

New model helping identify pregnant women whose previous kidney injury puts them, babies at risk

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Drs. Ellen E. Gillis (left) and Jennifer Sullivan. Credit: Kim Ratliff, Augusta University photographer

Young pregnant women, who appear to have fully recovered from an acute injury that reduced their kidney function, have higher rates of

significant problems like preeclampsia and low birthweight babies, problems which indicate their kidneys have not actually fully recovered.

Now scientists have developed a [rodent model](#) that is enabling studies to better understand, identify and ideally avoid this recently identified association, they report in the *Journal of the American Society of Nephrology*.

"We are talking about a population of young women that we usually think about as protected and healthy, and they are not if they have had a kidney insult," says Dr. Jennifer C. Sullivan, pharmacologist and physiologist in the Department of Physiology at the Medical College of Georgia and interim dean of The Graduate School at Augusta University. "We think there is injury, potentially even years later, in some of these young women that we are not seeing, and we need to be able to quantify how much injury is still there."

Acute kidney injuries, or AKIs, result from the rapid, temporary loss of adequate oxygen-rich [blood](#) to the organ that constantly filters our blood of toxins and resorbs essentials like water, glucose and potassium. An AKI can result from a literal blow to the kidney, like a car accident, from pharmaceuticals like the chemotherapy drug cisplatin, or from a major surgery or sickness that puts you in intensive care, like COVID-19, which is known to have a direct effect on the kidney.

The incidence of AKI has been on the increase, and the COVID pandemic very likely will accelerate that, says Dr. Ellen E. Gillis, senior postdoctoral fellow in Sullivan's lab and the study's corresponding author. A COVID-related AKI is associated with high mortality and considered an independent risk factor for death in patients with COVID. In fact, the clear emerging relationship was the focus of the virtual 25th Consensus Conference of the Acute Disease Quality Initiative.

"Any loss of blood flow to the kidneys can result in reduced function and an AKI," says Gillis. Pregnancy is one of the biggest stressors the kidneys face, she says. "Basically every system in your body changes during pregnancy."

Their new model is helping identify how calamity can occur when the two conditions collide, even if they are separated by years.

During pregnancy, maternal circulation must support fetal circulation so cardiac output increases, total body volume increases as well as plasma volume so the kidneys have an increased load to filter, Gillis says.

"There is an increase in plasma volume to ensure the high metabolic demands of both baby and mother are met," Sullivan adds. In this scenario, the baby actually gets preferential protection.

Two recent clinical studies and their new model suggest that even years later, some young women have lingering damage that can prevent these usual responses and protections. It can happen despite the fact that the mother's kidney function appeared normal before pregnancy, including normal creatinine levels, a waste product that healthy kidneys filter from your blood that is measured in the blood and/or urine as a standard assessment of kidney function.

Two clinical studies, one published in 2017 and the second a year later, looked at women an average age of 30, often years out from their AKI with multiple assessments that indicated their kidneys had recovered. The research led by Massachusetts General Hospital found significant increases in problems with both mother and baby, including preeclampsia, low birthweight and loss of the baby.

The MCG scientists now report the same findings in their animal model: they experience an AKI, they recover based on usual measures of kidney function, but problems with the mother and/or baby still occur.

Their model closely mimics what happens in humans: a period of compromised blood flow to the kidney followed by restoration of blood flow, called ischemia reperfusion injury, a known, common cause of AKI in humans, followed by a recovery period in which, again like the young women, creatinine levels returned to normal.

They monitored the rats throughout pregnancy, and watched uterine artery resistance go up, uterine blood flow go down and babies born smaller because they were not getting adequate nutrition. The uterine artery provides most of the blood to the uterus, where the baby develops, and should enlarge significantly during pregnancy.

"Typically during pregnancy your vasculature relaxes and blood pressure decreases to accommodate this increase in plasma volume," Gillis says. "You should see relaxation and vasodilation of the uterine artery," Sullivan adds. Normally there is some new blood vessel growth for the placenta to accommodate the demand, but not in the mother's kidneys. "The kidneys just have to work harder, which normally isn't a problem," Sullivan adds. But the previously injured kidney, which has functioned fine for the woman alone, may not be up for this additional significant task.

"You should see changes in the vasculature to promote increased perfusion, increased delivery to the pups. There are a lot of things that should be happening that the gross measurements we make today suggest aren't happening," Sullivan says.

Rather in their model, and in the young women, pregnancy appears to induce renal insufficiency, driving up levels of creatinine in the blood as well as urea, a byproduct of protein metabolism from your body and the food you eat, whose increased blood levels indicate kidney problems and/or high meat consumption. Creatinine levels should decrease in pregnant women because of that increased plasma volume, but the

limited clinical trials have shown they go up in women who have had AKIs.

Plasma volume, which should double, increases some, but not sufficiently, Gillis says. They don't yet know the exact mechanism for why plasma volume increase is insufficient, but suspect it's because the kidneys just can't handle the volume. Sullivan notes there is crosstalk between the kidneys, uterus and placenta that the previous insult to the kidney appears to change. Sodium retention is one way to increase plasma volume, so problems with sodium transport by the kidneys following an AKI could be an issue.

The rat mothers also have more waste product in their blood, another indicator the kidneys are not working at a premium. In fact, the high creatinine levels they are seeing would indicate that pregnancy itself has caused another AKI, Gillis says. The scientists note that it's widely acknowledged that creatinine levels are not an ideal indicator of kidney function, and one of the goals of their work is to find a better biomarker and better treatment.

Gillis is now exploring whether regulatory T cells, which help protect the fetus from the mother's immune system during pregnancy and also should increase in number in pregnancy, are part of the problem. Regulatory T cells can, for example, produce the powerful blood vessel dilator nitric oxide, and they don't see the increase in these calming T cells in their new model. Perhaps the AKI generated an altered inflammatory response that decreases the ability to prompt this important increase in regulatory T cells, Gillis says. If that is the problem, more regulatory T cells, an approach which already has been studied in humans, for example, to better protect their transplanted organ, could be given to help, Sullivan says.

They note that preeclampsia and low birthweight have long been

concerns, just not concerns associated with the kidneys. "We thought of them being placental disease," Sullivan says.

Still there have been known overlaps. AKIs increase the risk for chronic kidney disease, women are more likely to get chronic kidney disease and issues occurring during pregnancy may be one of the reasons, they say. Women with poor kidney function are known to have difficulties with pregnancy, but these [young women](#) are considered to be recovered from their kidney injury, the scientists emphasize.

And they are concerned the newly discovered association will only increase with rates of both AKI and maternal death on the rise. The Centers for Disease Control and Prevention reports that death rates of pregnant women are on the rise in the United States, which has the highest maternal mortality among developed countries.

COVID could worsen the problem. A study of more than 5,000 veterans hospitalized with COVID, for example, indicated that about 32% developed an AKI and that nearly half of them did not have fully recovered [kidney function](#) at discharge from the hospital. Veterans with an AKI were at increased risk of death and Black veterans were at most risk.

The first looks at pregnancy outcomes following what appeared to be full recovery from an AKI was a retrospective study of women who had babies between 1998 and 2016. It found that women who had an AKI had an increased rate of preeclampsia—the worse the AKI, the greater the preeclampsia risk—and that their infants were born at an earlier gestational age and were more likely to be small for their gestational age. The emerging association of AKI and preeclampsia and adverse fetal outcomes held even when matched with women of a similar age, race, body mass index and blood pressure—including rates of preexisting hypertension—at their first prenatal visit. Creatinine levels the six

months before conception also were similar in the nearly 40% of the women on whom that data was available.

Gillis last year received a K99 Pathway to Independence Award from the National Heart, Lung and Blood Institute to develop a model to further explore why pregnant women who seemed to recover from their acute kidney injury, had these associated problems.

Outcomes for an individual with an AKI include hypertension and chronic kidney disease, potentially including the need for [kidney dialysis](#). Preeclampsia is the most common complication of pregnancy and typically occurs in [women](#) with a previously healthy blood pressure. Traditional risk factors have actually included not having children as well as obesity and hypertension.

More information: Ellen E. Gillis et al. Adverse Maternal and Fetal Outcomes in a Novel Experimental Model of Pregnancy after Recovery from Renal Ischemia-Reperfusion Injury, *Journal of the American Society of Nephrology* (2021). [DOI: 10.1681/ASN.2020020127](https://doi.org/10.1681/ASN.2020020127)

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