SSRIs in Pregnancy Exert Small Teratogenicity Risk

Even with a large increase in risk, the absolute risk would still be less than 1%.

BY MARY ANN MOON
Contributing Writer

Two large-scale studies of the possible teratogenic effects of selective serotonin reuptake inhibitors have concluded that the absolute risk of birth defects related to the drugs is small.

Neither study could confirm previously reported associations between SSRIs and heart defects. Both suggested that a few individual SSRIs might raise the risk of a few specific defects, but these malformations are so rare that even a large increase in risk would still put the chance of having an affected child at well under 1%, the researchers said in separate reports.

In the first report, Carol Louik, Sc.D., of Boston University's Slone Epidemiology Center, and associates analyzed data from the center's Birth Defects Study, an ongoing case-control surveillance program of a wide range of malformations, which covers areas surrounding Boston, Philadelphia, Toronto, San Diego, and a portion of New York State. The researchers focused on births that occurred between 1993 and 2004, which included 9,849 neonates with malformations and 5,860 neonates without malformations who served as controls.

They found no association between maternal use of SSRIs during pregnancy and heart defects as a whole, nor was there any association with craniosynostosis, omphalocele, or neural tube defects. However, the use of sertraline raised the risk of a single heart defect (cardiac septal defect), based on 13 cases, and the use of paroxetine raised the risk of another single heart defect (right ventricular outflow tract obstruction), based on 6 cases.

In addition, the data "suggested" possible links between sertraline and both anal atresia and limb-reduction defects, and possible links between paroxetine and both neural-tube defects and clubfoot.

Despite the relatively large study population, the investigators said they had limited numbers to evaluate associations between rare outcomes and exposures. "We included results based on small numbers of exposed subjects in order to allow other researchers to compare their observations with ours, but we caution that these estimates should not be interpreted as strong evidence of increased risks," Dr. Louik and associates said (N. Engl. J. Med. 2007;356:2675-83).

In any case, "it is important to keep in perspective that the absolute risks of these rare defects are small. For example, the baseline prevalences of anal atresia and right ventricular outflow tract obstruction defects are each estimated to be about 5.5 cases per 10,000 live births; thus, even if a specific SSRI increased rates by a factor of four, the risk of having an affected child would still be only 0.2%," they noted.

In the second study, Sura Alwan of the University of British Columbia, Vancouver, and associates analyzed data from the National Birth Defects Prevention Study on infants born between 1997 and 2002 in eight study sites throughout the United States. This included 9,622 neonates with birth defects and 4,092 without birth defects who served as controls.

The baseline prevalence of anal atresia is estimated to be about 5.5 cases per 10,000 live births; thus, even if an SSRI increased rates by a factor of four, the risk would still be only 0.2%.

Again, no associations were found between SSRIs and most of the birth defects assessed, including heart defects as a group. However, a small but significant association was found between paroxetine use and right ventricular outflow tract obstruction, based on six cases.

There also were small but significant associations with anencephaly (based on 9 exposed neonates), craniosynostosis (based on 24 exposed neonates), and omphalocele (based on 11 exposed neonates).

"Our study did not show an increased risk of most birth defects, and SSRI exposure was present in only a small number of cases of certain defects. The absolute risks associated with SSRIs appear small in comparison with the baseline risks of birth defects that exist in every pregnancy," the researchers reported (N. Engl. J. Med. 2007;356:2684-92).

In an editorial comment accompanying this report, Dr. Michael F. Greene of Massachusetts General Hospital, Boston, said the findings of both studies make it clear that "neither SSRIs as a group nor individual SSRIs are major teratogens.

"Patients and physicians alike would prefer it if there were clear lines separating 'risk' and 'no risk' and if all studies gave consistent results pointing in the same direction. Unfortunately, this is often not the case, and the data to inform potential risks of SSRIs are no exception," he said (N. Engl. J. Med. 2007;356:2732-3).

Even with the association found between paroxetine and right ventricular outflow obstruction, the malformation is so rare and the number of neonates exposed to the drug so small that the absolute incidence in exposed neonates "is unlikely to exceed 1%, and the incidence of all congenital heart defects is unlikely to exceed 2%," Dr. Greene noted. ■

Drugs, Pregnancy, And Lactation

Autism and Exposure to Thimerosal

BY GIDEON KOREN, M.D.

The etiology of autism is not yet clear and the debate continues about whether the increase in prevalence noted in the past few decades is actual or is because of better diagnosis. However, the evidence for a genetic link is accumulating, as is evidence that mercury in vaccines is not behind the increased prevalence.

Because the disease appears in the second or third year of life, the potential association with early childhood vaccines has been the subject of many studies over the past 15-20 years. Children receive many vaccines during the first few years of their lives; until 2002, thimerosal, a preservative that contains ethylmercury, was used as a preservative in routine early childhood vaccines. To a lesser degree, prenatal exposure to Rh immune globulin—which, until 2001 in the United States, contained thimerosal—has also elicited concern. Because organic mercury is a proven developmental neurotoxin, exposure to it in utero or in early childhood has raised concerns.

In utero exposure to mercury in environmental accidents, especially organic mercury, has been associated with brain damage and pediatric diagnoses such as cerebral palsy—but not autism. Some of the most compelling evidence indicating that vaccines containing thimerosal are not a cause of autism was provided in studies that looked at population-based databases of children in Denmark, Sweden, and California.

Although the prevalence of autism increased in all three places from 1985 through the 1990s, the average exposure to vaccines containing mercury increased only in the United States. In Sweden and Denmark, where the use of mercury-containing vaccines began to decrease in the late 1980s and was eliminated by the early 1990s, there was still an increase in the diagnosis of autism.

An important study published this month provides compelling evidence that prenatal exposure to thimerosal in Rh immune globulin (RhIg) is not a likely cause of the increase in autism, either. These results should help allay lingering concerns about exposure to ethylmercury via thimerosal in vaccines and Rh immune globulin.

The new study analyzed records of families that have children with an autism spectrum disorder (ASD), who had been seen at the Thompson Center for Autism and Neurodevelopmental Disorders at the University of Missouri–Columbia, between 2004 and 2006. Of 214 mothers with 230 children diagnosed with ASD between 1995 and 2005, 33 (15.4%) were Rh negative, which was similar to the rates among mothers in control groups. Of these 33 women, 29 (88%) had received Rh immune globulin that contained thimerosal while pregnant. Based on comparisons with families of children with Down syndrome and other de novo chromosome disorders who came to the university for care, and two other populations—patients blood typed at the hospital in 2005 and 2006, and a population who had donated blood during 2005—the investigators determined that Rh-negative status was not higher among the mothers of children with autism. In addition, the mothers of children with autism were not more likely to have been exposed to antepartum Rh immune globulin containing thimerosal, and were not more likely to have an Rh-negative incompatible pregnancy. These findings were also true for autism subtypes. The authors concluded that the results "support the consensus that exposure to ethylmercury in thimerosal is not the cause of the increased prevalence of autism" (Am. J. Med. Genet. Part A 2007;143A:1397-407).

Therefore, based on the information currently available, it is fair to say there is no compelling evidence indicating that exposure of the developing brain to mercury, either in the fetus or the developing child, is a cause of autism. And as the authors point out, these findings also have implications for other countries, where multidose vials that contain thimerosal continue to be used.

As for other potential prenatal causes of autism, there have been more case reports of autism in children exposed in utero to valproic acid, isotretinoin, or alcohol than one would expect. But I emphasize that these are case reports and merely associations at this point, not proven causes.

Efforts are underway to further investigate the possible association between prenatal exposure to valproic acid and autism. At the Motherisk Program, a teratogen information service at the Hospital for Sick Children in Toronto, we are following the long-term development of children exposed in utero to valproic acid, which we hope will pick up an association with autism, if such a link exists.

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