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Exploring Prenatal Factors Linked to Autism Spectrum Disorder

Mila Sonkin
Santa Fe Christian Schools

Abstract:- Autism spectrum disorder is caused by a variety of determinants. This study focuses on how the mother's exposure to pesticides, ozone pollution, and infections, as well as the mother's pre-existing disorders, including diabetes and preeclampsia, result in the development of autism spectrum disorder in the child. It also examines the role that maternal immune activation and autoantibodies have on the risk of ASD in the mother's offspring. In addition, it analyzes specific circumstances during childbirth, which include maternal hemorrhage and the use of forceps, and addresses their potential impacts on the risk of autism in the child. Lastly, this study describes the association between incorrect brain development and ASD. Along with compiling the several different maternal circumstances during pregnancy that could cause autism, this study also mentions the link between early brain overgrowth and ASD. Essentially, it clears up any confusion about specific conjectures regarding possible maternal factors that contribute to autism spectrum disorder by presenting the data in a clear and organized manner.

I. INTRODUCTION

According to the Centers for Disease Control & Prevention (CDC), autism spectrum disorder (ASD) is a developmental disability that can cause significant social, behavioral, and communication challenges. Autism has become increasingly common over the past one hundred years with the latest CDC report stating that 1 in 36 children is diagnosed with ASD. Furthermore, there has been a great amount of research on the potential causes of autism, identifying a multitude of cause and effect relationships and associations between autism spectrum disorder and possible contributing factors. Although correlation doesn't equal causation, finding a correlation between two things is a crucial first step to proving a causal relationship.

- *Mother's Exposure During Pregnancy*

One factor that can contribute to the development of autism in a child is the mother's exposure to specific substances during pregnancy.

- *Pesticides*

A recent article published on the relationship between prenatal and infant exposure to ambient pesticides and the prevalence of autism spectrum disorder found that exposure to pesticides was a factor that contributed to autism spectrum disorder in the child. As stated by the primary author, Ehrenstein, the "risk of autism spectrum disorder increases with prenatal and infant exposure to several common ambient pesticides that have been shown to affect neurodevelopment in experimental studies." Therefore, a pregnant woman being in the vicinity of pesticides is a cause of the development of autism in the child.

- *Ozone Pollution*

Based on a meta-analysis from Harvard T.H. Chan School of Public Health, exposure to fine particulate air pollution (PM2.5) increased the risk of autism spectrum disorder by 31% during pregnancy, with the highest risk being found during the third trimester (Harvard T.H. Chan School of Public Health). Likewise, in a study entitled "Early Life Exposure to Air Pollution and Autism Spectrum Disorder: Findings from a Multisite Case-Control Study," the researchers determined that ozone exposure during a mother's third trimester of pregnancy was linked with the development of autism spectrum disorder in the child (McGuinn).

- *Maternal Infections*

Additionally, there are many possible circumstances where the gestational environment can cause issues in the development of the child. To start, the mother getting specific infections during pregnancy can contribute to autism spectrum disorder in the baby. According to the study "The Role of the Immune System in Autism Spectrum Disorder," infections, including rubella or influenza virus, "can create an inflammatory immune environment and spur the production of maternal cytokines." According to Atladóttir, "maternal influenza infection was associated with a twofold increased risk of infantile autism." In addition, many other studies show the link between influenza and autism spectrum disorder. Not only is the placenta likely affected, but also the infection "may cross the placenta and enter the fetal compartment to have lasting effects on the development of the fetus." Ultimately, rubella leads to infants with congenital defects. If the mother gets rubella, it is very likely that the child will develop congenital rubella syndrome (CRS). Consequently, multiple

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studies, including one done by Chess S entitled "Autism in children with congenital rubella," have shown that rubella is linked to autism spectrum disorder. In addition to rubella and influenza, a study done by Deykin and MacMahon titled "Viral Exposure and Autism" proposes that measles and mumps are linked to autism.

Moreover, bacterial infections in the mother are also connected to the development of autism spectrum disorder in the child. According to the study "Maternal Infection during Pregnancy and Autism Spectrum Disorders," "maternal bacterial infections during pregnancy, during the second trimester and the third trimester were associated with moderately increased ASD risk." The same study emphasizes that although there is a link between bacterial infections and autism spectrum disorder, there is no association between any maternal infection during pregnancy and ASD (Zerbo). In short, the maternal response to certain infections can lead to autism spectrum disorder in the child. Therefore, when there is an infection in the gestational environment, we should examine how the mother reacts to it.

- *Maternal Immune Activation*

Furthermore, the development of the child can also be impacted by maternal immune activation, most commonly caused by maternal viral infection (Massrali). According to Meltzer and Van de Water, "a generalized inflammatory response or loss of immune regulation" in the mother can contribute to a child having autism spectrum disorder. Maternal immune activation is triggered by the activation of inflammatory pathways, which increases "levels of cytokines and chemokines that cross the placental and blood-brain barriers altering fetal neural development" (Massrali). Additionally, as stated by Massrali, several studies "have confirmed the link between maternal infections, the role of abnormal levels of cytokines, and the possibility of developmental anomalies in the offspring." Additionally, a design involving pregnant rodents experiencing direct infection, specifically influenza, or the dsRNA mini poly shows substantial alterations in behavior and neurodevelopment in the progeny (Meltzer and Van de Water). Thus, activation of the maternal immune system during fetal development can certainly impact the development of the child and cause autism spectrum disorder. Huh, an associate professor of immunology at Harvard Medical School, explained how the link between a neurodevelopmental disorder, like autism spectrum disorder, and a dysregulated immune system is likely because the individuals "were exposed to this increase in inflammation during pregnancy" as stated by a study done by Harvard Stem Cell Institute titled *Gut-Brain Connection in Autism*.

- *Maternal Autoantibodies*

There have been several studies that examined and proved a link between autoantibodies in pregnant mothers and autism spectrum disorder. One particular study led by Zimmerman analyzed samples from eleven mothers with autistic children between the ages of two and eighteen. Subsequently, the researchers found serum reactivity to those proteins in the mothers who had autistic children and found no serum reactivity to those proteins in the mothers who acted as controls. However, considering the fact that this study had an extremely small sample size, its result is not enough to draw accurate conclusions. As a result, researchers executed a study with sixty-one mothers of autistic children and one hundred and two mothers who acted as a control group. In the end, they discovered that 37 and 73 kDa bands were present in 12% of samples from mothers who have children on the spectrum. On the other hand, they found that none of the mothers who served as the controls showed both bands. Therefore, the study determined that the two bands were undoubtedly more common among mothers who had children with autism. Despite the adequate number of participants, this study is also not sufficient alone to draw a valid conclusion (Meltzer and Van de Water).

In addition, a further study with a larger sample size aimed to offer additional support for the hypothesis that there is a connection between autism spectrum disorder and maternal autoantibodies. In short, the researchers identified a link between ASD behavior in the child and anti-fetal brain antibodies in the mother. They found that brain reactivity to the 37 and 73 kDa bands "correlated with lower expressive language," and this result was later determined by other studies as well (Meltzer and Van de Water).

Furthermore, research has been done by Braunschweig to establish a connection between maternal autoantibodies and autism. In the study, an RFB homogenate was divided into exactly one hundred ten fractions by molecular mass. The target regions of the proteins were 30-40 kDa, 39-50 kDa, and 60-85 kDa, and they meticulously examined the fractions that contained these on separate pairs of two-dimensional gels. The researchers then took one of the two-dimensional gels from each pair, relocated them to nitrocellulose, and lastly probed them with "diluted maternal plasma from a mother of a child with ASD who displayed reactivity to the bands in the region of interest" (Braunschweig). Subsequently, the observed spots on the two-dimensional western blots went through mass spectrometric analysis to identify developmentally regulated proteins in the fetal brain. From each spot, the protein with the highest confidence was further verified by western blot analysis. As stated by Braunschweig, "maternal IgG reactivity to LDH (37 kDa band), YBX1 (39 kDa band), STIP1 (upper 73 kDa band) and CRMP1 (lower 70 kDa band) or cypin, (a 44-kDa protein not noted in our initial studies) was observed in more than 75% of mothers of children with ASD." Overall, this study certainly advanced the ongoing research on the

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correlation between maternal autoantibodies and autism spectrum disorder (Braunschweig).

Additionally, a study done by Dudova explains how a potential factor that may contribute to the development of ASD is the "presence of maternal autoantibodies targeting fetal brain proteins." In the study, a considerable number of mothers who have children on the spectrum have maternal autoantibodies that destroy crucial fetal brain proteins that regulate normal brain development. Particularly, the targeting of collapsin response mediator proteins (CRMP1 and CRMP2), which regulate "neuron polarization, growth, guidance, and synapse refinement during the embryonic and early postnatal development of the nervous system," could lead to "defects in axon growth/guidance, cortical migration, or dendritic projection" by changing CRMP levels or allocation in the nervous system (Dudova).

- *Maternal Diabetes & Preeclampsia*

Several studies have linked diabetes and types of hypertension, including preeclampsia, in the mother with the development of autism spectrum disorder in the child. To start, according to the Centers for Disease Control and Prevention, gestational diabetes affects two to ten percent of pregnancies in the United States every year. Considering this substantial report of diabetes during pregnancy, several studies have been conducted to determine a relationship between gestational diabetes in the mother and autism spectrum disorder in the child. At Kaiser Permanente Southern California, researchers investigated the records of approximately 322,000 mothers to discover why about three thousand four hundred of their children were autistic. They made sure to account for the other possible contributing factors to the diagnosis of autism spectrum disorder in the children since they were specifically exploring the effect of diabetes on the risk of developing ASD. Gestational diabetes typically develops during a woman's 24th and 28th week of pregnancy. They observed that mothers who had gestational diabetes within twenty-six weeks of becoming pregnant were roughly 42% more likely to have a child with autism than women without gestational diabetes. In essence, based on this study, gestational diabetes increases the risk of having a child who is on the spectrum by about 0.5%. Additionally, the Boston Birth Cohort Study tested 2,734 children, including 102 who have autism spectrum disorder, from a minority population in Boston, Massachusetts. They ultimately determined that mothers who were obese and had diabetes before pregnancy were approximately three to four times more likely to have a child who is on the spectrum (Sarris).

Furthermore, a high blood pressure or hypertension disorder that can happen during pregnancy is preeclampsia. As stated by Ellis, "preeclampsia typically occurs during middle to late pregnancy and up to 6 weeks after delivery, though it can sometimes appear earlier than 20 weeks." In a study from the University of California, Davis' MIND Institute published in *JAMA Pediatrics*, the researchers discovered that children on the spectrum were more than twice as likely to be born to mothers who had preeclampsia. Ultimately, this discovery proposes a connection between autism spectrum disorder and maternal preeclampsia during pregnancy (Ellis). Additionally, based on a meta-analysis of ten studies conducted in the USA, Canada, Australia, Denmark, Finland, and Sweden, the risk of autism spectrum disorder was 32% higher in children "who had intrauterine exposure to pre-eclampsia compared with those not exposed" (Dachew). However, another study reports that there is a 50% higher risk of ASD in children whose mothers had preeclampsia after examining sixty-one reports on the connection between types of high blood pressure and developmental conditions (Zeliadt). In essence, these two studies with different sample sizes had results that varied to a small degree. However, they still proved the same thing: an association between autism spectrum disorder and maternal preeclampsia.

II. CIRCUMSTANCES DURING CHILDBIRTH

- *Forceps*

At times, during the second stage of delivery, the mother is not able to push the baby out of the birth canal and is in need of extra assistance. Consequently, in conjunction with contractions, doctors will use forceps, metal instruments used in order to aid in the process of delivering the baby. One important thing to note is that doctors only use forceps if the hospital can perform a cesarean section (Raynes & Lawn).

Furthermore, some severe risks come with the use of forceps for both the mother and the baby. Specifically, due to the pressure on the baby's head from the forceps, the baby has an increased risk of having skull fractures, minor external eye trauma, seizures, minor facial injuries, nerve injuries, facial palsy, and bleeding within the skull. Often, nerve damage resolves itself and facial muscles will go back to normal, but there is still a risk that the baby develops "more severe issues, such as cerebral palsy" (Raynes & Lawn). Cerebral palsy from the use of forceps is not only common but it is also extremely severe, affecting "the movement, balance, and muscle tone of the baby." A baby can develop cerebral palsy from an injury to the brain during or after birth; in roughly ten percent of cases, brain damage to the baby is due to the use of forceps (Raynes & Lawn). As stated by The Villari Firm, "the Autism and Developmental Disabilities Monitoring (ADDM) Network found that children with cerebral palsy may be up to 7 times more likely to have co-occurring ASD." Therefore, there is an indirect association between the use of forceps and autism spectrum disorder in the child.

- *Maternal Hemorrhage*

Moreover, antepartum hemorrhage is when there is bleeding from the genital tract during the second half of pregnancy (Giordano). Similarly, postpartum hemorrhage is when there is bleeding from the genital tract after labor. There

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are a lot of different perspectives about whether maternal hemorrhage causes ASD. One study states that maternal antepartum hemorrhage during the third trimester decreased the risk of autism spectrum disorder, suggesting that it does not cause ASD (Grivas). Likewise, in the Neonatal Brain Hemorrhage Study, researchers examined the brains of over one thousand newborns weighing between 1.1 pounds and 4.4 pounds using cranial ultrasounds and determined that hemorrhages don't increase the risk of ASD. On the other hand, according to a study titled "Prenatal, Perinatal, and Postnatal Factors Associated with Autism," the researchers determined that both antepartum hemorrhage and postpartum hemorrhage were contributing factors to autism spectrum disorder (Wang). Therefore, there is still a lot of research that needs to be done about this possible association between ASD and hemorrhage, but for now, we can't make any conclusions.

- *Child Development After Birth: Incorrect Brain Development*

As stated by *First Things First*, "From birth to age 5, a child's brain develops more than at any other time in life." Therefore, after birth, poor development of the child, specifically the child's brain, can increase the risk of autism. For instance, if the "frontal cortex of the baby's brain overgrows" momentarily after being birthed, there is a chance that the child can develop ASD (Miller)." Similarly, in a study called "Early Brain Overgrowth in Autism Associated with an Increase in Cortical Surface Area Before Age 2," the researchers observed enlargement of the cerebral cortex surface area in children who are on the spectrum (Hazlett). According to Zarbalis, about 20% of children on the spectrum "have early brain overgrowth," which highlights that incorrect brain development is quite common in children with ASD.

III. DISCUSSION

In summary, one thing that can be certain is that specific instances during pregnancy and after birth can alter the development of the child and potentially cause autism spectrum disorder. Research has been done that has indicated the following to be associated with ASD: pesticides, ozone pollution, maternal infections, maternal immune activation, maternal autoantibodies, maternal diabetes, maternal preeclampsia, the use of forceps, maternal hemorrhage, and incorrect brain development.

However, there is a lot of research that still needs to be done in order to draw valid conclusions for some of these connections. Particularly, there is controversy about whether maternal hemorrhage causes autism spectrum disorder in the child, and there is a demand for more research on that association. Additionally, we can conclude that there is a link between maternal autoantibodies and ASD because of the results of several clinical studies and animal models. However, the exact mechanism of how maternal autoantibodies caused the development of ASD is unclear so there is additional research that needs to be done to determine this process. Furthermore, further research is necessary to determine the effects of both maternal preeclampsia and gestational diabetes on the child to confirm the results previous studies have found which is that they are associated with the development of autism spectrum disorder. In the same way, studies have suggested an association between the use of forceps and cerebral palsy and other studies have determined a link between cerebral palsy and ASD, but there is not enough evidence yet to confirm that the use of forceps is a direct cause of autism spectrum disorder in the child.

Furthermore, despite the fact that there are different perspectives on whether pesticides are the only way to manage pests and disease carriers, there is a multitude of evidence suggesting that exposure to pesticides is harmful to human health and can potentially cause autism spectrum disorder in a child if their mother was regularly exposed to it during pregnancy. Additionally, there is a sufficient amount of evidence to support the association between maternal exposure to ozone pollution during pregnancy and the development of autism spectrum disorder in the child but there is still more research that can be done to further confirm this link. Furthermore, there are several replicable and transparent studies that suggest a connection between maternal infections and ASD in the child, but as expected, there are also a few unclear studies that state there isn't an association between maternal infections and autism spectrum disorder. In addition, there is a considerable amount of studies done on the relationship between maternal immune activation and ASD and the relationship between maternal autoantibodies and ASD, which suggests that there are strong associations between those variables and autism spectrum disorder.

IV. CONCLUSION

Overall, the mother's exposure during pregnancy can certainly cause changes in the development of the child. Studies have shown that maternal exposure to pesticides, as well as ozone pollution, is linked with autism spectrum disorder. In addition, during pregnancy, the gestational environment is very vulnerable to infections which could possibly lead to the child being diagnosed with ASD. Not to mention, maternal immune activation, commonly caused by infections, has strong evidence supporting its association with autism. Additionally, there have been several studies done on the link between maternal autoantibodies and ASD, one determining a possible solution to maternal autoantibody-related autism spectrum disorder: the elimination of specific pathological maternal autoantibodies. Moreover, an adequate amount of investigations have shown that maternal preeclampsia, gestational diabetes, and maternal hemorrhage are associated with ASD, but further research is essential in order to deduce their links. Similarly, the use of forceps and autism spectrum disorder are indirectly related, suggesting that there is more necessary research that must be done in order to

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affirm this connection. Lastly, the short period after birth is a crucial time when specific instances can occur that alter the development of the baby. One of which is early brain overgrowth, which studies have proven to be linked with ASD. In conclusion, the stretch during pregnancy leading up to the birth, during the birth, and after the birth are vital stages where certain circumstances can alter the development of the child. Therefore, we must be conscious of the various factors during pregnancy that are linked with autism spectrum disorder so that we can do everything we can to avoid the child being diagnosed with that life-long disorder.

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