Expensive immunotherapy shows no advantage over placebo for recurrent miscarriage patients

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(PhysOrg.com) -- The University of Chicago Recurrent Pregnancy Loss Program (RPL) recently completed a comprehensive study examining the use of immunotherapy to help couples that had experienced recurrent miscarriages for unexplained reasons achieve a successful pregnancy.

Miscarriage is the most common complication of pregnancy, impacting 15 percent to 20 percent of all clinical pregnancies. About 1 percent of couples experience recurrent miscarriage, defined as three or more miscarriages before 20 weeks of pregnancy.

Causes of recurrent miscarriage can be identified in about half of the cases. The other 50 percent of couples have unexplained recurrent miscarriage, meaning genetic, hormonal and other causes have been ruled out. An immunological cause has been suggested for more than 80 percent of unexplained recurrent miscarriages.

Intravenous immunoglobulin (IVIG) consists of antibodies produced by white blood cells that help fend off bacteria, viruses and other foreign bodies. Pooled from highly purified human plasma, IVIG is costly to process and, like all blood products, is not without risk. It is successfully used to treat immune disorders such as lupus, rheumatoid arthritis and other rheumatic diseases, and administered intravenously in a hospital setting. The University of Chicago Medical Center, along with six other medical centers in the United States and Canada, wanted to see if IVIG

would suppress the mother's adverse immunological responses to pregnancy and overcome miscarriage.

The study led by Mary Stephenson, MD, director of the University of Chicago Recurrent Pregnancy Loss Program, to be published in the September 9, 2010 issue of Human Reproduction, reported the largest randomized controlled trial to date evaluating the use of IVIG in couples with unexplained recurrent miscarriage. Eighty two women were randomized to either IVIG or saline, an inactive substance (placebo). The women were 18 to 44 years of age and had had one successful live birth followed by at least three unexplained consecutive miscarriages, all with the same partner. Known causes of recurrent miscarriage were ruled out.

The results showed no significant difference between the live birth rate for women receiving IVIG (70 percent) and women receiving the placebo (67 percent). The study's results were then combined with two smaller randomized trials, and again, no treatment benefit from IVIG was found.

Interestingly, 94 percent of women in both the IVIG and control groups had a live birth in the study, following an ultrasound at 6 weeks which revealed an embryo with cardiac activity. The impressive results are due to the supportive services offered, consisting of weekly blood tests in early pregnancy, close ultrasound monitoring and nurse contacts throughout the pregnancy, along with around-the-clock access to a RPL physician or nurse, according to Stephenson, professor of obstetrics and gynecology, University of Chicago.

In 2006, 42-year-old Teri Neri heard about Stephenson and the University of Chicago Recurrent Pregnancy Loss Clinic and joined the study. Neri and her husband Nick appreciated this high level of monitoring during the first trimester, which was a very frustrating and

anxious time for them. "We had been trying for seven years to have a child after our son Nicholas was born," Teri said. "The sense of comfort the program gave us, along with peace of mind in knowing we were doing everything possible once I got pregnant (after four months) to ensure I'd carry the baby to term, made a real difference in my pregnancy. You could tell they really cared about us. And if I hadn't gotten pregnant, we'd at least get to the bottom of it (the miscarriages)."

Given the cost of IVIG (as much as $5,000 per dose outside the trial) and concern about its safety and effectiveness, the therapy has been controversial for years. "Prior studies had suggested that IVIG may have a role to play in recurrent miscarriage," said Stephenson. "Given this devastating reproductive problem, and the possibility of finding an effective treatment, I designed a study to answer the question whether IVIG is effective in improving the live birth rate in couples who suffer from secondary recurrent miscarriage. With the risks associated with using a blood product, although it is highly purified and virally-inactivated, as well as the costs involved -- not usually covered by insurance -- this study sought to give a definitive answer."

At her fifth month of pregnancy, Teri's obstetrical care was transitioned to her local Ob/Gyn. "Our beautiful son Luke was born a few months later. Stephenson and all the others truly helped Nick and me realize a huge dream," in having a second successful pregnancy, she said.

The study was randomized and double-blinded, meaning the women were given either IVIG or a placebo by chance and neither the women nor the researchers knew who received which until after the study was completed. Patients were able to re-enter and receive the alternate infusion if they had another miscarriage, which ensured if the IVIG was of value that all participants had an opportunity to receive IVIG.

The infusions were started in a cycle in which the woman wished to

conceive. Once pregnant, the woman received the same infusion every four weeks through the second trimester.

"Recurrent miscarriage is an emotionally draining and frustrating reproductive problem for couples," Stephenson said. "We are pleased to have completed a definitive trial to assess the impact of using IVIG. Although the trial found that IVIG is not useful, preconception evaluation and frequent ultrasound monitoring and supportive care in the first trimester was found to be highly effective. Therefore, IVIG should be abandoned for unexplained secondary recurrent miscarriage and further research is needed to understand how close monitoring improves pregnancy outcome."

The study, which spanned more than ten years, was initially funded by a grant from, and IVIG supplied by the Canadian Blood Services. Subsequent funds and IVIG were provided by a University of Chicago Clinical and Translational Science Award, a University of Tennessee National Center for Research Resources Award and Talecris BioTherapeutics. Stephenson and her co-investigators declare no conflicts of interest.

More information: Paper: humrep.oxfordjournals.org/cgi/ … t/abstract/25/9/2203

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