Underlying Psychiatric Conditions Might Account for Increased ASD Risk in Offspring of Fathers Who Took SSRIs Before Conception

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January 28, 2018 – Underlying paternal psychiatric illness, rather than the use of SSRIs prior to conception, may be associated with increased ASD risk in offspring.

Maternal selective serotonin reuptake inhibitor (SSRI) use has recently been linked to an increased risk of autism spectrum disorder (ASD) in children. A new study reported that paternal SSRI exposure prior to conception increased the risk of ASD in children slightly. However, the increased risk was attenuated after adjusting for potential confounding factors, especially presence of psychiatric disorders in the fathers.

The new population-based cohort study, conducted by Dr Hong Liang from Key Laboratory of Reproduction Regulation of NPFPC, SIPPR, IRD, Fudan University, Shanghai, China and collaborators, was published online in *BMJ Open* on 22 December, 2017.

According to the authors, previous studies have demonstrated a significant link between prenatal exposure to SSRIs, which are commonly used to treat depression and anxiety-related conditions, and neuro-behavioral problems in children.[1] [Yang p1 Introduction col 2 L7-10] The authors referred to recent studies indicating that the increased risk of neurodevelopmental diseases in children associated with prenatal SSRI use may be confounded by related indications [Yang p1 Introduction col 2 L13-17], such as maternal psychiatric disorders.[2] In the current study, they address the impact of paternal SSRI use on ASD risk.

Risk factors for ASD

ASD is a complex neurodevelopmental disorder that currently affects approximately 1 in 45 children. [Yang p2 Introduction col 1 L1-2] ASD is characterized by impairment in social communication and interactions along with stereotypical or repetitive behaviors. The presentation and the level of impairment vary widely in ASD. Numerous genetic and environmental risk factors for ASD have been identified, perhaps accounting for its heterogeneity.

More than 20 pre-, peri-, and neonatal factors have been identified as contributing to ASD risk in recent meta-analyses and systematic reviews.[3] The risk factors include parental age, inter-pregnancy interval, and prenatal exposure to heightened or compromised immune functions, such as maternal hospitalization due to viral infections, as well as maternal use of medications during pregnancy, including the use of antidepressants and anti-epileptics. The ability of medications to cross the placenta and blood-brain barrier, as well as their transferability through breast milk, are likely to account for the enhanced risk of ASD with the maternal use of such medications during pregnancy. By extension, the authors suggest that paternal exposure to medications and the resulting alterations in the male gamete prior to conception may also impact ASD risk in offspring.

According to the researchers, previous studies have indicated that paternal SSRI use adversely affects the male gamete by impairing sperm quality and promoting aberrant sperm DNA fragmentation, effects which have been associated with reduced fertility, adverse pregnancy outcomes, and increased risk of childhood disease. [Yang p2 Introduction col1 L19-25]

Dr. Hong Liang and his colleagues at Fudan University collaborated with researchers at the Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark and found a slightly increased ASD risk in offspring associated with paternal SSRI use prior to conception, but reported that this increased risk may be attributable to underlying paternal factors, such as paternal psychiatric conditions or other confounding factors.

Association between paternal SSRI use and ASD risk

The authors used data from several national registers in Denmark to identify children who had been born alive to Danish parents in the period 1998-2008. A total of 669922 children were included in the analysis, after excluding children with extreme gestational age (≤23 weeks or ≥45 weeks), with missing parity, and without linkage to the father or mother.

Data pertaining to paternal SSRI use was obtained from the Danish National Prescription Registry,[4] a national repository for all redeemed prescriptions in Denmark that has been maintained since 1995. Children born to fathers who had redeemed SSRI prescriptions within a 74-day window prior to the date of conception were considered to have been exposed to SSRIs. Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram were included in the analysis.

ASDs in children were identified using the Danish Psychiatric Central Research Register (DPCRR) and the Danish National Patient Register (DNPR).[5-6] Data pertaining to psychiatric disorders in parents prior to birth of the children was also obtained from the DPCRR.

The researchers used 2 different models to adjust the variables for confounding factors before performing the Cox proportional hazards regression analysis. In model 1, they stratified the variables based on calendar year of birth (1998–2000, 2001–2003, 2004–2006, 2007–2008), gender of the child, parity (1, 2, ≥3), parental age at child birth (≤25, 26–30, 31–35, and >35 years), maternal smoking status during pregnancy, maternal history of psychiatric disorders before birth of child, and maternal antidepressant (AD) use during pregnancy. In model 2, they also adjusted for paternal history of psychiatric disorders before birth of child.

The study authors found that 1.03% of the children were born to fathers who had redeemed SSRI prescriptions in the 3 months immediately prior to conception. The incidence rate of ASD in their data set (169 per 100 000 person-years) corresponded to a 62% increased ASD risk in the group with SSRI exposure compared with unexposed children. The adjusted hazard ratio (aHR) of ASD was 1.54 (95% CI 1.27 to 1.88) after adjusting for potential confounders in model 1 and was decreased to 1.43 (95% CI 1.18 to 1.74) in model 2.

The researchers then extended the SSRI exposure window to 1 year prior to the date of conception and re-categorized the children into 3 groups based on whether their fathers had redeemed SSRI prescriptions only from the last year to 3 months prior to conception (former users), only within the last 3 months prior to conception (current users), or both (former and current users).

The readjusted analysis based on the window of SSRI exposure indicated a slightly elevated ASD risk for children of former users alone (aHR, 1.54 [95% CI 1.21 to 1.94]) and former and current users (aHR, 1.32 [95% CI 1.02 to 1.72]). However, the ASD risk for children of fathers who were only current users was not statistically significant (aHR, 1.17 [95% CI 0.75 to 1.82]; model 2). Of note, the ASD risk was not

affected by paternal SSRI use before conception in children born to fathers with an affective disorder (model 2: aHR, 1.10 [95% CI 0.61 to 1.98]).

The authors conducted an ASD risk analysis in siblings to account for unmeasured familial confounding factors. The ASD risk of exposed children was lower than that of their unexposed siblings (aHR, 0.74 [95% CI 0.34 to 1.59]), indicating that exposure to paternal SSRI use prior to conception was insufficient to confer an increased ASD risk in the children.

Key Conclusions

Presence or familial risk of neuropsychiatric disease has been associated with ASD risk.[7-8] Given the prevalence of depression and its treatment with SSRIs, as well as the correlation between both the underlying condition and SSRI use during pregnancy as risk factors for ASD in offspring, it is important to tease out the contributions of these factors in isolation and in combination in increasing ASD risk. The authors used several analytical strategies to account for confounding factors, such as underlying paternal depression, to address the effect of SSRI use on ASD risk. Their analyses showed that paternal psychiatric illness, rather than the use of SSRIs prior to conception, is associated with increased ASD risk. The authors also noted that there was increased ASD risk in children born to fathers not diagnosed with affective disorders, who had nevertheless used SSRIs. The authors caution that it is possible that these fathers may have had undiagnosed affective disorders. They concluded that the increased risk of ASD in the offspring of paternal SSRI users may thus be attributable to the underlying paternal diseases, rather than SSRI use.

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Article Summary: The modest increase in ASD risk in offspring of fathers who used SSRIs prior to conception may reflect the contribution of underlying paternal psychiatric disorders and/or other confounding factors, rather than the risk induced by paternal SSRI use alone.

Take Note:

- Paternal SSRI use in fathers who took SSRIs over 1 year before conception was associated with an increased ASD risk in children.
- ASD risk was not significantly increased in children when the data were adjusted for the presence of underlying paternal neuropsychiatric illness.
- Sibling analysis indicated similar ASD risk in children who had been exposed to paternal SSRI use and their unexposed siblings, suggesting that paternal depression or affective disorders and/or other confounding factors, rather than paternal SSRI use alone, increased ASD risk.

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