Rh sensitization treatment may be unnecessary in first trimester pregnancies

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A special immune treatment may not be necessary until after the first trimester of pregnancy, according to a new Penn State and University of Pennsylvania study. The researchers said their results could change

pregnancy care guidelines and possibly close global health equity gaps.

They published their findings in *JAMA*.

Human red blood cells have proteins on their surface called antigens. One of those proteins, Rh immunoglobulin, is what makes a person's blood type "positive" or "negative." An Rh-negative person can become pregnant with a fetus who is Rh-positive, since the trait that can be inherited from the other parent. At a certain point, the pregnant person's blood becomes exposed to the new antigen, causing the body to mount an immune response, known as Rh sensitization.

"Rh sensitization isn't a bad outcome on its own," said Sarah Horvath, MD, assistant professor of obstetrics and gynecology at Penn State College of Medicine, who led the study investigating if the first trimester is too early to treat for Rh sensitization. "If someone becomes sensitized during their first pregnancy, it only becomes problematic if they have a second pregnancy and if the fetus is Rh positive and if there is a high enough concentration of fetal red blood cells in the pregnant person's blood to then illicit an immune response."

When that immune response happens, fetal anemia could develop, requiring blood transfusions at birth, or in some cases, before birth. In a small handful of instances, fetuses could develop fatal hemolytic diseases. To prevent these immune responses, scientists treat Rh-sensitized pregnant people with Rh immunoglobulin to "block" their immune systems from reacting to Rh-positive fetal red blood cells.

Previous population-level evidence found only 9% to 10% of patients negative for Rh ever become sensitized during a full-term pregnancy. By routinely implementing Rh immunoglobulin treatment at delivery, only 1.1% to 1.6% of people became sensitized. Additional prophylactic treatment at 28 weeks of pregnancy decreased that rate to 0.2%.

But this rate was not reduced anymore in high resource countries that adopted Rh immunoglobulin treatment even earlier in pregnancy, which led scientists like Horvath to wonder if administering treatment early in pregnancy was necessary.

Overuse of Rh immunoglobulin, a finite human blood product, could increase costs and restrict availability of use in lower-resourced countries, according to Horvath, who set out to determine if the early treatment is actually beneficial.

"We found in our study that pregnant people weren't exposed to fetal red blood cells in a high enough capacity to become Rh sensitized during the first trimester," Horvath said. "Taking that data, we can now say with confidence that Rh sensitization happens after 12 weeks of gestation, which means we can change our approach to Rh sensitization prevention."

Horvath and colleagues collected maternal blood samples from 506 participants who were less than 12 weeks pregnant. Using flow cytometry, the researchers assessed the maternal blood samples for the presence of fetal red blood cells, which typically move across the placenta to circulate in the maternal blood by seven weeks into the pregnancy.

In a previous pilot study, Horvath and co-authors had determined the threshold of fetal red blood cell counts needed for a person to become Rh sensitized. Using that data, the team concluded that none of the participants from the present study had an elevated fetal red blood cell count high enough to become Rh sensitized.

According to Horvath, there is now enough evidence to change Rh immunoglobulin treatment guidelines in the United States—something that international organizations like World Health Organization, Society

of Family Planning, and Royal College of Obstetricians and Gynecologists have already done. By reducing unnecessary procedures and costs, Horvath said there is an opportunity to close health equity barriers.

"Our study shows that some prophylactic doses of Rh immunoglobulin in first trimester pregnancies are unnecessary," Horvath said. "By conserving this vital human blood product, we can have cost savings for patients in higher-resourced countries and allocate treatments to lower-resourced countries that may benefit from increased access to supply."

More information: Sarah Horvath et al, Induced Abortion and the Risk of Rh Sensitization, *JAMA* (2023). DOI: 10.1001/jama.2023.16953

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