

# Environmental factors influencing the risk of autism

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Autism is a developmental disability with age of onset in childhood (under 3 years old), which is characterized by definite impairments in social interactions, abnormalities in speech, and stereotyped pattern of behaviors. Due to the progress of autism in recent decades, a wide range of studies have been done to identify the etiological factors of autism. It has been found that genetic and environmental factors are both involved in autism pathogenesis. Hence, in this review article, a set of environmental factors involved in the occurrence of autism has been collected, and finally, some practical recommendations for reduction of the risk of this devastating disease in children are represented.

**Key words:** Autism, environmental factors, etiological factors

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## INTRODUCTION

Autism described by Asperger (in 1938) and Kanner (in 1943)<sup>[1]</sup> is a severe neurodevelopmental disorder and belongs to autism spectrum disorders (ASDs), including autism, Asperger syndrome, Rett syndrome, unidentified pervasive developmental disorders, and childhood disintegrative disorder.<sup>[2,3]</sup> Autism is 4–5 times more common among boys than girls.<sup>[4–6]</sup> The most prominent clinical and phenotypic features of autism are extensive disabilities in social and behavioral communications, language impairment or inability to speak, and strong tendency toward stereotyped and repetitive patterns of behavior.<sup>[7,8]</sup> Regarding statistical reports, the prevalence of autism had increased from 4–5 cases per 10,000 children in 1980s to 30–60 cases in 1990s,<sup>[9]</sup> and through astonishing increase, there are about 8.0 per 1000 children aged 8 years in 2004 and 9.0 per 1000 in 2006 or 1 in every 110 children aged 8 years in 2006. In 2012, a combined ASD prevalence of

11.3 per 1000 children aged 8 years or 1 in 88 children was published by the Autism and Developmental Disabilities Monitoring Network.<sup>[7,10]</sup> With regard to its progressive increase over the last two decades,<sup>[11]</sup> and lack of effective treatment, and moreover, the difficulties imposed on the society and families of autistic children, the importance of investigation on causes of this disease and effort to prevent it become clear. There is growing body of evidence about genetic factors enrolment which is supporting autism etiology through genetic mutations (e.g., heritability and twins).<sup>[12,13]</sup> According to the important role of epigenetics in autism etiology, a lot of genes have been studied, and in some cases, opposite results obtained.<sup>[14,15]</sup> Studying identical twins and lack of complete concordance among them and excessive genetic studies with no conclusive results unveils the importance of environmental risk factors and their role in etiology of autism.<sup>[16,17]</sup> Hence, the interactions between susceptible genes and environmental factors have been proposed as the major mechanism of autism etiology.<sup>[18,19]</sup>

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Currently, epigenetic and its complex mechanisms are presented as the most momentous mediator in the environment and genome interactions.<sup>[20]</sup> Environmental factors can affect the quality and quantity of gene expression without changing the DNA sequence through epigenetic mechanisms, including DNA methylation, changes in histone proteins, and expression of noncoding RNAs. This way, they can be transferred to the next cellular generation or even the next organism generation.<sup>[20,21]</sup> As a result, exposure to harmful environmental factors can change the expression of developmental key genes in critical periods of embryo formation and increases the risk of genomic imprinting diseases such as autism.<sup>[22,23]</sup>

None of the environmental factors is sufficient to yield autism, but rather a collection of them can be involved in the incidence of autism.<sup>[24]</sup> In this article, regarding mother and child exposure time to risk factors, they are divided into prenatal, natal, and postnatal risk factors.

## PRENATAL RISK FACTORS

Physical, mental, and psychological health and financial state throughout the pregnancy are important factors affecting fetal development and health. An unhealthy mother who is not mentally and physically healthy and well nourished might be unable to have a healthy neonate. A set of prenatal risk factors which increase a child's susceptibility to autism is presented in Table 1.

### Parental age

Advanced parental age (particularly paternal age) has been identified as one of the most important risk factors of autism.<sup>[25-29]</sup> In many studies, maternal and paternal age older than or equal to 34 years has been found associated with increased risk of autism in their offspring; however, in other studies, the relationship between child autism and the age of both parents<sup>[30]</sup> or even the age of one parent<sup>[24,31-34]</sup> is rejected. Intriguingly, the relationship between increased risk of autism and elevated paternal age has been approved in most studies.<sup>[28,32-40]</sup> Particularly, a study was conducted among Iranian people in 2010 to explore the presence or absence of association between parental age and risk of autism. Based on this study, autism risk increases by 29% for every 10-year elevation in fathers' age. In other words, fathers aged between 34 and 39 had a nearly two-fold greater risk, and those who are older than 40 have more than two-fold (2.58) greater risk to have an affected child in comparison to who ones aged 25-29 years old.<sup>[38]</sup> In other studies in Japan<sup>[34]</sup> and China,<sup>[40]</sup> similar relationships were explored between paternal age and increased risk of autism. Lack of any correlation between maternal age and susceptibility of autism in these three mentioned studies has critical importance. The probable

explanation for this phenomenon is the formation of *de novo* mutations in germline cells and modifications in DNA methylation, which can result in general epigenetic alterations in the expression of neural development genes and, finally, disorders in sperm genomic imprinting. As a result, the probability of neural impairments, such as autism, would be increased.<sup>[28,36,37]</sup> Advanced paternal age also affects immune system function and, consequently, the development of the nervous system.<sup>[35]</sup>

In studies that increase in maternal age manifests a correlation with autism,<sup>[24,30,31,41-44]</sup> chromosomal abnormalities and trinucleotide repeat expansion in the ovule,<sup>[42]</sup> and increase in the obstetric intervention<sup>[43]</sup> may be proposed as probable reasons. On the other hand, being small for gestational age can increase the risk of autism due to lack of physical maturity, inability, and poor maternal cares. Mothers who are younger than 20 may be exposed to intrauterine growth retardation of fetus and preterm birth, which both of them are potent for, associated with increased risk of autism.<sup>[30,31,41]</sup>

### Maternal physical health

Metabolic syndrome, bleeding, and mother infection during pregnancy are some of mother's physical diseases which are related to child autism.<sup>[45]</sup> Maternal bleeding during pregnancy which is associated with a significant 81% elevated risk of autism,<sup>[26]</sup> and metabolic syndrome, including diabetes,<sup>[26,46,47]</sup> hypertension,<sup>[31,48]</sup> and obesity,<sup>[48,49]</sup> paves the way for hypoxia (deficiency of oxygen) *in utero*<sup>[46]</sup> which results in deficient brain development and induction of myelination changes, membrane adhesion, and deficiency in hippocampal neurons (a brain area which is highly involved in autism).<sup>[23,50]</sup> Maternal viral infections in the first trimester of pregnancy, including rubella,<sup>[51-53]</sup> measles, mumps, chicken pox,<sup>[45,51]</sup> influenza,<sup>[45,51,54]</sup> herpes,<sup>[51,55]</sup> pneumonia, syphilis, varicella zoster,<sup>[55]</sup> and cytomegalovirus<sup>[45,56]</sup> and bacterial infections in the second trimester which require hospitalization, increase the risk of autism in embryo.<sup>[51]</sup> Such relationship is due to abnormal maternal immune activation and, consequently, elevated levels of inflammatory cytokines which affect the embryonic brain development and increase the risk of autism and other neuropathophysiological status.<sup>[57,58]</sup>

### Maternal mental health

According to the importance and impact of family unit, parental behavior, and their communication patterns on the formation of children's personality and emotions,<sup>[59]</sup> the association between parental psychiatric history and risk of child mental disorders, especially autism, is obvious. For example, the association of parental psychiatric history such as schizophrenia with a nearly three-fold increased risk of autism<sup>[30,60-63]</sup> or the relationship between mother's

**Table 1: Prenatal risk factors**

<b>Risk factors</b>	<b>Positive and negative association with autism</b>	<b>Reference</b>
Parental age	Positive	[25-29,114,115]
	Negative	[30]
Paternal age	Positive	[28,32-40]
	Negative	[24]
Maternal age	Positive	[24,30,31,41-44]
	Negative	[31-34]
Birth order	Positive	[24,25,40,91,118,140]
	Negative	[30,31,97,120,121]
Maternal physical diseases		
Preeclampsia	Positive	[94,141,142]
	Negative	[30]
Maternal gestational diabetes	Positive	[26,46,47]
	Negative	[31,94,143]
Hypertension/edema	Positive	[31,48]
	Negative	[26]
Nausea/vomiting	Positive	[119]
Other maternal diseases including psoriasis, asthma, hay fever, atopic dermatitis, rheumatoid arthritis, celiac disease, and mastocytosis	Positive	[57,144]
Maternal bleeding during pregnancy	Positive	[26,31,40,47,58]
Infections during pregnancy	Positive	[45,58]
Bacterial infection*	Positive	[145]
Viral infection*	Positive	
Influenza		[45,51,54]
Rubella		[45,51-53]
Cytomegalovirus		[45,56]
Measles		[45,51]
Mumps		[45,51]
Chicken pox		[45,51]
Herpes virus		[51,55]
Pneumonia		[55]
Syphilis		[55]
Varicella zoster		[55]
Maternal mental diseases		[30]
Schizophrenia	Positive	[30,60-63]
Depression	Positive	[20,30,60-63]
Anxiety and stress	Positive	[40,60,61,64-70]
	Negative	[146,147]
Personality disorders	Positive	[55]
Infant gender	Positive	[116,117]
Existence of >1 affected sibling	Positive	[116,117]
Maternal prenatal medication use	Positive	[26,45]
Antiepileptic drugs	Positive	[30,53,75,76,101,148,149]
	Negative	[95]
Psychotropic drugs	Positive	[122,150]
Antidepressant drugs	Positive	[78-80]
Beta 2 adrenergic agonist drugs	Positive	[83,84]
Paracetamol (acetaminophen)	Positive	[77,126]
Antipyretics	Positive	[151,152]
Thalidomide	Positive	[30,40,53,81,149]
Misoprostol	Positive	[82,122]
Exposure to certain chemicals heavy metals	Positive	[123,153-155]
Pesticides	Positive	[124,156,157]
Air pollutants	Positive	[123,154,158,159]
P-CB <sup>a</sup>	Positive	[43,53]
PBDE <sup>b</sup>	Positive	[160,161]

Contd...

Table 1: Contd...

Risk factors	Positive and negative association with autism	Reference
PAH <sup>c</sup>	Positive	[95,123,154]
Familial socioeconomic status		
Economic situation	Positive	[85,87,88,162]
	Negative	[30]
Social status	Positive	[40,65,66,70,85,86, 88-90,163]
Educational level	Positive	[85,88,91-93]
Mother born abroad	Positive	[24,31,32,42,61]
	Negative	[91]
Cigarettes or alcohol addiction of one parent	Positive	[31,40,49,129]
	Negative	[92,95,130]
Maternal iron, folate, and methionine deficiency	Positive	[50,113,131-133]
Maternal vitamin deficiency	Positive	[134-139,164]
Weight gain during pregnancy	Positive	[48,49]
Threatened abortion	Positive	[24,40,49]

<sup>a</sup>Polychlorinated biphenyls, <sup>b</sup>Polybrominated diphenyl ether, <sup>c</sup>Polycyclic aromatic hydrocarbons

depression,<sup>[20,60-63]</sup> anxiety,<sup>[40,61,64-70]</sup> and personality disorders<sup>[60]</sup> and susceptibility to autism has been proved in many studies.

In addition to mothers who have experienced mental illnesses throughout their lives and are recognized as mentally illness, those who undergo mental problems such as depression, anxiety, and considerable stress during 21–32 weeks of gestation, a period of heightened plasticity for fetal formation and development<sup>[71]</sup> can have irremediable effects, through epigenetic mechanism, on the expression of fetus stress response genes, the genes involved in neurobiology, metabolism, and physiology that can persist across the lifespan.<sup>[70]</sup> Mother’s inappropriate psychological state, especially great and long-lasting stresses<sup>[72]</sup> which may result in some other personality disorders such as aggression in mothers,<sup>[73]</sup> can expose the fetus to elevated levels of cortisol through interrupting mother’s HPA axis, amplifying adrenal steroids such as cortisol and increasing placental permeability to these hormones, basically. Consequently, fetal developmental programming (through epigenome) would be highly affected, and through interrupting the fetal stress response system, the way for different physical and mental impairments including autism would be paved.<sup>[20]</sup> On the other hand, rates of subclinical anxiety problems are increased among males and siblings in middle childhood.<sup>[74]</sup>

Maternal prenatal medication use

Maternal prenatal medication use can be associated with a 46% increased risk of fetus autism.<sup>[26]</sup> Researches about different kinds of drugs have revealed a significant 68% increased risk of autism in relation to prenatal psychiatric medication use.<sup>[26]</sup> The negative effect of prenatal medication use is caused by their placental crossing and disturbing fetal development, based on many studies. For example, use of antiepileptic drugs, as well as

valproic acid, leads to fetal valproate syndrome, increases oxidative stress and varied gene expression pattern, and subsequently results in developmental delays, deficient motor activities and social behaviors, and finally, postnatal growth alterations.<sup>[45,75,76]</sup> Moreover, it is confirmed that paracetamol (acetaminophen), which is widely used as an analgesic/antipyretic drug, can induce apoptosis and necrosis that are observed in autistic brains. In addition, paracetamol (acetaminophen) induces oxidative stress and immune dysregulation in humans.<sup>[77]</sup> Furthermore, positive connection between antidepressant medications and autism has been demonstrated in many studies.<sup>[78-80]</sup> The relationship between susceptibility to autism and taking some other medications has been identified, such as thalidomide, a painkiller,<sup>[81]</sup> misoprostol, a prostaglandin analog drug for the prevention and treatment of gastric ulcers,<sup>[82]</sup> in the first trimester, and  $\beta$ 2-adrenergic agonists such as terbutaline to treat asthma.<sup>[83,84]</sup>

Familial socioeconomic status

Considering economic, social, educational, and psychological aspects of family’s life, autistic children and their families are of poor state, mainly.<sup>[85]</sup> Basically, these families inevitably experience unhealthy, inappropriate sociality and unrehabilitated life conditions because of financial problems, occupational and psychological stresses.<sup>[86-88]</sup> Inaccessibility to health care and recreational facilities represented in infection and impaired physical health.<sup>[89]</sup> Furthermore, exposure to stress and anxiety (such as shared living place with couple’s families) imposes psychological tension for the parents, especially pregnant mother, and increasing susceptibility to child autism during pregnancy.<sup>[40,65,66]</sup>

On the other hand, isolation of mother and breakdown in communications and social interactions can negatively affect her psychological state and endanger both mother

and embryo’s health.<sup>[90]</sup> There are numerous researches evaluating the relationship between parental education and risk of child autism and have variable conclusions which confirmed the correlation between low level of parental education and risk of autism,<sup>[85]</sup> and some others indicate strength correlation between highly educated parents and incidence of autism.<sup>[91-93]</sup>

NATAL RISK FACTORS

Table 2 suggests natal risk factors which increase the fetal risk of autism. Abnormal gestational age, preterm (<35 weeks) and postterm pregnancy (>42 weeks), is associated with a significantly increased risk of autism.<sup>[30,40,47,92,94,95]</sup> Prenatal risk factors such as bleeding during pregnancy and natal risk factors such as fetal complications including fetal distress, umbilical-cord complications such as fetal nuchal cord and cesarean delivery (26% increased risk of autism)<sup>[47]</sup> are all involved in hypoxia (lack of oxygen) and consequently increasing susceptibility to child autism.<sup>[31,42,47,95]</sup> Fetal nuchal cord occurred significantly more frequent among children with autism (23.2%) regarding the controls (6.3%) and it causes fetal deficiency in blood, oxygen, and nutrition, which would affect fetal brain development and results in damage to the newborn central nervous system if the inadequate blood flow is severe or enough long-lasting.<sup>[40]</sup> Three brain regions, including basal ganglia, hippocampus,

and lateral ventricles, are highly vulnerable to hypoxia.<sup>[42]</sup> Autistic children’s brain exhibit larger lateral ventricles, morphological hippocampal abnormalities, and increased dopaminergic activity (what hypoxia causes).<sup>[96]</sup>

Postnatal risk factors: Lesser

Postnatal risk factors have crucial roles in susceptibility to autism, and a set of them is mentioned in Table 3. Low birth weight, jaundice, and postnatal infection are some of the most significant risk factors. A neonate with birth weight, which is the result of three potential factors (genetic growth potential, duration of pregnancy and rate of fetal growth)<sup>[30]</sup> minor than 2500 g considered as low birth weight and associated with a two-fold increase in the risk of autism.<sup>[31,47,93,97,98]</sup> Postnatal jaundice is a result of high bilirubin production caused by increased breakdown of fetal erythrocytes and a low hepatic excretory capacity resulting from general immaturity of the liver and it can be associated with death during a sensitive period (around the 40 weeks of pregnancy) or susceptibility to mental disorders, especially a four-fold increase in autism if survive.<sup>[30,40,47,99,100]</sup>

Table 2: Natal risk factors

Risk factors	Positive and negative association with autism	Reference
Abnormal presentation		
Preterm birth	Positive	[30,40,47,92,94,99]
Postterm birth	Positive	[40]
	Negative	[47]
Cesarean delivery	Positive	[26,31,40,47,165]
Fetal complications	Positive	[24,26,31,36,42,95]
Hypoxia (lack of oxygen)	Negative	[166-168]
	Positive	[24,40,49,50,96]
	Negative	[166,169-171]
Congenital anomalies	Positive	[30,31,47,172]
Fetal respiratory distress	Positive	[24,31,42,47,95]
Natal ulcers and bleeding	Positive	[30,47]
Umbilical cord complication	Positive	[24,26,31,40,42,47,95,97,121,170,173]
Maternal complications		
Maternal bleeding after childbirth	Positive	[24,47,95]
Venous thrombosis	Positive	[88]
Assisted conception (IVF)	Positive	[92]
Season of birth		
Winter	Positive	[99]
Summer	Positive	[30,47]

IVF = *In vitro* fertilization

Table 3: Postnatal risk factors

Risk factors	Positive and negative association with autism	Reference
Postnatal complications		
Low birth weight and size	Positive	[30,31,36,47,91,93,95,97,98,169,174-176]
	Negative	[40,142,143,166,167,170,177]
Jaundice and hyperbilirubinemia	Positive	[30,40,42,47,99,100,168]
	Negative	[166,177,178]
Encephalopathy	Positive	[94,100,143,179]
Birth defects	Positive	[31,94,95,170,176,180,181]
	Negative	[167,173,182]
Early infant infections	Positive	[94,101-103,149,183]
	Negative	[143,177]
Meningitis	Positive	[55]
Lack of breathing and infant resuscitation	Positive	[24,40,47,166,170]
	Negative	[170,171]
Postnatal anemia	Positive	[30,47]
	Negative	[143,184,185]
Weak or no	Positive	[24,40,47,166,170,186]
Crying after birth	Negative	[170,171]
Postnatal Vitamin D deficiency	Positive	[136,138]
Feeding difficulties	Positive	[30,47]
Medical intervention	Positive	[26]
Low levels of primary maternal	Positive	[64]
Care		
Postnatal chemical exposure to trihalomethanes, tetrachloroethylene, and trichloroethylene	Positive	[101]



In addition to prenatal maternal infection during pregnancy, postnatal infections such as meningitis<sup>[55]</sup> mumps, varicella, unknown fever, and ear infections<sup>[101]</sup> on the first 30 days of life are correlated with high risk of autism.<sup>[102,103]</sup>

## PROTECTIVE OR AUTISM-UNRELATED FACTORS

Among the environmental factors which are probable to cause autism, vaccines can be noted. Epidemiological studies have found no association between measles, mumps, as well as mumps, vaccines (as environmental risk factors), and increased risk of autism.<sup>[101,104]</sup> Contrary to directly related or unrelated factors to autism, some factors have protective roles. Unsaturated fatty acids can be cited as these factors. The biological effects of such fatty acids, such as linoleic acid, omega-3, and omega-6, on the retinal and brain development *in utero*,<sup>[105]</sup> signal transduction, gene expression, and as components of cell membranes<sup>[106,107]</sup> in the first 2 months of pregnancy (the most critical period of embryonic physical development) are highly important to such an extent that high maternal intake of omega-6 and linoleic acid is inversely associated with ASD risk in offspring, corresponding to a 34% reduction in autism risk, and in contrary, lower than 5% of  $\omega$ -3 fatty acid intake had significant increase in offspring ASD risk. Therefore, fatty acids consumption of different diets has an inverse effect on risk of autism.<sup>[108]</sup> In addition to unsaturated fatty acids, taking folic acid 3 months before pregnancy and during the 1<sup>st</sup> month of pregnancy can provide protection against autism in mothers and infants who have one copy of MTHFR 677 C>T allele at least. Maternal folic acid supplementation intake during early pregnancy is associated with less behavioral problems in offspring at 18 months age,<sup>[109]</sup> reduced risk of severe language delay at age 3,<sup>[110]</sup> improved verbal and attention competence at 4 years,<sup>[111]</sup> subordinate scores of childhood hyperactivity at age 8 years,<sup>[112]</sup> and particularly decrease the risk of autism.<sup>[113]</sup>

## DISCUSSION

Autism is a multifactorial neurodevelopmental disorder which is caused by genetic and environmental factors. The prevalence of autism has been increased over the last decades. About every disorder, prevention is more important than cure. Among the risk factors of autism, environmental ones attracted the attention of most of the scientists because prevention is possible by avoiding from them.

There are a lot of environmental risk factors which influence autism pathogenesis by their epigenetic effects. These factors are divided into three categories, included prenatal, natal, and postnatal risk factors. Each category allocates to the specific period of neonate development. A collection

of these factors is involved in the pathogenesis of autism. A comprehensive list of these factors is collected in this review. Regarding these factors, it would be essential to point out some requirements to prevent child autism. The following advice and suggestions are useful for parents to pass the highly significant period of pregnancy with confidence, especially those who have had experience of autistic children, and are about to prevent giving birth to another suffered infant.

## Recommendations

1. Advanced parental age (particularly paternal age) has important role in autism incidence in their neonate;<sup>[25-29, 32-40, 114,115]</sup> therefore, it is suggested that the best time to have a child (especially for father) is under the age of 35
2. Families with more than one autistic child would have increased risk to have an affected infant because the presence of more than one older affected sibling causes a two-fold increase in the risk of autism in the next children. These families are further at risk regarding those who have only one autistic child (32.2% of multiplex vs. 13.5% of simplex).<sup>[116,117]</sup> Therefore, genetic consultation is strongly suggested to families with more than two autistic children who decided to have more children
3. Considering the fact that autistic children are typically the primary child of their family and there is a significant (61%) increase in risk for first-born children compared with next children; if the first child of a family is autistic and the second child is unaffected, it will be less probable to have another autistic child.<sup>[26,53,55,56,118,119]</sup> However, such a relationship has not been observed in other studies<sup>[30,31,97,120,121]</sup>
4. Although the severity of autism is higher in the female gender, the prevalence of autism in boys is 3–4 folds greater than girls.<sup>[4,6]</sup> Hence, sex determination test is highly recommended to parents who are in danger for autism, to increase the probability of having healthy baby girls
5. The investigation of families and relatives of both autistic and healthy children has revealed the fact that familial psychiatric history is more common among autistic children's families and relatives with regard to healthy children;<sup>[30,60]</sup> hence, in addition to genetic susceptibility, environmental factors are also involved in the incidence of such diseases and make mental problems appear in children differently from their parents.<sup>[61]</sup> As a result, regarding the strong association between parental psychiatric history and higher risk of autism in their children<sup>[30,62,63]</sup> and, generally, the impact of parental behavior on children's personality and mental health,<sup>[59]</sup> parents will be advised to complete their treatment and recovery periods before pregnancy

6. Due to the direct effect of maternal emotional state on fetal health, mothers must avoid occupational and mental stresses. Mothers, who tolerate mental stresses such as family problems, stressful living places, financial problems, and loneliness, expose their children to different learning and mental problems such as autism<sup>[20,40,64,86,90,93,122]</sup>
7. Mother exposure to some chemicals such as pesticides, air and water pollutants, and heavy metals and other chemicals can affect fetal health negatively through epigenetic alterations of gene expression and neurodevelopmental process such as changing neuronal migration.<sup>[20,123,124]</sup> Consequently, parents must care about where they choose to live that be far from environmental pollutions and recreational and clinical facilities must be available. Moreover, newborns must not be exposed to trihalomethane, tetrachloroethylene, trichloroethylene, and other chemicals<sup>[101]</sup>
8. The quality of mother–infant interactions during the postnatal period has great importance; that’s why mothers are supposed to provide proper care for their children. The absence of such emotional mother–infant relation has a great effect on the postnatal development of neural and signaling pathways in addition to affecting secretion of some hormones such as dopamine, oxytocin, and serotonin.<sup>[64,125]</sup> They all can be involved in susceptibility to autism
9. Due to side effects of mother’s prenatal medication that is mentioned previously,<sup>[26]</sup> it is highly recommended that mothers should avoid taking any medication during pregnancy. Moreover, without prescription, the children must not be given medications such as paracetamol (acetaminophen) for pain and fever management following vaccinations in early infancy<sup>[77,126,127]</sup>.
10. Maternal smoking and alcohol consumption should be strictly forbidden during pregnancy, because in various studies, it has been proved that prenatal maternal smoking or even passive smoking includes polycyclic aromatic hydrocarbons, metals, and other chemicals with known adverse health effects, which may cause fetal hypoxia and affect fetal brain development.<sup>[31,40,49,128,129]</sup> Although in some studies, the connection between maternal smoking and risk of ASD has been rejected<sup>[130]</sup>
11. Natural childbirth has priority over cesarean section because cesarean is especially prevalent among mothers who give birth to autistic children<sup>[47]</sup>
12. Regarding the protective properties of unsaturated fatty acids<sup>[105-108]</sup> and folic acid<sup>[109-113]</sup>, in addition, the effects of iron deficiency, folate, methionine,<sup>[50,113,131-133]</sup> and vitamins<sup>[134-139]</sup> on susceptibility to autism highlight the importance of an appropriate diet during pregnancy. Considering the profound impacts of different

vitamins on physical health, the impact of Vitamin D on significant biological processes such as DNA repair and its anti-inflammatory quality on brain tissue,<sup>[134,135,137,139]</sup> and the roles of vitamin A and other vitamins in brain development,<sup>[53]</sup> it is better to eat foods enriched with different vitamins and iron in addition to taking vitamin supplements and folic acid during pregnancy. Furthermore, eating foods such as fish which is enriched with omega-3 and other unsaturated fatty acids help in the normal development of the embryo. Appropriate postnatal care prevents the problems with lack of Vitamin D and other crucial components<sup>[136,138]</sup>

13. Pregnancy obesity (>90 kg) and excessive weight gain during pregnancy are significantly associated with the incidence of autism;<sup>[48,129]</sup> therefore, mothers who are more susceptible to autism should be very careful about their dietary to prevent weight gain during pregnancy.
14. Based on some studies, prolonged exposure to elevated temperature during pregnancy and susceptibility to child autism are related.<sup>[47]</sup> Therefore, mothers must avoid taking long saunas and other forms of exposure
15. Due to the negative impacts of activation and aberrations of the maternal and fetal immune systems and increased level of cytokines on neural development of embryos and infants, mothers must care about their health during pregnancy as well as their newborn’s health to stop probable infections, especially in the 1<sup>st</sup> month of infant lives.<sup>[45,49,77,99,101,108,122]</sup>

## CONCLUSION

Given that autism is an epigenetic disorder in which environmental risk factors are the most momentous mediators in its pathogenesis, detection of these factors can help parents avoid the danger of autism onset in their children. By following the mentioned tips, parents can provide a lower risk condition for the outbreak of autism.

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## Conflicts of interest

There are no conflicts of interest.

## AUTHORS’ CONTRIBUTION

- PK, EK, SMM contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work . PK contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- MK contributed in the conception of the work, conducting the study, revising the draft, approval of

the final version of the manuscript, and agreed for all aspects of the work.

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