Vol 9 | Issue 1 | Pages 260-265

Journal of Pediatric Neurology and Neuroscience
ISSN: 2642-4797

Review Article

DOI: 10.36959/595/453

The Potential Risk of Autism Spectrum Disorder Associated with the Use of Depakin in Antenatal Care: A Systemic Review

Khajik Sirob Yaqob Qazaryan[1], Fatima Kamal Khalid[2] and Omer Qutaiba B Allela[3]*

[1]*Specialist pediatrician, children's nutrition and growth specialist, Zakho General Hospital, Kurdistan, Iraq.*

[2]*Assisstant professor of obstetrics and Gynecology, Zakho University, Kurdistan, Iraq*

[3]*Consultant and PhD in clinical Pharmacy, College of Pharmacy, Al- noor University, Ninevah, Iraq*

Keywords

Depakin, Antinatal care, Autism Spectrum Disorder, Folic acid, Timing of pregnancy, Monothaerapy, Polytherapy

Significance

Valproate, recognized as a broad-spectrum antiepileptic agent, is extensively employed in the treatment of epilepsy, as well as a range of neuropsychological disorders, including bipolar disorder and the prophylaxis of migraines. This medication represents a critical therapeutic option, particularly for women of child bearing potential who may have limited alternatives for the effective management of their conditions. However, it is imperative to acknowledge that prenatal exposure to valproate has been correlated with an increased risk of neurodevelopmental disorders, including autism spectrum disorders [1-3].

Evidence from research suggests that children who are exposed to valproate in utero may exhibit a higher prevalence of cognitive impairments and developmental delays. This necessitates that healthcare providers meticulously appraise the risks and benefits associated with the prescription of this medication to women who are either pregnant or contemplating conception [1-3].

Consequently, it is essential for clinicians to explore alternative therapeutic options and to engage in comprehensive discussions with patients concerning the potential risks associated with valproate use. Such discussions should occur during preconception counselling as well as throughout the course of pregnancy, ensuring that informed decision-making is prioritized in the management of these patients.

The exposure to antiepileptic drugs (AEDs) during pregnancy has been extensively studied and is associated with an increased risk of congenital malformations as well as developmental delays in cognitive abilities among offspring [4,5]. Notably, valproic acid, a commonly utilized AED, has been linked to higher incidences of such adverse outcomes. While the relationship between AED exposure and physical anomalies is well-established, the potential risk of other severe neuropsychiatric disorders, including autism spectrum disorder (ASD), remains inadequately characterized.

Numerous case series have reported the presence of autistic symptoms in children who were exposed in utero to valproic acid, suggesting a possible association [1-3,6]. Furthermore, research indicates that prenatal valproate exposure may serve as an experimental model for understanding the pathophysiology of autism in animal studies [7-9]. This line of inquiry raises important questions regarding how environmental exposures, particularly pharmacological ones, may influence neurodevelopmental trajectories.

Genetic factors also play a significant role in the susceptibility to autism, with evidence indicating that up to 25% of affected children possess identifiable genetic mutations related to the disorder [10], Nevertheless, these genetic predispositions must be considered in conjunction with environmental influences, as various factors may interact

***Corresponding author:** Khajik Sirob Yaqob Qazaryan, specialist pediatrician, children's nutrition and growth specialist, ADH, ASD specialist, Zakho General Hospital, Kurdistan, Iraq

Accepted: May 16, 2025

Published online: May 21, 2025

Citation: Qazaryan KSY, Khalid FK, Allela OQB. (2025) The Potential Risk of Autism Spectrum Disorder Associated with the Use of Depakin in Antenatal Care: A Systemic Review. J Pediatr Neurol Neurosci 5(9):260-265

to impact the risk of autism [11]. Within this framework, prenatal exposure to valproate constitutes a modifiable environmental risk factor deserving of careful scrutiny [11].

In light of these findings, it is imperative that healthcare providers engage in thorough evaluations and risk assessments when managing epilepsy in pregnant patients. This approach will ensure that the health of both the patient and the developing fetus are prioritized, while also emphasizing the need for continued research to better understand the complex interplay between genetic predispositions and environmental exposures in contributing to neuropsychiatric outcomes.

Definition, Diagnosis, and types of ASD

Autism spectrum disorders (ASDs) represent a diverse group of neurodevelopmental conditions that manifest primarily through challenges in social communication and the presence of restricted interests and repetitive behaviours [12]. The spectrum includes various classifications, notably childhood autism (often referred to as autistic disorder), Asperger syndrome, atypical autism, and other unspecified pervasive developmental disorders. Each of these classifications presents with unique symptomatology, but they all share core features that affect the individual's daily functioning and social interactions.

A diagnosis of childhood autism is predicated upon the presence of specific symptoms in three key domains: (1) stereotyped patterns of behaviour, which may include repetitive movements, insistence on sameness, and restricted interests; (2) significant impairments in social interaction, characterized by difficulties in understanding social cues, lack of emotional reciprocity, and limited engagement in shared activities; and (3) impairments in communication, which can range from delayed language development to challenges in both verbal and non- verbal communication [12]. It is essential that symptoms in at least one of these areas are evident before the age of three to meet diagnostic criteria [13].

In certain comprehensive population-based cohort study, they sought to investigate the association between maternal use of valproate—a commonly prescribed anticonvulsant medication-during pregnancy and the risk of developing ASD, specifically focusing on childhood autism in offspring [14]. This examination took into account the critical factors of parental history, including instances of epilepsy and various psychiatric conditions, both of which are known to influence neurodevelopmental outcomes. Through extensive data analysis, researchers aimed to elucidate any potential links between prenatal exposure to valproate and the incidence of ASDs [15].

As a consequence, understanding these associations is crucial, as it may inform clinical practices regarding medication use during pregnancy and contribute to the broader knowledge of environmental and genetic factors that play a role in the etiology of ASD. Such findings could have significant implications for prenatal care and future research directions in the field of neurodevelopment disorders.

Folic acid and ASD

The lack of comprehensive data on folic acid usage among pregnant women is particularly significant, especially considering that in Denmark, only high-dose folic acid (5 mg) requires a prescription. Various studies investigating the relationship between folate levels during the later stages of pregnancy and mental as well as psychomotor development in children at the age of five have yielded limited findings, revealing no substantial associations [16]. Nonetheless, it is noteworthy that periconceptional supplementation with folic acid has been linked to are markable 39% reduction in the risk of developing autistic disorder in children. This correlation is represented by an adjusted odds ratio of 0.61 (95% Confidence Interval, 0.41-0.90), suggesting a significant protective effect [17].

Furthermore, folic acid intake may play a crucial role in decreasing the likelihood of autism spectrum disorders, particularly among mothers who have been identified with suboptimal folate metabolism [18]. These findings underline the importance of the timing and adequacy of folate supplementation in pregnant women. It is also imperative to consider that pregnant women who are exposed to valproate—an anticonvulsant medication often prescribed for epilepsy—are likely to be more proactive in taking folic acid. This trend aligns with established recommendations which advocate for the use of folic acid among women of childbearing age who are managing epilepsy. Consequently, this behavior may inadvertently lead to an underreporting or underestimation of the actual risks associated with valproate exposure during pregnancy, thereby complicating the interpretation of the drug's safety profile in this population.

Objectives

The purpose of this investigation is to conduct a comprehensive analysis of the association between prenatal exposure to valproate and its potential correlation with an elevated risk of ASD in offspring. Researchers explore the underlying biological mechanisms and systematically review existing epidemiological data to clarify the relationship between maternal valproate usage during pregnancy and subsequent neurodevelopmental outcomes. By examining various parameters, including dosage, timing of exposure, and genetic predispositions, they aspire to enhance understanding of the implications related to valproate administration during the perinatal period [19-21].

Most important Outcomes and Measures

Studies rigorously examine the association between exposure to valproate during pregnancy and the subsequent development of ASD and childhood autism in offspring. Utilizing a population-based cohort design, they calculated the absolute risk (cumulative incidence) and hazard ratio (HR) of these neurodevelopmental outcomes in children subjected to inutero valproate exposure. The data indicate a significant increase in the risk of developing ASD and childhood autism among children born to mothers who utilized valproate during gestation, in comparison to those whose mothers did not receive this medication [22].

In addition to maternal valproate use during pregnancy, research findings revealed that children born to women who previously used valproate but discontinued its use prior to conception also exhibited elevated risks of ASD and childhood autism. While the results of another study are consistent with previous case series on this topic, it is noteworthy that our observed risk of ASD among valproate-exposed children was marginally lower. This discrepancy may be attributed to the larger, more diverse, and unselected cohort of valproate-exposed women included in our analysis, which potentially mitigates selection bias often associated with smaller case series. Given the profound and lasting implications of ASD for affected individuals and their families— ranging from social integration challenges to increased healthcare needs-even a modest increase in risk requires careful consideration from a public health perspective.

Research findings indicate that the absolute risk of ASD linked to valproate exposure remained below 5%. This threshold is critical to discuss with patients when advising on the implications of valproate use during pregnancy, emphasizing the need for informed decision-making and thorough risk-benefit analysis. Valproate is predominantly prescribed for the treatment of epilepsy, with additional applications in managing manic episodes in bipolar disorder and for the prophylaxis of migraine headaches. However, the ability to delineate the precise diagnoses that led to valproate prescriptions within study population was hampered by limitations in the available prescription data. It is reasonable to hypothesize that a subset of the women had an epilepsy diagnosis, which is the primary clinical indication for valproate use.

Studies comprehensive analysis indicates that the elevated risk of ASD extends beyond offspring of mothers diagnosed with epilepsy, encompassing those without such a diagnosis. This finding suggests a broader biological effect of valproate exposure, independent of the mother's underlying neurological condition. Additionally, the risk associated with valproate exposure was comparatively lower in the offspring of women with epilepsy than in the overall population of valproate-exposed children. This observation raises intriguing questions about the potential influence of maternal epilepsy itself, as well as the intricate interplay between individual genetic predispositions and the teratogenic effects of valproate [1-3].

Furthermore, it is imperative to acknowledge the possibility of ascertainment bias. Children born to mothers who used valproate during pregnancy may be monitored more meticulously for ASD due to heightened awareness of the risks linked with this medication. Such ascertainment bias could lead to an inflated perception of the relationship between valproate exposure and autism risk, necessitating cautious interpretation of our findings and the implementation of enhanced surveillance protocols for affected populations.

Another study underscores the necessity for ongoing research into the long-term neurodevelopmental outcomes of children exposed to valproate in utero [23]. It emphasizes the importance of informed clinical practices and patient counselling regarding the risks associated with valproate, particularly in reproductive-age women.

Assessing the correlation between valproate exposure timing and the risk of ASD

A research study investigate into the correlation between valproate exposure and the subsequent development of ASD, we found no statistically significant variation in the incidence of ASD among offspring of women who commenced valproate prescriptions in the early stages of gestation compared to those who initiated treatment later during pregnancy. However, it is imperative to note that the subgroup of women who initiated valproate therapy exclusively during the later trimesters was relatively small, which may pose constraints on the generalizability of the findings. The analytical estimates derived in this study relied on the trimester during which women filled their valproate prescriptions rather than the precise timing of ingestion. This methodological approach introduces the possibility of misclassification of the exposure timeline, potentially impacting the robustness of our conclusions [20,21].

Furthermore, sensitivity analyses demonstrated that adjustments made to the exposure window prior to conception had negligible effects on the observed association between valproate exposure and the risk of ASD. Consideration must also be accorded to the potential misclassification concerning the timing of conception itself; however, we anticipate that the impact of this misclassification would be minimal.

Certain study offers valuable insights into the relationship between valproate exposure and ASD, the limitations associated with the assessment of exposure timing and the diminutive sample size of certain cohorts necessitate cautious interpretation of the results [20,21]. Future investigations would benefit from larger and more rigorously executed studies to more accurately delineate the relationship between valproate exposure and developmental outcomes in offspring.

Risk of autism associated with antiepileptic treatment regimens in pregnancy

A research study examines the relationship between the administration of antiepileptic medications during gestation and the subsequent incidence of ASD in offspring. The findings underscore a statistically significant increase in the risk of ASD among children born to mothers who received prescriptions for valproate, both as monotherapy and in the context of polytherapy with other antiepileptic drugs, during pregnancy. It is imperative to acknowledge that the cohort of women who were exposed to valproate in a polytherapy context was relatively small, which may impact the robustness of our conclusions regarding this subgroup. Existing literature has consistently documented the teratogenic potential of valproate, positing that the risk may be magnified at higher daily dosages ingested during gestation [22]. Our analysis indicated an elevated risk associated not only with higher dosages but also with lower dosages of valproate [23].

A limitation of this research is the lack of detailed data concerning the specific dosages of valproate administered to participants, as well as any adjustments made throughout their pregnancies. These factors could significantly influence

the reliability of the findings. In contrast, the administration of other commonly prescribed antiepileptic medications, such as carbamazepine, oxcarbazepine, lamotrigine, and clonazepam, did not demonstrate a statistically significant association with increased risks of ASD or childhood autism.

The unique chemical structure of valproate, classified as a fatty acid derivative, may elucidate the divergent outcomes observed when compared to other antiepileptic agents studied herein.

Furthermore, it is plausible that women prescribed valproate during pregnancy may concurrently utilize additional medications, some of which might have potential neurodevelopmental implications [24]. However, in the study they chose not to adjust study analyses for concomitant prescription drug use during pregnancy due to the lack of consensus surrounding which medications may be associated with an elevated risk for autism in progeny. This highlights a critical area for future investigation aimed at elucidating the interactions between various pharmacological treatments and their cumulative effects on neurodevelopmental disorders.

Brain development, congenital malformations, and ASD: An overview of valproate exposure

The concerns regarding the potential adverse effects of valproate on the developing brain are substantial, particularly in the context of prenatal exposure [4,25]. Animal studies have notably demonstrated the emergence of autistic-like behaviours in offspring of mothers exposed to valproate during pregnancy. These behaviours encompass increased repetitive actions, stereotypic activities, heightened anxiety levels, and a significant reduction in social interaction [8,26]. While the exact mechanisms by which valproate contributes to these effects remain largely unclear, several hypotheses suggest potential disruptions in neurotransmitter systems critical for developmental processes. Key pathways may include alterations in cell migration and differentiation, induction of neuronal apoptosis, and changes affecting synaptic plasticity [27,28].

Moreover, various biochemical mechanisms may be involved, such as the attenuation of folic acid metabolism, inhibition of histone deacetylases, oxidative stress, and the generation of arene oxide intermediates [16-18,29,30]. Consistent with existing literature [22,23], research findings support an increased risk of congenital malformations among children exposed to valproate in utero. Notably, the association between valproate exposure and the development of ASD, along with childhood autism, persists even when analysis is restricted to children without congenital malformations.

Another research methodological approach operated under the assumption that a majority of women who filled prescriptions for valproate adhered to the treatment regimen during pregnancy. Previous research has shown a high concordance between maternal self-reporting of antiepileptic medication use and prescriptions recorded in the Danish Prescription Register [31]. However, a limitation of our study is the lack of data regarding antiepileptic drug consumption among pregnant women during hospitalizations; and because of this limitation, it is essential to note that valproate is rarely prescribed alone for short admission periods.

Consequently, the exclusion of pregnancies exposed to valproate might lead to an underestimation of the relationship between prenatal exposure and subsequent neurodevelopmental outcomes.

In further study analysis, they opted not to adjust for multiple comparisons, explicitly defining the primary outcome as the risk of ASD and childhood autism stemming from prenatal valproate exposure. The absence of multiple comparison adjustments heightens the potential for incidental findings; thus, secondary analyses should be interpreted cautiously and considered exploratory, warranting further investigation. The positive predictive value linked to epilepsy diagnoses within the Danish Hospital Register stands at 81%. Therefore, while our cohort includes individuals registered with epilepsy, it is plausible that a segment of these patients may not possess an active diagnosis of epilepsy.

Additionally, those diagnosed with epilepsy during childhood or early adulthood may not retain that diagnosis into later life. Nonetheless, the association between maternal valproate exposure and ASD was consistent across offspring of mothers with and without epilepsy, highlighting the pertinent relationship with valproate exposure itself. While seizure activity during pregnancy may introduce additional risks for the developing fetus, certain dataset did not provide the means to identify pregnant women experiencing seizures, leaving a gap in understanding the interplay between maternal seizures and autism risk.

The integrity of childhood autism diagnoses within the Danish Psychiatric Central Register was examined, revealing that 94% of diagnoses adhered to the International Classification of Diseases10th Edition (ICD-10) diagnostic criteria. Although the validation status of other autism spectrum disorder diagnoses within the register remains unestablished, the diagnostic quality is generally expected to be robust [32].

Another study identified a prevalence estimate of ASD at 1.53% (95% CI, 1.47%-1.58%) after 14 years of follow-up, comparable to reported prevalence rates of approximately 1.1% among US children aged 3 to 17 years based on parental reporting, and around 1% among 8-year-old children according to data from the Autism and Developmental Disabilities Monitoring Network.

Moreover, certain studies considered the analysis of parental psychiatric history-an established risk factor for ASD in offspring. Notably, adjusting for this factor did not significantly alter the estimates of risk associated with valproate exposure [13,33]. However, it should be noted that we lacked comprehensive data on alcohol consumption during pregnancy; we did adjust for diagnoses of alcohol abuse obtained from the Danish Psychiatric Central Register. It is important to recognize that not all individuals with a history of alcohol abuse or psychiatric disorders may be captured in the registers, thus introducing a potential for residual confounding.

Conclusion and discussion

Maternal use of valproate, a commonly prescribed antiepileptic medication, during pregnancy has been associated with a significantly increased risk of autism spectrum disorder (ASD) in offspring. Research indicates that children born to mothers who took valproate while pregnant have a higher likelihood of developing autism, even after controlling for potential confounding factors such as parental psychiatric disorders and pre-existing maternal epilepsy.

The mechanism behind this association may involve the effects of valproate on fetal brain development, as the drug is known to influence neurodevelopmental processes. This poses critical considerations for women of childbearing age who require antiepileptic treatment, particularly as valproate is often effective in controlling seizures in conditions such as epilepsy and bipolar disorder.

Given the importance of seizure control for maternal health, the findings necessitate a nuanced approach. Healthcare providers must engage in proactive risk assessment and open dialogue with women regarding the potential teratogenic effects of valproate. Alternative treatment options should be explored, and if valproate is deemed necessary, careful monitoring and planning can help mitigate risks, including the potential use of higher doses of folic acid and other strategies to support fetal health during pregnancy. Ultimately, these findings underscore the need for individualized treatment plans that weigh the benefits of seizure control against the risks of adverse developmental outcomes in children, emphasizing the importance of informed decision-making in the context of reproductive health.

Lastly, the periconceptional use of folic acid has been associated with a 39% reduced risk of childhood autism and use of folic acid may reduce the risk of autism spectrum disorder in mothers within efficient folate metabolism. However, we expect that pregnant women exposed to valproate would be more likely to take folic acid compared with those not exposed to valproate during pregnancy because of recommendations regarding the use of folic acid in fertile women with epilepsy, which would tend to underestimate the true risk associated with valproate [34,35].

References

1. MooreSJ, Turnpenny P, Quinn A, et al. (2007) A clinical study of 57 children with fetal anticonvulsant syndromes. J Med Genet 37: 489-497.
2. Rasalam AD, Hailey H, Williams JH, et al. (2005) Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 47: 551-555.
3. Bromley RL, Mawer G, Clayton-Smith J, et al. (2008) Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology 71: 1923-1924.
4. Holmes GL, Harden C, Liporace J, et al. (2007) Postnatal concerns in children born to women with epilepsy. Epilepsy Behav 11: 270-276.
5. Meador KJ, Baker GA, Browning N, et al. (2013) Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): A prospective observational study. Lancet Neurol 12: 244-252.
6. Bromley RL, Mawer GE, Briggs M, et al. (2013) The prevalence of neurodevelopmental disorders in children prenatally exposed to antiepileptic drugs. J Neurol Neurosurg Psychiatry 84: 367-643.
7. Markram K, Rinaldi T, La Mendola D, et al. (2008) Abnormal fear conditioning and amygdala processing in an animal model of autism. Neuropsychopharmacology 33: 901-912.
8. Wagner GC, Reuhl KR, Cheh M, et al. (2006) A new neurobehavioral model of autism in mice: pre- and postnatal exposure to sodium valproate. J Autism Dev Disord 36: 779-793.
9. Schneider T, Przewłocki R (2005) Behavioral alterations in rats prenatally exposed to valproic acid: Animal model of autism. Neuropsychopharmacology 30: 80-89.
10. Miles JH (2011) Autism spectrum disorders-a genetics review. Genet Med 13: 278-294.
11. Gardener H, Spiegelman D, Buka SL (2011) Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics 128: 344-355.
12. Diagnostic and Statistical Manual of Mental Disorders. (2000) American Psychiatric Association 4. Washington, DC: American Psychiatric Association.
13. Christensen J, Vestergaard M, Olsen J, et al. (2007) Validation of epilepsy diagnoses in the Danish National Hospital Register. Epilepsy Res 75: 162-170.
14. Pedersen CB, Gøtzsche H, Møller JO, et al. (2006) The danish civil registration system: A cohort of eight million persons. Dan Med Bull 53: 441-449.
15. Larsen H, Nielsen GL, Bendsen J, et al. (2003) Predictive value and completeness of the registration of congenital abnormalities in three Danish population-based registries. Scand J Public Health 31: 12-16.
16. Tamura T, Goldenberg RL, Chapman VR, et al. (2005) Folate status of mothers during pregnancy and mental and psychomotor development of their children at five years of age. Pediatrics 116: 703-708.
17. SurénP, RothC, BresnahanM, et al. (2013) Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA 309: 570-577.
18. Schmidt RJ, Tancredi DJ, Ozonoff S, et al. (2012) Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr 96: 80-89.
19. Symons MJ, Moore DT (2002) Hazard rate ratio and prospective epidemiological studies. J Clin Epidemiol 55: 893-899.
20. Kristensen J, Langhoff-Roos J, Skovgaard LT, et al. (1996) Validation of the danish birth registration. J Clin Epidemiol 49: 893-897.
21. Olesen AW, Westergaard JG, Thomsen SG, et al. (2004) Correlation between self-reported gestational age and ultrasound measurements. Acta Obstet Gynecol Scand 83: 1039-1043.
22. Jentink J, Loane MA, Dolk H, et al. (2010) EUROCAT Antiepileptic Study Working Group. Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med 362: 2185-2193.

23. Vajda FJ, HitchcockA, Graham J, et al. (2006) Foetal malformations and seizure control: 52 months data of the Australian Pregnancy Registry. Eur J Neurol 13: 645-654.

24. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators, Centers for Disease Control and Prevention (2012) Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveill Summ 61: 1-19.

25. MeadorKJ, Baker G, Cohen MJ, et al. (2007) Cognitive/ behavioral teratogenetic effects of antiepileptic drugs. Epilepsy Behav 11: 292-302.

26. Schneider T, Turczak J, Przewłocki R (2006) Environmental enrichment reverses behavioral alterations in rats prenatally exposed to valproic acid: issues for a therapeutic approach in autism. Neuropsychopharmacology 31: 36-46.

27. Bittigau P, Sifringer M, Genz K, et al. (2002) Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc Natl Acad Sci USA 99: 15089-15094.

28. Sui L, Chen M (2012) Prenatal exposure to valproic acid enhances synaptic plasticity in the medial prefrontal cortex and fear memories. Brain Res Bull 87: 556-563.

29. Ornoy A (2009) Valproic acid in pregnancy: How much are we endangering the embryo and fetus? Reprod Toxicol 28: 1-10.

30. Walsh CA, Morrow EM, Rubenstein JL (2008) Autism and brain development. Cell 135: 396-400.

31. Olesen C, Søndergaard C, Thrane N, et al. (2001) Do pregnant women report use of dispensed medications? Epidemiology 12: 497-501.

32. Mulvihill B, Wingate M, Kirby RS, et al. (2009) Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR Surveill Summ 58: 1-20.

33. Lauritsen MB, Jørgensen M, Madsen KM, et al. (2010) Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990-1999. J Autism Dev Disord 40: 139-148.

34. Kogan MD, Blumberg SJ, Schieve LA, et al. (2009) Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. Pediatrics 124: 1395-1403.

35. Lauritsen MB, Pedersen CB, Mortensen PB (2005) Effects of familial risk factors and place of birth on the risk of autism: A nationwide register-based study. J Child Psychol Psychiatry 46: 963-971.

DOI: 10.36959/595/453