

Her Doctor Said Her Illness Was All in Her Head. This Scientist Was Determined to Find the Truth.

After enduring severe nausea and vomiting in pregnancy, the geneticist Marlena Fejzo made finding the cause of her condition, hyperemesis gravidarum, her life's work.

By Alice Callahan

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Taped above a tidy wooden desk in the corner of her bedroom, right at eye level, is a piece of paper that Marlena Fejzo has saved for 24 years.

It's a portrait of Dr. Fejzo at age 31 during the worst ordeal of her life. Her face and body are drawn in the gaunt greens and yellows of illness; her hollowed cheeks are marked with tears. The colored pencil drawing, made by her sister in 1999, is the only image she has held on to from that time. The few photos her mother took "were too horrible" to keep, said Dr. Fejzo, now 55.

A little nausea and vomiting in pregnancy were normal, she knew. But she experienced weeks of debilitating illness when she was pregnant with her son, and when expecting her second child, Dr. Fejzo was so ill that she couldn't move without vomiting.

She couldn't go to work or care for her little boy, or swallow so much as a teaspoon of water, let alone a bite of toast or a prenatal vitamin. Her empty gastrointestinal tract would spasm so violently and for so long that she couldn't breathe.

"Every living moment was torture," she said.

For at least a month, Dr. Fejzo couldn't keep down any food or drink, and she received fluids through an IV. Her weight dropped to 90 pounds from an already slight 105, after which she grew too weak to stand on a scale.

"I was starving," she said, "and the doctor just kept trying higher doses of drugs and different drugs, and nothing helped."

Finally, her doctor agreed to deliver liquid nutrients through a catheter running into a large vein near her heart, but Dr. Fejzo believes this step came too late. Fifteen weeks into her pregnancy, the fetus's heart stopped beating.

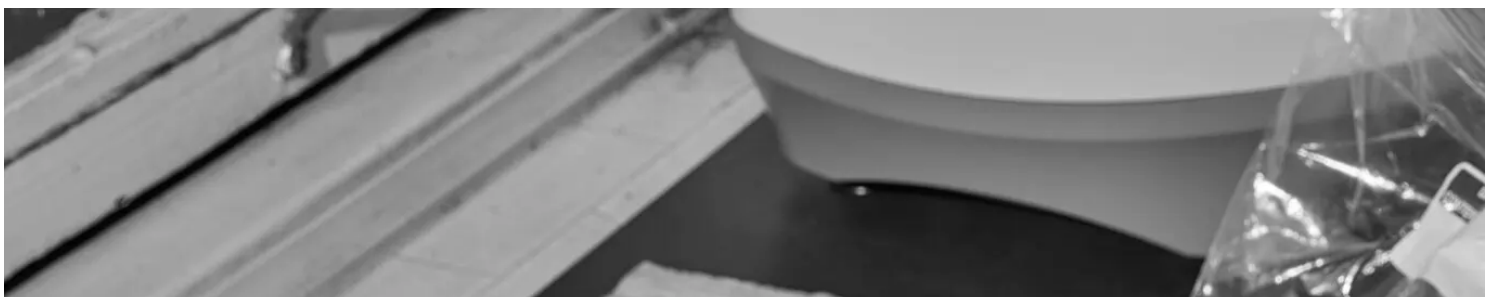
Dr. Fejzo was devastated. "All that incredible suffering for nothing," she said.

Dr. Fejzo, who was then a postdoctoral fellow at the University of California, Los Angeles, is now a faculty researcher in the department of obstetrics and gynecology at the University of Southern California Keck School of Medicine.

During her pregnancy, she suffered from hyperemesis gravidarum, a condition whose hallmark symptoms include nausea and vomiting so severe and relentless that it can cause dehydration, weight loss, electrolyte imbalances and hospitalization.

The complication is rare, affecting about 2 percent of pregnancies, but its consequences can be devastating. In surveys, women have described their experiences with the condition in harrowing terms: "I was depressed and bedridden for 20 weeks. I wanted to die," one wrote; "I am terrified to experience another pregnancy," another said.

Some wrote of feeling "miserable, with no hope"; or lonely and abandoned, with references to suicide. "I sobbed when I awoke in the mornings because I realized, I was still alive."



In a recent survey of more than 5,000 hyperemesis patients, 52 percent had considered — and 5 percent had gone through with — terminating a wanted pregnancy, and 32 percent reported contemplating suicide. Maggie Shannon for The New York Times



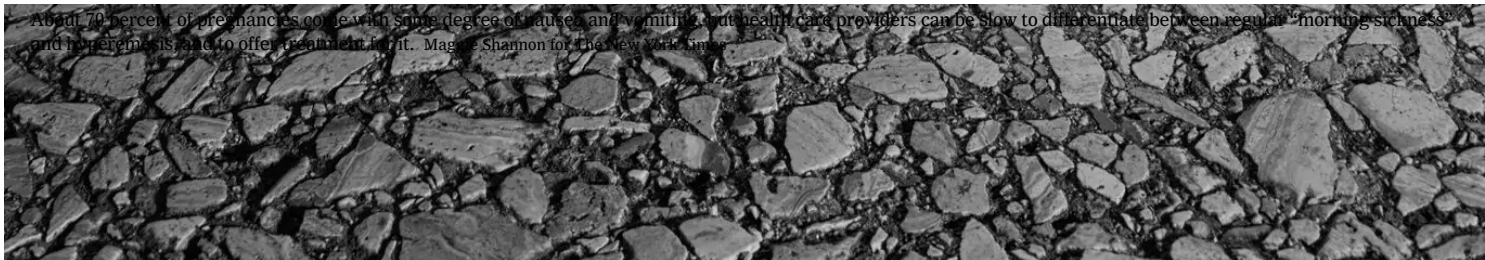
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at U.C.L.A. That was when, she said, she experienced the worst ordeal of her life, leading to 10 weeks of severe illness and her miscarriage.

Dr. Fejzo's sister, Melanie Schoenberg, now 45, a public defense lawyer for Los Angeles County, remembered seeing her at the end of her ordeal. She was in a wheelchair, too weak to walk and wrapped in a blanket, sobbing and shaking with grief.

"She looked like a ghost," Ms. Schoenberg said. "Like a pile of bones."

An under-researched condition

At age 31, as Dr. Fejzo regained her strength, she made two life-altering decisions. First, she said, she wouldn't try another pregnancy; her twin daughters would later be born with the help of a surrogate. Second, she was determined to find the cause of hyperemesis.

She scoured the medical literature for clues. Why had she gotten so sick when most pregnancies had far milder symptoms? "Nothing was known," she said. "There was so little research."

Hyperemesis has long been under-researched and insufficiently recognized, in part because about 70 percent of pregnancies come with some degree of nausea and vomiting, which is usually not dangerous, Dr. Trovik said. Health care providers can be slow to differentiate between the more common "morning sickness" and the rarer but more severe hyperemesis, and to offer treatment, including medications and nutrition, she said.



"It was so devastating what happened to me that I don't want that to happen to anyone else," Marlana Fejzo said of her experience with hyperemesis, and of her doctor's dismissal of the condition as being all in her head. Maggie Shannon for The New York Times

Before IV fluids became routinely available in the 1900s, hyperemesis killed pregnant women often enough that medical literature listed excessive vomiting as a reason to induce abortion because of the danger it posed to the mother's life. Some experts believe that the death of the author Charlotte Brontë in 1855 was most likely caused by hyperemesis, not tuberculosis, as was listed on her death certificate.

Today, deaths from hyperemesis are rare, but they do occur, as do serious complications.

Electrolyte imbalances caused by excessive vomiting and dehydration can bring about heart arrhythmias and cardiac arrest. Malnutrition and deficiency in the B vitamin thiamin can lead to a brain disorder called Wernicke's encephalopathy, which can result in miscarriage, brain damage and death.

Hyperemesis is also linked with a higher risk of pregnancy complications including preterm birth, pre-eclampsia and blood clots.

In a recent survey of more than 5,000 patients with hyperemesis in the United Kingdom, 52 percent had considered — and 5 percent had gone through with — terminating a wanted pregnancy; and 32 percent reported contemplating suicide. A 2022 study found that hyperemesis is one of the main predictors for postpartum depression.

Most babies born from hyperemesis pregnancies are healthy, but recent studies have shown that they have a small increase in risk of having low birth weight, and of having cognitive, mental health and behavioral difficulties in childhood — effects that could be caused by malnutrition and stress in the womb, researchers hypothesize.

Over the last century, physicians have claimed, without evidence, that hyperemesis is a subconscious attempt at “oral abortion,” as if trying to throw up a pregnancy; a rejection of femininity; a product of sexual frigidity; a strategy for taking a “time out” from stressful household responsibilities; or a bid for attention, as Dr. Fejzo's doctor had told her.

As a result, women have often been blamed and punished for their own illnesses. In the 1930s, hospitalized hyperemesis patients were “denied the solace of the vomit-bowl” and forced to lie in their own vomit.

To this day, patients hospitalized with the condition are sometimes isolated in a dark room and prohibited from having visitors or access to their cellphones. This treatment has been based in part on the theory that hyperemesis is caused by a woman's subconscious rejection of pregnancy, and that isolation would make her accept it, said Dr. Philippe Deruelle, a professor of obstetrics and gynecology at the University of Strasbourg, via email.

The practice is “misogynist” and “indefensible,” he said, but it still occurs at least occasionally in France and elsewhere in Europe. In 2022, the College of French Gynecologists and Obstetricians issued new guidelines that included a statement condemning it.

Dr. Fejzo was haunted by the dismissal of her illness as having a psychological cause, and by the lack of effective treatments to help her. Nothing would change as long as the condition's true cause was unknown, she thought.

A decade of Fridays

When Dr. Fejzo returned to her lab at U.C.L.A. after her miscarriage, she told her boss, the chair of the genetics department, that she wanted to find the cause of hyperemesis. “She just laughed at me,” Dr. Fejzo said, “like it was a joke.”

Unable to find a mentor interested in hyperemesis, Dr. Fejzo took a job studying ovarian cancer at the university, a position she stayed in, mostly part-time, for 20 years. But she began piecing together research on hyperemesis during her evenings and weekends and on Fridays when she wasn't working in the lab.

Her younger brother, Rick Schoenberg, 51, a statistician at U.C.L.A., helped her create an online survey of hyperemesis patients, and the Hyperemesis Education and Research (HER) Foundation offered collaborators and small grants to fund her work. In 2005, Dr. Fejzo also began partnering with obstetrician-gynecologists at the University of Southern California.

Tallying survey responses, “I saw right away that it was running in families,” Dr. Fejzo said. “The answers kept coming in where people were like, ‘Yeah, my sister has it; my mom has it.’”

In 2011, Dr. Fejzo and her collaborators published their findings in the American Journal of Obstetrics and Gynecology. Women who had sisters with hyperemesis, they found, had a 17-fold higher risk of developing the condition than those who didn't, providing some of the first clear evidence that the condition could be passed down from parents.

Dr. Fejzo knew that DNA analysis would be crucial to understanding the genetics of hyperemesis. So in 2007, she began collecting saliva samples from people who had experienced the condition and those who hadn't.

Every Friday for 10 years, she called study participants — more than 1,500 in all — to request their medical records and consent to participate, and mailed them saliva collection kits from her home.

But Dr. Fejzo wasn't sure how she would pay for the genetic analyses. Her grant proposals to the National Institutes of Health were rejected. Since 2007, the agency has funded only six hyperemesis studies, totaling \$2.1 million.

That amount is small in comparison with the economic burden of the condition, said Kimber MacGibbon, executive director of the HER Foundation. (Amy Schumer, who publicly documented her struggles with hyperemesis, is on the foundation's board of directors.)

Hyperemesis hospitalizations are thought to cost patients and insurers about \$3 billion per year, she said, and then there are the expenses of medications, home health care, lost work and complications like postpartum depression. "The costs of it are just astronomical," she said.

'This is it'

Without funding to analyze the saliva samples accumulating in the lab freezer, Dr. Fejzo discovered an alternative strategy when her older brother gave her a 23andMe DNA testing kit for her 42nd birthday.

After registering her kit, she received a standard email giving her the option of participating in the company's research studies by completing an online survey and consenting to the use of her genetic data.

"I saw what they were doing, which I thought was brilliant," she said.

She asked 23andMe if they would include a few questions about nausea and vomiting in pregnancy on their customer survey, and they agreed. A few years later, she worked with the company to scan the genetic data of tens of thousands of consenting 23andMe customers, looking for variations in their DNA associated with the severity of nausea and vomiting during pregnancy. The results were published in the journal Nature Communications in 2018.

A handful of gene mutations were flagged as significantly different, but the most striking was for one that makes a protein called growth differentiation factor 15, or GDF15. Dr. Fejzo had never heard of it, but as soon as she started reading about it, "I was like, 'Oh my God, this is it,'" she recalled.

GDF15 acts in a part of the brainstem that suppresses appetite and sets off vomiting, and it had already been shown to cause appetite and weight loss in cancer patients. Blood levels of the protein are naturally increased in pregnancy and have since been found to be even higher in those with severe nausea and vomiting.

Researchers speculate that GDF15 may have evolved to help pregnant women detect and avoid unsafe foods that might harm fetal development early in gestation. But in hyperemesis, this normally protective mechanism seems to run in overdrive, at least in part because of too much GDF15, said Stephen O'Rahilly, director of the metabolic diseases unit at the University of Cambridge, who now collaborates with Dr. Fejzo on GDF15 research.

In a study published in 2022, Dr. Fejzo and her colleagues confirmed the link between hyperemesis and GDF15 in the patients she had enrolled over a decade of Fridays. The analyses were conducted without charge by the biotechnology company Regeneron.

When that study was published, Dr. Fejzo wrote on Twitter, "My life's work is out."

But she isn't done. She's watching closely as several pharmaceutical companies have begun testing GDF15-based drugs that aim to reduce nausea and improve appetite in cancer patients, with promising early results.

A smaller number are working on similar medications for hyperemesis, Dr. Fejzo said. Among them is a newly formed company called Materna Biosciences, which recruited Dr. Fejzo as chief scientific officer.

There are significant hurdles to testing new medications in those who are pregnant, Dr. Fejzo said, but if done carefully, this step could improve treatment options for hyperemesis patients and definitively prove that GDF15 is the condition's primary cause.

And, Dr. Fejzo hopes, it could finally put to rest the idea that the condition is psychological.

"I would be devastated to see my daughters go through this without having tried everything in my power to make things better," Dr. Fejzo said. "If I don't keep going, who will?"

Edited by Julia Calderone. Audio produced by Kate Winslett.

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