How a cystic fibrosis drug given prenatally changed the lives of one family

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When a prenatal ultrasound in October of 2021 showed Michaela and Jacob Zalinski that the baby they were expecting was developing the same cystic fibrosis complication as her two brothers had, they were

devastated.

"It was like a brick hitting your chest," Michaela Zalinksi said. "We were freaking out."

Before birth, both of the couple's sons—Jaxon, born in 2018, and Elijah, born in 2020—developed bowel blockages related to cystic fibrosis, a genetic disease that primarily affects the lungs and digestive system. In their first few days of life, both boys needed surgery at Lucile Packard Children's Hospital Stanford to remove large portions of injured bowel. After the surgeries, Jaxon and Elijah faced extended hospital stays and long-term digestive complications.

When the ultrasound midway through Zalinski's pregnancy showed the beginnings of a bowel blockage in their daughter, the Zalinskis, who live in Magalia, California, a small town in Butte County, wondered if there was any way to set her on a different medical path.

Zalinski soon learned about a scientific report of a pregnant woman with CF who had taken a three-drug combination called Trikafta. Approved in 2019, Trikafta is part of a wave of new cystic fibrosis treatments that precisely target the gene mutations underlying the disease.

Though it was being given to treat the mother, the drug combination seemed to reduce signs of CF at birth in her baby. This gave the Zalinskis hope, but as far as they could tell, no one had tried the treatment for a mom who carried the CF gene, but didn't have the disease, and was pregnant with an affected fetus.

"I looked it up and thought, 'I wonder if there is a chance to get it approved for me, even though I don't have CF,'" Zalinski said. She called Natali Aziz, MD, the high-risk obstetrician at Stanford Medicine Children's Health who had cared for her during her pregnancies with her

sons, and said, "Do you think we can try?"

A challenging genetic disease

During Zalinski's pregnancy with Jaxon, she and her husband had learned they both carry the recessive gene for cystic fibrosis. The disease occurs when a child inherits two mutated copies of the gene, one from each parent. When two people who carry the gene have children, each child has a 25% chance of inheriting the disease.

The gene encodes a protein whose job is to maintain the balance of salt and water inside and outside the body's cells. In people with CF, the mutated version of the gene produces a malfunctioning form of this protein. The resulting disruptions in salt/water balance cause the body to produce thick, sticky mucus, which can damage the lungs, intestines and pancreas.

Intestinal problems have been the biggest challenge for Jaxon and Elijah, who are now four and three. Both boys were diagnosed in utero with meconium ileus, in which a bowel blockage develops in the final segment of the small intestine, sometimes causing the intestinal tissue nearby to become perforated or necrotic. Jaxon had a substantial amount of bowel removed three days after birth, and Elijah's bowel was in such bad shape that he was rushed to emergency surgery when he was three hours old. Both Jaxon and Elijah were hospitalized until two and a half months of age.

"For both boys, all their nutrients initially had to be given intravenously while their bowel recovered," said Carlos Milla, MD, a cystic fibrosis specialist and professor of pediatrics at Stanford Medicine who directs the Cystic Fibrosis Center at Stanford. The Zalinski children follow a complicated treatment regimen that is coordinated by Jacquelyn Spano, the CF newborn program coordinator at Stanford Medicine.

Although Jaxon and Elijah now eat fairly normally, their ability to absorb nutrients is reduced, and each has endured repeated hospitalizations for additional bowel blockages. "It's a pretty serious complication to deal with when there's a lot of bowel loss," Spano said.

Weighing the risks of a novel treatment

When Zalinski was 16 weeks pregnant with the daughter they would name Nora, an amniocentesis showed she had inherited two mutated copies of the CF gene. Soon after, the ultrasound revealed the developing bowel blockage.

At Zalinski's request, Aziz, Milla and their colleagues at Stanford Medicine Children's Health's Johnson Center for Pregnancy and Newborn Services carefully evaluated whether she should try Trikafta. The team reviewed the scientific literature—including evidence from animal studies that the drugs cross the placenta and help CF-affected fetuses—and brought the hospital's leaders, bioethics experts and the family's insurance company into the process.

"It was a high-risk situation. We knew this family had repeat, very severe meconium ileus," Milla said. That history, the ultrasound showing the same problem developing a third time and the option to try something new were all compelling, he said, adding, "In the past, we could intervene only after the baby was born."

Still, everyone was cautious. The drug combination carries side effects that had the potential to harm Zalinski, and it was impossible to know if, or how much, they would help Nora's bowel blockage.

"At most, we were hoping it would slow down or stabilize the progression," said Aziz, who is a clinical associate professor of obstetrics and gynecology at Stanford Medicine. In meconium ileus, not only can

the small intestine be damaged, but the fetus can also experience underdevelopment of the colon. The team hoped they might reduce both problems.

The team also planned how to monitor Zalinski's health, such as by checking on her liver function, as Trikafta can damage the liver.

"Our primary concern was that we could injure this mother who otherwise would not be taking Trikafta," said Susan Hintz, MD, professor of pediatrics and medical director of the Fetal and Pregnancy Health Program at Stanford Medicine Children's Health. "Michaela was extremely motivated. Our team knew her quite well and knew how challenging her journey with her other children had been, but we were still very thoughtful about proceeding as safely as possible."

Everyone agreed to go ahead, and the insurance company gave approval for a relieved Zalinski to take the drug. "It was a heroic effort on the team's part," Aziz said.

Zalinski didn't start taking Trikafta until she was 24 weeks pregnant, more than halfway through the gestation period, which worried the family as the previous mothers with CF had taken it from the outset.

"We had no clue if it was actually going to do anything for us," Zalinski said. "We were just hoping."

A disappearing blockage

An ultrasound a week later showed that the bowel blockage wasn't growing; subsequent scans showed that the blockage had stabilized.

Then, in January of 2022, when Zalinski was 32 weeks pregnant, Richard Barth, MD, professor of radiology, called her with news about

the latest fetal MRI.

"He didn't see a blockage," Zalinski said. Again, the Zalinskis felt a mixture of relief and fear. As Barth explained, the results could mean either that the blockage had healed, or that Nora's bowel had perforated. Until she was born, they wouldn't know.

Nora was born on March 12, 2022, by C-section, a week before her due date. The medical team took her to the neonatal intensive care unit and performed an X-ray with a contrast agent to give a good view of her digestive system. Michaela and Jacob Zalinski, their entire extended families, and the whole medical team waited on tenterhooks for the results.

The X-ray showed that Nora's digestive system appeared to be healthy. She did not have a bowel blockage or perforation. Her colon had developed normally. Unlike her brothers, she did not need surgery.

Aziz had been at Zalinski's side through all three pregnancies. After sharing the difficulties, she also shared her patient's thrilled sense of relief.

"The valor of this mother so impresses me," Aziz said. "We didn't know that the medication could have such an extensive benefit. For it to have completely resolved the microcolon findings was really astounding." Zalinski's lab tests remained normal, with no adverse effects from the medications.

When Hintz saw Nora's X-rays, she, too, thought about the challenging journey the family and medical team had navigated together. "Looking at her imaging, I was unexpectedly emotional," she said. "It's very humbling to think about how this could change the life of that little girl and her family."

Exciting changes

The Zalinskis were thrilled that, though third-time parents, they could have their first experience of taking a newborn home from the hospital.

"It was a big deal for everyone that she was actually coming home at four days old," Michaela Zalinski recalled, remembering that she had to learn how to adjust a car seat for a newborn as they left Packard Children's. "I wasn't used to bringing home such a small baby."

The medical team recently published a case report in *Annals of Internal Medicine* to share their story with CF experts at other hospitals. Another case report in *Journal of Cystic Fibrosis* from a different institution, published in July 2022, documented a similar experience for a mom and baby in South Carolina.

The Stanford Medicine team is developing a research protocol that will help systematically track similar cases, so they can get a broad sense of the risks and benefits from using Trikafta in pregnancy.

"Seeing that through a mother we can treat the fetus is very promising," Aziz said. "Now, we need large-scale studies formally assessing the benefit of these medications."

After she was born, Nora's lab tests showed some signs of CF, including decreased pancreatic function and elevated sweat chloride levels. Now just over a year old, she is taking a two-drug combination similar to Trikafta, and Spano is closely monitoring her. Unlike her brothers, she has had no major digestive difficulties. Her growth and development are right on track.

Jaxon and Elijah both recently began taking Trikafta, which was approved in April for children as young as 2. It's a bit early to know

exactly how much it will help them. Still, after years of navigating challenging medical issues, Zalinski is enjoying seeing her boys do normal kid things. They like playing outside, trying new sports, helping their parents in the garden and taking swimming lessons.

"I love watching them grow so strong," she said. "They have overcome so much, and it's great being able to watch them do everything anyone else can do."

As for one-year-old Nora, she has a typical toddler's high energy. "She loves jumping off of the furniture," Zalinski said.

"Our team is so encouraged to know there is a possibility to shift patients like Nora to a much easier road," Hintz concluded. "For all of us, that is the most exciting part of this work."

More information: Yair J. Blumenfeld et al, Treatment of Fetal Cystic Fibrosis With Cystic Fibrosis Transmembrane Conductance Regulator Modulation Therapy, *Annals of Internal Medicine* (2023). DOI: 10.7326/L23-0112

Sylvia Szentpetery et al, A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus, *Journal of Cystic Fibrosis* (2022). DOI: 10.1016/j.jcf.2022.04.005

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