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Improving autism perinatal risk factors: A systematic review

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ABSTRACT

Background: Current understanding of the etiology of autism is based on the interaction of multiple genes with each other and with environmental factors, leading to a neurodevelopmental process that results in the expression of autism spectrum disorder (ASD) in the child. This suggests that it might be possible to strengthen resilience to environmental stressors during the perinatal period to improve outcomes and possibly prevent the development of ASD.

Methods: We searched the MEDLINE database for multiple perinatal factors associated with the development of ASD published between January 1, 2005 and July 1, 2018. The search terms used were "autism" crossed with either "perinatal," "prenatal," "gestational," or "pregnancy," and crossed again with each perinatal risk factor highlighted in this review including topics on parental health, infections, medications, and environmental stressors. We then searched interventions that may improve neurodevelopmental outcome before and during pregnancy, including supplements, breastfeeding, and postpartum stress reduction. We identified recent or unique metanalyses and systematic reviews of the identified focus and on randomized controlled trials and summarized these using the most recent and comprehensive reviews.

Results: Folate, omega-3, vitamin D3, environmental toxin avoidance, correcting deficiencies, immune boosting, and prolonged breast feeding are all reported to be linked to the possible reduction of adverse pregnancy outcomes including ASD.

Conclusions: Studies of individual components for improving pregnancy outcomes and several uncontrolled preconception to infancy medical practices suggest that multiple interventions might improve the outcomes of pregnancies where there is risk for developing ASD.

Introduction

Autism Spectrum Disorder (ASD) is characterized by marked impairments in verbal and non-verbal communication combined with restrictive, repetitive patterns of behavior [1]. The prevalence of ASD has risen significantly since the 1980s from 3.3 cases of pervasive developmental disorders per 10,000 children. In 1996, the prevalence was 3.4 cases of autism per 1000 children [2]. Using data from 2012, the Autism and Developmental Disabilities Monitoring (ADDM) Network, estimated 1 in 68 children were affected [3] and recently, the Centers for Disease Control and Prevention (CDC) estimated autism prevalence to be 1 in 59 among the US children, based on an analysis of 2014 medical records and, where available, educational records of 8-year-old children from 11 monitoring sites [4].

The factors of this rise in prevalence is likely multifactorial. Possible explanations include 1) diagnostic expansion and substitution, 2) better reporting, 3) increased recognition, 4) increasing acceptability, and 5) immigration for services. However, other factors such as infection and immunity as well as exposure to environmental toxicants and other environmental factors may also play a role in increasing prevalence. Although as many as 25% of autism cases have a clear genetic etiology [5], concordance rates based on twin studies (monozygotic: 0.50–0.77, dizygotic: 0.31–0.36) support the combination of gene and environment interaction in the development of ASD [6].

Environmental agents may influence epigenetic processes through modifications of gene expression, rather than changes in the DNA sequence itself. Such changes in gene expression can also render some individuals more susceptible to the effects of certain toxicants [7]. The

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wide range of developmental phenotypes implies a complex and individualized process. Moreover, the dysregulation of neuronal connectivity by gene by environment (GxE) interactions may be heightened during critical periods of fetal development [8], suggesting the importance of GxE interactions during pregnancy. Such GxE interaction is seen at levels of gene expression beginning with histone modification and methylation [9] and may be influenced by the metabolic processes such as immune abnormalities/inflammation [10]; oxidative stress [11]; mitochondrial dysfunction [12]; free fatty acid metabolism [13]; and excitatory/inhibitory imbalance [14].

This review supports the possibility that interventions to normalize or mitigate these processes, particularly in the preconception or perinatal period, could lead to resilience and health in the developing and newborn child [15]. An intriguing retrospective case series of 294 general pediatric patients, many with a sibling on the spectrum, found that when the pediatrician gave mothers advice during their pregnancy including minimizing toxicant exposure and acetaminophen use, maximizing breast feeding, using probiotics, and limiting antibiotics, no new cases of autism arose from these families during a 7-year period [16].

Method

To identify factors associated with the perinatal period and the development and potential prevention of ASD in the offspring, we searched the MEDLINE database for studies published between January 1, 2005 and July 1, 2018 for perinatal risk factors and autism filtering for humans. We then searched for perinatal risk factors such as infections, medications, and environmental factors including non-chemical stressors, chemical and nutritional factors. Finally, we searched for interventions that may improve neurodevelopmental outcome including nutritional supplements during pregnancy, breastfeeding, and postpartum stress reduction. The search terms “autism,” “perinatal,” “prenatal,” “gestational,” and “pregnancy” were crossed with each risk factor discussed in this paper. We identified recent or unique metanalyses and systematic reviews of the identified focus and on randomized controlled trials and summarized those using the most recent and comprehensive reviews. Space requirements and focus limit the number of individual studies included. We report the findings from the strongest studies with adequate power, statistical significance, and consistency in replication divided into prenatal, gestational and post-natal influences and then review studies of interventions that are associated with improved ASD outcomes. This review will discuss the risk factors for developing ASD before and during pregnancy. First, we will discuss parental health before conception, then maternal health and environmental exposures during pregnancy, and conclude with interventions that can reduce the risk of developing ASD before and during pregnancy.

Results

Population reviews and meta-analyses

A meta-analysis from 37,634 children with autism and 12,081,416 neurotypical children highlighted numerous prenatal, perinatal and postnatal factors associated with autism prevalence, including maternal and paternal age ≥35 years, gestational hypertension, gestational diabetes, antepartum hemorrhage, cesarean delivery, gestational age ≤36 weeks, induced labor, preeclampsia, fetal distress, low birth weight, postpartum hemorrhage, male gender, and brain anomaly in the infant among the factors associated with the development of ASD [17]. A nest case- control study of Kaiser Permanente records found children with ASD were more likely to have been exposed to perinatal (HR = 1.15, 95% CI: 1.09–1.21), antepartum (HR = 1.22, 95% CI: 1.10–1.36), and intrapartum complications (HR = 1.10, 95% CI: 1.04–1.17) than neurotypical children [18]. Furthermore, a study of 8760 children with ASD age matched with 26,280 controls in the Military Health System database found associations with maternal epilepsy, obesity, hypertension, diabetes, polycystic ovary syndrome, infection, asthma, assisted fertility, hyperemesis, younger age, labor complications, and infant low birth weight, infection, epilepsy, birth asphyxia and newborn complications [19]. To investigate the link between perinatal factors and risk of ASD, future studies should consider risk specificity for ASD beyond nonspecific neurodevelopmental risk, timing of risk and protective mechanisms, and human and animal models to study mechanisms of gene-environment interactions [20] (See Table 1).

Table 1
ASD Perinatal Risk Factors and Possible Preventive Interventions.

Risk Factors	Interventions
Maternal & Gestational Diabetes	Glucose control, ? < oxidative stress, ?Tx < inflammation
Weight Gain	Diet, Exercise
Birth Spacing	> 18 < 60 months
Autoimmune & Inflammatory Disorders	Tx autoimmune d/o and inflammation
Advanced Parental Age	? programs to improve immunity and heath
Maternal infection & Fever	Reduce fever; ?antibiotics/antipyretics
Air pollution	Limit exposure; > immune
Environmental Chemicals	Limit exposure; > immune
Medications	Consider strongest studies & risk: benefit for use
Labor & delivery complications	Prenatal, labor & delivery skilled care
Postpartum Depression & Stress	Vigilance & Apprpriate Intervention

Parental health before and during pregnancy

Maternal and gestational diabetes and weight gain

Several studies report that pre-gestational and gestational diabetes mellitus (GDM) in the mother is associated with ASD in the offspring [21–24]. Pre-gestational diabetes may confer particular risk for ASD when it co-occurs with maternal obesity [25,26]. Most recently, unadjusted average annual ASD incidence rates per 1000 children were 4.4 for exposure to Type 1 diabetes in the mother; 3.6 for Type 2 Diabetes; 2.9 for gestational diabetes by 26 weeks; 2.1 for gestational diabetes after 26 weeks; and 1.8 for no diabetes [27]. A longitudinal study of 1311 mother-child pairs in the US found increased odds (OR 3.13; 95% CI, 1.10–8.94) of diagnoses of developmental delay and ASD in children of mothers who were simply obese [28], after adjusting for potential causal factors.

Proposed mechanisms for the association between maternal diabetes, obesity and ASD include increased fetal oxidative stress and in utero inflammatory processes [29,21]. The relationships between glucose control, timing of gestational diabetes, and offspring ASD seems an important area for ASD risk and should be a subject of future study.

Birth spacing

ASD was associated with both inter-pregnancy interval (IPI) of less than 18 months (aOR 1.5 [1.1–2.2]) and greater than 60 months (1.5 [0.99–2.4]). Both short and long IPI associations were stronger among ASD cases with high severity scores (aORs 2.0 [1.3–3.3] and 1.8 [0.99–3.2], respectively) [30].

Maternal autoimmune and inflammatory disorders

Altered immune responses are reported among persons with ASD and their parents. A Swedish study of 1227 children with ASD and 25 matched controls for each case (30,693 controls with parent data)

found parental autoimmune disorders, particularly maternal type I diabetes, idiopathic thrombocytopenic purpura, myasthenia gravis, and rheumatic fever, were weakly but significantly associated with offspring ASD (maternal OR = 1.6, 95% CI: 1.1–2.2; paternal OR = 1.4, 95% CI: 1.0–2.0) [31]. An increased risk of ASD is reported in children born to mothers with a history of celiac disease [32], rheumatoid arthritis [33] and systemic lupus erythematous (SLE) [34].

Anti-fetal brain autoantibody (Ab+) is shown to be present in 25% of 227 mothers of children with ASD in the Childhood Autism Risk from Genetics and the Environment (CHARGE) study [35]. This study showed that, of mothers of children with severe ASD, those with either type 2 or gestational diabetes were 2.7 times more likely to be Ab+ compared to healthy mothers (95% CI 1.1–6.6) [35].

The role of dysregulation between the mother's and infant's immune system as a risk factor for autism is currently an important area of investigation [36]. A systematic review and meta- analysis found significant associations between maternal autoimmune diseases developed during pregnancy or maternal thyroid disease and the risk of ASD in offspring (pooled OR, 1.30, 1.29, respectively) [37]. Such effect of maternal autoimmune disorders on neurodevelopment of the offspring may relate to the inflammatory effect of autoantibodies and cytokines, possibly through vertical transfer, rather than the maternal autoimmune disorder itself. Increased C-reactive protein (CRP) levels in mothers during pregnancy was significantly associated with autism in the offspring [38]. Adequately treating autoimmune and inflammatory disorders and preventing flare- ups during pregnancy may reduce perinatal risk factors for ASD.

Advanced parental age

Advanced maternal age is independently associated with ASD in several studies, though many of these lack standardized methodologies and statistical controls for paternal age, parity, birth order, or other confounding factors [39]. A meta-analysis in 2012 found statistically significant risk in mothers at least 35 years old, with relative risk increasing with rising maternal age [40].

The association between advanced paternal age and autism is increasingly reported [41]. A population-based cohort study of over 2 million individuals born in Sweden between 1973 and 2001 showed a 76% increased risk for ASD in children whose fathers were older than 45 years compared to children of fathers 20–25 years old (HR = 1.76, 95% CI = 1.36–2.28) [42]. A meta- analysis of 27 studies found the highest parental age category was associated with an increased risk of autism in the offspring, with adjusted ORs 1.41 (95% CI 1.29–1.55) and 1.55 (95% CI 1.39–1.73) for mother and father, respectively [43].

A large cohort study from five countries involving over 30,000 children with ASD found that advanced paternal and maternal age were independently associated with increased risk of ASD after adjusting for the other parent's age [44].

A focus of future study should be to understand whether the influence of parental age is through immunity or accumulated toxins or other mechanisms and if health-related programs to improve these vulnerabilities might improve outcomes. In addition, pregnancy planning programs should educate couples in this potential risk.

Maternal infection and fever during pregnancy

A meta-analysis of 15 studies found that maternal infection during pregnancy was associated with increased ASD risk (OR = 1.13, 95% CI: 1.03–1.23) and was likely modulated by type of infectious agent, time and site of exposure and possibly copy number variants [45]. Maternal exposure to second-trimester fever among 95,754 children with 583 cases of ASD born in Norway was associated with increased ASD risk, (adjusted odds ratio (aOR), 1.40; 95% confidence interval, 1.09–1.79), with a similar, but non-significant, point estimate in the first trimester. Risk increased markedly with exposure to three or more fever episodes after 12 weeks' gestation (aOR, 3.12; 1.28–7.63) [46].

Maternal congenital cytomegalovirus (CMV) infection and subsequent congenital CMV are associated with ASD [47], but too few reported events impose limits on generalizability and further studies are needed [47].

It is uncertain whether the effect of influenza is due to the virus itself, the body's immune response to it, or the effect of antibiotics/antipyretics use. To address this, a case-controlled study from the CHARGE study collected exposure information and found that while neither ASD nor developmental delays were associated with influenza during pregnancy, both were associated with maternal fever during pregnancy. Furthermore, fever-associated ASD risk was reduced among mothers who took antipyretic medications [48]. This suggests the association may be related to induction of inflammatory mediators rather than the viral illness itself. Additionally, low C- reactive protein during pregnancy has been associated with offspring ASD, suggesting a possible immune dysregulation that contributes to ASD [49].

Environmental risk factors during pregnancy

Environmental factors associated with ASD include air pollution, various neurotoxic and endocrine-disrupting pesticides, valproic acid, thalidomide, mercury, and misoprostol. Other chemicals such as polychlorinated biphenyls, toluene, lead, methylmercury, and arsenic also are implicated in developmental neurotoxicity [50].

Air pollution

Air pollution, consisting of hazardous air toxicants, particulate matter, ozone, nitrous oxide, and automobile exhaust-related pollution, is consistently associated with ASD during all trimesters of pregnancy in population-based case-control studies [51,52]. While a systematic review and meta-analysis of over 1000 references concluded that evidence of the association of air pollutants and risk of ASD was limited, the strongest evidence was for the association between prenatal exposure to particulate matter and ASD [53]. Two recent studies examined daily concentrations of particulate matter from air pollution monitors and found perinatal exposure to particulate matter increased ASD risk [54,55]. Nevertheless, low socioeconomic status is associated with maternal obesity and diabetes, lower education, and higher exposure to air pollution, all of which may be confounding risk factors for the ASD [56].

An epigenetic mechanism for neurodevelopmental toxicity associated with air pollution is suggested by a study showing that particulate matter (PM2.5) induced significant redox imbalance, DNA hypo- or hypermethylation, and a bnormal mRNA expression of autism candidate genes in neuronal cells [57]. The fine particles can induce oxidative stress, dysfunction in microglia, and ultimately neuroinflammation [58]. These preliminary studies again suggest that aberrant immune response may play a major role in poorer neurodevelopmental outcomes associated with air pollution.

Environmental chemicals

Insecticides are commonly designed to damage neurotransmission [59]. Maternal exposure to one of the most commonly used class of insecticides, organophosphate pesticides, measured by its urinary metabolite dialkylphosphate (DAP) levels during pregnancy was associated with increased risk of PDD in two-year olds from Latino farmworker families [60]. From the CHARGE case-control study, proximity of the mother during pregnancy to organophosphate pesticide application was associated with a 60% increase in odds of ASD. Particular risk was conferred during the 2nd trimester (OR = 3.3; 95% CI: 1.5, 7.4) and 3rd trimester (OR = 2.0; 95% CI: 1.1, 3.6). The same study also found pyrethroids insecticide application just before conception or in the third trimester increased risk. However, a recent study found an

increased risk of ASD among girls (OR for a doubling in the DMTP concentration: 1.64 (95%CI, 0.95; 2.82)) but not among boys (OR: 0.84, 95%CI: 0.63; 1.11) [61]. These findings suggest windows of vulnerability and gender differences that require further investigation.

Organochlorine compounds (OCs), including organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs), are organic pollutants, of which many have been banned in the United States since the 1970s. However, OCs are lipophilic and bioaccumulate in the food chain because of their long half-life, thus levels are still measurable in human blood today [62,63].

Matched controlled pairs from the Finnish Prenatal Study of Autism found the odds of autism among offspring are significantly increased with maternal p,p′-DDE (metabolite of DDT) levels that were in the highest 75th percentile (odds ratio = 1.32, 95% CI = 1.02, 1.71) while the odds of autism with intellectual disability were increased by greater than twofold (odds ratio = 2.21, 95% CI = 1.32, 3.69) [64].

Phthalates are widely used in cosmetics, plastics, carpets, flooring, toys, and medical and cleaning products, and can disturb hormones critical for brain development [65]. Prenatal exposure to phthalates is shown to be associated with social, communicative, and cognitive deficits, as well as with ASD in studies of several hundred participants [66–68].

Heavy metals such as lead and mercury are well-established toxicants of the developing nervous system, where high levels are associated with loss of cognitive functioning and behavioral problems [69]. Pregnant mothers living close to industrial facilities releasing lead, mercury, and arsenic, have increased offspring ASD risk [68,70]. An analysis of tooth-matrix biomarkers from twins discordant for autism, found that siblings who developed autism had higher levels of **lead** and lower levels of essential nutrients manganese and zinc during the prenatal period and first 5 months postnatally [71].

A comprehensive review of 91 studies focusing on the association of **mercury** and ASD found that 74% suggest mercury as a risk factor for ASD [72]. The authors concluded that mercury has both a direct and indirect effect on neuronal damage by causing oxidative stress, autoimmune activation, neuroinflammation and neuronal damage, which then correlate with ASD symptoms [71]. However, a large population study found no adverse effect of total prenatal blood Hg levels on diagnosed autism (AOR 0.89; 95% CI 0.65, 1.22) per standard deviation of Hg (P = 0.485) [73]. The CHARGE study cohort measured newborn bloodspot mercury concentrations and maternal reports of fish consumption during pregnancy and found no association between gestational methylmercury exposure, primarily from seafood consumption, and ASD risk (OR = 0.95, 95% CI: 0.95, 1.12) [74]. Although subject to memory bias, this study was the first to address prenatal cumulative methylmercury exposure and autism.

Medications and substance abuse during pregnancy

A review of prescription data, psychiatric registers, and birth records from 655,615 Danish children, found increased ASD risk in the 508 children who were exposed to **valproic acid** in utero, with a hazard ratio of 2.9 (95% CI: 1.4–6.0) [75]. With its significant teratogenic effects, maximum precautions should be taken to avoid valproic acid during pregnancy [76].

Thalidomide, used to ease morning sickness and help sleep, is a teratogen that has been associated with phocomelia and other developmental disorders. Hence it was banned for use during pregnancy but historically is associated with an increased incidence of autism [21].

Selective serotonin reuptake inhibitors (SSRIs) during pregnancy cross the placenta and are secreted in breast milk [21], exposing both the fetus and infant. Reports of elevated blood serotonin levels in patients with ASD suggest a possible association between prenatal SSRI exposure and ASD [77], although studies differ on which trimester shows the strongest association [78–82]. Two systematic reviews and meta-analyses concluded that prenatal SSRI exposure is associated with increased risk of ASD, though maternal psychiatric condition as a confounding factor could not be ruled out [76,83,84]. However, a meta-analysis of 4 case-control studies and 2 cohort studies concluded that the association between first trimester maternal exposure to SSRI and child autism was unclear, even after adjusting for maternal mental illness [85]. Health registry studies found no association between maternal use of SSRIs and offspring ASD after controlling for confounding factors such as a direct effect of affective disorder [21]. Further investigations of these associations with large sample sizes and study of maternal mental health surrounding pregnancy are needed.

A**cetaminophen** (paracetamol) use during gestation may be associated with problems in neurodevelopment and possibly ASD. In a Spanish birth cohort of 2644 mother-child pairs, children exposed to acetaminophen in utero had more ASD symptoms in males and attention- related problems in both sexes [86]. A meta-analysis of seven studies found increased risk for ASD (Risk Ratio = 1.23, 95% CI 1.13,1.32, I2 + 17% [87].

A link between **alcohol** exposure in utero and occurrence of ASD was first reported in the 1990s [21]. However, a large population-based cohort study found no positive associations between ASD and average alcohol consumption or number of binge drinking episodes during pregnancy [88].

Labor and delivery risk factors

Children with ASD are more likely to have complications around the time of delivery [18]. These include premature birth [89,90], long duration of delivery and acute fetal distress [91], and birth asphyxia and preeclampsia [18]. Cesarean section (CS) is significantly associated with an increased odds for ASD (OR: 1.26, 95% CI: 1.22–1.30) after adjusting for gestational age, site, maternal age and birth year [89]. This association may be influenced by the other complications during delivery that cause fetal stress, such as prematurity, prolonged labor, birth asphyxia, and others, which can necessitate emergency CS. Augmentation of labor with oxytocin is found to be modestly associated with an increased risk for autism in males (HR 1.13; 95% CI, 1.00–1.26; P = 0.04) in a sample of 557,040 children in Denmark [90], but the connection has not been confirmed.

Interventions that may improve neurodevelopmental outcome

Folate and folinic acid

The CHARGE study found that mothers of children with ASD had lower folic acid intake than mothers of typically developing children, and a mean daily folic acid intake of ≥600 μg was associated with reduced ASD risk [91]. Another recent study found increased odds of offspring ASD with low maternal folic acid intake (< 800 μg) and indoor pesticide exposure during pregnancy [92]. A meta-analysis of 12 articles with 16 studies consisting of 4514 cases found that supplementation with folic acid during pregnancy could reduce the risk of ASD [RR = 0.771, 95% CI = 0.641–0.928, I^2 = 59.7%, $P_{heterogeneity}$ = 0.001]. In addition, when folate receptor autoantibodies (FRAA) in the serum of 40 children with ASD and 42 gender and age matched children with typical development, serum FRAA were present in 77.5% (31/40) of children with ASDs compared with 54.8% (23/42) of TD children (P = 003746, Fischer's exact test)[93]. Further, among mothers with high folate intake (> 800 μg) in the first trimester, exposure to increasing levels of all air pollutants, except ozone, was associated with decreased ASD risk, while increased ASD risk was observed for the same pollutant among mothers with low folate intake (≤800 μg). The difference was statistically significant for NO_2 (e.g., NO_2 and low FA intake: OR = 1.53 (0.91, 2.56) vs NO_2 and high FA intake: OR = 0.74 (0.46, 1.19), P-interaction = 0.04) [94] (See Table 2).

Studies imply that more folate is not necessarily better. Although

Table 2
Evidence for Interventions that may Improve Neurodevelopmental Outcomes.

Agent	Evidence*
Folic and Folinic Acid	Grade B; Moderate Certainty
Omega-3 PUFA	Grade B; Moderate Certainty
Vitamin D	Grade B; Moderate Certainty
Multivitamins	Grade B; Moderate Certainty
Iron	Grade C; Moderate Certainty
Choline	Grade C; Low
Breastfeeding	Grade B; Moderate

* U.S. Preventive Services Task Force Quality Rating Criteria https://www.ncbi.nlm.nih.gov/books/NBK47515/.

maternal multivitamin supplementation of 3–5 times per week was associated with lower risk of ASD, high levels of maternal B12 (> 600 pmol/L) and folate (> 59 nmol/L) were associated with increased risk of ASD [95]. In fact, the highest risk was found in mothers who had both excess folate and B12. Thus, there may be an optimal level of folate during pregnancy for reducing the offspring ASD risk [94].

Omega-3 polyunsaturated fatty acid

A negative correlation between polyunsaturated fatty acids (PUFA) consumption and development of psychiatric disorders is reported [96], but the relationship between consumption during pregnancy and ASD is less clear. Of the PUFAs, omega-3 PUFAs, found mostly in fish, have been associated with decreased risk of ASD, while omega-6 PUFAs contained in vegetable oils and grains, are shown to have harmful effects [97,98]. However, other studies have yielded different results. In one study, mothers in the highest quintile of total PUFA and omega-6 fatty acid intake showed 34% reduction in risk of having a child with ASD, but no decrease in risk was associated with higher intake of omega-3. This may be due to the limited variability in the intake of these specific fatty acids and high correlation among the various dietary fatty acids in the study population [99].

PUFAs' protective mechanism remains unclear, but studies have linked a three- to four- fold increase in ASD in males to their negligible ability to convert a fatty acid precursor into docosahexaenoic acid (DHA), a particularly neuroprotective agent. Such metabolic advantage in females may be important for meeting the demands of fetal brain development during pregnancy, which requires an adequate supply of long chain-PUFAs [100]. These results suggest that omega-3 supplementation during pregnancy and lactation may confer some protection against ASD and should be strongly considered as pre- and perinatal supplements [95] but in need of additional clinical trials.

Vitamin D

Lower 25-hydroxyvitamin D (25(OH)D) levels at 18 weeks and 13.5 weeks gestation is associated with more language, mental, and psychomotor difficulties in the offspring at ages 5 and 10 [101,102]. A follow-up study found no difference in 25(OH)D level at 18 weeks gestation among mothers of children with and without ASD (n = 929) [103]. However, confounders such as socioeconomic status and low response rate in the follow-up study make generalizability difficult [104].

A recent study of over 4000 mothers found that those with gestational vitamin D deficiency (25(OH)D < 25 nmol) had children with worse Social Responsiveness Scale scores at 6 years [105]. A registry-based population study of over 500,000 mothers found an association between lifetime diagnosis of maternal vitamin D deficiency and ASD with intellectual disability, but not without intellectual disability, in the offspring (OR 2.52, 95% CI 1.22–5.16) [106]. Further supporting this, a study examining first trimester maternal serum vitamin D status found lower levels of 25(OH)D associated with increased risk of offspring ASD [107].

An open label trial of vitamin D for mothers with at least one child with ASD examined the effect of 5000 IU of vitamin D daily during pregnancy (n = 19) and either 7000 IU during breastfeeding or 1000 IU for newborn infants in the first three years of life if they did not breastfeed [108]. Despite being a small study, they found that recurrence rate of autism in newborn siblings was 5% compared to levels of up to 20% reported in the literature. Since this study had no controls or blinding, it is promising but preliminary and supports further investigation.

Multivitamin and nutritional supplementation

A prospective cohort study of more than 200,000 mother-child pairs found lowered prevalence of ASD with intellectual disability in children born to mothers who reported multivitamin (MV) supplementation during pregnancy, compared to mothers who reported no MV, iron, or folic acid supplementation (OR: 0.69, 95% CI: 0.57–0.84) [109]. However, maternal MV use was not associated with ASD without intellectual disability in the same study [108]. A recent systematic review of prenatal nutrients and childhood mental illness assessed randomized trials of folic acid, phosphatidylcholine and omega-3 fatty acid along with reports of Vitamins A and D and concluded that prenatal nutrients should be considered as "uniquely effective first steps in decreasing risk for future psychiatric and other illnesses in newborn children" [110].

Iodine and thyroid interventions

The presence of the maternal anti-thyroid peroxidase antibody during gestation is associated with verbal, perceptive, cognitive and motor disturbances, as well as almost 80% increase in the odds of having an offspring with autism (OR = 1.78, 95% CI = 1.16–2.75, p = 0.009) [111]. Therefore, checking for maternal anti-thyroid peroxidase may be valuable for determining potential ASD risk factors in the future.

Iron

A CHARGE study examined maternal iron intake and risk of ASD in the children. Findings showed that the highest iron intake was associated with reduced ASD risk, especially during breastfeeding [112]. In addition, low iron intake interacts with advanced maternal age and metabolic conditions, conferring a 5-fold increase in ASD risk [111]. Therefore, appropriate iron status and treatment of anemia during pregnancy is likely important for decreasing children's risk of ASD.

Choline/phosphatidylcholine

A recent double-blind placebo-controlled trial of oral phosphatidylcholine supplementation during pregnancy resulted in fewer attention problems and less social withdrawal in the treated group (N = 23) compared to placebo at 40 months of age, by parent ratings [113]. Although observational evidence of the benefits of choline during pregnancy for neurological health of the child exists, a systematic review concluded that interventional studies are insufficient [114].

Postpartum factors that may improve outcome

Breastfeeding

Breastfeeding, through the transference of oxytocin in breast milk, is shown to contribute to social recognition, social bonding, and neurodevelopment in the infant [115,116]. Maternal levels of oxytocin increase during lactation to reduce stress, protecting mothers from

anxiety while breastfeeding [117]. Numerous studies support oxytocin's role in maternal attachment and enhancing social development in the infant [118]. Therefore, oxytocin may be able to reduce stress for the mother and encourage social bonding in the newborn, perhaps helping to reduce risk of autism [118]. The potential therapeutic application of oxytocin is promising, and a more consistent dose, administration method, duration, and objective measurements in future research may reveal its potential protective effects.

Breastfeeding also transfers long-chain PUFAs. Breastfed infants or those born to mothers with PUFA intake from fish greater than 2–3 times per week during pregnancy score better on development scales (Bayley Scales of Infant Development) and mental scores (McCarthy Scales of Children's abilities) than non-breastfed or low duration breastfed infants [119,120].

Although the exact mechanism is unknown, sub-optimal breastfeeding is associated with risk of ASD, as well as other behavioral and cognitive deficits [121–123]. Thus, clinicians should educate parents about the medical and neurodevelopmental benefits of breastfeeding and encourage breastfeeding to minimize the risk of ASD in the child.

Postpartum depression and stress

Postpartum depression is common and occurs in 10–22% of mothers [124]. Although psychotropic drugs are generally considered safe to use postpartum [123], studies on the relationship between maternal use of antidepressants during pregnancy and development of ASD in children are inconclusive [125]. Future studies on the interplay between postpartum stress/depression, psychotropic use, and oxytocin levels, and risk of ASD are needed.

Discussion and summary

The search for the etiology of ASD is challenging due to influences from multiple domains of genetic and environmental factors. However, there is evidence that certain intervention during pregnancy may improve outcomes. These are the standards of care, such as quality and consistent perinatal care from skilled providers, nutritional diet, exercise, avoiding toxic exposures and breast feeding. Others suggested by this literature review are that we might be able to affect processes involved in epigenetic influences that improve resilience and neurodevelopment such as those that improve or impair inflammatory and immune processes, oxidative stress, mitochondrial health and free fatty acid metabolism.

Disorders associated with inflammation such as maternal diabetes, obesity, and autoimmune disorders are consistently associated with the risk for autism in the child, suggesting the critical role of the immune system to respond to environmental stressors that may lead to epigenetic changes. Chemical toxins in the environment are less clearly associated, but perinatal exposure to air pollution and its association with autism is strongly suggested. Other chemicals such as various pesticides, polychlorinated biphenyls, bisphenols, and phthalates have also been implicated but have been less frequently studied.

Valproic acid and thalidomide have consistently shown toxic effects on neurodevelopment. Perinatal SSRI exposure and association with autism is weak. Studies of acetaminophen's possible link to autism raise concerns because it is a pregnancy category B medication widely accepted for use during pregnancy.

Although environmental stressors and toxicants raise the risk for the development of autism, several hopeful interventions exist to improve resilience and neurodevelopmental outcome. One of the most studied is folate supplementation, which may have an optimal dose to prevent harm from over-supplementation. Supplementation with omega-3 and with vitamin D3 has support for a beneficial effect. Iodine and thyroid deficiencies, despite their uncertain direct associations with ASD, are harmful to neurodevelopment, and levels should be monitored and managed during pregnancy. Likewise, iron levels should be monitored and deficiencies supplemented. Because of concerns about toxicants and ASD, consumers might look for phlatates in the product labels, most commonly diethyl phthalate (DEP), di-*n*-butyl phthalate (DnBP), and di-isobutyl phthalate (DiBP), to prevent exposure to these chemicals [126]. Finally, postnatal factors such as breastfeeding and reducing postpartum stress may enhance the role of oxytocin in social development and help improve social bonding with the child.

Designing a strong study to support the usefulness of these interventions in reducing the number of new cases with neurodevelopmental disorders such as ASD would involve a large population where risk factors and interventions could be controlled prospectively, fidelity assessed, and outcomes reliably measured. Several countries around the world could do such a study. One small uncontrolled study described earlier [16] supports the idea that perinatal interventions support improved outcome odds. In the meantime, parents and their providers might consider the perinatal risk factors and preventive strategies described in this review to possibly improve neurodevelopmental outcomes of offspring during the perinatal period.

Conflict of interest

The authors declare that they have no conflict of interest in writing this review article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.03.012.

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