https://doi.org/10.31925/farmacia.2023.6.1 **REVIEW**

AUTISM SPECTRUM DISORDER – THE POSSIBLE TRIGGER OF PHARMACOLOGICAL INTERVENTIONS USED IN INFERTILITY TREATMENTS OR DURING PREGNANCY

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Abstract

The prescription of drugs for the treatment of infertility or during pregnancy has seen a sharp increase in recent years. The study aimed to review the main drugs used to evaluate the balance of benefits/risks of preconception during infertility treatment or during pregnancy. A 10-year PubMed database was searched to assess the association between medication use and offspring health outcomes. Careful analysis of pharmacovigilance reports regarding the potential risk of certain classes of drugs administered during infertility treatments or during pregnancy and ASD is the main strategy regarding the appropriate neurodevelopment of the offspring.

Rezumat

Prescrierea de medicamente pentru tratamentul infertilității sau în timpul sarcinii a cunoscut o creștere bruscă în ultimii ani. Studiul și-a propus să sumarizeze principalele medicamente utilizate pentru evaluarea echilibrului beneficii/riscuri ale preconcepției în timpul tratamentului pentru infertilitate sau în timpul sarcinii. Baza de date PubMed, pe o perioadă anterioară de 10 ani, a fost investigată pentru a evalua asocierea dintre utilizarea medicamentelor și rezultatele sănătății descendenților. Analiza atentă a rapoartelor de farmacovigilență cu privire la riscul potențial al anumitor clase de medicamente administrate în timpul tratamentelor pentru infertilitate sau în timpul sarcinii și al tulburării din sfera autismului (TSA) este strategia principală în ceea ce privește neurodezvoltarea adecvată a descendenților.

Keywords: autism spectrum disorder, infertility drugs, ART, pregnancy, perinatal pharmacological exposure, foetal brain development, maternal medication, child neurodevelopment

Introduction

Autism spectrum disorder (ASD) is a neuro-developmental condition of offspring characterized by dysfunctions in social communication, repetitive behaviours and hyperesthesia determined by genetic and/or environmental factors. The inflammatory process, mitochondrial dysfunction and oxidative stress at the cerebral and placental levels are the main mechanisms involved in the initiation of ASD [1].

Regarding the pathogenesis of ASD, environmental factors are identified in 17 - 50% of cases, but genetic factors of family co-aggregation can also play a special role [2]. Infectious processes during pregnancy increase immune activity with a pro-inflammatory effect on the release of cytokines (IL-6, TNF-α), which cross the placenta, reach the foetal circulation, cross the blood-brain barrier, determining a cerebral inflammatory status with neurodevelopmental disorders and behavioural type [3]. However, the study carried out by Wang *et al*. demonstrated a series of cerebrovascular changes in individuals with ASD [4].

An increase in the prevalence of ASD has been observed from 0.04 - 0.05% in the 1970s [5] to 0.5 - 2.9% or more in recent studies [6, 7], this increase has been due in recent years mainly to epigenetic factors. Epigenetic risk factors include medication related to ART, prenatal drug administration, maternal complications during pregnancy and advanced parental age. Genome-wide association studies on neurodevelopment have identified that ADHD/ASD has polygenic characteristics [8].

Various medications, including ovulation stimulants, hormonal therapies and other drugs prescribed for maternal health conditions during pregnancy, are under scrutiny for their potential role in influencing foetal brain development and ASD onset [3]. The review

will systematically evaluate these drugs, acknowledging their therapeutic benefits while also critically appraising the associated risks.

The escalation in the use of drugs for infertility and during pregnancy coincides with an increased incidence of ASD, prompting concerns about the potential neuro-developmental impact of these medications on the child [9]. This review, therefore, aims to analyse recent literature over the past decade, with a specific focus on the PubMed database, to assess the correlation between medication usage during the preconception period, infertility treatments, or pregnancy and offspring health outcomes, particularly the development of ASD.

The intersection of increasing ASD prevalence with the growing use of pharmacological interventions for infertility and during pregnancy necessitates a rigorous evaluation of the potential risks these drugs may pose to foetal neurodevelopment. It is an imperious need to critically examine the association between these medical interventions and the risk of ASD, against the backdrop of rising prescription trends for fertility and pregnancy-related medications. This review intends to synthesize current research to shed light on the possible link between such interventions and ASD risk [10]. By doing so, it hopes to contribute to a more informed and nuanced understanding of ASD aetiology, guiding future research and clinical practices in this domain.

Materials and Methods

In the present study we have investigated PubMed database on a 10-year time span; we dug the data-base to review the main drugs used to evaluate the balance of benefits/risks of preconception during infertility treatment or during pregnancy, to assess the association between medication use and offspring health outcomes.

We used keywords and phrases in the search: "autism spectrum disorder", "infertility treatments", "pregnancy medications", "folic acid", "antiepileptic drugs", "β2-adrenergic receptor agonists", "antipsychotics in pregnancy", "thyroid dysfunction and ASD", "SSRIs, SNRIs and ASD", "analgesic drugs and ASD", "antenatal corticosteroids and ASD", "tocolysis and ASD risk", "preterm birth and ASD", "antibiotic exposure and ASD", "epidural analgesia and ASD" and "anti-hypertensive medication and ASD".

Included in the review were observational studies, clinical trials, systematic reviews and meta-analyses that investigated the relationship between the aforementioned medications and the risk of ASD in offspring. Exclusion criteria consisted of non-English language articles, case reports, editorials, commentaries and studies focusing on non-pharmacological interventions.

Data extraction and study selection were conducted by three independent researchers, who reached a high level of agreement on the eligible studies. The process began with an initial screening of articles based on their titles and abstracts, followed by a detailed review of the full texts. Additionally, snowball searching was employed on pivotal papers to further enrich the sample. Any duplicates or articles that did not meet the predefined search criteria were excluded from the review. Data from the selected studies were extracted, including study design, sample size, medication types, dosage, timing of administration and outcomes related to ASD in offspring. This information was synthesized narratively to highlight patterns, correlations and emerging trends from the collected data.

The quality of the included studies was assessed using appropriate tools such the PRISMA checklist for systematic reviews and meta-analyses. The assessment focused on study design, methodology, data analysis and the robustness of the conclusions. The statistical analysis of the data was performed using Microsoft Excel® 2013 (Microsoft® Corporation, Redmond, WA, USA).

Infertility Drugs and ASD

The techniques of assisted reproduction are constantly growing worldwide, and as a result, there is a major interest in their development in subsequent life, being a public health problem. The tasks obtained by ART are frequently associated with an increased risk of premature birth, low birth weight (LBW), small for gestational age (SGA), perinatal morbidity and mortality and congenital anomalies [11]. The mechanisms of the appearance of ASD, the early neurodevelopment disorders, and the cognitive function in these cases it is not clear whether it is due to the prenatal complications or the medication itself [12].

Studies have not shown significant differences between these children and those conceived spontaneously. The monitoring of these subjects over a long time has shown an increase in the risk of cerebral paralysis and other neurological disorders, while other studies attribute these conditions to premature birth [13].

Prematurity [14, 15], foetal growth restriction, small for gestational age [16, 17], low birth weight [17], uncertain foetal status at birth, high blood losses and prenatal maternal drug use are risk factors for autism spectrum disorders [18]. The results are inconclusive regarding the measured sample, the follow-up of these patients, or the working methodology. Some studies have not found any significant association between ART and ASD [19, 20], while others have established a significant positive association [21]. Furthermore, Hvidtjorn *et al.* identified a relationship in women to whom FSH was administered for ART [22].

Children conceived ART show a slight increase in a possible psychiatric diagnosis compared to those conceived spontaneously. Studies have identified an increased risk of ASD in children born after the ICSI

procedure compared to conventional IVF [23, 24], because the ICSI procedure using manually selected spermatozoa increases the risk of autism gene methylation mutations compared to the one using zona pellucida-bound spermatozoa [25].

Drugs Administration in Pregnancy and ASD Risk

Folic acid supplementation and autism

Folic acid (FA) supplementation during pregnancy before and up to 12 weeks of gestation, in addition to the proven effect of preventing neural tube defects, can influence neurodevelopment and reduce the rate of disorders in the autistic spectrum [26]. At the beginning of pregnancy, the need for folate (vitamin B9) at the foetal level increases, a nutrient involved in DNA replication, amino acid synthesis and vitamin metabolism.

A multicentre prospective study observed that 57.3% of pregnant women consumed folic acid supplements of 0.4 mg/day, 25.2% of patients > 1 mg/day and 3.5% over 5 mg/day. The recommended daily dose of supplements containing folic acid is 0.4 - 1.0 mg/day, with doses > 5 mg/day associated with children with low scores regarding the psychomotor evaluation [27]. Moreover, periconceptional use of FA folic acid supplements < 0.4 mg/day or ≥ 1 mg/day has been shown to produce deficits in attentional function only in boys aged 4 - 5 years [28]. Long-term follow-up (7 - 9 years) of children born to mothers who used folic acid supplements beyond the periconceptional period identified deficits in attentional function different for boys and girls [29].

In contrast, the results of the 2006/2007 randomized controlled trial of 0.4 mg/day folic acid supplementation during the second and third trimesters (FASSTT) from the 14th week of gestation to the end of pregnancy, showed at 7 years beneficial effects regarding children's cognitive performance [30]. In children with ASD, an increased rate of serum autoantibodies against alpha folate receptor and methylene tetrahydrofolate reductase polymorphisms was observed. The beneficial dose of folic acid administration is 0.6 mg, the dose that improves neurological clinical manifestations in children diagnosed with ASD [31].

Antiepileptic drugs - Valproic acid

In women with epilepsy, a decrease in fertility was observed secondary to the disease but mainly to the administered treatment. The main mechanism of anti-epileptic medication is the inhibition of histone deacetylases, interfering with the control of the cell cycle and cell growth and differentiation. Valproate can be associated with an increased risk of congenital anomalies, as well as social behaviour disorders in the autistic spectrum. This risk can be reduced by administering an appropriate antiepileptic dose together with folic acid [32].

Christensen *et al*. showed in a cohort of 6584 new-borns of mothers with epilepsy, a 4.15% risk of autism spectrum disorder when exposed to valproate and a 2.95% risk of childhood autism. Thus, women of childbearing age with antiepileptic medication based on valproate must follow the benefits in relation to the potential risks by adjusting the doses [33]. Another study led by Bjørk *et al*. showed that only 1.5% of unexposed children of mothers with epilepsy had ASD, while exposure to topiramate and valproate monotherapy revealed a 4.3% and 2.7% rate of ASD, respectively. Prenatal monotherapy with lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, gapapentin, pregabalin, clonazepam or phenobarbital does not increase risk, whereas exposure to valproate, topiramate and dual therapies (levetiracetam with carbamazepine and lamotrigine with topiramate) have been associated with increased risks [34].

The prenatal administration of trans-resveratrol performed on an animal model (rat) proved to have a protective effect on the offspring against the adverse effect exerted by valproate, a study that will be important in neurodevelopmental disorders [35]. Dietary phytochemicals like curcumin, resveratrol, naringenin and sulforaphane serve as neurotherapeutics in ASD, offering benefits through antioxidant, immuno-modulatory, gut microbiota modulation and Nrf2 activation functions, so further research on brain targeted delivery methods to investigate their therapeutic value in ASD might be needed [36, 37]. Evidence suggests potential cognitive benefits in children from certain nutritional intervention in pregnancy and bio-molecules, *e.g.*, omega-3 fatty acid supplementation during pregnancy, but its effects on other developmental outcomes remain unclear [38].

Thus, the possible mechanism of action would be the upregulation of the expression of metabotropic glutamate receptors from group I and group II at the level of synapses of rats prenatally exposed to valproic acid, the modulation of the mGlu2/3 receptor being able to be beneficial in the treatment of ASD [39].

β2-adrenergic receptor agonist drugs

Prolonged treatment with β-2-adrenergic receptor agonists preconceptional or during pregnancy may be associated with an increased risk of ASD [40]. Instead, Nagata *et al*. in women with asthma treated during pregnancy with corticosteroids and β2-adrenergic agonists showed a safety profile of this association regarding the neurological development of the offspring [41].

Although the data are inconsistent regarding atopic conditions (asthma, allergy, eczema) in pregnancy and the occurrence of ASD, a series of evidence mentions that this association is possible and the need for additional research [42].

The safety profile of antipsychotic therapy in pregnancy

A series of studies did not highlight the risk of autism spectrum disorder after exposure in the first trimester

to antidepressants [43-45]. Sulpiride is an antipsychotic, along with chlorpromazine, with reduced autonomous side effects and an insignificant behavioural effect on the autistic component [46]. Andrade's study confirmed the fact that the risk-benefit analysis regarding anti-psychotic medication shows its safety profile, with the mention that aripiprazole requires additional research [44].

Benzodiazepines and Z-Drugs

The research conducted did not mention any causal relationship between the use of benzodiazepines and/ or Z-drugs during pregnancy for anxiety or sleep deficit and the risk of ASD [47]. Depression and anxiety during pregnancy affect approximately 10% of women [48]. Anxiolytic, antidepressant, hypnotic, or analgesic medication (opioids) in monotherapy or combination have as their main mechanism the neurotransmitter pathway of γ-aminobutyric acid, with rapid passage at the placental and haematoencephalic level with possible repercussions on foetal neurodevelopment.

The study by Vigod *et al.* observed a reduced association between third-trimester exposure to Z-hypnotics and a child's communication deficit without long-term repercussions [49]. The administration of these drugs as the first line must be justified by a correct diagnosis of the mental illness in adequate doses and for short periods.

Thyroid dysfunction, levothyroxine and ASD risk

Although there is no evidence that the use of levothyroxine in pregnancy is associated with ASD due to the higher risk of premature birth, the cautious administration of this treatment is recommended [50]. Pregnant women diagnosed with hypothyroidism were associated with an increased risk of ASD in their offspring depending on race-ethnicity, particularly evident in Hispanic children, so identifying and treating these cases can reduce the risk of ASD [51].

Offspring of pregnant women who were positive for thyroid peroxidase antibodies had a significantly increased risk of developing autism by almost 80% compared to the control group, with no changes in maternal thyroid hormone levels [52]. Andersen *et al.*, in a study evaluating thyroid dysfunction, showed that both maternal hypothyroidism and overt hyper-thyroidism were risk factors for the occurrence of ASD in children [53].

Antidepressants (Selective Serotonin Reuptake Inhibitors - SSRIs and Serotonin Norepinephrine Reuptake Inhibitors - SNRIs) and ASD

Administration of antidepressants during pregnancy has increased, reaching a percentage of 1 - 8% of all pregnant women [54]. Serotonin's role in neural development and maturation is known, with elevated levels observed in approximately one-third of children with abnormal neural circuits and autism [55]. In the treatment of depression and anxiety, selective serotonin reuptake inhibitors (SSRIs) (sertraline, fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine), first-line drugs during pregnancy [56]. No consensus has been reached regarding the association between exposure to SSRIs and SNRIs during pregnancy and ASD in the offspring, with some studies confirming this link [57-59], while other studies did not find these associations [60, 61].

SSRI/SNRI antidepressants cross the placenta and may be associated with a series of embryonic/foetal risks, such as congenital heart anomalies, which do not involve stopping treatment or initiating it due to the increased risk of relapse or exacerbation of clinical symptoms, with complications for both the mother and for infants [62]. Compared to SSRIs, tricyclic antidepressants have higher rates of transfer to the umbilical cord, not being associated with the risk of ASD in offspring [54].

Analgesic drugs

Analgesic medication (acetaminophen - paracetamol) used during pregnancy is associated with an increased risk of ASD in childhood, the recommendations being to reduce the dose if the situation requires its use to reduce the repercussions on foetal neurodevelopment [63]. Long-term prenatal exposure to acetaminophen consumption presents a higher risk of ASD among the female population [64]. The use of acetaminophen in large quantities during the first trimester of pregnancy requires a warning to pregnant women regarding the risk of ASD [65, 66].

Because there is an immediate dose-response effect through transplacental passage through passive diffusion, short-term use is recommended in case of high maternal fever or pain of increased intensity [67].

Antenatal corticosteroid exposure and ASD

The prenatal administration of corticosteroids is carried out to accelerate foetal lung maturation, being a gold standard starting at 23 0/7 weeks and 33 6/7 weeks of gestation in conditions with a risk of birth in the next 7 days. According to the guidelines, the administration of corticosteroids follows two regimes: the first being represented by two doses of 12 mg of intramuscular betamethasone every 24 h, and the second represented by four doses of 6 mg of intramuscular dexamethasone every 12 h [68]. Currently, a series of guidelines recommend the administration of corticosteroids even after 34 weeks but under 37 weeks, balancing the benefits and risks.

This treatment reduces neonatal morbidity by decreasing the number of NICU admissions and by reducing the hospitalization period. Studies have shown a decrease in postnatal complications (respiratory distress, ulcero-necrotic enterocolitis, intraventricular haemorrhage, sepsis). The long-term effects on the child's neuro-development, especially in children who are not born within 7 days and will be born at term, raise suspicions regarding the repercussions on the foetal brain because corticosteroids pass through the blood-brain barrier [68, 69].

An analysis carried out on a number of 16,847 (1.45%) prenatally treated with corticosteroids (< 28 weeks of gestation) out of a total of 1,163,443 infants mentioned both term and late preterm infants risks raised by mental disorders in childhood [70]. According to a meta-analysis of 1.6 million new-borns, Ninan *et al*. observed that approximately 40% of them, prenatally exposed to corticosteroid therapy, were born at term, which requires a better selection of cases due to the risk of adverse effects regarding neurodevelopment and behaviour disorder [71]. The prospective Odense Child Cohort study found that elevated maternal serum cortisol concentrations in the third trimester of pregnancy were associated with ASD in boys at age three, disappearing at age five [72].

Tocolysis, preterm birth and ASD risk

Tocolytic therapy with beta-sympathomimetics is necessary to delay delivery until the prenatal cortico-steroids accelerate pulmonary maturity, improving perinatal outcomes [73].

In a randomized multicentre study (follow-up of the APOSTEL III trial), van Winden *et al*. showed that there were no significant differences regarding adverse perinatal outcomes in the groups in which tocolysis was performed with nifedipine or atosiban in the case of the threat of premature birth [74]. Betamimetics (terbutaline, ritodrine) used to postpone preterm birth can cross the placenta and can have an adverse effect on foetal neurodevelopment, with an increased risk of autism in the child [75]. Instead, in a prospective case-control study, Altay *et al*. did not observe any risk of ASD regarding exposure to betamimetics during pregnancy [76].

Antibiotic exposure and the risk of ASD in the offspring

The prenatal administration of antibiotics initially changes the maternal microbiome, with a role in the microbiome-intestine-brain axis of the infant, a mechanism that can influence the neurodevelopment process and ultimately associate an autistic spectrum disorder.

In a cohort study of 569,953 children, 1.5% were diagnosed with ASD and 29.8% were prenatally exposed to antibiotics. An increased risk of ASD in offspring was observed in the case of administration during the first and second trimester of pregnancy and duration of administration ≥ 15 days, without influencing the appropriateness of administering antibiotics during pregnancy, but only to select as accurately as possible those cases that to require antibiotic therapy [77]. In the ORACLE II study, in which antibiotics were administered for threatened preterm labour, an increase in functional impairment was observed at a 7-year follow-up [78]. Almasri *et al.* did not observe any association between the peripartum administration of antibiotics and the increased risk of ASD [79].

Epidural analgesia in labour and ASD

In a retrospective longitudinal study, Qiu *et al*. observed that epidural analgesia in labour (LEA) is associated with a significantly higher rate of ASD risk along with the increase in the duration of exposure to the medication used in LEA, which caused a series of controversies regarding the methodology of the study [80]. Other studies based on robust epidemiological data and sibling matching analysis claim no significant association between LEA and ASD [81-83]. However, in a meta-analysis by Wang *et al*., it has been mentioned that LEA during birth can associate offspring with more chances of developing ASD [84]. In conclusion, additional studies will be needed to assess the possible risks of LEA.

The association of antihypertensive medication administered in preeclampsia with the risk of ASD in offspring

Prenatal hypertensive disorders, by increasing the rates of premature birth and SGA, can predispose to ASD, and as a result, antihypertensive medication can reduce this risk [85]. Maternal proinflammatory status, associated with preeclampsia and objectified by increased levels of C-reactive protein, can be a possible trigger for autism, increasing the risk by 43% compared to control cases [86].

Ignorance of the mechanisms underlying the action of preeclampsia on ASD makes therapeutic management difficult. A possible mechanism identified in an animal model (mouse) is the action of inflammatory cytokines TNFα in maternal serum and the increased signalling of nuclear factor kappa B (NFκB) in the foetal brain. Thus, the neutralization of TNFα during pregnancy improved the ASD phenotype [87]. Curran *et al*., using the Millennium Cohort Study of 13,192 children, assessed the association between preeclampsia and the double risk of ASD at age 7 years. Exposure of foetal cortical neurons to serum cytokines from preeclamptic women induced neuronal growth and branching *in vitro* [88].

Vaccines and immunoglobulins

Prenatal exposures to ethylmercury from thimerosal-containing vaccines [89], antibody-stimulating proteins and polysaccharides from vaccines [90] and immuno-globulin preparations [91] were not associated with increased risk of ASD. Prenatal influenza vaccination [91, 92], tetanus, diphtheria and acellular pertussis vaccination were not associated with risk of ASD in offspring [93]. Prenatal vaccination with maternal COVID-19 mRNA was associated with lower risks of perinatal death and NICU admission [94, 95], with no published association with ASD.

Discussion

The exploration of the potential link between infertility treatments, pregnancy medications and ASD is an area of growing concern and scientific inquiry. The

increase in ASD prevalence alongside the heightened use of various pharmacological interventions during infertility treatments and pregnancy necessitates a comprehensive understanding of the possible implications of these interventions on foetal neurodevelopment [1].

Infertility treatments often involve the use of medications such as ovulation stimulants and hormonal therapies. These drugs, while essential for addressing infertility, could potentially influence the neurodevelopmental trajectory of the foetus [2]. Similarly, the use of certain medications during pregnancy, intended to ensure maternal health, might also pose risks to the developing foetus, particularly in the context of neurodevelopmental disorders such as ASD [3]. Studies have pointed out that prenatal exposure to various drugs can have complex effects on brain development, modulated by factors like timing, dose and route of drug exposure [4] (Table I).

Table I

Effects of prenatal exposure to drugs and neurodevelopmental risk of ASD

Drugs	**Effects**		
	Yes	Possible	No
Folic acid supplementation	-	-	√
Antiepileptic drugs - valproic acids	√	-	-
β-2-adrenergic receptor agonists	-	√	-
Antipsychotic therapy	-	-	√
Benzodiazepines and Z-drugs	-	-	√
Levothyroxine	-	-	√
Antidepressants (SSRIs and SNRIs)	-	√	-
Analgesic drugs	√	-	-
Vaccines and immunoglobulins	-	-	√
Antenatal corticosteroids	-	√	-
Beta-sympathomimetics / tocolysis	-	-	√
Antibiotics	√	-	-
Epidural analgesia in labour	-	√	-
Antihypertensive medication	-	√	-

A systematic review of the long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics indicates potential adverse effects on neurodevelopment and behaviour. This finding is crucial as it underscores the need for rigorous evaluation of the safety profile of these drugs when prescribed to pregnant women or women undergoing infertility treatment. Moreover, the lack of high-quality clinical studies in this area highlights the need for further research, particularly studies that control for genetic predisposition and parental psychiatric illness [5].

The use of human-induced pluripotent stem cell-derived brain organoid technology has emerged as a promising approach to examining foetal neurobiology and the impacts of drug exposure [6]. This technology offers insights into how specific environmental stimuli, including medications, might affect cerebral development during critical periods of pregnancy. This discussion delves into the safety profiles and possible implications of different drug categories used during pregnancy and their association with ASD.

Folic acid is known for its protective role against neural tube defects. However, its impact on reducing the risk of ASD in offspring remains a subject of study. The role of folic acid in mitigating risks associated with other drug exposures during pregnancy is also an area worth exploring [1]. The use of anti-epileptic drugs, especially valproate, during pregnancy has been linked to a higher risk of ASD in children. Balancing the need for seizure control in pregnant women with the potential developmental risks for the foetus is a significant challenge [2].

These drugs, commonly used for asthma management, have raised concerns about their safety profile during pregnancy and their potential association with neuro-developmental disorders in children, including ASD [3].

Antipsychotics are essential for managing psychiatric conditions during pregnancy, but their impact on foetal brain development and the risk of ASD warrants careful consideration and further research [4]. The use of benzodiazepines and Z-drugs during pregnancy, especially when considering their potential for impacting foetal brain development, requires a cautious approach due to the possible association with ASD [5]. The use of SSRIs and SNRIs during pregnancy has been scrutinized for its potential link with an increased risk of ASD in children [7].

Maternal thyroid dysfunction and its treatment with levothyroxine have implications for foetal brain development. The association between these factors and the risk of ASD in offspring is an area that needs more definitive research [6]. Analgesics are frequently used during pregnancy, but their impact on the neurodevelopment of the foetus and the potential association with ASD, remains a critical area of investigation [8].

Corticosteroids are administered antenatally to promote foetal lung development in preterm births. However, their impact on neurodevelopment and the potential link with ASD is not fully understood [11]. Medications used for tocolysis to prevent preterm labour may have implications for foetal brain development. The association between these drugs, preterm birth and the risk of ASD in offspring is an emerging area of research [12]. Antibiotic use during pregnancy, especially considering the delicate balance of maternal-foetal microbiota, could potentially influence neuro-developmental outcomes, including ASD [14]. The use of epidural analgesia during labour and its potential association with ASD in offspring is a topic of growing interest, with some studies suggesting a possible link [15]. Antihypertensive medications are critical for managing preeclampsia in pregnancy. Research into how these drugs might impact foetal neurodevelopment and the risk of ASD is essential [16].

The expert consensus on neurodevelopmental outcomes in pregnancy pharmacovigilance studies recommends focusing on neurodevelopment as a core feature of pregnancy pharmacovigilance. This approach is vital in understanding the long-term impact of prenatal medication exposure beyond the immediate physical effects and into functional outcomes such as cognitive and motor skill development, educational achievements and the potential development of neurodevelopmental disorders like ASD [7].

In conclusion, the potential link between infertility treatments, pregnancy medications and ASD is a complex and multifaceted issue. It necessitates a balanced consideration of the therapeutic benefits of these medications against their possible risks. Ongoing research, employing both clinical and innovative methodologies is essential to unravel this intricate relationship and to guide clinical practices toward safer and more informed pharmacological interventions during pregnancy and infertility treatments.

Conclusions

The relationship between various pharmacological interventions during pregnancy and the risk of ASD in offspring is complex and multifaceted. Each drug category, from antiepileptics to antidepressants, presents unique challenges in balancing therapeutic needs with potential neurodevelopmental risks. Ongoing, multi-disciplinary research is crucial to inform safer clinical practices. We must pay special attention to the pharmacovigilance reports regarding the potential risk of some classes of drugs administered during infertility treatments or during pregnancy and ASD.

Conflict of interest

The authors declare no conflict of interest.

References

1. Usui N, Kobayashi H, Shimada S, Neuroinflammation and Oxidative Stress in the Pathogenesis of Autism Spectrum Disorder. *Int J Mol Sci.*, 2023; 24(6): 5487.
2. Maher GM, O'Keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, Khashan AS, Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring. *JAMA Psychiatry*, 2018; 75(8): 809-819.
3. Zawadzka A, Cieślik M, Adamczyk A, The Role of Maternal Immune Activation in the Pathogenesis of Autism: A Review of the Evidence, Proposed Mechanisms and Implications for Treatment. *Int J Mol Sci.*, 2021; 22(21): 11516.
4. Wang Y, Yu S, Li M, Neurovascular crosstalk and cerebrovascular alterations: an underestimated therapeutic target in autism spectrum disorders. *Front Cell Neurosci.*, 2023; 17: 1226580.
5. Christensen DL, Baio J, Van Naarden Braun K, Bilder D, Charles J, Constantino JN, Daniels J, Durkin MS, Fitzgerald RT, Kurzius-Spencer M, Lee LC, Pettygrove S, Robinson C, Schulz E, Wells C, Wingate MS, Zahorodny W, Yeargin-Allsopp M, Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR Surveill Summ.*, 2016; 65(3): 1-22.
6. Talantseva OI, Romanova RS, Shurdova EM, Dolgorukova TA, Sologub PS, Titova OS, Kleeva DF, Grigorenko EL, The global prevalence of autism spectrum disorder: a three-level meta-analysis. *Front Psychiatry*, 2023; 14: 1071181.
7. Salari N, Rasoulpoor S, Rasoulpoor S, Shohaimi S, Jafarpour S, Abdoli N, Khaledi-Paveh B, Mohammadi M, The global prevalence of autism spectrum disorder: a comprehensive systematic review and meta-analysis. *Ital J Pediatr.*, 2022; 48(1): 112.
8. Narita A, Nagai M, Mizuno S, Ogishima S, Tamiya G, Ueki M, Sakurai R, Makino S, Obara T, Ishikuro M, Yamanaka C, Matsubara H, Kuniyoshi Y, Murakami K, Ueno F, Noda A, Kobayashi T, Kobayashi M, Usuzaki T, Ohseto H, Hozawa A, Kikuya M, Metoki H, Kure S, Kuriyama S, Clustering by phenotype and genome-wide association study in autism. *Transl Psychiatry*, 2020; 10(1): 290.
9. Noda A, Ishikuro M, Obara T, Murakami K, Ueno F, Matsuzaki F, Onuma T, Watanabe Z, Shiga N, Iwama N, Hirotaka H, Otsuka T, Tachibana M, Tomita H, Saito M, Sugawara J, Kure S, Yaegashi N, Kuriyama S, Association between maternal infertility treatment and child neurodevelopment: findings from the Tohoku Medical Megabank Project Birth and Three-Generation Cohort Study in Miyagi and Iwate Prefectures, Japan. *BMJ Open*, 2022; 12(6): e060944.
10. Rönö K, Rissanen E, Bergh C, Wennerholm UB, Opdahl S, Romundstad LB, Henningsen AKA, Spangmose AL, Pinborg A, Gissler M, Tiitinen A, The neurodevelopmental morbidity of children born after assisted reproductive technology: a Nordic register study from the Committee of Nordic Assisted Reproductive Technology and Safety group. *Fertil Steril.*, 2022; 117(5): 1026-1037.

11. Wilkins-Haug L, Assisted reproductive technology, congenital malformations, and epigenetic disease. *Clin Obstet Gynecol.*, 2008; 51(1): 96-105.
12. Sutcliffe AG, Ludwig M, Outcome of assisted reproduction. Lancet, 2007; 370(9584): 351-359.
13. Goldsmith S, Mcintyre S, Badawi N, Hansen M, Cerebral palsy after assisted reproductive technology: a cohort study. *Dev Med Child Neurol.*, 2018; 60(1): 73-80.
14. Allen L, Leon-Attia O, Shaham M, Shefer S, Gabis LV, Autism risk linked to prematurity is more accentuated in girls. *PloS One*, 2020; 15(8): e0236994.
15. Mahoney AD, Minter B, Burch K, Stapel-Wax J, Autism spectrum disorders and prematurity: a review across gestational age subgroups. *Adv Neonatal Care*, 2013; 13(4): 247-251.
16. Jenabi E, Bashirian S, Asali Z, Seyedi M, Association between small for gestational age and risk of autism spectrum disorders: a meta-analysis. *Clin Exp Pediatr.*, 2021; 64(10): 538-542.
17. Lampi KM, Lehtonen L, Tran PL, Suominen A, Lehti V, Banerjee PN, Gissler M, Brown AS, Sourander A, Risk of autism spectrum disorders in low birth weight and small for gestational age infants. *J Pediatr.*, 2012; 161(5): 830-836.
18. Ng H, Kb K, Risk factors for autism and Asperger syndrome. Perinatal factors and migration. Autism, 2011; 15(2): 163-183.
19. Diop H, Cabral H, Gopal D, Cui X, Stern JE, Kotelchuck M, Early Autism Spectrum Disorders in Children Born to Fertile, Subfertile, and ART-Treated Women. *Matern Child Health J.*, 2019; 23(11): 1489-1499.
20. Robinson SL, Parikh T, Lin T, Bell EM, Heisler E, Park H, Kus C, Stern JE, Yeung EH, Infertility treatment and autism risk using the Modified Checklist for Autism in Toddlers (M-CHAT). *Hum Reprod.*, 2020; 35(3): 684-693.
21. Hansen M, Greenop KR, Bourke J, Baynam G, Hart RJ, Leonard H, Intellectual Disability in Children Conceived Using Assisted Reproductive Technology. *Pediatrics*, 2018; 142(6): e20181269.
22. Hvidtjørn D, Grove J, Schendel D, Schieve LA, Sværke C, Ernst E, Thorsen P, Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study. *J Epidemiol Community Health*, 2011; 65(6): 497-502.
23. Djuwantono T, Aviani JK, Permadi W, Achmad TH, Halim D, Risk of neurodevelopmental disorders in children born from different ART treatments: a systematic review and meta-analysis. *J Neurodev Disord.*, 2020; 12(1): 33.
24. Kissin DM, Zhang Y, Boulet SL, Fountain C, Bearman P, Schieve L, Yeargin-Allsopp M, Jamieson DJ, Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children. *Hum Reprod.*, 2015; 30(2): 454-465.
25. Wang L, Chen M, Yan G, Zhao S, DNA Methylation Differences Between Zona Pellucida-Bound and Manually Selected Spermatozoa Are Associated With Autism Susceptibility. *Front Endocrinol (Lausanne)*, 2021; 12: 774260.
26. Castro K, Klein Lda S, Baronio D, Gottfried C, Riesgo R, Perry IS, Folic acid and autism: What do we know?. *Nutr Neurosci.*, 2016; 19(7): 310-317.
27. Valera-Gran D, García de la Hera M, Navarrete-Muñoz EM, Fernandez-Somoano A, Tardón A, Julvez J, Forns J, Lertxundi N, Ibarluzea JM, Murcia M, Rebagliato M, Vioque J, Infancia y Medio Ambiente (INMA) Project, Folic acid supplements during pregnancy and child psychomotor development after the first year of life. *JAMA Pediatr.*, 2014; 168(11): e142611.
28. Compañ Gabucio LM, García de la Hera M, Torres Collado L, Fernández-Somoano A, Tardón A, Guxens M, Vrijheid M, Rebagliato M, Murcia M, Ibarluzea J, Martí I, Vioque J, The Use of Lower or Higher Than Recommended Doses of Folic Acid Supplements during Pregnancy Is Associated with Child Attentional Dysfunction at 4-5 Years of Age in the INMA Project. *Nutrients*, 2021; 13(2): 327.
29. Compañ-Gabucio LM, Torres-Collado L, Garcia-de la Hera M, Fernández-Somoano A, Tardón A, Julvez J, Sunyer J, Rebagliato M, Murcia M, Ibarluzea J, Santa-Marina L, Vioque J, Association between the Use of Folic Acid Supplements during Pregnancy and Children's Cognitive Function at 7-9 Years of Age in the INMA Cohort Study. *Int J Environ Res Public Health*, 2022; 19(19): 12123.
30. McNulty H, Rollins M, Cassidy T, Caffrey A, Marshall B, Dornan J, McLaughlin M, McNulty BA, Ward M, Strain JJ, Molloy AM, Lees-Murdock DJ, Walsh CP, Pentieva K, Effect of continued folic acid supplementation beyond the first trimester of pregnancy on cognitive performance in the child: a follow-up study from a randomized controlled trial (FASSTT Offspring Trial). *BMC Med.*, 2019; 17(1): 196.
31. Hoxha B, Hoxha M, Domi E, Gervasoni J, Persichilli S, Malaj V, Zappacosta B, Folic Acid and Autism: A Systematic Review of the Current State of Knowledge. *Cells*, 2021; 10(8): 1976.
32. Reynolds EH, Green R, Valproate and folate: Congenital and developmental risks. *Epilepsy Behav.*, 2020; 108: 107068.
33. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M, Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA.*, 2013; 309(16): 1696-1703.
34. Bjørk MH, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, Gilhus NE, Gissler M, Hálfdánarson Ó, Igland J, Sun Y, Tomson T, Alvestad S, Christensen J, Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. *JAMA Neurol.*, 2022; 79(7): 672-681.
35. Schwingel GB, Fontes-Dutra M, Ramos B, Riesgo R, Bambini-Junior V, Gottfried C, Preventive effects of resveratrol against early-life impairments in the animal model of autism induced by valproic acid. *IBRO Neurosci Rep.*, 2023; 15: 242-251.
36. Majhi S, Kumar S, Singh L, A Review on Autism Spectrum Disorder: Pathogenesis, Biomarkers, Pharmacological and Non-Pharmacological Interventions. *CNS Neurol Disord Drug Targets*, 2023; 22(5): 659-677.

37. Coc LMC, Lacatusu I, Badea N, Penes O, Cobelschi CP, Pop A, Meghea A, Curcumin co-loaded with a lipid mediator in the same nanostructured lipid delivery system. *Farmacia*, 2022; 70(5): 932-943.
38. Nevins JEH, Donovan SM, Snetselaar L, Dewey KG, Novotny R, Stang J, Taveras EM, Kleinman RE, Bailey RL, Raghavan R, Scinto-Madonich SR, Venkatramanan S, Butera G, Terry N, Altman J, Adler M, Obbagy JE, Stoody EE, de Jesus J, Omega-3 Fatty Acid Dietary Supplements Consumed During Pregnancy and Lactation and Child Neurodevelopment: A Systematic Review. *J Nutr.*, 2021; 151(11): 3483-3494.
39. D'Antoni S, Schiavi S, Buzzelli V, Giuffrida S, Feo A, Ascone F, Busceti CL, Nicoletti F, Trezza V, Catania MV, Group I and group II metabotropic glutamate receptors are upregulated in the synapses of infant rats prenatally exposed to valproic acid. *Psychopharmacology (Berl.)*, 2023; 240(12): 2617-2629.
40. Gidaya NB, Lee BK, Burstyn I, Michael Y, Newschaffer CJ, Mortensen EL, *In utero* Exposure to β-2-Adrenergic Receptor Agonist Drugs and Risk for Autism Spectrum Disorders. *Pediatrics*, 2016; 137(2): e20151316.
41. Nagata A, Masumoto T, Nishigori H, Nakagawa T, Otani S, Kurozawa Y, Japan Environment and Children's Study Group, Neurodevelopmental Outcomes Among Offspring Exposed to Corticosteroid and B2-Adrenergic Agonists *In Utero*. *JAMA Netw Open*, 2023; 6(10): e2339347.
42. Seker A, Qirko-Gurakuqi A, Tabaku M, Javate KRP, Rathwell I, Maternal atopic conditions and autism spectrum disorder: a systematic review. *Eur Child Adolesc Psychiatry*, 2023.
43. Hálfdánarson Ó, Cohen JM, Karlstad Ø, Cesta CE, Bjørk MH, Håberg SE, Einarsdóttir K, Furu K, Gissler M, Hjellvik V, Kieler H, Leinonen MK, Nørgaard M, Öztürk Essen B, Ulrichsen SP, Reutfors J, Zoega H, Antipsychotic use in pregnancy and risk of attention/deficit-hyperactivity disorder and autism spectrum disorder: a Nordic cohort study. *Evid Based Ment Health*, 2022; 25(2): 54-62.
44. Andrade C, Attention-Deficit/Hyperactivity Disorder, Autism Spectrum Disorder, and Other Neurodevelopmental Outcomes Associated with Antipsychotic Drug Exposure During Pregnancy. *J Clin Psychiatry*, 2022; 83(3): 22f14529.
45. Straub L, Hernández-Díaz S, Bateman BT, Wisner KL, Gray KJ, Pennell PB, Lester B, McDougle CJ, Suarez EA, Zhu Y, Zakoul H, Mogun H, Huybrechts KF, Association of Antipsychotic Drug Exposure in Pregnancy With Risk of Neurodevelopmental Disorders: A National Birth Cohort Study. *JAMA Intern Med.*, 2022; 182(5): 522-533.
46. Härnryd C, Bjerkenstedt L, Björk K, Gullberg B, Oxenstierna G, Sedvall G, Wiesel FA, Wik G, Aberg-Wistedt A, Clinical evaluation of sulpiride in schizophrenic patients--a double-blind comparison with chlorpromazine. *Acta Psychiatr Scand Suppl.*, 1984; 311: 7-30.
47. Chan AYL, Gao L, Howard LM, Simonoff E, Coghill D, Ip P, Lau WCY, Taxis K, Wong ICK, Man KKC, Maternal Benzodiazepines and Z-Drugs Use during Pregnancy and Adverse Birth and Neurodevelopmental Outcomes in Offspring: A Population-Based Cohort Study. *Psychother Psychosom.*, 2023; 92(2): 113-123.
48. Vigod SN, Wilson CA, Howard LM, Depression in pregnancy. *BMJ.*, 2016; 352: i1547.
49. Vigod SN, Dennis CL, Benzodiazepines and the Z-Drugs in Pregnancy—Reasonably Reassuring for Neurodevelopment But Should We Really Be Using Them?. *JAMA Netw Open*, 2019; 2(4): e191430.
50. Ge GM, Cheung ECL, Man KKC, Ip P, Leung WC, Li GHY, Kung AWC, Cheung CL, Wong ICK, Association of maternal levothyroxine use during pregnancy with offspring birth and neurodevelopmental outcomes: a population-based cohort study. *BMC Med.*, 2022; 20(1): 390.
51. Getahun D, Jacobsen SJ, Fassett MJ, Wing DA, Xiang AH, Chiu VY, Peltier MR, Association between maternal hypothyroidism and autism spectrum disorders in children. *Pediatr Res.*, 2018; 83(3): 580-588.
52. Brown AS, Surcel HM, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Bao Y, Sourander A, Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. *Prog Neuropsychopharmacol Biol Psychiatry*, 2015; 57: 86-92.
53. Andersen SL, Andersen S, Vestergaard P, Olsen J, Maternal Thyroid Function in Early Pregnancy and Child Neurodevelopmental Disorders: A Danish Nationwide Case-Cohort Study. Thyroid, 2018; 28(4): 537-546.
54. Sørensen MJ, Grønborg TK, Christensen J, Parner ET, Vestergaard M, Schendel D, Pedersen LH, Antidepressant exposure in pregnancy and risk of autism spectrum disorders. *Clin Epidemiol.*, 2013; 5: 449-459.
55. Brennan PA, Dunlop AL, Croen LA, Avalos LA, Salisbury AL, Hipwell AE, Nozadi SS, Sathyanarayana S, Crum RM, Musci R, Li M, Li X, Mansolf M, O'Connor TG, Elliott AJ, Ghildayal N, Lin PD, Sprowles JLN, Stanford JB, Bendixsen C, Ozonoff S, Lester BM, Shuster CL, Huddleston KC, Posner J, Paneth N, Prenatal Antidepressant Exposures and Autism Spectrum Disorder or Traits: A Retrospective, Multi-Cohort Study. *Res Child Adolesc Psychopathol.*, 2023; 51(4): 513-527.
56. Leshem R, Bar-Oz B, Diav-Citrin O, Gbaly S, Soliman J, Renoux C, Matok I, Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) During Pregnancy and the Risk for Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) in the Offspring: A True Effect or a Bias? A Systematic Review & Meta-Analysis. *Curr Neuropharmacol.*, 2021; 19(6): 896-906.
57. Boukhris T, Sheehy O, Mottron L, Bérard A, Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. *JAMA Pediatr.*, 2016; 170(2): 117-124.
58. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C, Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ.*, 2013; 346: f2059.
59. Fatima Z, Zahra A, Ghouse M, Wang X, Yuan Z, Maternal SSRIs experience and risk of ASD in

offspring: a review. *Toxicol Res (Camb.)*, 2018; 7(6): 1020-1028.
60. Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN, Association Between Serotonergic Antidepressant Use During Pregnancy and Autism Spectrum Disorder in Children. *JAMA.*, 2017; 317(15): 1544-1552.
61. Sujan AC, Rickert ME, Öberg AS, Quinn PD, Hernández-Díaz S, Almqvist C, Lichtenstein P, Larsson H, D'Onofrio BM, Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. *JAMA.*, 2017; 317(15): 1553-1562.
62. Grigoriadis S, Graves L, Peer M, Mamisashvili L, Tomlinson G, Vigod SN, Dennis CL, Steiner M, Brown C, Cheung A, Dawson H, Rector NA, Guenette M, Richter M, Maternal Anxiety During Pregnancy and the Association With Adverse Perinatal Outcomes: Systematic Review and Meta-Analysis. *J Clin Psychiatry*, 2018; 79(5): 17r12011.
63. Ji Y, Azuine RE, Zhang Y, Hou W, Hong X, Wang G, Riley A, Pearson C, Zuckerman B, Wang X, Association of Cord Plasma Biomarkers of *In Utero* Acetaminophen Exposure With Risk of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder in Childhood. *JAMA Psychiatry*, 2020; 77(2): 180-189.
64. Alemany S, Avella-García C, Liew Z, García-Esteban R, Inoue K, Cadman T, López-Vicente M, González L, Riaño Galán I, Andiarena A, Casas M, Margetaki K, Strandberg-Larsen K, Lawlor DA, El Marroun H, Tiemeier H, Iñiguez C, Tardón A, Santa-Marina L, Júlvez J, Porta D, Chatzi L, Sunyer J, Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. *Eur J Epidemiol.*, 2021; 36(10): 993-1004.
65. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH, Prenatal paracetamol exposure and child neurodevelopment: A review. *Horm Behav.*, 2018; 101: 125-147.
66. Masarwa R, Levine H, Gorelik E, Reif S, Perlman A, Matok I, Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. *Am J Epidemiol.*, 2018; 187(8): 1817-1827.
67. Nilsen K, Staff AC, Krogsrud SK, Paracetamol use in pregnancy: Not as safe as we may think?. *Acta Obstet Gynecol Scand.*, 2023; 102(6): 652-656.
68. Committee on Obstetric Practice, Committee Opinion No. 713: Antenatal Corticosteroid Therapy for Fetal Maturation. *Obstet Gynecol.*, 2017; 130(2), e102-e109.
69. Sweet DG, Carnielli VP, Greisen G, Hallman M, Klebermass-Schrehof K, Ozek E, Te Pas A, Plavka R, Roehr CC, Saugstad OD, Simeoni U, Speer CP, Vento M, Visser GHA, Halliday HL, European Consensus Guidelines on the Management of Respiratory Distress Syndrome: 2022 Update. *Neonatology*, 2023; 120(1): 3-23.
70. Lin YH, Lin CH, Lin MC, Hsu YC, Hsu CT, Antenatal Corticosteroid Exposure Is Associated with Childhood Mental Disorders in Late Preterm and Term Infants. *J Pediatr.*, 2023; 253: 245-251.e2.
71. Ninan K, Gojic A, Wang Y, Asztalos EV, Beltempo M, Murphy KE, McDonald SD, The proportions of term or late preterm births after exposure to early antenatal corticosteroids, and outcomes: systematic review and meta-analysis of 1.6 million infants. *BMJ.*, 2023; 382: e076035.
72. Andreasen JJ, Tobiasen BB, Jensen RC, Boye H, Jensen TK, Bilenberg N, Andersen MS, Glintborg D, Maternal cortisol in 3rd trimester is associated with traits of neurodevelopmental disorder in offspring. Odense Child Cohort. *Psychoneuroendocrinology*, 2023; 154: 106293.
73. Wilson A, Hodgetts-Morton VA, Marson EJ, Markland AD, Larkai E, Papadopoulou A, Coomarasamy A, Tobias A, Chou D, Oladapo OT, Price MJ, Morris K, Gallos ID, Tocolytics for delaying preterm birth: a network meta-analysis (0924). *Cochrane Database Syst Rev.*, 2022; 8(8): CD014978.
74. van Winden T, Klumper J, Kleinrouweler CE, Tichelaar MA, Naaktgeboren CA, Nijman TA, van Baar AL, van Wassenaer-Leemhuis AG, Roseboom TJ, Van't Hooft J, Roos C, Mol BW, Pajkrt E, Oudijk MA, Effects of tocolysis with nifedipine or atosiban on child outcome: follow-up of the APOSTEL III trial. *BJOG.*, 2020; 127(9): 1129-1137.
75. Chae J, Cho GJ, Oh MJ, Park K, Han SW, Choi SJ, Oh SY, Roh CR, *In utero* exposure to ritodrine during pregnancy and risk of autism in their offspring until 8 years of age. *Sci Rep.*, 2021; 11(1): 1146.
76. Altay MA, Görker I, Aslanova R, Bozatlı L, Turan N, Kaplan PB, Association between Beta-Sympathomimetic Tocolysis and Risk of Autistic Spectrum Disorders, Behavioural and Developmental Outcome in Toddlers. *Open Access Maced J Med Sci.*, 2017; 5(6): 730-735.
77. Nitschke AS, do Valle HA, Vallance BA, Bickford C, Ip A, Lanphear N, Lanphear B, Weikum W, Oberlander TF, Hanley GE, Association between prenatal antibiotic exposure and autism spectrum disorder among term births: a population-based cohort study. *Paediatr Perinat Epidemiol.*, 2023; 37(6): 516-526.
78. Kenyon S, Pike K, Jones DR, Brocklehurst P, Marlow N, Salt A, Taylor DJ, Childhood outcomes after prescription of antibiotics to pregnant women with spontaneous preterm labour: 7-year follow-up of the ORACLE II trial. *Lancet*, 2008; 372(9646): 1319-1327.
79. Almasri J, Barazi A, King KS, Walther-Antonio MRS, Wang Z, Murad MH, Murray JA, Absah I, Peripartum Antibiotics Exposure and the Risk of Autoimmune and Autism Disorders in the Offspring. *Avicenna J Med.*, 2021; 11(3): 118-125.
80. Qiu C, Lin JC, Shi JM, Chow T, Desai VN, Nguyen VT, Riewerts RJ, Feldman RK, Segal S, Xiang AH, Association Between Epidural Analgesia During Labor and Risk of Autism Spectrum Disorders in Offspring. *JAMA Pediatr.*, 2020; 174(12): 1168-1175.
81. Ren T, Zhang J, Yu Y, Pedersen LH, Wang H, Li F, Henriksen TB, Li J, Association of labour epidural

analgesia with neurodevelopmental disorders in offspring: a Danish population-based cohort study. *Br J Anaesth.*, 2022; 128(3): 513-521.
82. Butwick AJ, Abrams DA, Wong CA, Epidural labour analgesia and autism spectrum disorder: is the current evidence sufficient to dismiss an association?. *Br J Anaesth.*, 2022; 128(3): 393-398.
83. Król JW, Stanirowski PJ, Mazanowska N, Majewska A, Wielgoś M, Bomba-Opoń D, Is There an Association between the Use of Epidural Analgesia during Labor and the Development of Autism Spectrum Disorder in the Offspring?-A Review of the Literature. *Int J Environ Res Public Health*, 2022; 19(12): 7202.
84. Wang X, Li J, Liu D, Effects of epidural analgesia exposure during parturition on autism spectrum disorder in newborns: A systematic review and meta-analysis based on cohort study. *Front Psychiatry*, 2022; 13: 974596.
85. Wang LW, Lin HC, Tsai ML, Chang YT, Chang YC, Preterm birth and small for gestational age potentiate the association between maternal hypertensive pregnancy and childhood autism spectrum disorder. *Sci Rep.*, 2023; 13(1): 9606.
86. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, McKeague IW, Sundvall J, Surcel HM, Elevated maternal C-reactive protein and autism in a national birth cohort. Mol Psychiatry, 2014; 19(2): 259-264.
87. Liu X, Liu H, Gu N, Pei J, Lin X, Zhao W, Preeclampsia promotes autism in offspring *via* maternal inflammation and fetal NFκB signaling. *Life Sci Alliance*, 2023; 6(8): e202301957.
88. Curran EA, O'Keeffe GW, Looney AM, Moloney G, Hegarty SV, Murray DM, Khashan AS, Kenny LC, Exposure to Hypertensive Disorders of Pregnancy Increases the Risk of Autism Spectrum Disorder in Affected Offspring. *Mol Neurobiol.*, 2018; 55(7): 5557-5564.
89. Price CS, Thompson WW, Goodson B, Weintraub ES, Croen LA, Hinrichsen VL, Marcy M, Robertson A, Eriksen E, Lewis E, Bernal P, Shay D, Davis RL, DeStefano F, Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism. *Pediatrics*, 2010; 126(4): 656-664.
90. DeStefano F, Price CS, Weintraub ES, Increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines is not associated with risk of autism. *J Pediatr.*, 2013; 163(2): 561-567.
91. Becerra-Culqui TA, Getahun D, Chiu V, Sy LS, Tseng HF, Prenatal Influenza Vaccination or Influenza Infection and Autism Spectrum Disorder in Offspring. *Clin Infect Dis.*, 2022; 75(7): 1140-1148.
92. Ludvigsson JF, Winell H, Sandin S, Cnattingius S, Stephansson O, Pasternak B, Maternal Influenza A(H_1N_1) Immunization During Pregnancy and Risk for Autism Spectrum Disorder in Offspring. *Ann Intern Med.*, 2020; 173(8): 597-604.
93. Becerra-Culqui TA, Getahun D, Chiu V, Sy LS, Tseng HF, Prenatal Tetanus, Diphtheria, Acellular Pertussis Vaccination and Autism Spectrum Disorder. *Pediatrics*, 2018; 142(3): e20180120.
94. Varlas VN, Borș RG, Năsui BA, Mititelu M, Gheorghi ARA, Pop AL, Key points in fertility preservation treatment strategies during COVID-19 pandemic. An update on pharmacological therapies. *Farmacia*, 2021; 69(2): 189-199.
95. Jorgensen SCJ, Drover SSM, Fell DB, Austin PC, D'Souza R, Guttmann A, Buchan SA, Wilson SE, Nasreen S, Schwartz KL, Tadrous M, Wilson K, Kwong JC, Newborn and Early Infant Outcomes Following Maternal COVID-19 Vaccination During Pregnancy. *JAMA Pediatr.*, 2023; 177(12): 1314-1323.