Mental health

Gene variants associated with increased risk of congenital heart defects with SSRI use

Common variants in genes related to folic acid, homocysteine and glutathione/transsulfuration metabolic pathways are associated with an increased risk of congenital heart disease in the offspring of women who take SSRIs in the periconceptual period, a US case control study has found.

The study used data from the National Birth Defects Prevention Study. Three categories of congenital heart disease were investigated: conotruncal (e.g. Fallot's tetralogy), left ventricular outflow obstruction (e.g. aortic stenosis) and right ventricular outflow obstruction (e.g. pulmonary valve stenosis). Affected children were identified from congenital malformation registers in ten US states.

Overall, 1,180 liveborn children with congenital heart disease and 1,644 controls without any major birth defect were included in the study. Their mothers took part in a telephone interview in which they were asked about SSRI use during the periconceptual period (from one month before until three months after conception). Buccal swab DNA from affected children and their parents was genotyped.

Several hundred variants (single nucleotide polymorphisms) in genes involved in the folic acid, homocysteine and glutathione/transsulfuration metabolic pathways were included in the analysis. The problem with multiple comparisons is that they generate too many false positives. To control for this, associations were only reported when the Bayesian false discovery probability (BFDP) was < 0.8.

The children of women who took SSRIs in the periconceptual period were at increased risk of congenital heart defects if their mothers had one of the following risk modifying gene variants. Compared with women without the variant, women who were heterozygous or homozygous for the rs9909104 SHMT1 (folic acid) gene variant were respectively 2.4 and 5.9 times more likely to have affected offspring (BFDP = 0.69). Women who were heterozygous or homozygous for either the rs492842 or rs542852 BHMT (homocysteine) gene variants were respectively twice as likely and over four times as likely to have affected offspring (BDFP = 0.74 and 0.79 respectively). Women who were heterozygous or homozygous for the rs2075237 MGST1 (transsulfuration) gene variant were respectively 2.8 and 8.0 times more likely to have affected offspring (BDFP = 0.79).

The study also identified six offspring gene variants which were associated with an increased risk of congenital heart disease when their mothers took SSRIs in the periconceptual period.

It is surprising that septal heart defects were excluded from the study as these are the most common type of congenital heart defect and have been linked to SSRI exposure in some,[1,2] but not all, previous studies. The method of ascertaining maternal SSRI use is prone to recall bias. The BFDP is a compromise between reducing the number of false positives (type 1 errors) and not missing too many interesting associations (type 2 errors).[3] Therefore, the results should be interpreted as possible rather than proven associations.

If there is an association between SSRI use and congenital heart disease, this could be due to SSRIs themselves, maternal depression or poor maternal health behaviours.[2] It is biologically plausible that SSRIs may cause congenital heart defects by disrupting serotonin signalling in the developing fetus,[2] and the authors of the present study suggest that variations in genes associated with the folic acid pathway may increase sensitivity to changes in serotonin levels.

An alternative explanation could be that maternal depression is linked to congenital heart disease by a common association with low folic acid levels. Folic acid is required for the synthesis of monoamines, deficiency of which may lead to depression.[4] Folic acid is also required for the metabolism of homocysteine, an amino acid which is thought to cause endothelial damage and increase the risk of congenital heart defects. A meta-analysis has found that maternal folic acid supplementation is associated with a significant reduction in the risk of congenital heart defects.[5]

In conclusion, this study suggests that SSRIs may only cause congenital heart disease when mothers or their babies are genetically susceptible. It is important to remember that the absolute risk, if any, is low.[1]

There is some evidence to support the promotion of periconceptual folic acid supplementation as a way of reducing the risk of both maternal depression and congenital heart disease in offspring.

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