comparison of C3G-TMA case series

Parameter	Ravindran et al. (5) (n = 5)	Chabannes et al. (4) (n = 16)
Hematologic indices		
Hemoglobin (avg, g/dL)	8.8	8.5
Presence of schistocytes	20%	25%
Thrombocytopenia	20%	44%
Presence of monoclonal immunoglobulin	20%	25%
Complement pathway/genetics		
C3 (mg/dL, avg)	67.6	72.4
C4 (mg/dL, avg)	20.8	30.4
C5b-9 level (ng/mL)	N/A	596.2
Factor H level (% of normal range, avg)	N/A	103.3
Factor I level (% of normal range, avg)	N/A	110.3
Presence of anti-factor H antibodies (%, avg)	N/A	25%
Histopathologic features[a]		
Sclerotic glomeruli (% of total glomeruli, avg + range)	16.3% (0–37.5%)	16.9% (0–56%)
Presence of crescents (% of all biopsies)	20%	37.5%
Presence of double contours (% of all biopsies)	60%	75%
Interstitial fibrosis/tubular atrophy >50%	0%	19%

N/A, not applicable.
[a]Due to differences in assessment of specific histologic features of C3G and TMA between studies, some features could not be compared directly.



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From left to right: Shannon McGurry, RN (Fresenius Kidney Care Home Therapy Nurse); Christin Giordano McAuliffe, MD, FACP; Ms. C with Baby M; Candy Strombeck, RN (Fresenius Kidney Care Home Therapy Program Manager)

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 preconception to managing kidney diseases during pregnancy and lactation. Additional articles will appear in the August issue of *Kidney News.*

REFLECTION
ON THE PRIVILEGE OF CARING FOR PREGNANT PATIENTS WITH CHRONIC KIDNEY DISEASE

By Christin Giordano McAuliffe

I met Ms. C when she was pregnant at 15 weeks gestation. She was referred for proteinuria, hematuria, and abnormal kidney function. Over the course of the next few weeks, we weighed the pros and cons of a kidney biopsy, home vs. in-center dialysis, genetic testing, and more. I spoke with multiple physicians, including nephrologists and obstetricians featured in this section, for guidance and reassurance. As her pregnancy progressed, and her kidney function worsened, Ms. C, her team, and I used shared decision-making to decide to start her on home hemodialysis, which would ultimately allow her to dialyze at her rural home while her child recovered in the neonatal intensive care unit. There was an anxious moment as her home-training nurse started the machine, but Ms. C did great. She completed her training in a record timeframe—under 4 weeks. When her blood pressure began to rise at the end of treatment, we collectively agreed it would be best to admit her for the remainder of her pregnancy. While her husband was several hours away, she went into labor overnight. I headed to the hospital and had the ultimate privilege of being with her as she labored. After her son was born, we talked through the challenges of breastfeeding, and I reached out to lactation experts to learn more than what I knew from my own experiences. Through a team of experts and caring physicians, Ms. C has thrived as a patient receiving home hemodialysis, and her son has grown and exceeded all expectations.

Having children is important to many of our patients and with the advancements in reproductive assistive therapies and the younger age at which patients are affected by kidney diseases, we will continue to see more opportunities to assist our patients with having the families they desire in the healthiest and safest way possible. Taking care of these patients is an incredible, sometimes harrowing experience. Pregnancy in women with chronic and end stage kidney disease has been a keen interest of mine. However, despite my reading, research, and prior experiences, I had to call upon a team of experts to provide my patient with the best care. My hope is that this special section in this issue of ASN *Kidney News* will provide nephrologists with a window into the awe-inspiring and transformative experience of providing care for these women and their children and will be a resource of both knowledge and encouragement for those facing these challenges with their own patients. ■

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The author and section co-editors report no conflicts of interest.

Preconception Counseling for Women with Chronic Kidney Disease

By Mala Sachdeva

The prevalence of chronic kidney disease (CKD) is slightly higher in women than men. Women of childbearing age make up a small, yet important portion of this population (1, 2). Asking women in this age group about their future family plans can prevent unplanned pregnancies, provide timely education and intervention, and decrease adverse fetal and maternal outcomes associated with CKD. Still, for some women or for some nephrologists, speaking about pregnancy may be an uncomfortable and unfamiliar topic of conversation during an office visit. Discussed below are pertinent topics of conversation that can allow nephrologists to start an impactful conversation with their patients (Table 1).

Timing of pregnancy should be discussed so that pregnancies can be planned. This can be dependent on numerous factors, such as remission or relapse of their underlying glomerular disease, control of hypertension, rate of progression of their current kidney disease, age, and their status for kidney transplantation. If glomerular disease is in remission for 6 months to 1 year, it may be an ideal time to try to conceive. If the rate of kidney function decline is rapid, then pregnancy should be postponed, as CKD progression may accelerate. Ideally, if kidney transplantation is possible, then postponing pregnancy until 1–2 years post-transplantation would be preferred. Still, post-transplantation pregnancies carry their own maternal and fetal risks, including preterm deliveries, cesarean sections, preeclampsia, gestational diabetes, and pregnancy-induced hypertension (3). Likewise, if age permits, pregnancy can be postponed until the patient is well optimized.

For women who are not planning pregnancy, conversations regarding contraception should be initiated, and these can be followed up with more detail provided by a gynecologist. Individual preference, timing of conception, adherence to medications, along with underlying comorbid conditions, such as hypertension, thrombogenic conditions, and CKD, should be taken into consideration when discussing risks and benefits of certain contraceptive methods (4). Different methods of contraception are provided in Table 2.

Fertility is an important topic to consider in women with CKD. This is of particular concern with past use of medications, such as cyclophosphamide, or even living with CKD, which can impact fertility potential. When treating women of childbearing age, nephrologists need to be mindful of what the woman's future family plans are so that fertility can be preserved as much as possible. If a woman chooses the use of assisted reproductive technologies (ARTs) to aid infertility, similar preconception counseling and assessment should be performed before beginning any ART. ART comes with inherent risks to the mother and fetus, which are likely similar to those for CKD yet not completely understood (5). ART increases risk of hypertensive disorders of pregnancy, including preeclampsia, preterm deliveries, and low birth-weight infants (6).

Laboratory testing to help prognosticate kidney outcome, as well as maternal and fetal outcomes, should be appropriately performed. Pre-pregnancy, 24-hour urine for proteinuria, creatinine clearance, and serum creatinine levels can all help with counseling. Checking hemoglobin A1c levels will be helpful for those with diabetes mellitus. Assessing autoimmune activity in patients with lupus vasculitis, for example, should be performed. Since challenges of performing a kidney biopsy during pregnancy exist in women with proteinuria of undetermined etiology, performing a kidney biopsy pre-pregnancy may be indicated to ensure there is a pre-pregnancy glomerular diagnosis so that appropriate therapy can be initiated during pregnancy if indicated. Likewise, in women with advanced CKD, performing a kidney biopsy may help prognosticate their post-pregnancy kidney outcome, as well as offer treatment if the disease progresses during pregnancy.

Based on lab assessment, it is important to discuss risk with these women. Some women may be oblivious to the risks that their kidney disease poses on a pregnancy. Risks of relapse, progression of their underlying kidney disease or proteinuria during pregnancy, and adverse outcomes of CKD to the mother and fetus should all be discussed. Women with CKD have a higher likelihood for preterm deliveries, gestational hypertension, preeclampsia or eclampsia, and cesarean sections (7). Adverse fetal outcomes include small gestational-age and lower birth-weight infants and increased admissions to neonatal intensive care units (8).

Appropriate medication adjustments should be made before conception. In women treated with immunosuppressive agents, such as mycophenolate mofetil, whether for post-transplantation or for the treatment of glomerular disease, pregnancy should ideally be postponed until teratogenic medications are successfully removed for a reasonable amount of time or substituted for non-teratogenic agents. Similarly, women who are being treated with antihypertensive agents that are teratogenic, such as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, should be switched to other, safer alternatives, such as labetalol, hydralazine, calcium channel antagonists (e.g., nifedipine), or methyldopa. Blood pressure should be followed up to ensure optimal control preconception. Sodium-glucose cotransporter-2 inhibitors have been shown to affect kidney development in animal studies, especially in the second and third trimesters; hence, these medications should be avoided until more is known about their use in pregnancy. Diuretics should be used with caution to

Table 1. Components of preconception counseling

Discussion on the timing of pregnancy
Contraception counseling
Assessment of fertility status
Use of assisted reproductive technologies
Medication reconciliation
Assessment of kidney disease, kidney function, and proteinuria
Control of blood pressure
Counseling on adverse fetal and maternal outcomes associated with CKD
Referral to appropriate subspecialists
Referral to high-risk obstetrician

Table 2. Types of contraception

	Short-acting contraception	Long-acting, reversible contraception	Permanent contraception
Progestin only	Depo-Provera injection	Levonorgestrel intrauterine device (LNG IUD)	
	Progestin-only pills	Etonogestrel implant (ENG implant)	
Combined estrogen/ progestin	Combined oral contraceptive pills		
	Transdermal patch		
Non-hormonal methods	Male or female condoms	Copper IUD	
	Diaphragms		
	Vaginal sponges		
	Cervical caps		
Surgical			Sterilization vasectomy
			Tubal ligation
			Salpingectomy

prevent volume depletion. Since CKD is a risk factor for preeclampsia, low-dose aspirin is ideally initiated before 16 weeks gestation to decrease risk (9).

One nephrology office visit can suffice to initiate and discuss most issues that encompass preconception counseling. Follow-up on the recommendations from this visit are still recommended. Referral to a high-risk obstetrician and other subspecialists in a timely manner can further supplement appropriate preconception counseling and stratification. ■

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Hypertension Management During Pregnancy

By Kelli King-Morris

Hypertension during pregnancy is defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure ≥90 mm Hg on two separate occasions at least 4 hours apart. Hypertension complicates 10% of pregnancies worldwide (1). Classically, the presence of hypertension prior to 20 weeks gestation has been attributed to the presence of preexisting, essential hypertension. However, with an aging maternal population, rising obesity rates, and the success of fertility improving in those with chronic illness, the development of earlier onset blood pressure derangements is notable (2). The Survey of Neonates in Pomerania (SNiP) study found that 27% of American women of childbearing age experienced one or more chronic diseases (3).

Healthy maternal alterations in prostaglandins, activation of the renin-angiotensin-aldosterone system (RAAS), and a subsequent increase in glomerular filtration rate typically result in lowering of maternal systemic blood pressure. One can expect up to a 0.4- to 0.8-mg/dL reduction in serum creatinine and lowering of approximately 10 mm Hg in blood pressure by the second trimester, with mean values of 105/60 mm Hg (4). Markers of preeclampsia, either superimposed or de novo, include the development of new-onset hypertension, reduced kidney function, thrombocytopenia, pulmonary edema, or neurologic symptoms, such as headache or visual stigmata. The glomerular endotheliosis present with preeclampsia is associated with sodium retention despite intravascular depletion (5). Placental factors have been implicated in its development.

Pharmacologic treatment of hypertension during pregnancy remains largely unchanged in this population. Treatment mainstays are non-dihydropyridine calcium channel blockers, β-blockers, clonidine, and, now less commonly, the centrally acting α-2 adrenergic agonists (methyldopa) (Table 1). Postpartum care may include RAAS blockade agents, such as enalapril, which has been documented to have less accumulation for lactating mothers. In 2022, the investigators of the Chronic Hypertension and Pregnancy (CHAP) trial found that using 140/90 was a threshold for initiation or titration of medical therapy for chronic hypertension in pregnancy, rather than the previously recommended threshold of 160/110 (6). In the setting of preeclampsia-induced hypertension, magnesium sulfate infusion triggers vasodilation affecting blood pressure reduction and particularly cerebral events and prevention of eclamptic events (7).

Long-term cardiovascular complications of hypertension experienced during pregnancy are becoming more well established. Once exposed to gestational hypertension or preeclampsia, the risk of subsequent hypertension was increased 5.3-fold (range, 4.9–5.8) after gestational hypertension, 3.6-fold (range, 3.4–3.8) after mild preeclampsia, and 6.1-fold (range, 5.5–6.8) after severe preeclampsia. Of those with chronic hypertension, 25% will develop preeclampsia (8). Primary prevention strategies for cardiovascular morbidity or mortality may be warranted for those who have experienced a hypertensive disorder in pregnancy (9). ■

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Table 1. Pharmacologic treatment of hypertension during pregnancy

Antihypertensive	Dosing strategy
Oral	
Nifedipine	20–120 mg/day once daily or in two divided doses
Labetalol	300–2400 mg/day in three or four divided doses
Clonidine	0.1–0.3 mg orally two to three times daily
Methyldopa	500–2000 mg/day in three or four divided doses
Intravenous[a]	
Hydralazine	5 mg IV bolus; then if needed, 5–10 mg IV to a maximum of 45 mg
Labetalol	20 mg IV; then if needed, 40 mg and then 80 mg to a maximum of 300 mg

IV, intravenous. Adapted from Mol et al. (8).
[a]Reserved for severe hypertension (blood pressure >160/110 mm Hg).

The Diagnostic Dilemma of Kidney Stones in Pregnancy

By Cynthia O'Sullivan and Nadya York

Young, pregnant patients presenting with loin or back pain and associated hydronephrosis on imaging create a diagnostic dilemma. The challenge is establishing the causal link between the pain and imaging while limiting or minimizing radiation exposure. Although back pain in pregnancy is common, it can be secondary to physiological changes in pregnancy or pathological causes, which may be obstetric or non-obstetric in nature. Kidney stones are the most common cause of pathological pain (1).

The incidence of kidney stones is increasing and affects 10% of people at some point in their lives. A stone event occurs in 1 out of every 200–1500 pregnancies, with 80%–90% presenting in the second and third trimesters (2). Although the incidence of stones is no higher in pregnant women than in the non-pregnant population, a stone event during pregnancy represents a unique clinical situation that poses risk to both the mother and the fetus.

Pregnancy is a complex state that alters the risk factors for stone formation. Increased stone promoters are offset by an increase in stone inhibitors. Urinary stasis promotes stone formation, and hydronephrosis during pregnancy occurs in 90% of pregnant women, often physiological from compression at the pelvic brim by the growing uterus and smooth muscle relaxation induced by elevated progesterone levels (2). These normal anatomical changes during pregnancy can make it challenging to determine the diagnosis.

On the basis of symptoms alone, a preliminary diagnosis can be made but can be incorrect in at least 30% of patients (2). Ultrasound remains the first-line imaging modality given its lack of radiation exposure. Although the specificity is as high as 94%, it has a low sensitivity of up to 45%, therefore failing to rule out stones. In one study examining kidney stones in pregnancy, only 60% of stones were identified using ultrasound (1–3).

This leads to a further diagnostic dilemma: what to do next. The best second-line imaging is controversial, with magnetic resonance imaging (MRI) previously being the recommended choice for its lack of radiation. However, it is often limited by availability and relies on secondary signs of a stone such as dilation (2).

Low-dose computed tomography of the kidney, ureter, and bladder (CT KUB) is increasingly being used because it has a higher positive predictive rate (>95%) than an ultrasound or MRI (2) but raises the question of the effect of radiation on the fetus. The good news is that fetal risk of anomalies, growth restriction, and abortion have not been reported with radiation exposure <50 mGy, which is endorsed by The American College of Obstetricians and Gynecologists (4, 5). The risk of carcinogenesis as a result of in utero exposure to ionizing radiation is unclear but is probably very small. A CT intravenous pyelogram has 10–15 mSv used for investigation of hematuria; however, a low-dose CT KUB has an average dose of 1–3 mGy, well below the concerning levels mentioned above (2).

Pregnancy is a complex state that alters the risk factors for stone formation.

The American Urological Association (5) and the European Association of Urology (6) advise that CT KUB should not be withheld if clearly indicated because the material benefit for early and accurate diagnosis may outweigh the theoretical harm to the fetus. Locally, we are endorsing the use of low-dose CT KUB in pregnancy as a second-line imaging modality following discussion in a multidisciplinary setting, including radiology, urology, and obstetrics specialties.

Managing proven kidney stones in pregnancy is a complex situation. Intrarenal stones will be managed conservatively along with uncomplicated ureteric stones. However, in the case of infection, uncontrolled pain, or worsening kidney function, an urgent de-obstructive procedure must be performed, either a stent or nephrostomy tube. Definitive stone treatment will be deferred until the woman is postpartum, or if an intervention is required, ureteroscopy or laser lithotripsy is safest in the second trimester. ■

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Pregnancy Among Patients with Lupus: Progress, Problems, and Promise

By Cassidy Onukwuli and Anika Lucas

Over the last several decades, we have made progress in the management of pregnant patients with lupus. Pregnancy is no longer prohibited in this patient population, and many patients have successful pregnancies without complications. We also have more knowledge about this disease and have more treatment options. We know that lupus disease activity should be quiescent for at least 6 months prior to conception (1). Individuals with prior kidney involvement, even with partial or complete remission, have a higher risk of developing active nephritis and additional pregnancy complications (2). Hypocomplementemia, including low C4, has been associated with renal flare during pregnancy (2).

Medications such as hydroxychloroquine have been associated with a reduced risk of developing high disease activity during pregnancy and pregnancy-related lupus flare, potentially improving long-term kidney outcomes (3) (Table 1). Low-dose aspirin use has also been associated with a reduced risk of preeclampsia in patients at high risk of preeclampsia, such as those with lupus (4). At many medical centers within the United States, interdisciplinary teams composed of nephrologists, rheumatologists, perinatologists, advanced practice providers, nurses, and other medical professionals provide care for pregnant people with lupus. The advancement in therapeutic options for lupus has also provided unique opportunities for treatment during pregnancy. For example, the Belimumab (Benlysta®) Pregnancy Registry (GSK study BEL114256; NCT01532310) has been established to evaluate pregnancy outcomes among pregnant patients exposed to belimumab. However, enrollment for this prospective study has been low—with only 55 participants reportedly recruited from a goal of 500 participants—over the course of 10 years (5).

Although there have been advances in the care for pregnant patients with lupus, many challenges still remain. Changes in immunosuppressant therapy may result in lupus flares in previously stable patients. Medications such as mycophenolate mofetil are discontinued during pregnancy due to their teratogenicity (6), with patients switching to azathioprine or tacrolimus as an alternative therapy. Pregnant patients with lupus still experience high rates of adverse pregnancy outcomes.

A recent study evaluating adverse pregnancy outcomes among patients prospectively enrolled in lupus pregnancy cohorts at tertiary and quaternary academic medical centers in North America found that at least two of five pregnant patients with lupus experienced an adverse pregnancy outcome. Patients with lupus nephritis had double the odds of preeclampsia (odds ratio [OR], 2.04; 95% confidence interval [CI], 1.01–4.13) and fetal loss (OR, 1.90; 95% CI, 1.10–3.56) compared with individuals without a history of lupus nephritis (7). Those with active lupus nephritis (defined by at least >500 mg/g on a spot urinary protein-to-creatinine ratio) had a sixfold higher odds of fetal loss (OR, 6.29; 95% CI, 2.52–15.70) and a threefold higher odds of poor pregnancy outcome (OR, 3.08; 95% CI, 1.31–7.23) compared with individuals without a history of lupus nephritis (7). Similar findings have been reported in other prospective lupus pregnancy cohorts around the globe. Pregnant patients with lupus continue to experience higher odds of adverse outcomes compared with the general population (8). Additionally, distinguishing between active lupus nephritis and preeclampsia during pregnancy may be difficult for even well-trained clinicians. Although kidney biopsies may offer a definitive diagnosis, performing this procedure during pregnancy is not without risk (9). Circulating angiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt 1) and placental growth factor (PlGF), have shown promise as biomarkers (10) but are not widely available in the United States.

To continue to improve outcomes for pregnant patients with lupus and their offspring, rigorous prospective cohort studies and pragmatic clinical trials will need to be conducted. Moreover, a biopsychosocial approach should be adopted to address the sociopolitical context of our patients and understand the structural barriers that may impact health outcomes. Finally, there is still more investigation needed to facilitate the identification of novel biomarkers, therapeutics, development of risk-stratification tools, and incorporation of the sFlt1/PlGF ratio as a screening test for preeclampsia into clinical practice to ensure even greater success for pregnant patients with lupus. ■

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Table 1. Safety of medications for SLE and blood pressure management in pregnancy and lactation

Agent	Safety in pregnancy	Lactation
Immunosuppression		
Hydroxychloroquine	Yes	Compatible
Azathioprine	Yes	Compatible
Tacrolimus	Yes	Compatible
Cyclosporine	Yes	Compatible
Mycophenolate	No	Limited data, not recommended
Cyclophosphamide	No. If life-threatening disease, can consider late in pregnancy	Not recommended
Glucocorticoids	Yes	Compatible
Voclosporin	No	Not recommended
Biologics		
Rituximab	Limited safety data, not recommended	Limited data, not recommended
Belimumab	Limited safety data	Limited data
Antihypertensives		
ACE inhibitors	No	Limited data available (no adverse effects observed in breastfed infants exposed to captopril or enalapril due to low levels in breast milk)
Angiotensin receptor blocker	No	No data available
Mineralocorticoid receptor antagonists	No	Limited data available
Diuretics	Yes. Use with caution	Can be used with close monitoring
Labetalol	Yes	Compatible
Hydralazine	Yes	Compatible
Nifedipine	Yes	Compatible
Clonidine	Yes (not recommended first line due to side effects)	Not recommended

ACE, angiotensin-converting enzyme; SLE, systemic lupus erythematosus. See also Singh (6) and Castro-Gutierrez et al. (11).

The Nephrologist's Role in Supporting and Promoting Lactation

By Anna Sadovnikova and Nandakishor Kapa

Breastfeeding has myriad benefits for both the mother and infant. For instance, breastfeeding is associated with a decreased risk of maternal hypertension, diabetes, and heart disease and reduced risk of gastrointestinal and respiratory illnesses for the infant (1). Nephrologists should select medications that support lactation and optimize maternal and infant outcomes. Nephrologists should also educate patients and colleagues about the effect of kidney diseases and their treatment on a patient's lactation potential. It is paramount that nephrologists advocate for patients to receive timely and skilled lactation support in the hospital and community. Herein, we present three case vignettes to spotlight the nephrologist's critical role in lactation support.

CASE 1. The obstetrics team consulted nephrology about a primigravida with stage 4 chronic kidney disease (CKD) who was induced at 36 weeks gestation due to preeclampsia and worsening kidney function.

1 How is milk production affected by CKD? Does the patient need specialized lactation support?

Patients with CKD can breastfeed successfully (2). This is despite the fact that they often deliver preterm, undergo induction, have cesarean deliveries, and receive intrapartum intravenous fluids that contribute to excess breast edema (3). Each of these factors can result in a delay in lactogenesis II, which is defined as the onset of copious milk production, typically occurring between 48 and 72 hours postpartum (4). Because of this, patients with CKD require lactation support early and often. Determining medication compatibility with lactation should be a priority to prevent delays in breastfeeding initiation. Knowledge of breast milk volume per 24 hours can be used to guide decisions about ultrafiltration, diuresis, fluid intake, and dry weight (2, 4). Daily breast milk volume increases rapidly, from <100 mL in the first 2 days postpartum (1–10 mL per feed) to >500 mL by day 7 postpartum (30–60 mL per feed) (4). Maternal perception of breast fullness on day 3 postpartum suggests normal onset of copious milk production; many women with chronic medical conditions, preterm deliveries, or obstetric complications will have a delay in lactogenesis II or report never feeling breast fullness (4). Full milk supply is defined as >600 mL per day between months 1 and 6 postpartum, with the average individual producing approximately 750 mL (4). Oversupply or hyperlactation is the production of more breast milk per day than is required by the infant for optimal growth, usually >1000 mL per day (4).

2 Are her medications safe for milk production and her infant?

Most medications are compatible with lactation and are safe for the infant, primarily because there is no risk for teratogenicity, as there is during pregnancy, and exposure to the maternal medication via breast milk is virtually always less than via placental transfer (Table 1 and Figure 1) (5, 6). When in doubt, write "[medication name] LactMed" into your search engine to access free, up-to-date, evidence-based information from the Drugs and Lactation Database (LactMed) of the National Institutes of Health.

CASE 2. A 33-year-old female is admitted to the intensive care unit with COVID-19 pneumonia. Her hospital course is complicated by septic shock, acute kidney injury, and need for hemodialysis. What should the nephrologist consider?

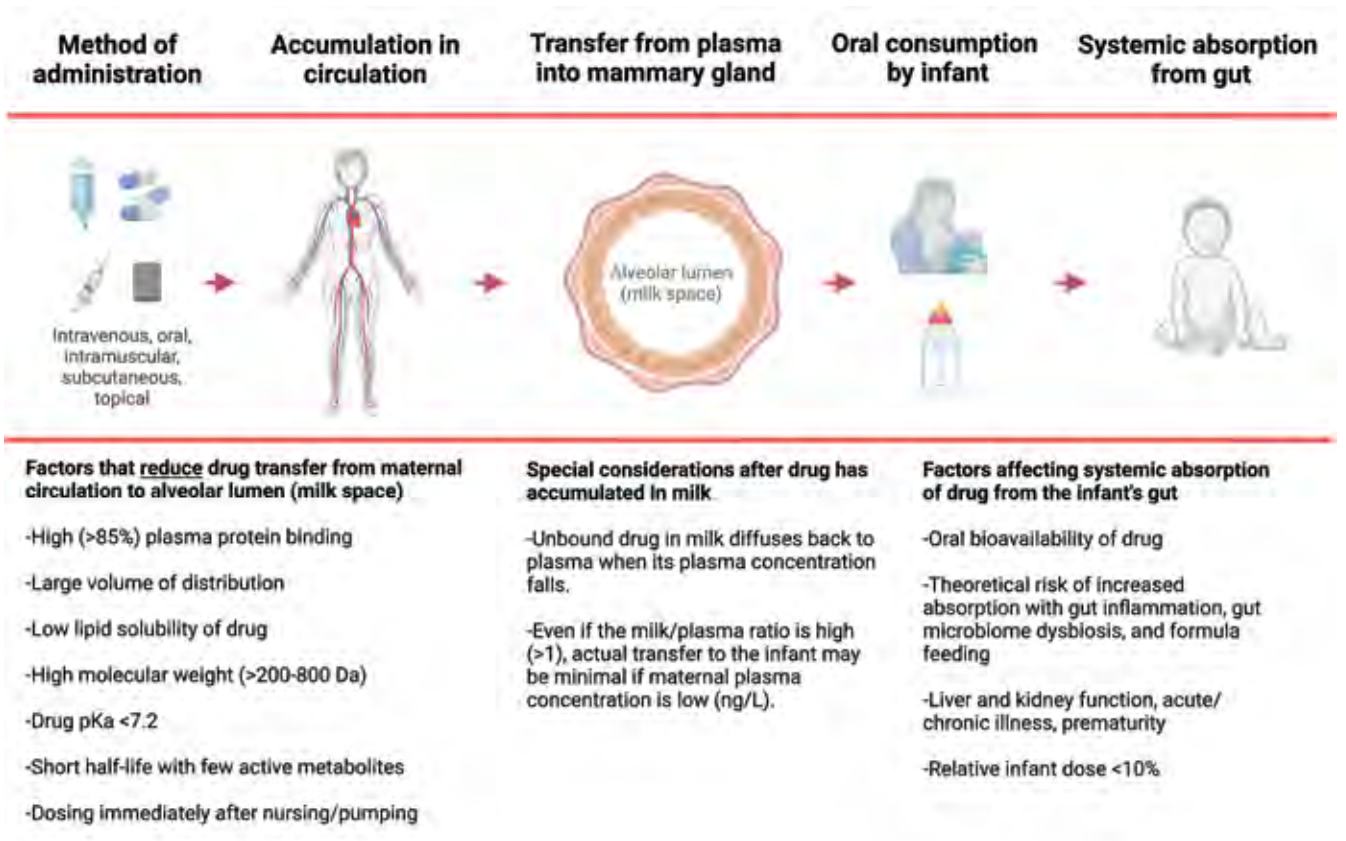
1 Is the patient lactating? If yes, does continued lactation in critical illness lead to issues in management?

Asking about lactation should be just as routine as asking about (or screening for) pregnancy. It is important to continue removing milk regularly by hand or pump or, if possible, allowing the infant to nurse to prevent milk stasis, breast infection, or sepsis. Nephrologists should, at a minimum, know how to contact lactation services and refer to the Academy of Breastfeeding Medicine, Clinical Protocol #35: Supporting Breastfeeding During Maternal or Child Hospitalization for additional information (7).

2 If she were to receive imaging with contrast or hemodialysis, would she need to discard ("pump and dump") breast milk?

Imaging with contrast is safe, and there is no need to pump and dump (8). There is not sufficient evidence to support interruption of breastfeeding for patients undergoing peritoneal dialysis or hemodialysis; expressing breast milk immediately before dialysis and saving it to mix with post-dialysis breast milk can be suggested. For the first 6 months postpartum, most women need to remove milk every 2–4 hours, so prioritizing home dialysis to limit maternal-infant separation is key (4).

Figure 1. Determinants of drug transfer from maternal plasma to breast milk and subsequent systemic absorption from the gut by the infant



In general, drugs that bind plasma proteins, have a large volume of distribution, low lipid solubility, or a high molecular weight are less likely to appear in breast milk. Whenever possible, drugs with short half-lives and few active metabolites should be considered and dosed immediately after nursing or pumping. If maternal plasma concentration of the drug is low, then actual transfer to the infant is low, even if the milk-to-plasma ratio is high. Finally, even if the accumulation of the drug in the milk is high, if it is not orally bioavailable, it is unlikely to have systemic negative effects because it will not be absorbed in high quantities by the infant's gut into the bloodstream. Physicians can select drugs with a relative infant dose <10%. For additional information, refer to Anderson's article, "Drugs in lactation" (9).

Figure created with BioRender.com.

CASE 3. **A 46-year-old, exclusively breastfeeding patient treated with azathioprine is found to have a lupus nephritis flare at 7 weeks postpartum.**

1 **Should she continue to breastfeed if she needs pulse-dose steroids or different immunosuppressive agents?**

Although oral corticosteroids are generally safe (5), injected or intravenously administered high doses of steroids may cause transient suppression of milk production (4). Patients can be advised to pump and save breast milk to mix it in small increments with breast milk free of exogenous steroids. Many common maternal immunosuppressants, including biologics, are considered safe for the infant (Figure 1 and Table 1) (5, 6). ■

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Table 1. Common drugs prescribed to patients with kidney diseases and their compatibility with lactation

Drugs	Compatibility
Calcium channel blockers (e.g., nifedipine, amlodipine)	✔
β-Blockers (e.g., metoprolol, labetalol)	✔
Angiotensin II receptor blockers (e.g., candesartan)	✔
Angiotensin-converting enzyme inhibitors (captopril, enalapril preferred)	✔
Erythropoiesis-stimulating agents (ESA) and per-oral/intravenous iron	✔
Phosphorus and potassium binders	✔
Alkalinizing agents (sodium bicarbonate, sodium citrate)	✔
Vitamin D analogs	✔
Sodium-glucose cotransporter-2 (SGLT2) inhibitors[a]	Unknown
Heparin[b]	✔
Azathioprine	✔
Tacrolimus/cyclosporine	✔
Rituximab	✔
Hydroxychloroquine	✔
Mycophenolate	✘
Sirolimus/everolimus[c]	✘
Cyclophosphamide[d]	✘

Drug information was derived from LactMed. Nephrologists should refer to LactMed to confirm medication compatibility with breastfeeding.

[a]These drugs are highly protein bound, so very little is expected in breast milk. Yet because there are no human studies, these drugs are not yet recommended in lactation.
[b]Caution only with certain preparations containing benzyl alcohol (potential toxic/anaphylactoid reaction for infants).
[c]One case report suggested that no adverse effects were experienced by an infant whose mother was taking an unspecified dose of sirolimus.
[d]Excreted in milk. If preservation of milk production is desired, patients can pump and discard milk for 72 hours postinfusion.

Fellows First

Beyond Fertility and Pregnancy: Women's Health in Kidney Care Must Become a Research Priority

By Anjali Muraleedharan

Current discourse on women's health in nephrology largely focuses on reproductive health and pregnancy, overlooking other sexual functions impacted by chronic kidney disease (CKD). The majority of women with CKD are beyond the typical child-bearing age. This population is predisposed to gynecologic problems such as decreased libido, menstrual cycle abnormalities, and early menopause, which may be directly impacted by their kidney disease or its treatment. Some of these common women's health issues outside of reproduction were touched upon during the recent Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on Women and Kidney Health (1). However, the main focus of this conference was on pregnancy and fertility, reflecting the lack of attention that matters outside this arena receive.

Women's health in CKD is a topic that is well outside of the comfort zone of many practicing nephrologists. In a 2019 survey of 154 nephrologists from the United States and Canada, only 55% reported having fellowship training in women's health. A significantly smaller percentage felt confident counseling on common women's health issues, like contraception, menstrual disorders, or menopause, compared with counseling on issues related to pregnancy (2). This is not surprising given the relatively sparse literature on this subject.

Many of the investigations into the prevalence and pathophysiology of sexual dysfunction and premature menopause in CKD were done in the 1970s through early 2000s. These investigations laid the groundwork for what we know today. In women with CKD and end stage kidney disease, there is disruption of the hypothalamic-pituitary-gonadotropin axis due to loss of pulsatile gonadotropin-releasing hormone (GnRH) (3, 4). This results in low follicle-stimulating hormone (FSH) and luteinizing hormone secretion by the pituitary and thus low estradiol production by the ovaries. The etiology of the loss of pulsatile GnRH is not fully understood, but excess prolactin, catecholamines, and endogenous opioids may contribute (3, 5, 6).

The consequences of this hormonal dysregulation are widespread. In a survey of 659 women with CKD, 84% reported sexual dysfunction, based on the female sexual function index score, and only 35% reported being sexually active (7). This significantly impacts the quality of life of patients with CKD. While similar findings in the male population have spurred research on interventions for erectile dysfunction in CKD, sexual dysfunction in women with CKD remains an under-investigated area in nephrology. Another survey showed that women with CKD tended to experience menopause, on average, 4.5 years before those without CKD, putting them at increased risk of cardiovascular disease and osteoporosis (8–10). In a cross-sectional study that made national news in 2023, Faubion et al. (11) estimated that missed work days due to menopause symptoms in the general population cost the United States a whopping $1.8 billion yearly.

Barriers to research of sexual dysfunction in CKD are many: varying definitions of sexual dysfunction, stigma, and multifactorial etiologies, to name a few (12). Premature menopause, although still multifactorial, is a relatively easier target. However, laboratory diagnosis of menopause is difficult in advanced CKD due to amenorrhea in the setting of low FSH levels, as opposed to the high FSH characteristic of menopause (13). As a result, many studies on menopause in CKD rely on self-reported questionnaires of menopausal symptoms. In spite of these obstacles, several treatment options have been explored. Restoration of menstruation was noted in amenorrheic premenopausal women with kidney failure after successful kidney transplantation, hormone replacement, or bromocriptine use (14–16). The lack of adequately powered randomized clinical trials on the safety of hormone replacement or prolactin-lowering medications in CKD means that there are no guidelines for their use. The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients from 2005 suggested that guidelines from the North American Menopause Society may be followed (17). However, these have changed since 2005 due to more data about cancer risk in the general population on long-term hormone-replacement therapy, and KDOQI recommendations have not been readdressed since.

The remarkable paucity of research and lack of funding in nephrology for women's health outside of reproduction are glaringly apparent (18). Time and time again, reports and reviews have shown the burden of sexual dysfunction and premature menopause on women with CKD, highlighted the gaps in data, and demonstrated the need for a trans-disciplinary approach to investigation. In recognition of this, the National institutes of Health started the Office of Research on Women's Health in 1990 and continues to mandate that investigators include sex as a variable in basic research and female trial participants in grant submissions (19). However, we as a nephrology community must pursue additional efforts to close these gaps of knowledge. Academic centers may be able to help shine the spotlight on this topic by providing more fellowship training on women's health outside reproduction. This could spur more participation in interdisciplinary conversations to better align patient priorities with research directions. ■

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Kidney Biopsy During Pregnancy: Risks Exist but Not Without Benefit

By Natalie McCall and Anna Burgner

Pregnancy has been described as a "great occasion" for the diagnosis of kidney disease. Kidney diseases are estimated to affect 3% of women of childbearing age (1). When kidney disease is newly diagnosed or flares during pregnancy, there are many issues concerning whether and in what circumstances kidney biopsy should be performed. This decision should be based on several factors, including the stage of pregnancy, severity of the kidney disease, and suspected underlying diagnoses.

The early diagnosis of glomerular diseases can have a profound therapeutic impact on the mother and the fetus. If kidney biopsy results offer a chance at a significant alteration in patient management, then a biopsy should be considered. A diagnosis that allows for immediate initiation of targeted treatment may allow progression of pregnancy to fetal viability with maternal protection. It also can be the grounds for discussion about the risk of continuing a pregnancy if the severity of the glomerular disease is high, and due to the side effects of medications, only a course of suboptimal therapy can be offered.

Kidney biopsies are typically performed in the prone position. As the pregnancy progresses, a gravid uterus can make the standard position untenable. In pregnant patients, biopsies have been successfully and safely performed with the patient sitting upright or in the lateral decubitus position. Kidney biopsies during pregnancy should be performed under ultrasound guidance and not computed tomography guidance to limit radiation exposure to the developing fetus. Otherwise, the logistics of performing a kidney biopsy during pregnancy are unchanged from the nonpregnancy technique.

The major risk of kidney biopsy is bleeding, which can range from minor to major. Major bleeds result in the need for blood transfusion, selective angiography and embolization, or death (2). In pregnancy, there is additional risk to the fetus with severe bleeding; not only would blood flow to the placenta be compromised, but shielding the fetus from radiation exposure during angiography is challenging.

The rates of complications from kidney biopsy during pregnancy range from 4% to 7% (3–6). Complications increase with gestational age of pregnancy and collectively are higher during pregnancy than in the postpartum period (7% vs 1%, respectively) (3). A meta-analysis of kidney biopsy performed in pregnancy found that kidney biopsy in early pregnancy (0–21 weeks, before fetal viability at 22 weeks) was not associated with increased risk of complications. At 23–28 weeks, more major bleeding episodes occurred that were associated with severe obstetric complications, including early preterm delivery and presumed fetal death. Late pregnancy biopsies (after 28 weeks) were rare (3).

Consensus is to biopsy before the 28th week (beginning of the third trimester), although clinical practice guidelines in the United Kingdom suggest limiting kidney biopsies to the first and early-second trimesters. The potential risks to the fetus are likely too great after 28 weeks. Management options in the third trimester include empiric treatments that are considered safe in pregnancy (e.g., steroids and azathioprine), early induction of labor followed by kidney biopsy, or delayed treatment and biopsy until after delivery.

Kidney biopsies can and should be performed in selected women during pregnancy. Extensive counseling about the risks and benefits of the procedure is important. In women with presumed rapidly progressive glomerulonephritis, in which the results of the biopsy would lead to immediate changes in therapy, kidney biopsy should be considered to allow for the best possible outcomes. ■

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The authors report no conflicts of interest.

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Policy Advances During the Dogs Days of Summer

ASN's advocacy efforts take to the sky

Although transplantation is the ideal therapy for those living with kidney failure, there are nearly 90,000 people, including 1100 children, on the U.S. kidney waitlist. And albeit that the nation's organ transplantation system has made many gains in recent years that are worth celebrating, many opportunities are also within reach to better serve our patients by maximizing access to kidney transplantation.

ASN recently joined other organizations in advocating that congressional leaders urge the Federal Aviation Administration (FAA) to make a key change in how donated organs can be transported through the nation's commercial aviation system. As a result of protocol revisions brought about by the federal response to the September 11, 2001, attacks, organs are now transported in the cargo area of the airplane instead of the passenger area, unaccompanied and at greater risk of logistical issues in the cargo hold. Delays that increase cold ischemic time also increase the risk that an organ cannot be transplanted or may face reductions in quality, ultimately impeding patients' access to a successful kidney transplant. ASN and 17 other groups, including patient organizations and other health professional organizations, urged the U.S. Senate Committee on Commerce, Science, and Transportation and the U.S. House Committee on Transportation and Infrastructure to consider a legislative provision in the FAA's reauthorization for the next 5 years that would require the FAA to develop regulations to enable the safe and efficient transportation of a donated organ in the passenger cabin instead of in a cargo hold of an airplane (1). This change is one of several opportunities for improvement that ASN is requesting to ensure that transportation and logistical challenges cease to be a barrier to transplant for any patient.

The nation can secure its future for transplantation with the SUS OPTN Act

Introduced by Representatives Larry Bucshon, MD (R-IN), and Robin Kelly (D-IL) in the House and by Senators Ron Wyden (D-OR) and Chuck Grassley (R-IA) and six other bipartisan lead sponsors in the Senate, the Securing the U.S. Organ Procurement and Transplantation Network (SUS OPTN) Act provides an opportunity to help ensure that the nation's organ transplant network is as effective and efficient as possible (2). This bill would grant the Health Resources and Services Administration (HRSA) the statutory authority to fully implement HRSA's OPTN Modernization Initiative, which would include enabling more competition and new ways of thinking about certain aspects of the transplant system, ensuring good governance, and increasing the amount of funding that can be invested in improving the system. These changes aim to make certain that patients are served by the best in class in every aspect of the nation's transplant system and that the system is as transparent and efficient as possible for patients, nephrologists, and every other member of the care team involved in a patient's journey.

The House Committee on Energy and Commerce passed its version with unanimous bipartisan support on May 24, 2023, and the Senate version of the bill was referred to the Senate Committee on Health, Education, Labor, and Pensions on May 17, 2023.

"The SUS OPTN Act allows for reforms that represent crucial, foundational changes to ensure America's kidney health ecosystem serves patients as optimally as possible," remarked ASN President Michelle A. Josephson, MD, FASN, on the bill's introduction.

The SUS OPTN Act is a result of years of advocacy by ASN and community stakeholder organizations to allow HRSA the flexibility to make improvements to—and greater investments in—the transplant system (3, 4). ASN plans to hold an advocacy day on Capitol Hill this summer in support of the bill. ASN will continue to work with Congress and the HRSA to ensure that the OPTN Modernization Initiative fulfills its aims, including that the HRSA works closely with patient organizations, health professional organizations, and other stakeholders in the policy development and implementation process.

ASN urges CMS to increase access to dialysis for people receiving hospice services

In May, ASN responded to the hospice request for information issued by the Centers for Medicare & Medicaid Services (CMS) in the fiscal year 2024 Hospice Wage Index and Payment Rate Update, Hospice Conditions of Participation Updates, Hospice Quality Reporting Program Requirements, and Hospice Certifying Physician Provider Enrollment Requirements proposed rule (5).

Only 25% of dialysis patients receive hospice services compared with 50% of the general Medicare population, and, of those on dialysis, nearly half receive hospice for less than 3 days. These figures are likely caused by how the current care model views dialysis and barriers caused by payment and reimbursement. Dialysis is narrowly portrayed as a therapy to prolong life rather than as a treatment that might be customized to manage symptoms and maximize comfort concurrently with hospice services. ASN believes that dialysis strongly aligns with the goals of hospice services to reduce symptoms and enhance quality of life for patients with a limited prognosis. Dialysis costs often greatly exceed a hospice service's daily reimbursement. Hospices receive a flat per diem rate between $150 and $200, whereas the base rate of dialysis averages approximately $250 per session.

ASN encouraged CMS to support the following:

1. Broader coverage of concurrent hospice and dialysis (including transportation)
2. Patients' ability to dialyze in a dialysis center with palliative approaches to dialysis care, allowing flexibility in the dialysis prescription to achieve patients' goals served with palliative or customized dialysis with hospice. This may involve exceptions to classical Quality Incentive Program measures.
3. Upstream models of care including palliative care to assist with symptoms and goals of care for patients receiving or planning for maintenance dialysis. This would improve the patient experience as well as promote a more timely and smooth transition to hospice services.

ASN urged CMS to pursue reforms within its authority and to consider both concurrent hospice and dialysis as well as more palliative and customized dialysis approaches, while sharing that ASN will be reviewing necessary statutory changes with Congress.

HHS encourages states to adopt new strategies in Medicaid redeterminations

As the nation emerges from the COVID-19 pandemic, and Medicaid returns to its prior operations with full Medicaid renewals beginning, it is important to protect individuals and families from procedural termination. Noting that a number of individuals were unnecessarily losing coverage while monitoring Medicaid and the Children's Health Insurance Program enrollment, the Secretary of the Department of Health and Human Services (HHS) Xavier Becerra penned a letter to U.S. governors calling for each state to review its elected flexibilities and consider additional policy options to protect eligible individuals and families from losing coverage due to administrative processes. Secretary Becerra highlighted several existing and new flexibilities for states to consider adopting, including:

- Spreading renewals over 12 months for all populations, providing more time to prevent systems from getting backlogged while ensuring that those eligible for continued coverage do not experience a gap in care, and those no longer eligible can easily transition to other sources of coverage
- Strategically using data sources by renewing individuals based on their eligibility for other programs, such as the Supplemental Nutrition Assistance Program or Temporary Assistance for Needy Families, reducing the need for some individuals to complete and return a Medicaid renewal form
- Partnering with managed care plans to help beneficiaries complete these forms and using data available from the U.S. Postal Service to update beneficiaries' contact information so they actually receive the renewal forms that states are disseminating

A full list of strategies that states are encouraged to use and adopt to protect eligible beneficiaries from inappropriate coverage losses is available (6). ■

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Heat Stress and Kidney Dysfunction in Salt Pan Workers: Insights from an Indian Study

By Xavier Fernando Vela Parada

In their recent work on heat stress and kidney diseases in salt pan workers, Jakobsson and coworkers (1) shed light on the lesser-understood consequences of hot temperatures on nonagricultural workers, for which their causes are still subject to debate. This is in contrast with the well-known condition of chronic interstitial nephritis in agricultural communities (CINAC), in which hot climates and pesticides are often cited as important risk factors (2). Salt pan workers extract salt from large, shallow depressions, allowing seawater or brine to evaporate and to produce salt for commercial use.

The study focused on seven salt pans in Tamil Nadu, located in the southern region of India. Most workers (87%) exceeded the wet bulb globe temperature threshold limit value for heat stress. Furthermore, the authors noted a severely limited water intake among workers, possibly due to their preference to avoid excessive urination during work. The authors observed a high urine-specific gravity (>1.020) in 28% of the workers. Kidney function assessment indicated an estimated glomerular filtration rate (eGFR) of 60–89 mL/min in 41% of all workers, and 7% had an eGFR below 60 mL/min.

In my opinion, this observational study does a good job of describing heat stress-related symptoms and kidney function among salt pan workers in India. However, it is important to consider potential caveats to fully utilize the findings. One area of focus involves the individuals with eGFR values <60 mL/min, because understanding the unique characteristics of this group can provide valuable insight and enrich the findings. Additionally, given the wide age range (18–85 years), it is crucial to evaluate whether the observed changes in kidney function can be attributed to age-related decline or other factors, for example, by assessing the kidney function of salt pan workers compared with a sex- and age-matched group from the general population. Lastly, to avoid recall bias, the authors implemented structured questionnaires and validation measures during a pilot study before evaluation of the target communities; however, the risk of recall bias may not be fully eliminated.

With these considerations, the issue of heat stress causing kidney diseases remains an important question to address. This study is not aimed to demonstrate that, but further research can build on it. Let us not forget that kidney diseases are complex, and a host of factors play a role, many of which are embedded in the intertwined reality of poverty, lack of health care access, and social disparities. This may be the larger picture. ■

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The author reports no conflicts of interest.

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Stroke in Patients with Kidney Diseases: A Not-So-Silent Killer?

By Rasha Raslan

In February 2020, while news of a novel virus was beginning to spread beyond the eastern hemisphere, a multidisciplinary group of experts convened in Dublin as part of Kidney Disease: Improving Global Outcomes' (KDIGO's) fourth clinical Controversies Conference on the heart, kidney, and vasculature (1). Of the many goals that the committee set out to achieve, one priority was to address existing knowledge gaps regarding cerebrovascular disease in patients with advanced chronic kidney disease (CKD).

Although cardiac disease is one of the leading causes of death in patients with end stage kidney disease, the relationship between non-cardiac vascular diseases and kidney diseases is not well understood. A recent review article by Bobot et al. (2) discusses an important, but often ignored, cause of significant morbidity and mortality in patients with underlying kidney diseases: stroke. The incidence of stroke is 13.4 per 1000 person-years in patients with CKD, and this increases for patients receiving dialysis (2). Understanding the unique features of this patient population allows us to provide better and more targeted care.

Although there are traditional risk factors, such as diabetes and hypertension, that predispose patients with kidney diseases to stroke, there are also kidney disease-related, nontraditional risk factors. These include the accumulation of uremic toxins, reactive oxygen radicals, and increased inflammatory products. In addition, patients receiving hemodialysis also have dialysis-specific risk factors, such as left ventricular hypertrophy, vascular calcifications, dialysis-induced dysregulation of cerebral blood flow, and intradialytic hemodynamic instability. More information is needed regarding the interplay of these risk factors to optimize and identify novel therapeutic targets.

Most of the current available therapies revolve around prevention and lifestyle modification. Anti-hypertensive agents, lipid-lowering therapies, and sodium-glucose cotransporter-2 inhibitors comprise the majority of current preventative therapies. As for individuals receiving hemodialysis, certain adjustments to the dialysis prescription and using cooled dialysate can lead to fewer hemodynamic variations during treatments.

Despite the increased morbidity in patients with advanced kidney diseases, fewer therapeutic options are available to them in cases of an acute stroke. For example, patients with CKD have less access to revascularization techniques, like thrombolysis and thrombectomy (3). Also, patients with advanced kidney diseases and those receiving dialysis are typically excluded from or under-represented in large randomized clinical trials. The ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) trial was a multicenter, randomized trial comparing low-dose to standard-dose alteplase in patients with acute ischemic stroke. Patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 had a twofold increased mortality risk compared with those with normal kidney function (4). However, patients with advanced kidney diseases comprised only about 3% of the study population. Since patients with advanced kidney diseases are disproportionately affected, more trials are needed that include this unique population to decipher optimal management.

The 2020 KDIGO meeting was the first step in describing best practices in the diagnosis and management of patients with dialysis and cerebrovascular disease, as well as proposing areas that require further research and investigation. Many aspects of care remain unanswered, and further research is needed to better elucidate the pathophysiological mechanisms that predispose patients with kidney diseases to higher rates of cerebrovascular disease. ■

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The author reports no conflicts of interest.

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ASN American Society of Nephrology

Mehrotra Named Senior Editor-in-Chief of ASN Journals

By Karen Blum

After serving as editor-in-chief of the *Clinical Journal of the American Society of Nephrology* (*CJASN*) for nearly 7 years, Rajnish Mehrotra, MD, MS, FASN, will assume a new role next January, as editor-in-chief of the *Journal of the American Society of Nephrology* (*JASN*) and senior editor-in-chief for the ASN journal portfolio of *CJASN*, *JASN*, and *Kidney360*.

Mehrotra, the Belding H. Scribner Endowed Chair in Medicine and head of the Division of Nephrology at the University of Washington School of Medicine in Seattle, talked to *Kidney News* (*KN*) about this move and what innovations he has in store.

KN: What interested you in taking on this new role overseeing the portfolio of ASN's journals?

Mehrotra: ASN's three journals have not functioned in a coordinated manner as part of a portfolio. Each journal has set its own independent vision and has had its own strategic direction. This is the first time that ASN has moved to create a portfolio that allows for coordinating the efforts. Because I've been the editor-in-chief of one of the three journals, it positions me well to take on this inaugural role. Collectively, it is the most elite of all journal portfolios in nephrology. The possibility of having an impact on the field in assuming the role is what attracted me.

KN: Tell us more about how you will help foster collaboration and teamwork across the journals.

Mehrotra: There will be three editors-in-chief, one for each journal. I will be one, and I'll be leaving the second, so I understand fully the opportunities and challenges. For us to work together, we need to define explicitly for our authors and our readers the scope of each of the three journals, how they differ from each other, and where they overlap and ensure that we work in a way that we avoid overlap between content [so] that we solicit and maximize the impact that we have.

I would plan annual face-to-face and virtual meetings for the editors to help build engagement, trust, and buy-in for the three journals to view themselves as part of a single portfolio.

KN: What types of changes or innovations can readers expect to see as these journals move toward a more cohesive approach?

Mehrotra: *CJASN* publishes original research that is patient-oriented but has a broader scope, including anything and everything that affects the clinical practice of nephrology—whether it is public policy, an approach on how to implement the recent findings from research in clinical practice, or as we have reintroduced in the past 7 years, what we call the patient voice, where we provide patients a platform to comment on research published in *CJASN*. In terms of coordinating efforts, it's an important niche that *CJASN* occupies.

JASN has been traditionally focused primarily on research, which is appropriate. But I think there's an opportunity to broaden the scope to put into context how to apply the findings to further advance research and innovation. My hope is to introduce a new article type that could be called "Evidence Updates," a set of articles that provides a comprehensive, state-of-the-art summary of our knowledge regarding the pathophysiology of kidney diseases or their complications more broadly. *Kidney360* has a special place in being the open access journal for nephrology within the ASN portfolio and focuses on kidney disease care models around the world.

There are synergies in infrastructure [that] we hope to create across the three journals to further enhance the quality of the output that we publish. Research methods used to advance science have evolved considerably, and there are people who have specific expertise in individual research methods. I envision teams of statistical editors and visual abstract editors across the journals, with a lead editor for each to oversee those teams. I would also like to see a coordinated approach to disseminate the content that we publish. Right now, we publish them online, and there is a paper copy for *JASN* and *CJASN*, but there is cross-cutting content published across the three journals. My hope is [that] we can create collaborative approaches to disseminate the content, such as webinars or podcasts. Topics could include recent advances in managing diabetic kidney disease, advancing wearable technologies for dialysis, or challenges with equity in health outcomes for kidney diseases. Those are some ideas.

KN: What are your plans for the near term and down the road?

Mehrotra: The immediate short-term, up to this December, is to identify the new editor-in-chief for *CJASN* and assemble a team of editors for both *JASN* and *CJASN*. Then, starting in January 2024, we will implement the infrastructure across the three journals, such as shared statistical expertise and shared dissemination strategies. We will have social media strategies and programs to provide opportunities for trainees to be involved in journal work. By the end of 2024 into 2025, my hope is that you will see new content in the pages of *JASN*, such as the evidence updates and new perspectives.

KN: What are you most proud of in your time as editor-in-chief of *CJASN*?

Mehrotra: A tremendous increase in rigor and impact of the content that we publish. Rigor means a lot of different things. It is the internal and external validity of the science that we publish. But it's also ensuring that we follow the highest standards of presentation of clinical research from article to article. What has followed is a substantial increase in impact, whether you measure that by the number of articles that are downloaded or our presence on social media. I think collectively, it has enhanced the value of the journal for our readers. I have heard repeatedly that authors around the world value the opportunity to publish their work in *CJASN*. I find that the highest measure of success. ■

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C3G, complement 3 glomerulopathy; IgA, immunoglobulin A.

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