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Anxious Mom, Allergic Kid?

A mother's distress not only affects her interactions with her baby —it can also throw the baby's immune system off-kilter

As anyone who has been around children knows, babies instantly pick up on their mothers' moods. Mom smiles, baby smiles. Mom's upset, baby fusses. Mom is stressed out ... baby gets an allergy? Is that even possible, and how might it work?

AllerGen investigator Dr. Anita Kozyrskyj, a professor in the Department of Pediatrics at the University of Alberta, is looking for answers to these questions.

Dr. Anita Kozyrskyj, Professor
University of Alberta

Studies have linked a mother's distress during and after pregnancy to her child developing an allergy, but exactly how one leads to the other has been unclear. A separate line of research has connected childhood allergies with disruptions in a baby's developing immune system.

Dr. Kozyrskyj and her team are weaving these two threads together to better understand how a mom's distress could lead to immune changes in her newborn, and how this link may translate into allergies down the road.

In 2017, Dr. Kozyrskyj's team conducted a study with 403 mothers and their babies participating in the CHILD Study—AllerGen's national birth cohort project collecting a vast range of health, lifestyle, genetic and environmental exposure information from thousands of Canadian families.

Mothers completed a questionnaire consisting of 20 questions about depression experienced during their pregnancies and after their babies were born. The questions, which covered a range of symptoms—from feeling lonely or sad to experiencing restless sleep—were designed to assess a mother's overall level of distress. The research team then categorized the participants based on the timing of the symptoms they reported: while pregnant, after birth, during both these time periods, or not at all.

Mothers also provided information about their breastfeeding and other infant feeding practices, as well as medication use and details about the home environment.

Antibodies on guard

When the infants were three months old, the researchers collected their stool samples to measure levels of secretory IgA (sIgA), an immune antibody, secreted in the gut. A critical marker of immune maturation in infants, sIgA "prevents harmful bacteria from penetrating the lining of the gut but allows harmless environmental molecules to pass through, thereby teaching the immune system to distinguish between good and bad foreign substances," explains Dr. Kozyrskyj.

Because sIgA does not pass from mom to baby through the placenta, newborns have negligible amounts of this antibody at birth. During their first few months of life, infants receive sIgA primarily from their mothers' breastmilk, after which their guts begin to independently produce the molecule.

Why zero in on sIgA as the marker of a strong immune system? Dr. Kozyrskyj says that previous studies have found respiratory infections and allergic disorders tend to occur more frequently in people with sIgA deficiency, suggesting that sIgA may help to prevent these conditions.

And why explore the link between sIgA and stress? An animal study in which sIgA levels fell in mice exposed to stress caught Dr. Kozyrskyj's attention. "This finding made me wonder whether stress during pregnancy and after birth could affect the developing immune system in humans as well," she says.

Of note, sIgA levels were not lowered in infants of mothers who were distressed only during pregnancy or only after their baby's birth. It would seem that "a continuous stretch of maternal distress has a greater influence on infant gut immunity than pre- or post-natal distress in isolation," says Dr. Kozyrskyj, adding that "this study highlights the importance of maternal wellbeing throughout the pregnancy and birth journey."

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Mother's stress, baby's immune system

Examining the questionnaire responses, Dr. Kozyrskyj's team found that 12% of women experienced significant distress symptoms only during pregnancy (prenatal period); 8.7% of women had symptoms only after they gave birth (postnatal period); and 9.2% of women had symptoms both before and after the birth (pre- and post-natal periods). It was in this last group that the findings were most compelling: infants born to mothers who experienced distress both during and after pregnancy had the lowest levels of sIgA among all infants in the study. Specifically, infants born to these women were "three times as likely to have reduced sIgA levels compared to infants whose mothers were not depressed, which is highly significant," Dr. Kozyrskyj says.

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According to Dr. Kozyrskyj, this is the first study to identify a plausible explanation for the link between maternal distress and childhood allergy. "Earlier studies were not able to explain the 'why,'" says Dr. Kozyrskyj. "One of the hypotheses floating around was that distressed mothers were more likely to smoke and less likely to breastfeed—behaviours that could theoretically lower sIgA levels and weaken the child's immune system."

But that's not what the Kozyrskyj study found. Using information from health questionnaires, the researchers classified the infants into three categories: exclusively breastfed, partially breastfed, and not breastfed. They found that while the formula-fed infants had lower sIgA levels than the breastfed infants overall, "formula-fed infants with more severely depressed mothers had lower sIgA than other formula-fed babies," says Dr. Kozyrskyj. "The connection between depression and lower sIgA levels held true, even when breastfeeding status was considered in our analysis."

Their analysis also examined the impact of a mother's allergies or antidepressant use and found no connection to lower sIgA in the infants.

So what's next for this research team? There are several more "intriguing threads to follow," says Dr. Kozyrskyj. Having established a connection between a mother's psychological wellbeing and her newborn's immune health, Dr. Kozyrskyj would like to dig deeper into how exactly the one impacts the other. "The B cells which secrete sIgA into the intestine start to be produced by the fetus. Stress during pregnancy elevates maternal cortisol levels which could lower fetal production of B cells and subsequently sIgA levels after birth," says Dr. Kozyrskyj, though she admits this is just conjecture. "In truth, we don't yet know what physiological mechanisms could account for our results. Stay tuned for follow-up studies."

She also plans to investigate whether the severity of maternal depression tracks with the magnitude of sIgA reduction in the infant in what is known as a "dose-response effect."

Longer term, Dr. Kozyrskyj hopes to find out if the low-sIgA children in her study grow up to have higher rates of asthma and allergy. "The CHILD Study is unique in that it has been following families and their babies since before birth—and the children are now eight years old. This incredibly rich trove of health data and samples will allow us to finally answer the question of whether or not maternal depression ultimately raises the risk of childhood allergy."

The microbial connection

Dr. Kozyrskyj has one more lead she plans to follow: the possibility that maternal stress perturbs the infant's gut microbiome—a known contributor to immune health.

An expert in the gut microbiome—the community of micro-organisms or bacteria that live in the digestive tracts of humans —Dr. Kozyrskyj leads the $2.5 million SyMBIOTA (Synergy in Microbiota Research) project funded by the Canadian Institutes of Health Research (CIHR).

The idea that maternal depression affects bacteria in the child's gut has some support: animal studies have shown that stressing pregnant mothers affects the composition of bacteria in their gut and vagina, which in turn alters their offspring's gut microbiome. In humans, an early report has found reduced levels of lactic acid bacteria in infants born to stressed pregnant mothers.

According to Dr. Kozyrskyj, the infant gut microbiome goes through a series of predictable changes in the first year of life. When the maturation process unfolds normally, the infant develops a protective bacterial barrier as part of a healthy immune system. Disturbances in the microbiome, however, can steer the immune system toward dysfunction. As an example, "lactic acid bacteria appear to stimulate IgA production, so having fewer of these bacteria in early infancy could cause IgA to drop," she says. By the same token, "IgA plays a key role in establishing the gut microbial composition—so it seems that the influence goes in both directions."

Getting the word out

Dr. Kozyrskyj also has an immediate task at hand: sharing the current study's results with the media, the public and the scientific community. "I'm fortunate to have Liane Kang, a graduate student at the University of Alberta, on the case," she says. "Liane has run with the study from beginning to end and she was the lead author of the *Brain, Behavior & Immunity* journal article published in November 2017."

Kang created an explanatory video to help readers interpret these research results. She also received an AllerGen Research *SKETCHES* grant, which facilitated her translation of the academic paper into a clear-language summary for a general audience.

Dr. Kozyrskyj, for her part, was "surprised and pleased" when the children's charity UNICEF noted her team's paper in one of its blog posts, praising the study for "generating breakthrough insights about child health," and asking the provocative question: *Will decision-makers listen and act on the new insights through improved policies and programs?*

Dr. Kozyrskyj sees several ways this could happen. For instance, "our findings encourage the development of community programs and policies to assist mothers in distress, and highlight the need for family and healthcare professionals to support the psychosocial wellbeing of women during pregnancy and in the months after birth."

Given that depression affects between seven to 12% of women during pregnancy and seven to 19% of women after giving birth, Dr. Kozyrskyj hopes that this research will prompt pregnant and new mothers to "speak out, seek treatment, and ask for social support."