In utero stem cell transplants may replace riskier childhood transplants for multiple conditions

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Tippi MacKenzie, MD, a pediatric and fetal surgeon at UCSF Benioff Children's Hospital San Francisco, is the principal investigator for a clinical trial that will use in utero stem cell transplants to treat fetuses with an inherited disorder that restricts the blood's ability to carry oxygen to vital organs. Credit: Cindy Chew

UCSF Benioff Children's Hospitals in San Francisco and Oakland will pioneer stem cell transplants for a uniquely challenging patient population: second-trimester fetuses stricken with a potentially fatal

disease.

The two hospitals are enrolling 10 pregnant women in the first phase of a clinical trial to treat fetuses with an inherited disorder that restricts the blood's ability to carry oxygen to vital organs. The trial, the first of its kind in the world, is funded by a $12.1 million grant from the California Institute for Regenerative Medicine.

Alpha thalassemia (ATM) affects 5 percent of the world's population, but is significantly more prevalent in China, Southeast Asia, India and the Middle East – parts of the globe where many residents of the San Francisco Bay Area claim their origins. In its most extreme form, alpha thalassemia major (ATM), the condition leads to progressive anemia and heart failure before birth. Standard treatment in the United States includes lifelong blood transfusions.

Stem cell transplants from a matched donor in childhood have proven to be curative in some cases, but patients face risks, including graft-versus-host disease and serious side effects from immune-suppression drugs.

The trial is based on the premise that risks could be minimized by harnessing the "tolerance" between the pregnant woman and fetus before birth, said principal investigator Tippi MacKenzie, MD, a pediatric and fetal surgeon at UCSF Benioff Children's Hospital San Francisco.

Hope That Procedure Could Be Adopted Worldwide

"In performing the procedure in utero when the fetus's immune system is underdeveloped, we can avoid the aggressive treatments required for postnatal transplants for children with alpha thalassemia," MacKenzie said. "Eventually, the procedure may become a treatment option in parts of the world where ATM is most common. Due to lack of treatment possibilities in many countries, most pregnancies are either terminated

on diagnosis or result in fetal demise," she said.

The trial follows a decades-long odyssey marked by triumphs and tribulations for researchers in the field. Fetal transplants using stem cells from other fetuses to treat blood disorders were carried out in the 1980s, but were only marginally successful due to engraftment failure. Researchers around the world searched for answers by turning to animal studies.

'Eureka Moment' Spurred Sea Change

"The fetus, unlike a fully developed human, can accept foreign cells, because its immune system is not yet primed to fight bacteria and viruses," said MacKenzie. "This undeveloped immune system benefits the fetus throughout the pregnancy, because it prevents it from launching an immune response to its mother's cells that are naturally circulating in its bloodstream."

Further research led to Mackenzie's "eureka moment," when it was discovered that the mother's immune system is actually responsible for rejecting other cells that are transplanted into the fetus. If the mother's cells are transplanted, they can engraft without being rejected. "This led to a sea change in our strategy to use maternal cells for the transplants," she said.

In the trial, bone marrow will be collected from women who are between 18 and 25 weeks pregnant, with a fetal diagnosis of ATM. The bone marrow cells will be processed and hematopoietic cells – immature stem cells that can evolve into all types of blood cells – will be singled out from the mix. They will then be injected through the woman's abdomen, into the umbilical vein of the fetus, where they can circulate through the bloodstream, developing into healthy mature blood cells.

The procedure is not without risks to the fetus and the pregnant woman. To minimize risks, the researchers restricted the trial to ATM, since the fetus is already undergoing blood transfusions. "An additional procedure for the transplantation is not necessary, since the maternal stem cells are infused at the same time as an in utero blood transfusion," said Elliott Vichinsky, MD, director of hematology/oncology at UCSF Benioff Children's Hospital Oakland, who will head the hematologic management of the fetus and newborn. "This should reduce additional risks to the fetus." Since the underlying disease causes complications, the woman will be monitored throughout her pregnancy and the fetus will continue to receive blood transfusions until birth.

UCSF is a pioneer in thalassemia research and the birthplace of fetal surgery. UCSF Benioff Children's Hospital Oakland is home to the Northern California Comprehensive Thalassemia Center, which was established in 1991 and is now the largest such program nationwide, with a focus on caring for patients and leading research into new treatments.

"We are excited about launching this trial, which combines the expertise of UCSF Benioff Children's Hospitals in San Francisco and Oakland. This study offers families with a usually fatal ATM pregnancy the chance of survival and cure," said Vichinsky, who founded the Northern California Comprehensive Thalassemia Center.

Treatment May Be Tested for Sickle Cell Anemia

Patient recruitment will continue for five years, during which pregnant women and their babies will be followed after birth for 30 days and one year respectively. If successful, the procedure will be carried out for fetuses with beta thalassemia, a more common and less serious variant of the disorder, as well as sickle cell anemia, in collaboration with Children's Hospital of Philadelphia. Other conditions requiring stem cell transplants after birth may be considered, said MacKenzie.

The incidence of ATM is unknown because most fetuses with the disorder die before delivery. The condition occurs when both parents are carriers for thalassemia. In places where women have access to prenatal care, ATM is usually suspected on ultrasound and confirmed by DNA analysis in the second trimester.

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