

SPRING/SUMMER 2016

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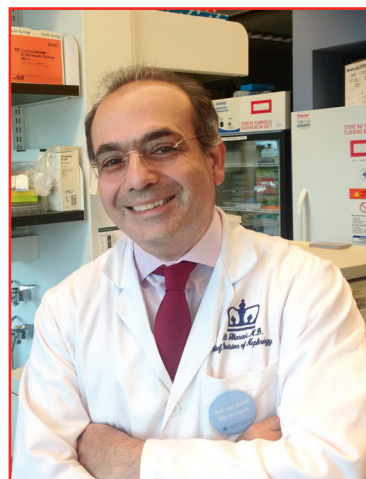
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Pursuing Personalized Medicine in Kidney Disease

The advent of next-generation sequencing and microarray technologies has brought about an unprecedented number of discoveries in the field of nephrology, providing many opportunities for incorporating genomic diagnostics into clinical care. “The use of genetic testing, particularly in pediatrics, can provide accurate diagnoses in puzzling cases, resolve misclassification of disease, and identify subsets of individuals with treatable conditions,” says **Ali G. Gharavi, MD**, Chief, Division of Nephrology at NewYork-Presbyterian/Columbia University Medical Center, and Director of the Columbia Institute of Genomic Medicine Initiative for Kidney Diseases.



Dr. Ali G. Gharavi

“For the past 5 or 10 years, we have been seeing significant technological advances, particularly in the area of genomics, which can change our approach to the diagnosis and treatment of patients with kidney disease,” says Dr. Gharavi, a leading kidney disease researcher who has served and continues to serve as principal investigator on several R01 and other studies funded by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health and the New York State Empire Clinical Research Investigator Program.

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Pregnancy, Hypertension, and Preeclampsia: Advancing Understanding of a Complex Relationship

In the opening of her 2013 article, “Preeclampsia: A ‘Nephrocentric’ View” for the National Kidney Foundation publication *Advances in Kidney Disease*, **Phyllis August, MD, MPH**, Ralph A. Baer Professor of Research in Medicine, Director of the Hypertension Center in the Division of Nephrology and Hypertension at NewYork-Presbyterian/Weill Cornell Medical Center, and the Theresa Lang Director of the Lang Center for Research and Education at NewYork-Presbyterian/Queens, emphasizes the complex and multifaceted features of preeclampsia and how physicians in the past have focused on single attributes of preeclampsia. She draws an analogy to the well known fable of the six blind men describing the unique features of an elephant – each one emphasizing only the part that he can feel, while oblivious to the whole animal – eloquently captured by the 19th century poet

John Godfrey Saxe. “Though each was partly in the right. And all were in the wrong!”

“We have a holistic view of preeclampsia and a true interdisciplinary approach to treatment at NewYork-Presbyterian,” emphasizes Dr. August. “A very close research and clinical collaboration with obstetricians, neonatologists, and researchers has ensured that patients seeking care at our Hospital have unprecedented access to a team of specialists. Acknowledging that while the obstetricians and nephrologists may have different perspectives about preeclampsia, at NewYork-Presbyterian, the ongoing collaboration and communication has resulted in unique opportunities to make scientific discoveries and translate these discoveries to render excellent care for patients.”

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Pursuing Personalized Medicine in Kidney Disease (continued from page 1)

Dr. Gharavi's work has identified multiple regions of the genome that confer risk of IgA nephropathy and has yielded novel insight into the mechanisms of kidney injury underlying the condition. His research also includes the genetic causes of congenital abnormalities of the kidney and the urinary tract. Dr. Gharavi is one of the principal investigators of a prestigious Cohort Program of President Barack Obama's Precision Medicine Initiative – a large-scale research effort to improve our ability to prevent and treat disease based on individual differences in lifestyle, environment, and genetics.

"These technologies were primarily in the research domain up until a few years ago, but now are being incorporated into the practice of medicine," says Dr. Gharavi. "In clinical practice we know that in hypertension, diabetes, cancer, and coronary heart disease, patients present differently, their clinical course is different, and their response to treatment is different. Now we know that there are actually molecular differences and that large subsets of disease can be identified through genomic approaches, providing us with the opportunity to make a precise diagnosis for many patients and individualize care based on the specific molecular mechanism of disease."

The Importance of Genomics in Kidney Disease

By sequencing the genome, says Dr. Gharavi, it is possible to identify the underlying mutations that may cause disease. This has important ramifications for individuals who are diagnosed with kidney disease that is likely hereditary and yet no family history of it. "If it is a true diagnosis of a hereditary disease in which they developed a mutation that will have consequences for the patients, their family members, and their children," says Dr. Gharavi. "Or is it misdiagnosed? In order to answer these questions we have begun to perform gene sequencing in young people who present with chronic kidney disease, have a family history, or an undiagnosed disease."

There are more than 300 known genes for monogenic kidney disorders that have been catalogued and, notes Dr. Gharavi, every month there are new mutations that cause kidney failure. "Most of these mutations are rare. There is a lot of variability under traditional diagnostic categories and mutations in many different genes can cause the same disorders. For example, there are more than 20 genes for focal segmental glomerulosclerosis. In some cases, mutations in the same gene can cause different disorders – the complement factor H (CFH) gene mutation can cause membranoproliferative glomerulonephritis or hemolytic uremic syndrome."

According to Dr. Gharavi, recent studies indicate that chromosomal microarrays can identify rare genomic imbalances that can clarify the etiology of neurodevelopmental and cardiac disorders in children; however, the contribution of unsuspected genomic imbalance to the incidence of pediatric chronic kidney disease is unknown. This led the Columbia researchers to perform chromosomal microarrays to detect genomic imbalances in children enrolled in the Chronic Kidney Disease in Children (CkiD) prospective cohort study, a longitudinal prospective multiethnic observational study of North American children ages 1 to 16 years with mild to moderate chronic kidney disease.

"We compared 419 unrelated children enrolled in the national

cohort to multiethnic cohorts of 21,575 children and adults that had undergone microarray genotyping for studies unrelated to chronic kidney disease," says Dr. Gharavi of the study, the results of which were published in the July 2015 *Journal of Clinical Investigation*. "We found that a genetic disorder not diagnosed by clinical evaluation was present in less than 10 percent of the study group. In many cases, genetic diagnosis completely reclassified the disease."

A genetic diagnosis can be highly informative for the care plan, says Dr. Gharavi. "There may be additional tests that one has to do because you find that these individuals are predisposed to other complications or may be at risk for neuropsychiatric disease or metabolic problems that require monitoring. In many cases, if a precise diagnosis identifies a structural defect in the kidney that is not usually responsive to immunotherapy, the patient should not be subjected to the side effects of some of these therapies."

In an article in *Current Opinion in Nephrology and Hypertension*, Dr. Gharavi further extrapolates on the importance of genetic testing and the increasing role of genetics and genomics in healthcare. Key points include:

- Genetic testing is increasingly recognized as a highly useful test in diagnosing and managing kidney disease.
- Ongoing technological improvements are expected to continue uncovering new mechanisms of disease, identify targets of therapy, and increase the use of genetics in the coming years.
- Gene interpretation and patient management will warrant the collaboration of scientific laboratories, geneticists, nephrologists, and bioethicists to properly counsel patients with genetic kidney disease.

Although there are already many benefits of genomics in the diagnosis and management of rare kidney disorders, the promise of genomic medicine remains to be realized for the more common forms of kidney disease, believes Dr. Gharavi. Therefore, large-scale sequencing efforts in kidney disease patients are needed to define the optimal indications for genomic diagnostics and to enable discovery of additional genes that can be targeted for therapy.

"Finally, the integration of genomics data into clinical medicine will require the development of tools for data management and communication via electronic health records, as well as significant investment in education for both physicians and patients. The NIH Precision Medicine Initiative in which we will participate aims to provide many of these answers for the community," says Dr. Gharavi.

Reference Articles

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For More Information

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Pregnancy, Hypertension, and Preeclampsia (continued from page 1)

Dr. August believes that the intriguing relationship between kidney function and pregnancy outcomes and overall maternal health requires a more encompassing understanding from all those who treat women with preeclampsia. “You have young women at the prime of their lives and you don’t want to permit them to get into a situation that would be life-threatening – for them or for their babies,” says Dr. August. Dr. August’s work has focused on the interrelationships of kidney function, blood pressure regulation, and pregnancy, particularly in women with hypertension and those at risk for preeclampsia.

Significance of Hypertension to Preeclampsia

Preeclampsia is a syndrome of pregnancy diagnosed after 20 weeks and characterized by mild to severe hypertension, proteinuria equal to or more than 300 mg/day, or evidence of organ dysfunction – particularly in the kidney. “A very interesting and unique relationship exists between kidney function and having a healthy pregnancy,” says Dr. August, who is one of only a handful of nephrologists in the country with a major clinical focus on hypertension in pregnancy. “If kidney function is impaired at all, a pregnant woman is at risk for a myriad of complications. In addition to causing high blood pressure, abnormal kidney function may result in early delivery or a smaller than normal newborn. The other interesting aspect is that it’s a bidirectional relationship.”

Preeclampsia is one of the most common medical disorders of pregnancy and affects between 3 to 10 percent of pregnancies. Preeclampsia profoundly affects the kidney, causing, in addition to proteinuria, reduced function and other more subtle defects, such as impaired calcium excretion by the kidney, first reported by Dr. August and her colleagues in the *New England Journal of Medicine* in 1987.

“Elevated blood pressure is often the first clinical sign that preeclampsia is present,” says Dr. August. “It is a clinical feature that often leads to preterm deliveries and an important risk factor for one of the most lethal sequelae of preeclampsia – maternal intracerebral hemorrhage. Subtle increases in blood pressure are detectable weeks before preeclampsia is diagnosed.” Dr. August’s research has also focused on why blood pressure is elevated in women with preeclampsia, and has found that alterations in the renin angiotensin system, a key hormonal system that regulates blood pressure and kidney function, are routinely present in women with hypertension in pregnancy and preeclampsia.

Dr. August appreciates the older name for preeclampsia – toxemia – as it implies that the cause is a circulating toxin in the blood, a theory that persists to this day. “Although we have learned a lot about this disorder, there remain important gaps in our knowledge. We don’t yet know what causes the abnormalities in the placenta that ultimately lead to preeclampsia,” says Dr. August. While the condition generally improves after the baby is delivered, one of the important features of toxemia that Dr. August and others have reported is that the women who have had this disorder in pregnancy are at increased risk for cardiovascular disease, and possibly kidney disease later in life. “We are very interested in why this is the case.”



Dr. Phyllis August

Dr. August’s research in obstetric nephrology spans 25 years, with studies on factors that cause toxemia, how the kidney is affected, preventive treatments, as well as how blood pressure is regulated during pregnancy. She conducted clinical trials of low dose aspirin to prevent preeclampsia – an approach that is widely used today. She also studied the impact of calcium supplementation on blood pressure and development of preeclampsia. She began her clinical focus on pregnancy, hypertension, and kidney disease during fellowship training, and her first research project, in collaboration with **Manikkam Suthanthiran, MD**, Stanton Griffis Distinguished Professor of Medicine and Chief of Nephrology and Hypertension at NewYork-Presbyterian/Weill Cornell, was

a study of the immunologic alterations that are present in women with preeclampsia. This area of research addresses an important aspect of mechanisms of preeclampsia. Other key mentors, **John H. Laragh, MD**, and **Jean E. Sealey, MD**, played an important role in stimulating her research in the renin angiotensin system and pregnancy.

As a young physician she sought out the guidance of nephrologist **Marshall D. Lindheimer, MD**, at the University of Chicago Medical Center, who had essentially “written all the chapters on the subject in any textbook I consulted,” recalls Dr. August. “He became a mentor, a close friend, and a colleague, and we continue to talk about cases and research.” Dr. August’s clinical practice is an important aspect of her work. Women with all forms of kidney disease and hypertension are referred to her from all over the country. Today, Dr. August is one of the go-to physicians in this still very small field of subspecialists worldwide, receiving emails regularly from physicians around the country.

“A woman is pregnant and her obstetrician discovers she has high blood pressure,” says Dr. August as she describes a typical path that brings patients to her practice at the Hypertension Center of Weill Cornell. “Maybe the patient knew about her hypertension before; maybe she didn’t. But the OB will say, ‘We need to have somebody look at this.’ And they’ll send her to me.”

“Or, she is a woman who had previously known kidney disease and either wants to get pregnant or is pregnant and she comes to see me to help manage her pregnancy in the context of having kidney disease,” continues Dr. August. “Then there are the women who have had a pregnancy that ranged from mildly problematic to devastating loss and want to have another baby. They will come to me to see if we can prevent the problems from recurring.”

The Challenges of Treatment

“One of the more challenging aspects of preeclampsia – whether you take the obstetric or nephrocentric perspective – is that despite considerable understanding regarding some of the key pathogenetic features, treatment options are fairly limited,” says Dr. August, who served on the 2013 Task Force on Hypertension

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Advances in Nephrology

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Pregnancy, Hypertension, and Preeclampsia *(continued from page 2)*

in Pregnancy convened by the American Congress of Obstetrics and Gynecology. “Antihypertensive therapy can prevent severe maternal hypertension, but not preeclampsia. We have become somewhat better at predicting who is at higher risk and can thus implement closer surveillance for women with a past history of preterm preeclampsia and those with multiple gestations, chronic hypertension, diabetes, preexisting kidney disease, and obesity. The early pregnancy identification of women with chronic hypertension – which alone is an important risk factor for preeclampsia – would permit more intensive surveillance, more aggressive care, and hopefully better maternal and fetal outcomes.”

So how should the treatment of hypertension be approached in women who are or may become pregnant? In young women considering pregnancy, identifying and treating hypertension is important. Dr. August notes that although most women with hypertension in the beginning of pregnancy have what is known as essential hypertension, and do quite well during pregnancy, the experience of her and her colleagues, supported by limited published evidence, suggests that identification of secondary causes of hypertension is important and often overlooked. These conditions – pheochromocytoma, renovascular hypertension, obstructive sleep apnea, Cushing’s syndrome, and primary aldosteronism – are not common, but they are associated with considerable risks not only to the expectant mother with hypertension, but also to the unborn fetus who is at risk for preterm birth, morbidity due to prolonged hospitalization associated with prematurity, and death. If appropriately diagnosed, they can be cured, and subsequent pregnancy outcomes much improved – and often quite normal.

According to the ACOG guidelines, a blood pressure greater than or equal to 160/105 should be treated. For women with chronic hypertension whose delivery is imminent, safe medications include IV labetalol, IM or IV hydralazine, calcium channel blockers, or diazoxide. Those with a delayed delivery can be prescribed methyldopa, labetalol, calcium channel blockers, alpha or

beta blockers, or hydralazine. “In women who have a history of preterm preeclampsia and want to have another baby, we consider recommending low-molecular-weight heparin and baby aspirin to prevent complications.”

Important Lines of Investigation

Dr. August and her colleagues – maternal-fetal medicine specialist **Daniel W. Skupski, MD**, and third-year fellow **Line Malha, MD** – continue to pursue research to further expand the understanding and treatment of hypertension and preeclampsia. “We are collaborating with the Suthanthiran laboratory and beginning to look at biomarkers in women who are at risk for but have not yet developed preeclampsia to identify the microRNAs that determine who will get into trouble as the pregnancy progresses,” says Dr. August. “We have previously established clinical markers and related tests that are useful for predicting who will get preeclampsia, but we are interested in looking at the genetic basis with the hope that this will point us in the direction of understanding more about the mechanism of preeclampsia and, in particular, defining treatments to prevent recurrent preeclampsia in subsequent pregnancies.

“Our evidence base to guide our use of antihypertensive treatment in women with preeclampsia can be improved, and important questions regarding thresholds for beginning antihypertensive therapy and treatment targets remain,” continues Dr. August. “For the nephrologist, preeclampsia is an exciting field. There are significant opportunities for progress as the disorder encompasses many aspects of nephrology and obstetrics, and despite the sometimes dramatic presentations accompanied by maternal and fetal morbidity and mortality, overall the outcomes are generally happy ones.”

For More Information

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