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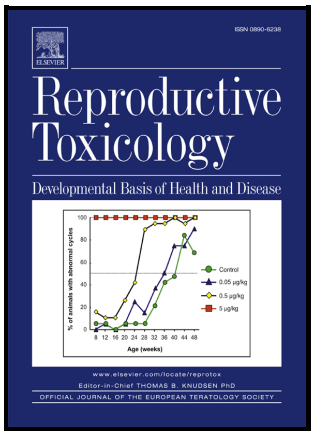

Folate in maternal Rheumatoid Arthritis-filial Autism Spectrum Disorder continuum

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Title

Folate in maternal Rheumatoid Arthritis-filial Autism Spectrum Disorder continuum

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Abbreviations

RA: Rheumatoid Arthritis; ASDs: Autism Spectrum Disorders; RFC: Reduced Folate Carrier; PCFT: Proton-Coupled Folate Transporter; FPGS: Folylpolyglutamate Synthase; GGH: γ-Glutamyl Hydrolase; FR: Folate Receptor; DHF: Dihydrofolate; THF: Tetrahydrofolate; DHFR: Dihydrofolate Reductase; MTHFR: 5,10-MethyleneTHF Reductase; SHMT: Serine-hydroxymethyltransferase; MTR: Methionine Synthase; MTRR: Methionine Synthase Reductase; MAT: Methionine Adenosyltransferase; SAHH: SAH hydrolase;SAM: S-Adenosyl-Methionine; SAH: S-Adenosyl-Homocysteine; tHcy: total homocysteine; MTX: Methotrexate; SSZ: Sulfasalazine; GART: Glycinamide Ribonucleotide Formyltransferase; ATIC: AICAR-TF/IMP Cyclohydrolase; ROS: Reactive Oxygen Species; FRβ: Folate Receptor β; DMARD: Disease-modifying antirheumatic drugs; MTXGlu: MTX-Polyglutamates; *TYMS*: Thymidylate Synthase; NTDs: Neural Tube Defects; FA: Folic Acid; CSF: Cerebrospinal Fluid; 5MTHF: L-5-Methyltetrahydrofolate; BBB: Blood Brain Barrier; FRAA: Folate Receptor Alpha Autoantibody; MAPK: Mitogen Activated Protein Kinase; GSH: Glutathione; TS: Thymidylate Synthase.

Abstract:

Rheumatoid Arthritis (RA) is an inflammatory autoimmune disease that affects women three times more than men. Epidemiological studies found that the incidence of Autism Spectrum Disorder (ASD), a neurological and developmental disorder, in children born to mothers suffering from RA is higher compared with the control population. Considering that the pathogenesis of ASD could be traced back to pregnancy and in uterine conditions, and the evidence of reduced folate levels in the brain of ASD-affected children, we aimed to study the role of folate, as an important nutritional factor during pregnancy, in associating maternal RA to ASD development in the offspring. Folate balance during RA could be influenced twice, initially during the immune activation associated with disease onset, and later during the treatment with anti-folate drugs, with a potential consequence of folate deficiency. Maternal folate deficiency during pregnancy could increase homocysteine levels,

oxidative stress, and global DNA hypomethylation, all known risk factors in ASD pathogenesis. These effects could be intensified by genetic polymorphisms in the folate system, which were also found as genetic risk factors for both RA and ASD. The available evidence suggests that folate level as an important factor during RA, pregnancy and ASD could have pathological and therapeutical significance and should be carefully monitored and investigated in the RA-pregnancy-ASD axis.

Keywords:

Rheumatoid Arthritis, Autism Spectrum Disorders, Folate, Pregnancy, Genetics

Background

Autoimmune diseases, as one of the leading causes of death and disability, have a prevalence higher than 5% (1). Most autoimmune diseases are more common in females than males and could occur during the reproductive age (1,2). Epidemiological studies have identified a positive association between maternal autoimmune diseases and neurodevelopmental disorders in the offspring (3,4). This is further supported by animal studies demonstrating that maternal immune activation could affect normal brain development and function in littermates (5–7). Accordingly, a positive correlation between maternal Rheumatoid Arthritis (RA) and an increased risk of filial Autism Spectrum Disorders (ASDs) has been identified (8,9) (Figure 1). RA is one of the most common systemic autoimmune diseases during which autoantibodies, increased circulating immune cells, and inflammatory cytokines are activated (10). ASD is a neurodevelopmental disorder with a global prevalence of approximately 1–2% and is characterized by impairments in social interaction and communication, restricted interests, and repetitive behaviours (11).

There are at least two possible explanations for the increased risk of ASD in the offspring of women suffering from RA. One is the disturbance of the intrauterine environment caused by the activated maternal immune system (12,13) which through affected placenta induces alterations in brain morphologic features and leads to atypical foetal brain development accompanied by future behavioural deficits and risk of later development of ASD (14,15). The other relates to the inheritance of genetic risk loci such as human leukocyte antigen (HLA)-DRB1*04A ((16–19), C4B null allele (20), PTEN, MET, and RELN (21,22) which predispose the mother to systemic immune dysregulation and the fetus to neurodevelopmental impairment in the brain (8,9,23,24).

By considering several pieces of evidence, such as a) the prevalence of RA is three times higher in women compared to men (25), b) the shift of childbearing towards later ages (26), c) the observed increasing number of children being born to mothers with RA (27,28), and d) the growing incidence of ASD (29), having more autistic children being born to mothers with RA is increasingly foreseen. Therefore, it is important to study the different connecting aspects of maternal RA to filial ASD. Nutrition is an essential aspect of a healthy lifestyle and its changes could have pathological, consequential, or therapeutical significance. Folate is one of the essential vitamins for health and development, and its disturbance has been associated with both RA (30,31) and ASD (32,33). Folate is necessary for normal cell metabolism and homeostasis especially during periods of rapid growth like pregnancy, as all pregnant women should get 600 µg of folic acid per day in order to prevent some birth defects such as anencephaly and spina bifida (34). In this study, we reviewed the role of folate, as an important player during RA, pregnancy, and ASD, in associating maternal RA with ASD in offspring.

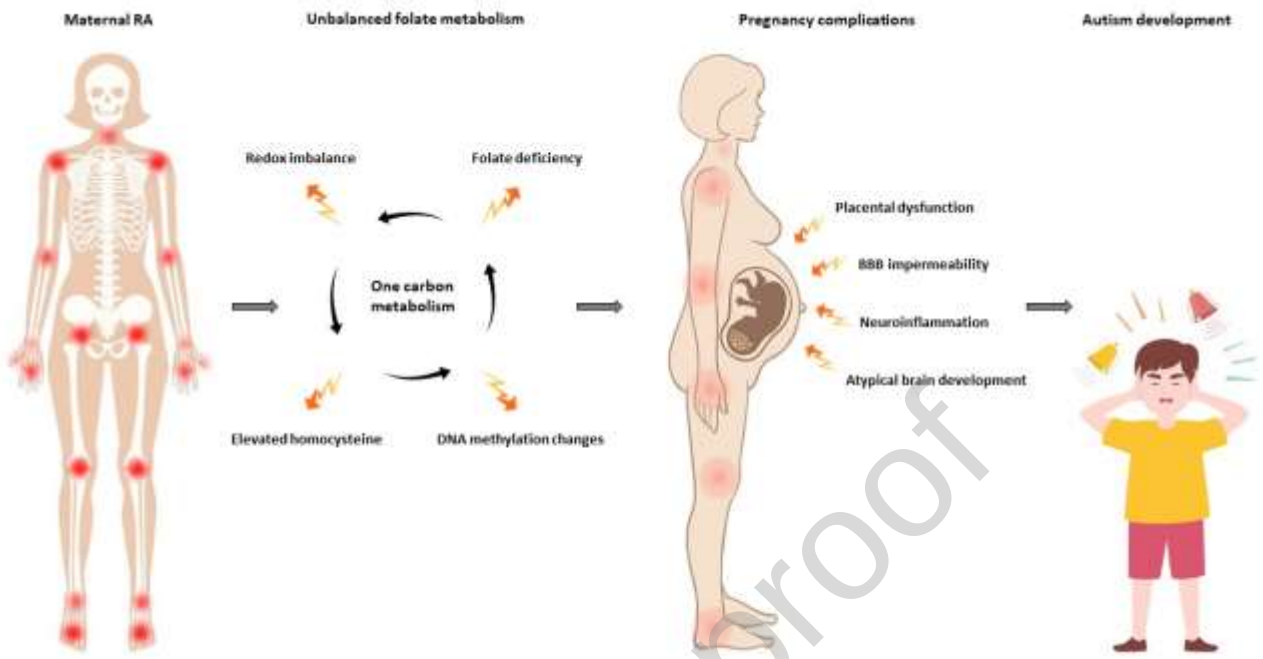

Figure 1. Maternal RA-Folate Status-ASD Axis. Maternal RA could influence folate status and affect pregnancy outcomes, including increasing the risk of ASD. BBB: Blood Brain Barrier (The figure was partially designed by Freepik; www.freepik.com).

Folate

Folate, also known as vitamin B9, plays a fundamental role in maintaining normal metabolism, regulation, division and homeostasis in human cells by providing one-carbon units (35). Once folate ingested, cellular absorption starts primarily in the duodenum and jejunum mainly by folate-specific entries named reduced folate carrier (RFC) and proton-coupled folate transporter (PCFT) (36). After entering the cell, two enzymes folylpolyglutamate synthase (FPGS) and γ-glutamyl hydrolase (GGH) maintain intracellular folate homeostasis. Through the polyglutamylation process, FPGS adds glutamate residues to the folate molecules, which promotes intracellular folate retention and a steady supply for folate-dependent reactions. On the other hand, GGH hydrolyzes polyglutamylated folate into monoglutamylated for export from the cell, as it is the only form of the folate available in circulation (37) and through folate receptors (FRs) enters the cells (37,38). In the cell, through two reduction steps in the folate cycle, polyglutamated folate is converted first to dihydrofolate (DHF) and then tetrahydrofolate (THF) by the dihydrofolate reductase (DHFR) enzyme. Afterward, 5,10-methyleneTHF reductase (MTHFR) converts THF to 5-methylTHF (5MTHF). By the activity of methionine synthase/methionine synthase reductase (MTR/MTRR) enzymes, 5-methylTHF could be recycled to THF and methionine. In the methionine cycle, subsequently, methionine is used to produce S-Adenosyl-methionine (SAM), S-adenosyl-homocysteine (SAH) and homocysteine. SAM is the main cellular methyl donor for DNA, RNA, protein, and phospholipid methylation (39) (Figure 2).

Through these cycles, folates function as coenzymes in methionine regeneration, transsulfuration pathway, thymidine production, de novo purine synthesis, and influence the intracellular pools of glutathione, serine, glycine, and NADPH. Folates are necessary for nucleic acid synthesis,

transmethylation pathways, and maintaining a redox state, and therefore an adequate supply of folates is essential for health and normal development (35,40,41). Folate supply is primarily determined by the amount and bioavailability of dietary intake (35). However, malabsorption (e.g. due to alcoholism), an increased requirement (e.g. during pregnancy), medications (e.g. anti-folate drugs) (42), and polymorphisms in genes encoding folate enzymes and receptors (43) may all have an impact on its effective bioavailability. The classical symptom of folate deficiency is megaloblastic anemia (44). During folate deficiency, reduced serum or plasma folate levels and decreased red blood cell (RBC) folate occur (44) and all of the reactions in which folate is involved are compromised to a varying degree, as could be marked by the accumulation of various substrates and metabolic intermediates (35) such as elevated serum or plasma total homocysteine (tHcy) concentrations (hyperhomocysteinemia) (35) or alteration in DNA methylation (45) and oxidative stress (46), which all are associated with deleterious consequences (35,47,48).

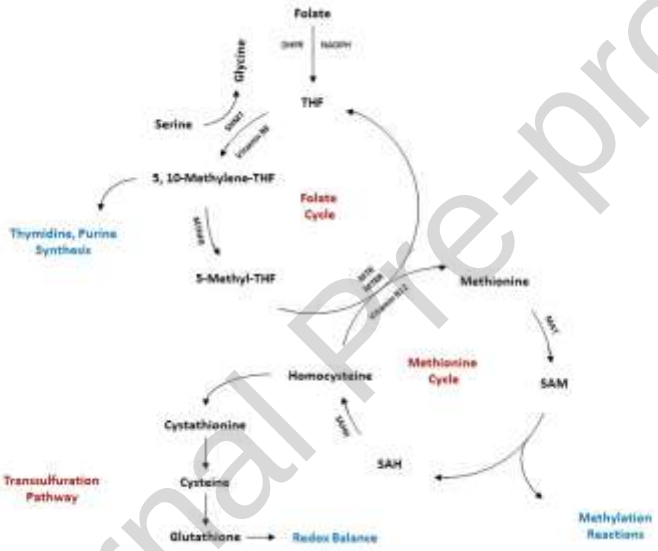

Figure 2. One carbon metabolism. DHFR: Dihydrofolate Reductase; THF: Tetrahydrofolate; SHMT: Serine Hydroxymethyltransferase; MTHFR: 5,10-MethyleneTHF Reductase; MTR: Methionine Synthase; MTRR: Methionine Synthase Reductase; MAT: Methionine Adenosyltransferase; SAHH: SAH hydrolase; SAM: S-Adenosyl-Methionine; SAH: S-Adenosyl-Homocysteine;

Folate in RA

A complex interaction between environmental and genetic factors triggers RA pathogenesis during which aberrant activation of innate and adaptive immune systems occurs. This immune activation is characterized by a breakdown of immune tolerance, presenting autoantigen by T cells, activation of dendritic cells, neutrophils, and macrophages, B cell activation and autoantibody production, and release of inflammatory cytokines, ending in synovitis followed by joint and bone damage (49,50). During the RA course, the folate supply undergoes two significant changes, the first during immune activation leading to disease onset, and the second after starting the therapy with first-line drugs, methotrexate (MTX) or sulfasalazine (SSZ).

Immune activation, which is accompanied by proliferation and lymphopoiesis, has an increased need for nucleotide generation that is provided by folate-dependent purine and pyrimidine de novo

biosynthesis, as evidenced by elevated expression of folate-dependent enzymes glycinamide ribonucleotide formyltransferase (GART), DHFR, and AICAR-TF/IMP cyclohydrolase (ATIC) in blood cells of untreated RA patients (30). Since immune activation is associated with the production of reactive oxygen species (ROS) and oxidative stress, increased consumption of tetrahydrofolates, as an *in vivo* antioxidant vitamins, occurs (51) and could diminish blood concentrations of tetrahydrofolate (52,53). Another piece of evidence is the expression of folate receptor β (FRβ) on activated macrophages of RA patients (49), which has been suggested to play a role in delivering folates for biopterin metabolism, which enhances the production of ROS in macrophages (54), or to create a folate-deficient environment for depriving pathogens from nutrients (55), or for involvement in signalling processes (56,57).

Disease-modifying antirheumatic drugs (DMARD) such as MTX and SSZ are well known to interfere with folate metabolism (58). MTX/Folate homeostasis is tightly controlled at several levels, including a) cellular uptake and efflux, b) intracellular metabolism and retention, and c) expression of folate-dependent enzymes (30). MTX, by being structurally similar to folates, acts as a folate antagonist and blocks the activity of the DHFR enzyme, as its affinity for DHFR is approximately 1000 higher than that of folate (59). Moreover, MTX-polyglutamates (MTXGlu) probably inhibit the activity of the thymidylate synthase (TS) enzyme. The activities of DHFR and TS are necessary for de novo biosynthesis of pyrimidines and purines required for DNA replication and cellular proliferation. Accumulation of dihydrofolate polyglutamate and MTXGlu after DHFR inhibition could inhibit the activity of other downstream enzymes such as GART and MTHFR (60,61), which are important in de novo biosynthesis of purine and methylation of DNA, RNA, and proteins (30). On the other hand, SSZ, which is less studied compared with MTX, by inhibiting PCFT-mediated folate transport in the proximal small intestine, interferes with folate absorption (36). In addition, SSZ causes malabsorption of folates by inhibition of DHFR, MTHFR, serine-hydroxymethyltransferase (SHMT) (62), and GGH into the absorbable form (63). In RA patients, to reduce the side effects of MTX and SSZ, due to folate antagonism and malabsorption, folate administration is provided: a weekly dose of 5-10 mg folic acid (FA) in the case of treatment with MTX (64) and only a folate intake recommendation in case of SSZ treatment.

Folate in ASD

Pathogenesis of ASD is the result of gene-environment interactions (65–68). As evidenced by post-mortem and genetic studies, ASD develops because of developmental impairment in the brain affecting the frontal cortex, hippocampus, cerebellum, and amygdaloid nucleus (69). Different cellular, neural, and anatomical processes such as neurogenesis, neuritogenesis, synaptogenesis, neuronal migration, maturation, differentiation, and degeneration are involved in ASD pathogenesis (70–72). Since folate deficiency before or during early pregnancy, i.e. first trimester, is associated with the increased risk of neural tube defects (NTDs) and this risk could be significantly reduced with periconceptional folate supplementation, milder forms of neurodevelopmental disorders like ASD in early childhood could be associated with folate deficiency without being specifically limited to pre-conception and early gestation folate status (73). Folate plays a critical role in brain development as it is required for neurogenesis, neurotrophic factors, gene expression, DNA methylation, and myelin formation (74) and could be explained by its active transport in the placenta and its higher levels in the fetal brain compared with the adult brain (75). Animal studies showed that eliminating folic acid one week before birth is associated with lower brain weight (76) and prenatal folate deficiency is correlated with anxiety-related behaviour (77). Neuropsychiatric conditions such as ASD were found to be correlated with low levels of 5MTHF in cerebrospinal fluid (CSF) (78–80). Low levels of folate in CSF could be caused by: a) insufficient folate intake and absorption, as FA supplementation in autistic children with low levels of 5MTHF in CSF was shown to reduce the ASD symptoms (81); b) inflammation of the blood brain barrier (BBB) which impairs efficient transport of folate to CSF. The choroid plexus and BBB control the transport of folate between blood and CSF (82). BBB has three

major transporters: folate receptor alpha (FR∝), PCFT and RFC (83); c) mutations and polymorphisms in folate transporters and carriers genes (FR∝, PCFT and RFC) and folate metabolizing enzymes (i.e. DHFR, MTHFR, MTR and MTRR); and d) presence of folate receptor alpha autoantibody (FRAA) (31) that inhibits the transfer of folate to the brain, considering that folates are more concentrated in the brain than the plasma and its active import by FRα is crucial (84).

RA-Pregnancy-ASD

The consequences of folate deficiency in RA patients could contribute to elevated serum and plasma homocysteine (85,86), increased oxidative stress (87) and global hypomethylation of DNA (88,89). Patients who began MTX therapy while receiving FA supplementation had lower serum/plasma homocysteine levels (85), increased oxidative stress (90) and normalized DNA methylation (91). RA patients before conception should consult a gynaecologist and a rheumatologist to receive timely medication and meet pregnancy restrictions and requirements. Since MTX is in category X of the FDA, it should be discontinued 3 months before conception, as its active metabolites remain for several months in tissue with a 4 to 10-week median time of being undetectable in red blood cells (92,93). On the other hand, SSZ could be continued during pregnancy while supplemented with FA (94). SSZ can cross the placenta and reach maternal concentrations in the growing fetus (95), and its use is associated with elevated homocysteine (96) and oxidative stress (97).

In addition to folate deficiency, which can directly affect the complex biological pathways such as DNA synthesis and cell division required for embryogenesis, fetal growth and development (98), elevated maternal homocysteine, oxidative stress and DNA hypomethylation could complicate pregnancy outcomes. During placentation, folate is involved in critical processes such as extravillous trophoblast proliferation, invasion of placental trophoblasts, and angiogenesis (99,100). Its deficiency is known to affect placental development, resulting in impaired fetal growth (101) and is considered a risk factor for ASD development (102). Elevated homocysteine may cause atherosclerosis by damaging the endothelial layer and enhancing inflammation (103,104), causing vascular injury in the placenta (105), and also by influencing the permeability of the BBB (106) could impair the transport of nutrients to the developing fetus. Chronic hyperhomocysteinemia, by having proinflammatory effects, could increase IL-6 and IL-1β cytokines in the maternal blood, which could cross the placental barrier and affect the development of the fetal brain (107–109). As evidenced in rat models, elevated Hcy is associated with increased IL-1β, the number of astroglial and microglial cells, and the phosphorylation level of p38 MAPK (mitogen activated protein kinase), indicating the development of neuroinflammatory processes (110,111). Accordingly, neuroinflammation, as an independent risk factor, was observed during ASD (21,112–114) and could be supported by the observation of increased levels of Hcy in the biological fluid of ASD children (115). Oxidative stress is involved in the pathophysiology of RA and could be found in the serum and different tissues of affected individuals (116). Correspondingly, oxidative stress could be raised in the cord blood and the placental tissue (117,118). Regulating oxidative stress in the placenta is vital for maintaining its physiological activities and normal immune microenvironment (119). Oxidative stress is considered another contributing factor to ASD, and folate, by regulating the redox potential of the neurons, could play a preventive role. During cortical folate deficiency, depletion of glutathione (GSH), which is an important antioxidant produced by the transsulfuration pathway, occurs and leads to stimulation of cortical excitability (72,120). RA patients with active disease experience global DNA hypomethylation, which is correlated with the relative degree of expression of folate genes, such as *MTR* and *MTHFR* (91). Treatment with MTX reverses this global DNA hypomethylation (91) and normalizes the up-regulated folate pathway genes (30). It was found that children born to mothers with RA have altered DNA methylation compared with controls (121), and ASD patients, similar to RA patients, experience global DNA hypomethylation (122,123), which could be an implication of folate deficiency (124), as maternal supplementation with FA during pregnancy could change the DNA methylation in genes related to brain development in cord blood (125).

Inheritance of genetic factors related to the folate pathway could be a contributing factor in giving birth to an autistic child in mothers with RA. There are several genetic polymorphisms in folate pathway genes with different effects on folate metabolism. These polymorphisms include *MTHFR* c.677C>T (rs1801133), *MTHFR* c.1298A>C (rs1801131), *MTR* c.2756A>G (rs1805087), *MTRR* c.66A>G (rs1801394), *SLC19A1* c.80A>G (rs1051266), *MTHFD1* c.1958G>A (rs2236225), *DHFR* 19bp del/ins (rs70991108) and a 28bp repeats in *TYMS* gene (rs45445694) (44,126). Some of these variants are identified in both RA and ASD as risk factors, which include *MTHFR* c.677C>T (127–129), *MTR* c.2756A>G (130,131) and *SLC19A1* c.80A>G (132,133). However, the latter polymorphism in the mothers of autistic children is associated with autism in the foetus, not its presence in the foetus itself (133).

Conclusion and future directions

RA and ASD are two distinct pathologies with different pathogenesis pathways. The occurrence of ASD in early childhood and tracking its development back to the in utero period highlights the pregnancy conditions during which folate is considered a fundamental player. Immune activation during RA and its treatment with anti-folate agents could affect the folate cycle twice and leave systemic influences with varying consequences, as signs of folate deficiency are first seen in serum and plasma and later in RBC. This systemic influence, which may be exacerbated by genetic polymorphisms in the folate system, may affect uterine conditions by reducing folate supply for fast growing fetuses, impairing placenta function by elevated homocysteine levels, disrupting the redox balance required for normal pregnancy, and influencing DNA methylation processes. These changes, besides contributing to folate deficiency in the brain, could influence normal development and function of the brain and increase ASD risk. Although folate supplementation in ASD children showed improvement in autistic behaviours, excessive supplementation was also reported to be associated with ASD (134). Therefore, having a precisely balanced and steady supply of folate during pregnancy should be advised, although it is not an easily controllable condition in RA patients. Besides, there are three different commercially available synthetic folates that do not resolve the folate deficiency and its consequences equally, and supplementation with them might have different impacts on both RA treatment and brain development (31,135) as they enter the folate cycle from different points (135). Therefore, it is imperative to conduct further research on the maternal RA-folate status-filial ASD axis by taking into account the genetic background of the folate system in women with RA, carefully monitoring serum/plasma and RBC folate concentration before and during pregnancy, and the type of folate supplemented during both RA treatment and pregnancy. In conclusion, maternal RA as well as folate imbalance as environmental factors could contribute to ASD development in genetically predisposed offspring, and folate interventions might have important impact on ASD prevention and management in the fetus of mothers with RA.

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Declaration of interests

☒The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- Folate balance is important for a healthy pregnancy
- Maternal RA could influence folate balance during disease onset and treatment
- Folate status is associated with ASD
- Maternal RA by influencing folate balance might contribute to filial ASD