NEWS

Study challenges link between antidepressants, autism

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Unraveling risk: The mother's depression could explain the increased chance of autism in some children exposed to antidepressants in utero.

Taking antidepressants while pregnant doesn't boost the risk of autism in the child, according to the largest study yet to search for a link, published 15 November in *Clinical Epidemiology*[1]. However, the subgroup analyses that question the connection are based on numbers too small to draw a firm conclusion, say several experts.

Antidepressant use **during pregnancy** has risen in the past few decades, as have autism diagnoses, prompting researchers to ask whether the two are connected. Two studies, one published in 2011 and the other earlier this year, have **reported** that taking antidepressants while pregnant **increases a woman's risk** of having a child with autism[2,3].

"In our study we don't find that same association," says Merete Sørensen, a child and adolescent psychiatrist at Aarhus University Hospital in Risskov, Denmark, who led the current work.

The two previous studies each had significantly fewer participants than the new one. The 2011 study included medical records from 298 children with autism and 1,507 typically developing children in a California health network covering more than 3.2 million people. The study from earlier this year included 4,429 children with autism and 43,277 age-matched controls identified through a

Swedish national database.

Both studies left worrisome questions about whether the rise in autism risk has to do with antidepressants themselves or with the depression they were prescribed to treat.

In the new study, researchers analyzed the medical records of 655,615 children born to 428,407 mothers in Denmark between 1996 and 2006, using several population-based registries. They mined the data to identify 8,833 children who had been exposed to antidepressant medication prenatally, and 5,437 children who were diagnosed with autism. The analysis includes 104 children who fall into both camps.

Disappearing risk:

To determine prenatal exposure to antidepressants, the team identified women who had filled a prescription for an antidepressant during pregnancy or up to a month before conception. When the researchers analyzed data from all of the children, they found a statistically significant increase in autism risk in those exposed to antidepressants before birth.

But when they analyzed subgroups of participants to control for parents' mental health and other factors that could be driving this finding, the risk disappeared.

"We cannot say exactly what those factors are, but we are quite convinced that they point to medication not being a problem," says Sørensen.

Emily Elert

In one of the analyses, for example, the researchers looked at a subset of 6,080 children whose mothers were diagnosed with affective disorder, a condition that includes depression and manic depression, as opposed to anxiety or another condition.

When they compared women in this group who had taken antidepressants with those who had not, they found no significant increase in autism risk in their children. The finding suggests that at least some of the risk identified in the main analysis is likely to be associated with the underlying depressive disorder, Sørensen says.

In another analysis, the team examined the records of 2,765 families with at least two children, and at least one who has autism. If the drugs contribute to autism risk, they reasoned, then the 96 children exposed to the drugs *in utero* should show a higher risk of autism than the 6,046 not exposed. But the researchers found no difference in autism risk between the two groups of children.

“I think these analytic strategies are really good,” says **Dheeraj Rai**, clinical lecturer at the University of Bristol in the U.K., who was not involved in the study. Rai led the study on antidepressants and autism risk published earlier this year. “Other groups should be doing the same,” he says.

However, Sørensen’s subgroup analyses are based on too few individuals for their results to be convincing to some.

“It reduces the numbers quite significantly, so the imprecision becomes higher,” Rai says.

Many more women in the study took antidepressants during pregnancy than were diagnosed with depression, notes **Alan Brown**, professor of clinical psychiatry and epidemiology at Columbia University in New York, who was not involved with any of the three studies. “This suggests that mothers with affective disorders may have been missed by the registry,” he says.

Lisa Croen, director of the autism research program at Kaiser Permanente, a healthcare management organization in Oakland, California, lauds the additional analyses included in the study. However, she questions whether separating mothers with a depression diagnosis truly disentangles the effect of antidepressants from that of the underlying condition.

“In those women, the antidepressant drugs didn’t change the risk for autism,” says Croen, who led the 2011 study that reported a connection between maternal antidepressant use and autism risk in the children. “But I don’t think you can infer from that that there is no additional independent risk from the antidepressants themselves.”

Sørensen agrees that unraveling the confounding factors is difficult, and that study numbers remain a problem even in a population-based study such as hers. “Autism is rare, antidepressant use during pregnancy is rare, and so the combination is quite rare,” she says.

Even larger studies, perhaps those that combine different databases, will be needed to resolve whether antidepressants increase autism risk, she says. Several ongoing efforts are continuing to address this question, including one based on a collaborative platform called iCARE, which **allows multiple large registries to pool** their data.

References:

1: Sørensen M.J. *et al. Clin. Epidemiol.* **5**, 449-459 (2013) **PubMed**

2: Croen L.A. *et al. Arch. Gen. Psychiatry* **68**,1104-1112 (2011) **PubMed**

3: Rai R. *et al. BMJ* **346**, f2059 (2013) **PubMed**