New Drugs Raise Old Questions About Treating Cancer During Pregnancy

About 1 in 1,000 pregnant women is diagnosed with cancer. Do newer treatments, such as immunotherapy, work in this group of patients?

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In the fall of 2020, Leticia Ramos-Mateo was 13 weeks pregnant when she received some unwelcome news: Her cancer had come back.

Three years earlier, Ms. Ramos-Mateo had been treated for Hodgkin lymphoma. But she'd had no signs of the disease since completing treatment. Now, at age 31 and at the end of her first trimester, she was facing a recurrence.

Doctors at her local hospital in New Jersey had detected multiple tumors, including a volleyball-sized mass growing in her upper abdomen. "I was worried that I might not survive," recalled Ms. Ramos-Mateo, who had decided not to terminate the pregnancy.

But she did survive. And she recently celebrated the first birthday of her son, who was born without any signs of harm from the treatment his mother received while pregnant with him.

"The baby is healthy and talks a lot," Ms. Ramos-Mateo said. "He's small, but we don't worry about his size because I am also tiny."

Ms. Ramos-Mateo was treated with the immunotherapy drug nivolumab (Opdivo), a type of immune checkpoint inhibitor. By blocking proteins called immune checkpoints, these drugs restore the ability of immune cells to attack cancer cells.

Nivolumab is approved to treat Hodgkin lymphoma. But Ms. Ramos-Mateo may have been the first pregnant person with a lymphoma to be given immunotherapy intentionally.

Although Ms. Ramos-Mateo's story has a happy ending, her experience underscores how little is known about using newer therapies, such as targeted therapies and immunotherapy drugs, to treat cancer during pregnancy, according to Andrew Evens, DO, MBA, MSc, of the Rutgers Cancer Institute of New Jersey.

Evens, who specializes in treating pregnant women with lymphoma, led the multidisciplinary team that took over the care of Ms. Ramos-Mateo from her local hospital when she was 19 weeks

pregnant.

Focusing on a uniquely vulnerable population of patients

The team recently published a case study describing Ms. Ramos-Mateo's treatment in the American Journal of Hematology. After Evens presented the study at a scientific meeting last year, several doctors contacted him seeking advice about how to treat their pregnant patients with cancer.

About 1 in 1,000 pregnant women is diagnosed with cancer. Lymphoma is among the cancers that occur most frequently during pregnancy.

"Cancer during pregnancy may be more common than we realize, perhaps because it does not get reported and talked about," said Evens. "We're sharing our findings in part because we want people to practice evidence-based medicine, even though there's not a great deal of published data."

Pregnant people are excluded from clinical trials of new drugs to ensure that they and their developing fetuses are not exposed to potentially toxic treatments. A result is that no one knows whether many newer cancer treatments are safe and effective during pregnancy.

"We need a national effort to evaluate standard treatments for cancer in pregnant patients," he said. "Our new case report can help shine a light on the need to help a uniquely vulnerable population of patients."

Crowdsourcing questions about immunotherapy and cancer during pregnancy

Ms. Ramos-Mateo's experience illustrates the need to expand treatment options for pregnant people with cancer. Beginning in week 19 of her pregnancy, she received a chemotherapy regimen that has been used to treat pregnant women with cancer after the first trimester (the first 13 weeks of pregnancy).

Her symptoms, such as severe abdominal pain caused by a tumor, improved temporarily. But by the 26th week of her pregnancy, multiple tumors, including one near the baby, were growing unchecked. Evens estimated that she had weeks to live.

Nivolumab is very effective in many patients with Hodgkin lymphoma, noted Evens. "We thought the drug would work, but we wanted to have some confidence that it would be safe for the mother and the baby," he said.

There were no published studies demonstrating the safety of immunotherapy in pregnant women with relapsed Hodgkin lymphoma. And there were few case reports describing the use of immunotherapy drugs in pregnant women with any type of cancer.

After reviewing the scientific literature, Evens posted a message on Twitter asking if anyone in the medical community had experience using immune checkpoint inhibitors during pregnancy. He received a helpful response.

Elad Sharon, MD, MPH, of NCI's Cancer Therapy Evaluation Program, replied that he had some unpublished data from a case series. He'd never met Evens, but they began a conversation that led to a collaboration.

Sharon's team had identified reports of nine participants in NCI-sponsored clinical trials who had unexpectedly become pregnant while receiving immune checkpoint inhibitors. Seven of these women decided to continue their pregnancies, and all gave birth to healthy infants.

"These pregnancies turned out just fine," said Sharon. "We thought this was scientifically interesting and potentially important for public health, at least for women who experience cancer while pregnant."

The anecdotal information—along with some case reports describing similar outcomes—gave Evens and his team confidence that nivolumab might benefit Ms. Ramos-Mateo. Despite the potential risks, she agreed to try the therapy.

Testing blood levels of an immunotherapy drug in the umbilical cord

"The drug worked better than I expected," said Dr. Evens. "The patient's tumors melted away, she went into a complete remission, and gave birth to a healthy baby boy."

A few weeks after giving birth, Ms. Ramos-Mateo had a stem cell transplant, and her cancer has remained in remission.

In addition to being the first pregnant person with a lymphoma to intentionally receive an immune checkpoint inhibitor, Ms. Ramos-Mateo received her final dose of nivolumab when she was 37 weeks pregnant. There were no previous reports of pregnant people receiving immune checkpoint inhibitors beyond 33 weeks of pregnancy.

Ms. Ramos-Mateo gave her doctors permission to collect blood samples, including from the umbilical cord and the placenta, for research purposes. A team at NCI's Center for Cancer Research documented, perhaps for the first time, the blood levels of an immunotherapy drug in a placenta and an umbilical cord during pregnancy.

"We wanted to learn as much as we could from the care of this individual patient to inform what we would do for the next patient," said Sharon.

One question was whether nivolumab had reached the fetus. The researchers did not collect any blood from the fetus, but they found nivolumab in the umbilical cord blood, which meant that the drug had reached the fetus, according to Sharon.

“We did not observe any harmful effects of the drug on the baby,” Sharon said. “The questions now are which factors may be more likely to cause harm to a developing fetus and what should we be watching out for. That will be the focus of future research.”

Building a registry about pregnant patients with cancer

The decision to treat cancer during pregnancy involves “weighing the risk of exposing the fetus to medication versus the risk to the mother’s untreated illness if you don’t expose the fetus to medication,” said Elyce Cardonick, MD, an obstetrician at Cooper University Health Care who specializes in high-risk pregnancies.

There’s a growing recognition among doctors, Cardonick continued, that if a pregnant woman with cancer cannot delay treatment until delivery, it is generally safe to use chemotherapy in the second and third trimester.

If a woman has a very aggressive tumor in the first trimester, however, “then unfortunately we may have to discuss termination of the pregnancy, because we can’t use aggressive chemotherapy in the first trimester,” Cardonick added. (Chemotherapy is not used during the first trimester because the drug could affect developing organs in the fetus.)

Dr. Cardonick runs a registry of people with cancer who were diagnosed during pregnancy. Launched in 1997, the database now has information on the treatment and outcomes of about 450 women and their children.

The registry includes a wealth of information about pregnant women treated with older drugs. “With the newer drugs, we are really starting over,” Cardonick said. “We have to collect information about the new drugs one case at a time, just as we have done with chemotherapy.”

But she welcomes the challenge, she said. New drugs may offer hope to pregnant people with certain cancers, like melanoma, that haven’t responded to chemotherapy.

Immunotherapy has helped to transform the care of people with advanced melanoma. And although more research is needed, there is some evidence that immunotherapy may benefit pregnant patients with the disease.

“Before the recent approval of new drugs, we had not been able to help pregnant women with melanoma outside of surgery—it was really sad,” said Cardonick. “But now, with immunotherapy, we have something else we can offer them, which is amazing.”

A growing need for information on immunotherapy during pregnancy

The expanding use of immunotherapy to treat cancer has created “a great need for information about using these drugs in pregnancy,” said Frédéric Amant, MD, PhD, of the University of Leuven

in Belgium, who studies cancer during pregnancy.

Most of what is known about the use of immunotherapy during pregnancy comes from patients in their first few months of pregnancy, because women have tended to stop immunotherapy once they have learned that they were expecting, he noted.

Long-term studies of children who are exposed to cancer treatments in utero and their mothers should be priorities for the field, Amant continued.

Exploring questions about including pregnant women in clinical trials

Experts agree that to improve the care of pregnant women with cancer, new studies—and particularly those that collect biological samples such as blood—are needed.

Such studies could shed new light on all aspects of treating cancer during pregnancy, including how pregnancy affects the biology of different types of cancer.

Although well intentioned, the practice of keeping pregnant women from participating in clinical trials of cancer treatments has had unintended consequences, according to Sharon.

“By excluding pregnant women from clinical trials, we’re really not learning anything that could help us treat the next pregnant patient,” said Sharon. “And that’s probably a flaw in how we conduct medical research.”

One solution, he explained, would be to conduct “dedicated observational trials.” In these trials, patients with cancer who are pregnant and have no choice but to receive therapy could be monitored to assess the benefits and risks of newer drugs. “This would allow us to learn more so that we could help future patients who are in the same situation,” Sharon said.

The inclusion of pregnant and lactating participants in clinical trials will be discussed June 16–17 at a workshop hosted by the National Academies of Sciences, Engineering, and Medicine. The meeting will highlight gaps in knowledge about the use of drugs during pregnancy and lactation, as well as barriers and opportunities for including people who are pregnant or lactating in clinical trials.

In the meantime, Ms. Ramos-Mateo hopes that her story can help other pregnant women who are diagnosed with cancer. She is planning to bring her son to her next appointment with Evens.

“Because of COVID restrictions, Evens has never seen the baby,” said Ms. Ramos-Mateo. “But they will soon meet, and it will be a blessing.”

Studying Cancers Found by Noninvasive Prenatal Tests

Noninvasive prenatal tests (NIPT) that pregnant women use to detect common chromosomal abnormalities in a fetus can also suggest that the mother may have cancer. Though it is uncommon, noninvasive prenatal tests have detected abnormal chromosomes resulting from an undiagnosed cancer in the mother rather than chromosomal abnormalities in the fetus.

Christina Annunziata, MD, PhD, an investigator in NCI's Center for Cancer Research Women's Malignancies Branch, is leading a study to learn more about the biology of these cancers. "The big question we are trying to answer is, 'What's the frequency of cancer when the prenatal screening test finds abnormal chromosomes and the baby's chromosomes are normal?'" said Annunziata.

Although the number of participants is still small, she continued, many of the women enrolled in the pilot study had cancer. Her team plans to enroll 100 people total.

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