Small Absolute Risk of Birth Defects With SSRIs

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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.

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." 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%," he noted (N. Engl. J. Med. 2007;356:2732-3). ■