Diagnostic Test Warns Mothers Before Preeclampsia Strikes

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Preeclampsia is a potentially dangerous complication of pregnancy that can strike women as early as the 20th week of gestation with little notice. It is characterized by a sudden spike in maternal blood pressure, edema and protein in the urine. In severe cases, preeclampsia escalates to eclampsia, which can cause the mother to suffer potentially fatal complications and lead to forced premature delivery of the infant.

Preeclampsia adds significantly to infant mortality rates in all countries and regions, but most especially so in areas where there are insufficient resources to save and treat premature infants. According to the Preeclampsia Foundation, this disease strikes 5 to 8 percent of all pregnant women in any given population, some 200,000 annually in the U.S. alone.

> *The foundation also estimates that preeclampsia is responsible for more than 70,000 maternal and 500,000 infant deaths globally per year. The only cure for preeclampsia is forced labor or*

> *cesarean section to deliver the infant prematurely.*

Despite the severity and high prevalence of preeclampsia, an ancient affliction, very little is known about mechanisms behind development of preeclampsia and less yet about early diagnosis and potential therapies.

"In an average OB-GYN practice in the United States, the doctor will see 25 to 50 women with preeclampsia every year," says Ananth Karumanchi, M.D., a Howard Hughes Medical Institute investigator and associate professor of the Division of Nephrology and the Division of Vascular Biology at Beth Israel Deaconess Medical Center (BIDMC), a teaching hospital of Harvard Medical School located in Boston. "Even though doctors know they will see many women with the disease, there has not previously been a way to tell which of them has preeclampsia until the onset of signs and symptoms," says Karumanchi.

Finding the Warning Markers

That is, until now. Karumanchi and his team of researchers are developing the first diagnostics test for preeclampsia. It is work born from years of careful research.

Starting with the knowledge that after the placenta is delivered, the disease gets better, Karumanchi became intrigued with the role of the placenta in preeclampsia. A kidney specialist by training, he hypothesized that the placenta must be secreting toxic substances into the mother's blood, either subsequent to the disease process or as the cause of the disease.

"We took a molecular approach to studying this hypothesis. We took an approach that was not possible in the past because the technology did not yet exist," explains Karumanchi, who began this research in 2001.

The BIDMC research team studied placentas to find the molecules that might cause high blood pressure, kidney protein spillage, vascular impact and/or seizures in a pregnant woman — all symptoms of preeclampsia. "We found a number of molecules, but one in particular proved very important," explains Karumanchi.

That molecule is a protein called sFlt-1 — an antagonist of circulating vascular endothelial growth factor and placental growth factor (PlGF). sFlt-1 was later confirmed to be present in large quantities in the bloodstream of patients with preeclampsia.

"We found that the sFlt-1 protein levels increased several weeks ahead of signs and symptoms. By finding that early warning marker, we now have a way to predict which women will suffer from the disease, and we can prepare early to address the problem," says Karumanchi.

Co-investigator Vikas P. Sukhatme, M.D., Ph.D, Victor J. Aresty professor of medicine at Harvard Medical School and chief academic officer and Harvard faculty dean for academic programs at BIDMC, adds. "Down the road, the contemplated treatment would be through administration of drug therapies that neutralize the effects of sFlt1," he says.

Identified but not Arrested

However, the discovery of the sFlt-1 protein did not arrive in a lightning strike. It was a painstaking process. "There was no Eureka! moment," reports Karumanchi. "It took time for us to appreciate the discovery, and it took time for a number of colleagues across the field to confirm the findings."

By testing the sFlt-1 protein in pregnant rats, Karumanchi discovered that sFlt-1 reproduces the characteristics of preeclampsia: high blood pressure, protein in urine and glomerular endotheliosis — a classic lesion found in

preeclampsia cases. This established a relationship between excess sFlt-1 in the bloodstream and the presence of the disease. Working with scientists at the National Institutes of Health, Karumanchi and his team were able to demonstrate that circulating sFlt-1 and PlGF levels can be used for the clinical diagnosis and prediction of preeclampsia.

The team is currently studying the role of certain placental cells in the regulation of sFlt-1 production. They are concurrently characterizing other elevated gene products that may also play a role in preeclampsia and may serve as biomarkers for early disease detection.

Moving this knowledge into clinical trials, and then commercial use, whereby it can potentially save thousands of women and infants, however, requires more than the efforts of the scientists in the lab.

Finding a Champion

"The technology piqued a lot of interest, but we had difficulty licensing it," explains Mark Chalek, director of Technology Ventures Office (TVO) at BIDMC. "We spent the better part of one year trying to find a big pharmaceutical company to license the technology. Most large pharmaceutical companies were concerned that the clinical trials would be too risky and that the preeclampsia market would be too small to justify an investment."

But the support for the diagnostic could not be denied.

"It was vital to bring this technology to the bedside, which is consistent with BIDMC's mission and its unique strength in translational medicine," says Karumanchi. "We are fortunate to have highly competent staff in TVO, capable in acting as catalysts to accelerate the project."

Part of that acceleration was making the decision in 2005 to license the technology to Nephromics, a Massachusetts based startup company.

Spearheading the negotiations was TVO's Christine Jost, who serves as associate director. She explains that Nephromics is a private startup company based on intellectual property (IP) arising from both BIDMC and Massachusetts General Hospital. While this maneuver established a focused champion, it also posed both funding and management difficulties.

The initial laboratory research that led to this discovery was funded by the National Institutes of Health. However, Nephromics was precluded from sponsoring Karumanchi's research in compliance with Harvard's and BIDMC's rules.

Yet Nephromics needed capital to market the IP to companies that would actually develop a commercial test kit and handle the clinical trials, testing, manufacturing, marketing and distribution. The company also required managers to complement the scientific expertise of Karumanchi and others.

"We are not venture capitalists in the traditional sense of managing a fund," explains Patrick Jeffries, president of Nephromics. "We are good at the business side; and the scientists, such as Karumanchi, are good at the science side. We complement each other.

"In essence, our team believed in the science, trusted the scientists and figured out how to work well together to attract larger companies as sub-licensees to get this product out," Jeffries says.

This approach — to offer nonexclusive sublicenses to several manufacturers — would allow the test to get to patients faster by creating a competition between the companies.

"For example, when we began to negotiate with Abbott, Roche pushed back hard, claiming there must be only one

manufacturer for the purpose of competitive exclusivity," Jeffries says. "We explained that the big companies such as Roche, Abbott and others compete in laboratory testing equipment, but not in individual tests, so no exclusive license was warranted. We won that argument."

Nephromics has now successfully sublicensed the preeclampsia diagnostic to several leading diagnostic companies such as Beckman Coulter, Roche Diagnostics, Johnson & Johnson and Abbott Pharmaceuticals.

"Our objectives are to get the diagnostic kit standardized across the sub-licensees, get it to market and get doctors ready to use the kit to save lives," says Jeffries.

Over time, the discovery may be offered as a point-of-care test in a doctor's office. A pregnant woman and her doctor would know her preeclampsia risk in a matter of minutes, rather than in several days, when a result comes back from a lab.

The interest in this discovery is, for now, focused mainly on diagnostics rather than therapeutics. "That begs the question, of course, as to why we should use the test if there is no specific treatment. Babies will still need to be delivered early," says Karumanchi. "By eliminating the guesswork in diagnosis, we may prevent unnecessary premature deliveries." Despite the current absence of a cure, a future treatment may indeed eventually result from the research under way today. "We are hopeful that the markers will prove useful in developing new therapies and may lead us to a cure one day," Karumanchi says.

"Thus far," Jeffries says, "we have awakened the scientific community to the importance of markers we can now utilize to find a cure. We are a long way off, but we are definitely on that path." At some point, the test may enjoy a groundswell of public support.

"This story is a tremendous example of the marriage of great science, effective technology transfer and commercialization, leading to the development of a preeclampsia diagnostic," says Chalek. "And if we are lucky — it will be accomplished in less than a decade."

Even luckier still are the mothers and their children who might be spared unnecessary risks. As Jeffries says, "Nearly everyone would want to prevent the risks of complications stemming from premature delivery."

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