NEWS

As the pandemic wanes, will autism diagnoses rise in its wake?

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In January 2020, during her fifth month of pregnancy, Erin Knipe came down with a sore throat, ear infection and relentless cough. She was exhausted: She had made it through the morning sickness of her first trimester only be to be knocked out by what seemed like a bad cold.

When Knipe wasn't getting better after a few days, her doctor prescribed an antibiotic for a possible bacterial infection and a steroid inhaler to treat her asthma, which had been exacerbated by the cough. After four miserable weeks, she recovered — just before the first wave of the COVID-19 pandemic ramped up in the United States. She gave birth in May and, eager to do her part to advance scientific research, immediately enrolled herself and her daughter in a study of children born during the pandemic.

Knipe expected that she and her daughter would be part of the study's control group. But an initial blood test revealed that they both had antibodies to SARS-CoV-2, the virus that causes COVID-19. Having those antibodies, the research team told her, meant that she had unwittingly contracted the virus while she was pregnant, possibly back in January. And with such a new pathogen and disease, they couldn't yet tell her what that infection would mean for her baby.

A mild illness during pregnancy is not usually cause for concern. "Most women will be exposed to viral and bacterial infections during pregnancy, and most go on to have neurotypical offspring," says **Melissa Bauman**, professor of psychiatry and behavioral sciences at the University of California, Davis, who is not involved in the study Knipe joined.

Severe infections, though, particularly those that require hospitalization, have been linked to a

slightly increased likelihood of having a child with autism or other psychiatric conditions. And although it's new, severe COVID-19 has already been tied to an increased risk of certain **pregnancy complications**, including preterm birth, that are, in turn, associated with an increased chance of a **child having autism**.

Because of these associations, scientists and clinicians are searching for clues as to whether the COVID-19 pandemic will **boost the incidence** of neurodevelopmental conditions over the next few years. They're tracking the long-term development of prenatally exposed children, such as Knipe's daughter, and comparing the immunological responses of pregnant people who contract the virus with those who do not.

Although some indirect evidence suggests that prenatal exposure to SARS-CoV-2 can alter neurodevelopment — particularly in cases of severe infection — the earliest data on babies born during the pandemic hint at only minimal effects. But it's still not clear if that pattern will hold up over time, or what else may influence a child's developmental outcomes in conjunction with maternal infection.

"We now think of exposure to infection during pregnancy as a disease primer that, in combination with other genetic and environmental risk factors, may increase the risk of altered neurodevelopment for a subset of exposed pregnancies," Bauman says. "The major challenge is to understand which pregnancies are at risk and which are resilient to prenatal immune challenge."

SARS-CoV-2 is a novel pathogen, but researchers have been studying how viruses and other infectious agents can shape **prenatal brain development** for decades.

Some pathogens affect development by passing directly from a pregnant woman to her fetus — what clinicians call 'vertical transmission.' One prominent example is the Zika virus, which can cross the placenta and interfere with fetal brain growth, leading to microcephaly and, even in mild cases, language difficulties and other **developmental problems**.

The vertical transmission of viruses is rare, however. The evidence so far suggests that it is **possible but uncommon with SARS-CoV-2**, and even in these cases there don't appear to be significant effects.

"We were reassured early on that it doesn't seem to cause vertical transmission in the same sense that Zika would," says **Karin Nielsen-Saines**, professor of pediatrics at the University of California, Los Angeles, who has studied Zika and works on the COVID-19 study in which Knipe is enrolled.

But even if a pathogen never infects the fetus, the woman's immune reaction to the invader can still wreak havoc on fetal brain development, according to the 'maternal immune activation theory.' To collect evidence in support of this idea, researchers have **injected pregnant mice**, rats

and **monkeys** with compounds that mimic viruses or bacteria to stimulate the animal's immune system. And the immune signaling molecules released in response to the mock infection, they have found, can make their way to the placenta, **alter fetal brain structure** and increase the offspring's likelihood of having autism-like traits.

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The exact mechanisms are not fully understood, but studies in mice suggest that these atypical maternal immune profiles affect the developing fetal brain by **interfering with microglia** — specialized immune cells that help **prune connections between neurons**.

In people, certain immune signaling molecules, particularly inflammatory cytokines that help rally a woman's immune system, are also associated with an increased likelihood of autism in her child. Some women with autistic children, for example, have **unusually high gestational levels of inflammatory cytokines** called interferons and interleukins, research shows. And exposure to these immune signals, such as **IL-6**, in utero is also linked to atypical brain connectivity. Women with **autoimmune conditions**, which dysregulate levels of these molecules, are more likely to have autistic children as well.

Infection with SARS-CoV-2 during pregnancy can lead to **similarly atypical immune profiles**, studies are finding. In one analysis of 23 pregnant women, those infected with SARS-CoV-2 had **increased levels of the cytokine IL-8**, which has been previously linked to **atypical brain development**. And among 93 pregnant women, roughly 20 percent had severe COVID-19 cases, Nielsen-Saines and her colleagues discovered, which produced **significantly more inflammation** than milder illness.

In that same cohort, Nielsen-Saines' team also noted that infants with prenatal exposure to SARS-CoV-2 showed dysregulation of the Wnt signaling pathway, a core developmental signaling cascade involved in brain development. Disruption to this pathway is **linked to autism and schizophrenia**. Although more research is needed, Wnt's connection to COVID-19 adds another reason for concern over the long-term consequences of SARS-CoV-2 infection during pregnancy.

"It could potentially signal that, in the future, there could be issues with neurodevelopment in babies who are born to women with severe disease," Nielsen-Saines says.

Despite such findings, the earliest data on babies prenatally exposed to SARS-CoV-2 are encouraging. Most of these babies show no obvious signs of atypical development so far.

A fetal imaging study in Germany, for example, **found age-appropriate brain development** in

babies of women who had mild or moderate COVID-19 during pregnancy, and no differences from babies whose mothers had not been infected. And infants born in New York City from March to December 2020 to women who had mild or moderate COVID-19 showed **no signs of delayed motor or social development**, according to a study published in January.

“This does not mean that we should allow pregnant women to get infected,” says the New York study’s lead investigator, **Dani Dumitriu**, assistant professor of pediatrics and psychiatry at Columbia University. “But if they do get infected, they don’t need to feel desperate about the outcome.”

The studies that have produced results so far are all relatively small, says **Brian Lee**, associate professor of epidemiology and biostatistics at Drexel University in Philadelphia, Pennsylvania, who investigates links between prenatal exposures and autism. But if SARS-CoV-2 altered brain development to the level that’s seen with Zika, it would likely be apparent, he says.

“It seems that on the scale of severity of potential neurodevelopmental outcomes, we’ll be looking for more subtle effects.”

Such subtle changes will likely take time to emerge, and it may be challenging to identify the biggest contributing factors.

The earliest studies may not have included enough severe COVID-19 cases to discern how disease severity tracks with changes in fetal neurodevelopment, for instance. Pregnancy itself is a **risk factor for having severe COVID-19**, but only about **4 percent** of infected pregnant women in the U.S. were admitted to an intensive care unit between January 2020 and February 2022, according to the Centers for Disease Control and Prevention. Some 20 percent were hospitalized, but that figure likely includes women admitted for a variety of reasons.

> “It seems that on the scale of severity of potential neurodevelopmental outcomes, we’ll be looking for more subtle effects.” Brian Lee

There are plenty of confounding factors to consider, too, says **Anna-Sophie Rommel**, assistant professor of psychiatry at the Icahn School of Medicine at Mount Sinai in New York City, who is working on a study, dubbed Generation C, of more than 2,500 women who received obstetrical care in the Mount Sinai Health System during the pandemic, and their babies. For example, it can be difficult to tell if a pregnancy complication **arises because of COVID-19** or because people who are more likely to contract COVID-19, such as those who have been economically and socially marginalized, are also more likely to have pregnancy complications, Rommel says.

But so far, it seems that infection with SARS-CoV-2 does not “add to an already elevated risk of adverse maternal and neonatal outcomes,” she says.

The studies best poised to untangle those factors are the large, long-term projects collecting extensive data on the mothers' health and the children's outcomes, such as Generation C and the University of California, Los Angeles study in which Erin Knipe is participating. But because many neurodevelopmental conditions are diagnosed after the first few years of life, it may still be too early to tell if autism diagnoses have increased.

"Most of the children exposed to the virus in utero are still quite young or yet to be born," says **Lisa Croen**, senior research scientist at the Kaiser Permanente Division of Research in Oakland, California, who is helming a long-term study of the effect of maternal inflammation on children's neurodevelopmental outcomes. In addition to tracking how SARS-CoV-2 exposure shapes these outcomes, Croen and her colleagues have an eye on another source of maternal inflammation — environmental stress — that some researchers say could end up having more impact than the virus.

For example, the same study that found no association between maternal COVID-19 and atypical development in 6-month-old babies did find a link between development and just being born during the pandemic. In particular, children who were in utero and in the first trimester when New York City experienced its first pandemic peak had poorer motor and social skills than children born pre-pandemic.

In some ways, the finding is not surprising, says **Gráinne McAlonan**, professor of translational neuroscience at King's College London in the United Kingdom. "We know that conditions like depression and stress in pregnancy do have outcomes which affect some of the offspring," at least potentially, she says. "If you look back at 2020 — if you were pregnant at that point, it would be a very worrying time."

McAlonan is leading an imaging study to **compare the trajectories of brain development** in children exposed to different forms of maternal stress and inflammation. Because that project was ongoing before the pandemic, she and her colleagues may be able to tease out any changes that arise specifically from prenatal exposure to SARS-CoV-2 — something they hope to begin looking at in the next few months.

"I expect to see something," McAlonan says. "Having said that, whether those changes turn out to really cause something that's developmentally of concern, I think the jury would be out. And I'm certain it will be way more complex than we think."

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