

Rare, deadly genetic disease successfully treated in utero for first time

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Patient Ayla Bashir. Credit: University of California, San Francisco

Using a protocol developed at UC San Francisco, physicians have successfully treated a fetus with a devastating genetic disorder for the first time, and the child is now thriving as a toddler, a case study in the

New England Journal of Medicine reports.

"This treatment expands the repertoire of fetal therapies in a new direction," said co-senior and corresponding author Tippi MacKenzie, MD, a pediatric surgeon at UCSF Benioff Children's Hospitals, co-director of UCSF's Center for Maternal-Fetal Precision Medicine and director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research. "As new treatments become available for children with genetic conditions, we are developing protocols to apply them before birth."

The child's disorder, infantile-onset Pompe disease, is one of several lysosomal storage diseases that begin to cause severe damage to major organs, such as the heart, before birth. By initiating enzyme replacement therapy during [fetal development](#), physicians aimed for better outcomes than are typical with post-birth treatment—outcomes that can include death in early childhood, very low muscle tone or ventilator dependency.

After six prenatal enzyme replacement treatments at The Ottawa Hospital, the child, Ayla, was born at term. She is receiving postnatal enzyme therapy at CHEO (a pediatric hospital and research center in Ottawa, Canada), and doing well at 16 months of age. She has normal cardiac and motor function and is meeting developmental milestones.

"When we were having Ayla, we didn't know if she'd be able to walk," said Zahid Bashir, Ayla's dad. "We didn't know if she'd be able to talk. We didn't know if she'd be able to eat. We didn't know if she'd be able to laugh. So, as she hits each of these milestones, we continue to be amazed at her progress. So, yeah, it's quite something, that I think sometimes we may take for granted, but most of the time we're quite aware that she's a miracle."

A triumph of collaboration

The successful treatment is a feat of collaboration between UCSF, where an ongoing clinical trial on the treatment is based; CHEO and The Ottawa Hospital, where the patient was diagnosed and treated; and Duke University, home to the world's top experts on Pompe disease.

"We really needed this multidisciplinary group of people to lend their deep expertise to all aspects of care," said MacKenzie, who holds a Benioff UCSF Professorship in Children's Health and a John G. Bowes Distinguished Professorship in Stem Cell and Tissue Biology. "Enzyme replacement therapy is a new frontier in the field of fetal therapy; it has been exciting to see it grow from a research project in my laboratory to impact the outcome for this family ultimately. UCSF is considered the birthplace of fetal surgery, and it is a special privilege for us to continue to expand the technologies and treatments available to help families facing a difficult diagnosis during pregnancy."

Under usual circumstances, the patient's family would have traveled to the UCSF Benioff Children's Hospital Fetal Treatment Center to participate in the clinical trial. When COVID-19 restrictions made international travel unfeasible, experts from the two Canadian and two American hospitals met the family as a team by video to discuss alternatives. UCSF shared the treatment protocol with the team in Ottawa, where the family lives. Throughout the process, the entire team met weekly by video to discuss the health of the mother and fetus and to monitor the response to treatment.

"We have been treating our fetal patients using intrauterine therapy for more than 30 years," said Karen Fung-Kee-Fung, MD, the family's maternal-fetal medicine specialist at the Ottawa Hospital and professor of obstetrics and gynecology at the University of Ottawa. "The emergence of a new medical treatment to lift the burden of Pompe

disease for this family, and potentially help other families affected by devastating genetic diseases, is both exciting and incredibly satisfying. We feel very privileged and honored to be a part of this international collaboration to help make this first-in-the-world treatment a reality."

Pranesh Chakraborty, MD, a pediatrician and metabolic geneticist at CHEO and co-lead of the [case study](#), has provided care to the family for years. "This treatment is very promising, and I am so happy for Ayla and her family," said Chakraborty, who is also a researcher at the CHEO Research Institute and an associate professor at the University of Ottawa. "Having had the privilege and heartbreak of walking alongside families who have lost children to these devastating diseases, this work is very important to me."

A big step forward for fetal therapy

Babies born with infantile-onset Pompe disease typically have enlarged hearts and die within two years if untreated. The disease is very rare, seen in less than 1/100,000 live births, and is caused by mutations in a gene that makes acid alpha-glucosidase, an enzyme that breaks down glycogen. Without it or with limited amounts, glycogen accumulates dangerously in the body.

"From our long-standing work at Duke treating patients with Pompe disease, we know first-hand the critical importance of earlier initiation of treatment," said Jennifer Cohen, MD, co-lead author of the study and assistant professor in the Division of Medical Genetics in the Department of Pediatrics at Duke University School of Medicine. "Our ability to offer a new treatment opportunity to this family and potentially change the course of this difficult disease has made this collaboration and project groundbreaking," added Cohen.

Duke has played a pivotal role in many advances in the field of Pompe

disease, including developing alglucosidase alfa as the first Food and Drug Administration-approved enzyme replacement therapy (ERT) for Pompe disease, identifying the role of high and sustained antibody titers to the ERT, using biomarkers to follow treatment response, and establishing immune tolerance induction protocols for the most severe patients, noted Priya Kishnani, MD, co-senior author, division chief of Medical Genetics at Duke University School of Medicine. "All of these advances were crucial to this particular patient's treatment and response," said Kishnani. "The intrauterine therapy represents a new frontier for patients with Pompe disease."

Pompe is one of eight lysosomal storage diseases that UCSF has received FDA approval to treat with enzyme replacement therapy in utero for a Phase 1 clinical trial of 10 patients. The other diseases are Mucopolysaccharidosis types 1, 2, 4a, 6 and 7, Gaucher disease types 2 and 3, and Wolman disease.

The researchers hope the success of this first application and publication of the case study will increase awareness of the UCSF clinical trial among parents at known risk of passing on these diseases and the physicians who treat them.

"Seeing how well Ayla is doing, it is important to pursue clinical trials to establish whether this kind of fetal therapy will be a good option for other families when treatment in the newborn period just isn't early enough," said Chakraborty, who directs the provincial program Newborn Screening Ontario based at CHEO. "We are working hard to try to improve access to this trial for other Canadian families."

Two additional patients with different lysosomal diseases have now been enrolled in the UCSF clinical trial and both have completed their course of prenatal [enzyme replacement therapy](#). The first patient gave birth in late October 2022, and the second will deliver in early November 2022.

Both are doing well.

"It's exciting to continue this research, which is an important step in the evolution of fetal therapy, from surgery for anatomic conditions to medical therapies for genetic conditions," said MacKenzie.

More information: Jennifer L. Cohen et al, In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease, *New England Journal of Medicine* (2022). 10.1056/NEJMoa2200587. www.nejm.org/doi/full/10.1056/NEJMoa2200587

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