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Autism and Pregnancy, Is It Preventable?

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Review Article

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Abstract

Autism Spectrum Disorder is an early-onset neurodevelopmental disorder characterized by qualitative impairments in social interaction, verbal and non-verbal communication combined with repetitive or restricted patterns of behavior. The prevalence of autism appears to be increasing; although it is not entirely clear whether this increase is related to the changes in diagnostic criteria and rise in public awareness of the subject matter or whether it is due to a true increase in incidence. Although researchers have already confirmed a significant heritable component to the etiology of ASD, the exact pathogenesis of it is still unknown. A new focus point undergoing intense studying in recent years has been Environmental exposures and their contribution to an increased ASD risk. There have been long-standing debates over various prenatal, perinatal and postnatal factors and whether they could be associated with a higher risk of ASD in the offspring. These factors range from the presence of maternal diseases/conditions during pregnancy such as Diabetes (Gestational and Pre-gestational), Pre-eclampsia, Autoimmune/Inflammatory disorders and infections to exposures during pregnancy such as medications, chemicals, and various environmental agents. This literature review paper aims to study the pattern of Autism Spectrum Disorder in association with maternal peri-natal risk to identify modifiable risk factors during the gestational period which could be targeted to reduce the overall incidence of ASD.

Keywords: Autism spectrum disorder ASD, Developmental delay DD

Introduction

Autism spectrum disorder in a new clinical entity established in the DSM (V) in 2013 that subsumes the various earlier entities mentioned in DSM (IV) [1]. (i.e. diagnosis of early infantile autism, childhood autism, Kanner autism, high-functioning autism, atypical autism, pervasive development disorder–not otherwise specified, childhood disintegrative disorder, and Asperger.) This clinical entity has 3 major domains of clinical

characteristics, present during early childhood development, that are central to its diagnosis: Impairments in social interaction, deficits in both verbal and non-verbal communication and lastly stereotyped ritualistic behavior patterns. Although these three domains are the triad hallmark of ASD, the presentation of these symptoms and their severity is highly variable among different patients. Studies have linked Autism to several factors in pregnancy. A pregnant women's diet, medication use, her mental, metabolic and immune conditions during pregnancy are all implicated as a possible causative factor. Preeclampsia, Diabetes, and exposure to certain chemicals (pesticide) have been claimed to increase the risk of Autism as well. Even though a considerable number of researches in recent years have tried studying the potential of all the above risk factors in contributing to the etiology of ASD, the relationship between many of these factors and Autism is still speculative as researchers cannot ethically expose pregnant women to possible risks; observational studies can only identify correlations, not causes; and the results of animal studies don't always extrapolate to people. In general, however, experts believe autism arises from genetic susceptibility and yet unknown environmental factors. Ultimately, it's a complex interplay between candidate genes and environmental exposures. Researchers have managed to find a few hundred genes that are linked to autism risk. And although there is no definite environmental culprit, studies have tied certain factors during pregnancy to an increased risk, including exposure to high levels of air pollution, low intake of vitamins such as folate and Vitamin D and viral infection.

Discussion

Although the exact pathogenic mechanism and cascade underlying ASD are unknown, the leading theory is that disrupted neuronal activity is precipitated primarily by genetic factors resulting in alterations in early brain development. Twin studies and family aggregation studies have provided clear evidence for the important role of genetics in autism aetiology [2].

The only clearly identifiable group known for certain to have substantively elevated ASD risk is siblings of affected individuals [3]. The prevalence of autistic disorder among siblings of individuals with autistic disorder ranges from 2% to 6%. Certain rare genetic medical disorders, tuberous sclerosis, fragile X, and epilepsy are also believed to place individuals at moderately higher risk for ASD [4,5]. Because the absolute ASD prevalence among males is still low, males cannot be considered at high risk for ASD but, for unknown reasons, ASD does occur from three to four times more often in males than in females [6].

Maternal diseases/Conditions during pregnancy

Hannah G, et al. [7] published a meta-analysis in the British journal of psychiatry 2008 and examined the prenatal fetal, maternal and environmental factors linking Autism. Over 50 prenatal factors have been examined. The factors associated with autism risk in the meta-analysis were advanced parental age at birth, maternal prenatal medication use, bleeding during pregnancy, gestational diabetes, being firstborn vs. third or later, and having a mother born abroad. The factors with the strongest evidence as to play a role in autism risk included previous fetal loss and maternal hypertension, proteinuria, pre-eclampsia, and swelling. There was insufficient evidence to implicate a single prenatal factor in autism etiology, although there is some evidence to suggest that exposure to pregnancy complications may increase the risk.

Similarly results from the Northern California–based Childhood Autism Risks from Genetics and the Environment (CHARGE) [8] study has also concluded that the ASD risk was two times as great and the DD risk five times as great compared to children whose mothers didn't have preeclampsia. An important aspect of this subject that is yet to be analyzed by researches is the relationship between glycemic control and ASD risk, and this could be an interesting direction for future studies studying Maternal Diabetes as a risk factor for ASD.

There is extensive evidence linking Diabetic pregnancies to adverse pregnancy outcomes [9-11] including autism. The pathogenesis most likely involves diabetes-associated hormonal and metabolic abnormalities, epigenetic changes altering fetal gene expression fetal oxidative stress impacting normal fetal neurodevelopment and growth [10,12]. Interestingly, a Boston-based cohort study conducted by Li. et al. [13] went a step further and linked pre-gestational obesity too along with Maternal diabetes to an increased risk of ASD in the offspring. In mothers with Pre-gestational Diabetes and obesity, the hazard ratio (HR) for ASD was 3.91 (95% CI 1.76–8.68) and in obesity and Gestational Diabetes, the HR was 3.04 (95% CI 1.21–7.63) 26. An important aspect of this subject that is yet to be analyzed by researches is

the relationship between glycemic control and ASD risk and could prove to be an interesting direction for future researches examining the same subject matter.

Martin et el has also raised the possibility of increasing maternal and paternal age at birth and as a contributing factor to the rising prevalence of autism [14]. Maternal age at birth over 30 was associated with an increased risk with effect estimates ranging from a 27% increased risk (30–34 v. 25–29) to a 106% increase in risk (40+ v. 50). A 5-year increase in maternal age was associated with a 7% increase in risk19,20. Increased paternal age at birth was also found to be a significant risk factor (trend P = 0.004), with a 5-year increase in paternal age associated with a 3.6% increase in risk [15].

There is also a growing body of research already linking prenatal Vitamin D deficiency to various neurodevelopmental disorders including Schizophrenia, which shares genetic traits with ASD. This evidence was embedded in a population-based prospective cohort study, done on a multi-ethnic population in Rotterdam, which was specifically designed to study if prenatal Vitamin D deficiency could also play a role in the pathogenesis of ASD [16]. The results showed that 25-OH-Vitamin D deficiency [25(OH)D < 40 ng/ml], assessed at mid-gestation and birth was associated with an increase in Autism-related traits in 6-year-old children. However, a causative relationship between the two variables can only be established after further scrutiny using randomized control studies of Vitamin D supplementation during pregnancy.

Medications/Chemical exposure

Jacob and koops [17] performed a population-based study on Maternal use of valproate during pregnancy, as monotherapy or polytherapy, and found out that it is associated with a significantly increased risk of autism spectrum disorder and childhood autism in offspring, even after adjusting for maternal epilepsy. However, exposures to carbamazepine, oxcarbazepine, lamotrigine, and clonazepam monotherapy were not associated with increased risks of autism spectrum disorder and childhood autism, citing the different chemical structure of valproate being responsible for the possible difference in results. The study does not, however, shed light on the relationship between the timing of exposure of valproate during pregnancy (early vs late) and the risk of ASD.

Autistic children have demonstrated higher serotonin levels in SERT [18] study, SSRI's have since then came under intense examination as a potential risk factor. Unlike valproate, where an association has clearly been established, studies analyzing SSRI's have given conflicting results with a few studies suggesting an association of SSRI's usage with autism risk in offspring [19,20] and other studies showing no association between the two, after adjusting for confounding variables like familial risk factors and maternal history of affective disorders [21,22]. A recently published large cohort study [23] analyzed their results and suggested that the association between Autism and in-utero exposure to antidepressants cannot be solely attributed to confounding and the results should not be considered particularly alarming since, despite the observed relative risks, 95% of pregnant women taking antidepressants during pregnancy do not give birth to an ASD offspring. Therefore, keeping in mind the absolute risk of having an ASD offspring due to in-utero anti-depressant exposure is small as compare to the adverse consequences of untreated maternal depression, mothers are advised to continue their Anti-depressant medications during pregnancy, including SSRI's, despite the above-mentioned conflicting results.

Another environmental exposure with extremely conflicting results is Air pollution. Multiple population-based cohorts conducted in the United states [24,25] have found a positive association between the two, however, European population-based cohorts [26] revealed contradicting results. Another Case-control study [27] examining 15,387 children suggest that air pollutant exposure in early infancy but not during pregnancy increases the risk of being diagnosed with autism and Asperger among children. Again, larger well-controlled studies would be needed to gain conclusive results.

When it comes to Autistic regression, where children seem to have normal neurodevelopment up until 15-30 months of age but are abruptly noted to have regression in both their language and social skills, the focal point of researchers has been to investigate immunizations given to children at about the same type as when the regression is often noted and their associations with this disorder, if any. Despite the intense scrutiny, reviews of existing data on measles-mumps-rubella immunization and ASD, including reports by the Institute of Medicine [28], the Medical Research Council [29], and an expert panel convened by the American Academy of Pediatrics [30], concur that there is insufficient evidence to support

measles-mumps-rubella as an ASD risk factor. Additionally, recently completed Institute of Medicine expert review of mercury in thimerosal, used as a preservative in routine immunizations until 2001, and ASD found the totality of existing evidence to be inconclusive [28].

Although existing epidemiologic and genetic research on ASD supports a complex etiology. However, in summary, the four main potential sources of risk for ASD are the following: 1) genetic predisposition of the mother, 2) environmental factors acting on the mother, 3) genetic predisposition of the child, and 4) environmental factors affecting the child. Exposure to an environmental factor can predispose a genetically susceptible individual to autism or not is still unclear and require further adequately powered studies to prove an association [15,31-33].

Conclusion

There is insufficient evidence to implicate just a single prenatal factor in autism etiology, although there is some evidence to suggest that increase parental age and exposure to pregnancy complications like Hypertension, preeclampsia, and Diabetes may increase the risk. Other environmental factors implicated should further be investigated using large scale randomized control studies to reach on a firm conclusion.

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