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Prenatal Use of Serotonin Reuptake Inhibitors (SRIs) and Congenital Heart Anomalies (CHA): An Exploratory Pharmacogenetics Study

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Abstract : Prenatal use of SRIs was previously associated with Congenital Heart Anomalies (CHA). The aim of the study is to explore whether pharmacogenetics plays a role in this teratogenicity using a gene-environment interaction study. A total of 33 case-mother dyads and 2 mother-only (children deceased) registered in EUROCAT Northern Netherlands were included in a case-only study. Five case-mother dyads and two mothers-only were exposed to SRIs (paroxetine=3, fluoxetine=2, venlafaxine=1, paroxetine and venlafaxine=1) in the first trimester of pregnancy. The remaining 28 case-mother dyads were not exposed to SRIs. Ten genes that encode the enzymes or proteins important in determining fetal exposure to SRIs or its mechanism of action were selected: CYPs (CYP1A2, CYP2C9, CYP2C19, CYP2D6), ABCB1 (placental P-glycoprotein), SLC6A4 (serotonin transporter) and serotonin receptor genes (HTR1A, HTR1B, HTR2A, and HTR3B). All included subjects were genotyped for 58 genetic variations in these ten genes. Logistic regression analyses were performed to determine the interaction odds ratio (OR) between genetic variations and SRIs exposure on the risk of CHA. Due to low phenotype frequencies of CYP450 poor metabolizers among exposed cases, the OR cannot be calculated. For ABCB1, there was no indication of changes in the risk of CHA with any of the ABCB1 SNPs in the children and their mothers. Several genetic variations of the serotonin transporter and receptors (SLC6A4 5-HTTLPR and 5-HTTVNTR, HTR1A rs1364043, HTR1B rs6296 & rs6298, HTR3B rs1176744) were associated with an increased risk of CHA, but with too limited sample size to reach statistical significance. For SLC6A4 genetic variations, the mean genetic scores of the exposed case-mothers tended to be higher than the unexposed mothers (2.5 ± 0.8 and 1.88 ± 0.7, respectively; p=0.061). For SNPs of the serotonin receptors, the mean genetic score for exposed cases (children) tended to be higher than the unexposed cases (3.4 ± 2.2, and 1.9 ± 1.6, respectively; p=0.065). This study might be among the first to explore the potential gene-environment interaction between pharmacogenetic determinants and SRIs use on the risk of CHA. With small sample sizes, it was not possible to find a significant interaction. However, there were indications for a role of serotonin receptor polymorphisms in fetuses exposed to SRIs on fetal risk of CHA which warrants further investigation.

Keywords : gene-environment interaction, heart defects, pharmacogenetics, serotonin reuptake inhibitors, teratogenicity
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