Stress can have lasting impacts on sperm and future offspring

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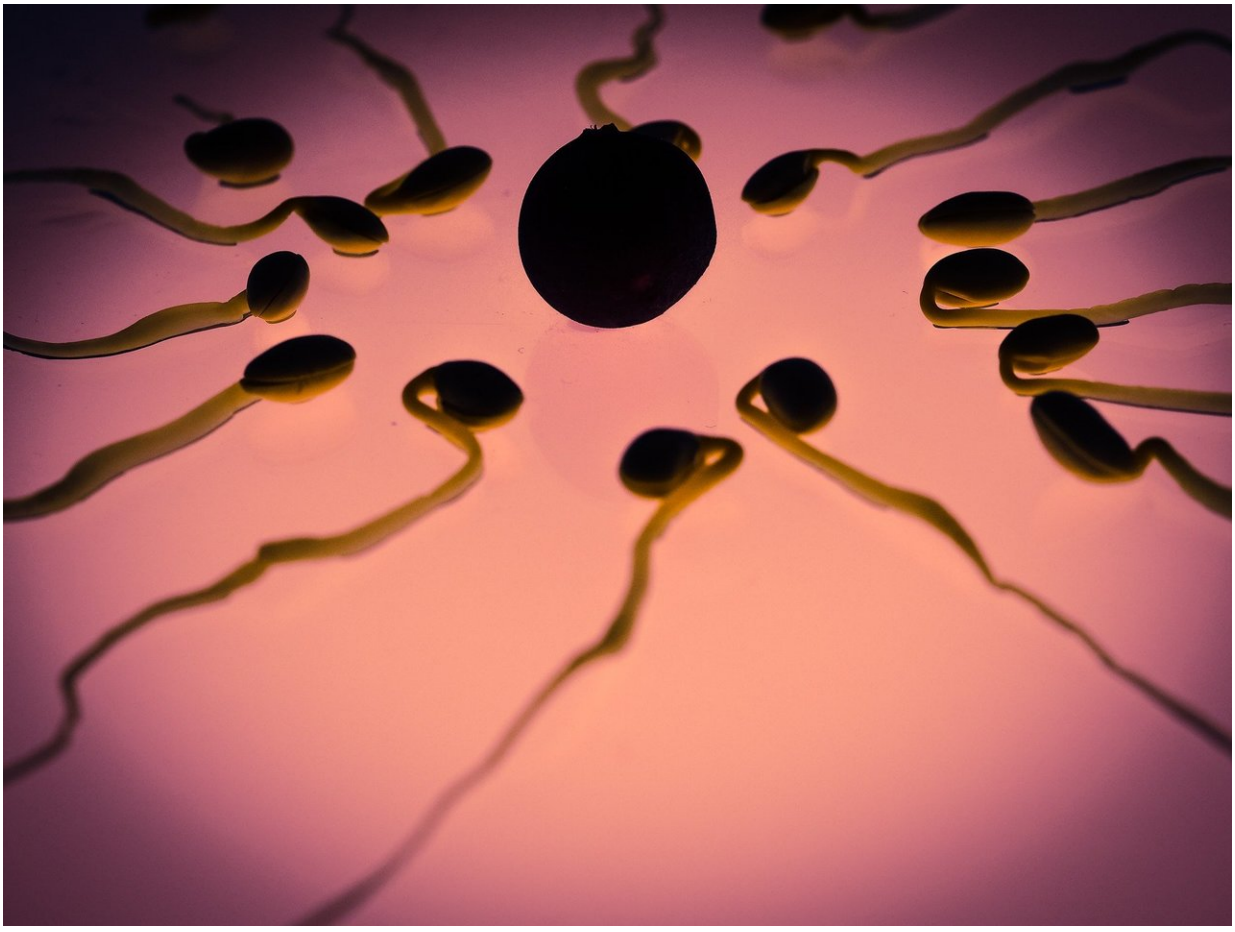

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Prolonged fear and anxiety brought on by major stressors, like the

coronavirus pandemic, can not only take a toll on a person's mental health, but may also have a lasting impact on a man's sperm composition that could affect his future offspring. That is the finding of a provocative new study published in the journal *Nature Communications* by researchers at the University of Maryland School of Medicine.

The research outlines a biological mechanism for how a father's experience with stress can influence fetal brain development in the womb. The effects of paternal stress can be transferred to offspring through changes in the extracellular vesicles that then interact with maturing sperm. Extracellular vesicles are small membrane-bound particles that transport proteins, lipids, and nucleic acids between cells. They are produced in large amounts in the reproductive tract and play an integral role in sperm maturation.

"There are so many reasons that reducing stress is beneficial especially now when our stress levels are chronically elevated and will remain so for the next few months," said study corresponding author Tracy Bale, Ph.D., Professor of Pharmacology and Director of the Center for Epigenetic Research in Child Health & Brain Development at the University of Maryland School of Medicine. "Properly managing stress can not only improve mental health and other stress-related ailments, but it can also help reduce the potential lasting impact on the reproductive system that could impact future generations."

She and her colleagues did not specifically study those who were under stress due to the coronavirus pandemic.

To examine a novel biological role for extracellular vesicles in transferring dad's stress to sperm, the researchers examined extracellular vesicles from mice following treatment with the stress hormone corticosterone. After treatment, the extracellular vesicles showed dramatic changes in their overall size as well as their protein and small

RNA content.

When sperm were incubated with these previously "stressed" extracellular vesicles prior to fertilizing an egg, the resulting mouse pups showed significant changes in patterns of early brain development, and as adults these mice were also significantly different than controls for how they responded to stress themselves.

To see if similar differences occurred in human sperm, the researchers recruited students from the University of Pennsylvania to donate sperm each month for six months, and complete questionnaires about their perceived stress state in the preceding month. They found that students who had experienced elevated stress in months prior showed significant changes in the small RNA content of their sperm, while those who had no change in stress levels experienced little or no change. These data confirm a very similar pattern found in the mouse study.

"Our study shows that the baby's brain develops differently if the father experienced a chronic period of stress before conception, but we still do not know the implications of these differences," said Dr. Bale. "Could this prolonged higher level of stress raise the risk for mental health issues in future offspring, or could experiencing stress and managing it well help to promote stress resilience? We don't really know at this point, but our data highlight why further studies are necessary."

The research team did find that stress-induced changes in the male reproductive system take place at least a month after the stress is attenuated and life has resumed its normal patterns. "It appears the body's adaptation to stress is to return to a new baseline," Dr. Bale said, "a post-stress physiological state—termed allostasis."

This research was funded by the National Institute of Mental Health and included co-authors from the Institute for Genome Sciences at the

University of Maryland School of Medicine and the Department of Pharmaceutical Science at the University of Maryland School of Pharmacy, as well as the University of Pennsylvania.

"This research represents a critical step in understanding important mechanisms that underlie the field of intergenerational epigenetics," said UMSOM Dean E. Albert Reece, MD, Ph.D., MBA, who is also the Executive Vice President for Medical Affairs, University of Maryland, and the John Z. and Akiko K. Bowers Distinguished Professor. "Such knowledge is crucial to identify early interventions to improve reproduction and early childhood development down the road."

While the study did not test stress management interventions to determine what effects they might have on attenuating the changes in sperm composition, Dr. Bale, who goes for regular runs to reduce the stress of the current COVID-19 pandemic, contends that any lifestyle habits that are good for the brain are likely good for the reproductive system.

"It is important to realize that social distancing does not have to mean social isolation, especially with modern technologies available to many of us," said Joshua Gordon, Director of the National Institute of Mental Health in his web message about coping with coronavirus. "Connecting with our friends and loved ones, whether by high tech means or through simple phone calls, can help us maintain ties during stressful days ahead and will give us strength to weather this difficult passage."

The Centers for Disease Control and Prevention has tips on "stress and coping" page on their COVID-19 site that recommends the following to "support yourself":

- Take breaks from watching, reading, or listening to news stories, including social media. Hearing about the pandemic repeatedly

can be upsetting.

- Take care of your body. Take deep breaths, stretch, or meditate. Try to eat healthy, well-balanced meals, exercise regularly, get plenty of sleep, and avoid alcohol and drugs.
- Make time to unwind. Try to do some other activities you enjoy.
- Connect with others. Talk with people you trust about your concerns and how you are feeling.

More information: Jennifer C. Chan et al, Reproductive tract extracellular vesicles are sufficient to transmit intergenerational stress and program neurodevelopment, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15305-w

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