Prenatal antidepressant exposure as a risk factor for autism spectrum disorder: an examination of the evidence

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Background

- Serotonin has a key role in the development of the human central nervous system. Serotonergic neurons form early in development, at the fifth gestational week, and innervate most areas of the growing brain.[1]
- Serotonergic input regulates the assembly of neural circuits[2] and directs neuronal differentiation and migration, synaptogenesis, and dendritic pruning.[3]
- As a trophic factor, serotonin may influence the ability to manipulate and process information by directing the differentiation and microstructural organization of the cortex[4,5]; it may also influence the ability to apprehend sensory stimuli via its role in the development of the somatosensory cortex.[6,7] As a neurotransmitter, serotonin may, either alone or in conjunction with the neuropeptide oxytocin, have an effect on the modulation of social behavior.[8]
- Autism spectrum disorder (ASD) is characterized by abnormalities in these same three domains: information processing, the interpretation of sensory stimuli, and social behavior.
- Furthermore, ASD has been repeatedly associated with abnormalities of the serotonin system: peripheral hyperserotonemia, for example, may occur in 25 to 41% of individuals with ASD.[9,10,11]
- By far the most commonly prescribed antidepressants are selective serotonin reuptake inhibitors (SSRIs)[12], which directly alter extracellular serotonin levels in the brain and are known to cross the placenta.[13]
- Therefore, in principle, there is a plausible mechanism of action by which maternal use of SSRI antidepressants could be an ASD risk factor for the developing fetus.
- Is there evidence to suggest that such a risk actually exists?

Methods

- A search of the MEDLINE and Web of Science Core Collection databases identified six case-control studies and four cohort studies that specifically examined a potential association between prenatal antidepressant exposure and ASD.
- Methodologies, inclusion and exclusion criteria, adjusted covariates, and results were qualitatively compared.

Results

#	Year	1st Author	Design	Population	*n*	AOR/AHR (95% CI)	Notes
1	**2011**	**Croen**[14]	**Case-control**	**USA: Kaiser Northern CA**	**298 cases 1,507 controls**	**2.2 (1.2 – 4.3)**	**AOR 3.8 in 1st trimester**
2	2013	Sørensen[15]	Cohort	Denmark: national registry	646,782 unexposed 8,833 exposed	1.5 (1.2 – 1.9)	AHR 1.2 for mothers with an affective disorder
3	**2013**	**Rai**[16]	**Case-control**	**Sweden: national registry**	**4,429 cases 43,277 controls**	**1.83 (1.10 – 3.04)**	**AOR 2.37 for ASD without ID AOR 1.09 for ASD with ID**
4	2013	Hviid[17]	Cohort	Denmark: national registry	620,807 unexposed 6,068 exposed	1.20 (0.90 – 1.61)	Relatively low upper bound of CI
5	**2014**	**Harrington**[18]	**Case-control**	**USA: CHARGE enrollees**	**492 cases 320 controls**	**2.91 (1.07 – 7.93)**	**Significant association in boys only; strongest in first trimester (OR 3.22)**
6	**2014**	**Gidaya**[19]	**Case-control**	**Denmark: national registry**	**5,215 cases 52,150 controls**	**2.0 (1.6 - 2.6)**	**Controlled for parental age**
7	2014	Clements[20]	Case-control	USA: Partners HealthCare	1,377 cases 4,022 controls	1.10 (0.70 – 1.70)	Controlled for maternal depression
8	**2016**	**Boukhris**[21]	**Cohort**	**Canada: QPC enrollees**	**140,732 unexposed 4,724 exposed**	**1.87 (1.15 – 3.04)**	**AHR 2.17 for SSRIs AHR 1.75 when controlled for maternal depression**
9	2016	Castro[22]	Case-control	USA: 3 MA EHR systems	1,245 cases 3,405 controls	0.90 (0.50 – 1.54)	Antidepressant use before but not during pregnancy associated with higher risk
10	2016	Malm[23]	Cohort	Finland: national registry	31,394 unexposed 15,729 exposed	1.40 (1.02 – 1.92)	ASD risk comparable to unmedicated maternal psychiatric illness

- 2, 4, 6: Appeared to draw on substantially the same Danish datasets.
- 5: Found increased risk of DD in boys exposed to antidepressants (AOR 3.39), strongest in third trimester (AOR 4.98) .
- 7: Found increased risk of ADHD with antidepressant exposure (AOR 1.81), even when controlling for maternal depression. Not replicated by 9.
- 9: Replication of 7 that used a novel methodology combining EHR data from Partners HealthCare with two other Massachusetts hospital systems.
- 10: Found increased risk of adolescent depression with SSRI exposure (compared to unmedicated maternal psychiatric illness): AHR 1.78.

Interpretation

- 4 of 6 case-control studies and 1 of 4 cohort studies found a significant increase in ASD risk with maternal antidepressant use.
- If an increase in risk exists, it may be highest in the first trimester.
- Major potential confounders (including maternal psychiatric illness, advanced maternal age, and advanced paternal age) were not controlled for in all studies.
- Even in studies where an association was found, absolute risk was modest.

Conclusions

- Data are equivocal regarding whether prenatal antidepressant exposure is an ASD risk factor: existing studies are heterogeneous in design and adjusted covariates, and have yielded conflicting results.
- Any possible risk would have to be weighed against the risks of untreated maternal depression.
- More research in this area is needed so that clinicians and patients can make informed decisions regarding treatment of depression during pregnancy.

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