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>> From the JAMA Network, this is JAMA Pediatrics Author Interviews. Conversations with authors exploring the latest clinical research, reviews and opinions featured in JAMA Pediatrics.

>> Hi, this is Aaron Carroll. I'm the digital media editor for JAMA Pediatrics. This podcast, we talk about interesting articles featured in the journal, and what they might mean to you. This week I'm focusing on association of exposure to diethylstilbestrol during pregnancy with multi-generational neurodevelopmental deficits by Marianthi-Anna Kioumourtzoglou and colleagues. And, I hope I got that name right.

The prevalence of many neurodevelopmental disorders is increasing. One of these is attention deficit hyperactivity disorder, or ADHD. While some may minimize ADHD as something which is not that serious, kids with ADHD have been shown to have issues with quality of life and educational attainment. They can even have problems that persist into adulthood, including premature death. We still don't know what causes ADHD, or other neurodevelopmental disorders for that matter.

One theory involves endocrine-disrupting chemicals, which have been linked to a number of neurodevelopmental disorders, including ADHD. EDC's as they are otherwise known, can involve an epigenetic reprogramming of the germ line. This means they can cause DNA changes that are passed on to future generations. In mice, studies have shown that EDC exposure can change behavior and stress responses in third-generation offspring. And, social interaction changes have been seen in fifth-generation offspring. Few multi-generational cohorts exist to allow us to explore similar hypotheses in adults. But, some do exist.

In this study, researchers used data from the Nurses' Health Study 2, to look at potential third-generation outcomes of ADHD from diethylstilbestrol exposure. Diethylstilbestrol, which is a potent potential EDC, was given to many pregnant women between 1938 and 1971 to prevent complications of pregnancy. Somewhere between 5 and 10 million pregnant women received it. It was banned in 1971 because it had serious harms associated with it, and few if any benefits, as studies later showed. The Nurses' Health Study is a pretty big cohort study. In 1989, more than 116,000 female registered nurses between 25 and 42 years of age enrolled in it. All of the women were born during a time when diethylstilbestrol was being used. In 1993, the study asked these women if their mothers had used diethylstilbestrol during pregnancy. They also collected information on the women who were participating in the study's children.

More than 2,000 of the participants responded to questions about their mothers' exposure to diethylstilbestrol during pregnancy, and most of them were certain, or somewhat certain about this potential exposure, and were therefore included in the study. In 2001, they asked many of the participants' mothers themselves about this question, and observed very good agreement with what the participants had reported in prior times. The main outcome of interest was whether the participants' children were ever diagnosed with ADHD.

Co-variants were only considered for the participants' mothers, because the researchers felt that potential confounders could only be variables that preceded the diethylstilbestrol use. They collected data on socioeconomic status at the birth of the participants, as well as lifestyle, education, occupations, race, ethnicity, year of birth, and smoking status. They also adjusted for depression history in a sensitivity analysis.

The gist of the analysis was to check if basically a grandmother's exposures to diethylstilbestrol, an EDC, was related to grandchildren, or third-generation, ADHD after controlling for other factors. Well, let's get to the results. Data were available for more than 47,500 grandmothers, 1.8% of whom were exposed to diethylstilbestrol. They had more than 106,000 thousand grandchildren, 5.3% of whom were diagnosed with ADHD.

The use of diethylstilbestrol was associated with an increased odds of a grandchild being diagnosed with ADHD, with an odds ratio of 1.36. This association held, after controlling for the grandmother's age at delivery, and after for controlling for a history of depression. Further sub-analyses showed that this association was pretty much limited to diethylstilbestrol use in the first trimester, when the odds ratio was 1.63. But, it was a sub-analysis, and we shouldn't give it too much weight.

Before we go any further, let's talk about some limitations for this study, because this is pretty inflammatory stuff. The main outcome of interest, ADHD, did depend on maternal reports, but there's no reason to think that maternal report would be linked to grandmothers' diethylstilbestrol use, so it's hard to see how this would bias things too much. There could also be misclassification of diethylstilbestrol use, as it was asking for something that happened some time ago. Again though, these data were collected long before the data on ADHD were collected, so it's hard to argue that the latter would bias the former. More concerning, is that there could be some unmeasured confounder that could be related to both diethylstilbestrol use and the later diagnosis of ADHD, but I don't know what that would be. That's the problem with unmeasured confounders, though. We don't necessarily know what they are.

The biggest limitation though, is that we can't measure the means by which this mechanism is working, at least how we think it is. The hypothesis is that the diethylstilbestrol altered the grandmothers' germ lines, leading to genetic changes inherited by the grandchildren, and that these genetic changes somehow led to an increased risk of ADHD. We don't know that's true. We don't know what genes to measure, and that wasn't part of this study.

Even taking all of that into account, this study found that there was an increased risk in the third generation having ADHD, when the first generation was exposed to diethylstilbestrol, an EDC, during pregnancy. While diethylstilbestrol isn't used any more, other EDC's do exist. Before you panic, the EDC's we're exposed to in the environment are at a much, much lower dose than what pregnant women were exposed to with diethylstilbestrol. That's not the point of this study.

What is novel, and ground-breaking, is that these results are exactly what you'd expect if an epigenetic cause of ADHD existed. It may be time to sink some serious time and money into looking at epigenetic causes of neurodevelopment disorders, as an accompanying editorial argues better than I could here. You should go read that, and the paper of this study, because it's free this week online at JAMAnetwork.com/journals/JAMApediatrics.

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