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Leucovorin is a More Efficacious Folate Source in High-Risk Pregnancies

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ABSTRACT

Background: Autism spectrum disorder is a multifactorial neurodevelopmental disorder with fetal origins. Insufficient maternal folate due to folate receptor alpha autoantibodies is associated with a higher risk of autism in offspring. Folinic acid (leucovorin) supplementation has been demonstrated to alleviate autism symptoms in children with this antibody. Leucovorin may be a biologically targeted solution to reduce autism spectrum disorder risk and provide a superior folate source to folic acid.

Methods: We here review clinical evidence for leucovorin use in autism and examine its application at the earliest moments in development, throughout the perinatal period.

Observations: A pilot randomized trial by Giorlandino *et al.* (2026), together with emerging clinical data on infertility and preclinical evidence of a negative impact of excess folic acid, suggests that leucovorin may be the optimal folate source for prenatal care. For at risk pregnancies, where maternal folate receptor autoantibodies are present, standard folic acid supplementation resulted in 60% of births later diagnosed as autistic, while those using leucovorin resulted in 10% diagnosed autistic.

Conclusion: This striking difference is evidence of the importance of the appropriate form of folate for perinatal care, with leucovorin proving the safer option, and perhaps the optimal choice when maternal folate receptor autoantibodies are present.

Introduction

AUTISM AND FOLATE

Autism spectrum disorder (ASD) is a multifactorial neurodevelopmental condition with fetal origins.[1] Folate is essential for early brain development, and inadequate maternal folate status has been associated with a higher risk of ASD in offspring. Interest in this relationship has expanded from prevention to treatment, with recent studies evaluating whether folate supplementation, particularly folinic acid, may improve clinical outcomes in children with ASD.[2–4] The biological plausibility of this association is strengthened by folate's central role in one-carbon metabolism, DNA synthesis, methylation, and epigenetic regulation. These pathways are critical for neurodevelopment and may help explain why folate-related disturbances have been implicated in ASD pathophysiology.[5]

Folate is required for neural tube closure during embryogenesis, a process completed within the first month of pregnancy. Deficiency during this period is a well-established risk factor for neural tube defects such as spina bifida and anencephaly. Beyond neural tube formation, folate supports neuronal proliferation, migration, and synaptogenesis during early brain development.[6–8] Experimental studies in rodents indicate that maternal folate deficiency can impair neurogenesis, alter brain structure, and produce behavioral abnormalities resembling ASD, including reduced social interaction and increased repetitive behaviors.[9] These findings support the view that folate availability during gestation is important not only for structural neural development but also for later neurobehavioral outcomes.

Epidemiological studies further support an association between maternal folate status and ASD risk. Low maternal folate levels and lack of periconceptional folic acid supplementation have both been linked to increased ASD risk in offspring. In a large Norwegian cohort, maternal folic acid use around conception was associated with a lower risk of autistic disorder in children.[10] A subsequent meta-analysis also reported that maternal folic acid supplementation was associated with a significant reduction in ASD risk.[11] Although observational findings cannot establish causality, the consistency of these data across populations suggests that adequate periconceptional folate intake may contribute to favorable neurodevelopmental outcomes.

Mechanistically, folate is a major methyl donor in DNA methylation, a key epigenetic process regulating gene expression during brain development. Alterations in DNA methylation have been described in ASD, including dysregulated expression of genes involved in synaptic signaling and neurodevelopment. Folate deficiency may also increase homocysteine concentrations, which are potentially neurotoxic and may interfere with neuronal migration, synapse formation, and myelination. Elevated maternal homocysteine during gestation has been associated with a greater risk of neurodevelopmental disorders in offspring, further implicating disrupted one-carbon metabolism in ASD risk.[12] In animal models, maternal folate supplementation has been shown to reverse methylation abnormalities and improve behavioral deficits in offspring exposed to environmental risk factors for ASD.[9] These findings suggest that folate may influence ASD risk and phenotype through converging effects on genetic stability, methylation, and neurodevelopmental programming.

More recent clinical studies have examined folate as a potential therapeutic intervention in ASD. High-dose folinic acid has shown promise in improving core ASD symptoms, particularly in children with mitochondrial dysfunction or folate receptor autoantibodies.[2,3,13] These subgroup findings are especially relevant because they suggest that response to treatment may depend on underlying metabolic or immune-related abnormalities. Taken together, current evidence supports a role for folate in both the prenatal origins of ASD and the possible modulation of symptoms after diagnosis. Future research should prioritize individualized approaches

guided by genetic, metabolic, and immunologic profiling to identify children most likely to benefit from folate-based interventions.

PERICONCEPTIONAL FOLATE AND ASD RISK

Previous work has indicated that the periconceptional period and first trimester are the most critical windows for folate exposure in relation to ASD risk.[7,13–17] Large cohort and case-control studies suggest that folic acid supplementation initiated before conception and continued through early pregnancy is associated with a lower risk of ASD in offspring.[13,14,16,17] In the Norwegian Mother and Child Cohort Study, maternal folic acid use from four weeks before to eight weeks after conception was associated with a 40–45% reduction in risk of autistic disorder. Similarly, a meta-analysis found that folic acid supplementation during pregnancy was associated with a significant reduction in ASD risk. These findings support the view that adequate folate exposure during early gestation may be important for optimal neurodevelopment.[13–17]

The first month of pregnancy is particularly sensitive to folate insufficiency because neural tube formation and closure occur during this interval. Folate is therefore essential not only for preventing neural tube defects but also potentially for reducing ASD risk. Evidence also suggests that uninterrupted supplementation across the periconceptional and prenatal periods may provide the greatest protective effect. Women who did not supplement during either period appear to have had the highest risk of having a child with ASD. This pattern reinforces the importance of early initiation and sustained use of folate-containing supplements during pregnancy.

Some evidence suggests that the specific form of folate may be clinically relevant. In two women with folate receptor autoantibodies and a prior child with ASD, periconceptional folinic acid at 7.5 mg/day continued throughout gestation was associated with neurotypical development in the offspring at three years of age. These observations raise the possibility that folinic acid may be preferable in selected high-risk groups, particularly where folate transport or metabolism is impaired. However, this evidence remains limited and should be interpreted cautiously until supported by larger studies.

There is also emerging evidence that maternal folate status may follow a U-shaped association with ASD risk, such that both low and excessively high folate levels could be associated with increased risk, while moderate intake appears most favorable. This risk with high folate appears to apply only with folic acid and not with folinic acid, as the folinic acid study did not show a high-folate risk. This seems to indicate that supplements with folic acid are not warranted, while supplementation with leucovorin would be the safe choice if there is may be an autism risk in the pregnancy. Overall, timely folate supplementation has a preventive role in neurodevelopmental disorders, and for at risk pregnancies a reduced folate (such as leucovorin, a natural form of folate) diminishes risk while oxidized folate (folic acid, a synthetic form of folate) appears to increase neurodevelopmental disorder risk.[7,14–18]

Maternal folate intake appears to be most important during a critical periconceptional and early gestational window, beginning at least 1 month before conception and continuing through the first trimester of pregnancy. This period coincides with neural tube closure and early brain development, when folate-dependent pathways are especially important for normal fetal neurodevelopment. It is now becoming clear that while the first months are critical for neural tube formation and essential aspect of nervous system formation, subsequent months in the pregnancy may have critical periods during which neurotypical development cannot proceed apace unless adequate natural folate is available.[13,14,16–21]

CLINICAL EVIDENCE THAT GESTATIONAL NATURAL FOLATE IS KEY TO REDUCING AUTISM

In this light, the clinical trial reported by Giorlandino et al[22] builds on their previous study indicating that for pregnancies at risk for autism, prenatal supplementation with calcium folinate (leucovorin) is a much more efficacious source of folate than folic acid, minimizing autism development in these at

risk pregnancies.[18,22] Their previous study has been also been replicated by another group, revealing the same finding that women who have an autistic child and are put on leucovorin for a subsequent pregnancy eliminated the risk for autism in the second child, with no children in either study (n=2 and n=7) diagnosed for developmental disorders by age 3.[18,23]

Leucovorin (folinic acid, calcium folinate) has emerged as a promising alternative to folic acid for pregnancy, particularly in women with folate receptor alpha autoantibodies (FRAA) and those with folate metabolism polymorphisms. We here examine the pilot randomized trial by Giorlandino *et al.* (2026)[22] in FRAA-positive pregnancies alongside clinical observations with infertility and preclinical data on excess folic acid exposure. In the trial, calcium folinate supplementation, compared with folic acid, was associated with markedly lower autism spectrum disorder (ASD) incidence, reduced ASD symptom severity, and higher Bayley-4 cognitive scores in offspring, despite a small sample size. Case series in women with *MTHFR* polymorphisms and infertility suggest that switching from folic acid to a reduced folate (folinic acid or methylfolate) can restore fertility and lead to successful pregnancies, highlighting the form of folate as a modifiable determinant of reproductive outcome. Preclinical work further indicates that excess prenatal folic acid can alter cortical DNA methylation and gene expression networks, raising concern that high-dose folic acid may perturb brain development in susceptible populations. Together, these converging lines of evidence support a shift from a one-size-fits-all folic acid paradigm toward precision folate strategies that incorporate FRAA status, genetic background, and folate form, and they motivate the central question of whether leucovorin is a more efficacious folate source for pregnancy in defined high-risk groups.

A BIOMAKER FOR AUTISM RISK IS PARENTAL PRESENCE OF FRAA

Giorlandino *et al.* (2026) intervened along a mechanistically coherent causal chain in which FRAA impair folate receptor-mediated transport across the placenta and blood–brain barrier, causing cerebral folate deficiency despite normal systemic folate.[22] FRAA block folate receptor alpha and diminish 5-methyltetrahydrofolate (5-MTHF) delivery to the fetal brain, a mechanism linked to ASD, infantile-onset cerebral folate deficiency, and related neurodevelopmental syndromes. This follows their 2025 case report of two FRAA positive mothers, each with an earlier child who is ASD. When these mothers took calcium folinate throughout the next pregnancy, the children born had no developmental disabilities at age three.[18]

Folate receptor autoantibodies are substantially more prevalent in ASD children and in mothers of ASD-affected children, defining an immune-mediated endophenotype within the broader ASD spectrum. In ASD children with cerebral folate deficiency, open-label and case series data indicate that approximately two-thirds improve with leucovorin, especially in communication and irritability, and experimental models show that maternal FRAA exposure induces offspring behavioral changes that leucovorin can prevent, supporting a causal role for impaired folate transport.[2,3]

Within this framework, the Giorlandino trial is the first randomized human study to test whether correcting FRAA-related folate transport failure during pregnancy can modify early ASD risk markers instead of treating established ASD postnatally. The results were evident. For FRAA-positive women entering pregnancy, one in ten who took calcium folinate had an ASD diagnosed child, while near two in three who took folic acid had ASD diagnosed children.

PREVENTION SIGNAL IN FRAA-POSITIVE PREGNANCIES

In the trial, 210 women planning pregnancy were screened and 17.1% were found to be FRAA-positive, indicating that this immune risk factor is not rare in the general preconception population. Among the 29 FRAA-positive women who conceived and were randomized, 18 completed follow-up (10 received calcium folinate, 8 received folic acid) with supplementation initiated after pregnancy

confirmation and continued to delivery.[22] Figure 1 provides a visual summary of their study.

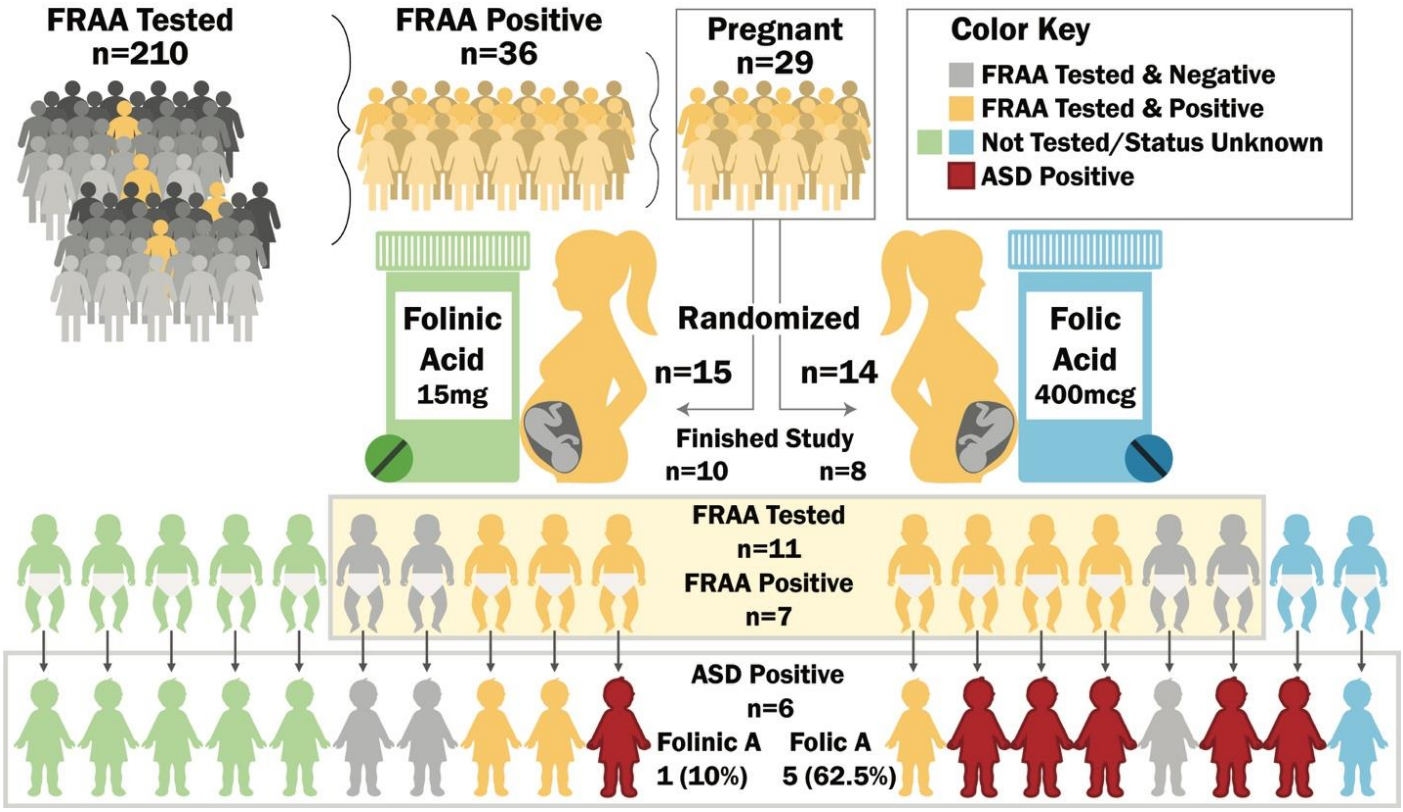

Figure 1. Visual depiction of trial. Half the recruited women received folic acid and half received leucovorin. Children were assessed for autism by 30 months. Of the leucovorin arm, one child was diagnosed ASD for a 10% prevalence, of the folic acid arm, 6 children were diagnosed ASD for a 62.5% prevalence.[22]

The neurodevelopmental signal, although generated from a small per-protocol sample, is striking: ASD incidence at 24-30 months was 10% in the leucovorin group versus 62.5% in the folic acid group (Fisher's exact p = 0.043), corresponding to an odds ratio around 0.07–0.08 and an estimated relative risk reduction of approximately 84%. Learning disorders were less frequent in the calcium folinate arm (10% vs. 50%; odds ratio 0.13), and ASD symptom severity (ADOS-2) was significantly lower while Bayley-4 cognitive scores were substantially higher, each with very large effect sizes (Cohen's d > 1.4–1.5).[22]

The single ASD case in the calcium folinate arm carried a pathogenic *SHANK2* variant, illustrating that folate-immune mechanisms represent one etiological route among many and that pathway correction cannot prevent strongly genetic forms.[8] The clustering of greater ASD severity and lower cognition in the folic acid group, plus a strong negative correlation between ADOS-2 scores and Bayley-4 indices, reinforces a consistent pattern of folate-mediated neuroprotection when FRAA-positive pregnancies receive leucovorin.

WHY LEUCOVORIN MAY OUTPERFORM FOLIC ACID

Standard prenatal folic acid policy assumes intact folate receptor alpha-mediated transport to deliver 5-MTHF to the placenta and choroid plexus, an assumption that fails in FRAA-positive women. In FRAA-positive pregnancies, this receptor pathway is partially blocked or dysfunctional, creating cerebral folate deficiency despite apparently adequate circulating folate, and undermining the protective intent of folic acid.[24,25]

Leucovorin differs from folic acid in two clinically relevant ways: it enters cells through alternative transport systems, notably the reduced folate carrier

and proton-coupled folate transporter, thereby bypassing antibody-blocked folate receptor alpha, and it is already in a reduced, metabolically active form that more directly supports nucleotide synthesis and methylation, processes essential for neurogenesis and synaptogenesis.[5,24,26] Preclinical data indicate that high-dose folic acid can, in some settings, be associated with adverse neurodevelopmental effects, whereas leucovorin shows neuroprotective benefits without the same concern profile, underscoring that the chemical form and transport route of folate are critical variables rather than interchangeable means of raising total folate.[27]

Taken together, these observations suggest that leucovorin may be a more physiologically appropriate folate source in contexts of impaired receptor-mediated transport or altered folate metabolism, including FRAA positivity and certain genetic variants.

REVERSAL OF INFERTILITY BY SWITCHING FOLATE FORM

An underappreciated but highly relevant strand of evidence comes from a clinical series in women with infertility and *MTHFR* polymorphisms, in whom changing the folate form alone appears to restore fertility and enable healthy pregnancies. In a case series by Ledowsky *et al.* (2022), women with diagnosed infertility and *MTHFR* variants who had been using folic acid were transitioned to alternative folate formulations, leucovorin or methylfolate, resulting in successful conceptions and healthy births after prior unsuccessful attempts.[28]

These infertility cases highlight several important principles for pregnancy folate policy: first, that folic acid is neither universally benign nor uniformly effective across genotypes, and second, that correcting the form of folate, without altering the nominal dose, can reverse a clinically significant reproductive phenotype. When viewed alongside FRAA-positive pregnancies in the Giorlandino trial, these data suggest that both immune-mediated and genetically mediated impairments of folate handling may respond more favorably to reduced folate forms, including leucovorin.

From a translational perspective, the infertility experience strengthens the argument for individualized folate formulations, incorporating both autoantibody status and genetic polymorphisms (such as *MTHFR*) into preconception and early-pregnancy risk assessment. It also broadens the rationale for leucovorin and related reduced folates from neurodevelopmental prevention into the domain of reproductive success, positioning folate form as a modifiable determinant of both conception and subsequent fetal brain development.[29]

EXCESS FOLIC ACID AND ALTERED BRAIN DEVELOPMENT

Preclinical work demonstrates that more folic acid is not necessarily better and that high-dose folic acid exposure during vulnerable developmental windows can perturb brain development at the epigenomic and transcriptomic levels. In a recent study, excess prenatal folic acid altered cortical DNA methylation and gene expression networks, indicating that supra-physiologic levels of this synthetic vitamin can reprogram neurodevelopmental trajectories in ways that may not be benign.[27]

A recent clinical study on folic acid use observed that of the 1200 women followed, those with folic acid supplementation in the second trimester had children with higher rates of behavioral problems at age four. Similarly, the women with folic acid supplementation during preconception and second trimester had children with poorer cognitive development.[30]

These findings carry several implications for pregnancy folate policy: they challenge the assumption that increasing folic acid intake is uniformly protective and highlight the importance of using physiological folate forms that align more closely with endogenous metabolism. They also raise the possibility that, in susceptible subgroups, including those with FRAA, *MTHFR* polymorphisms, or other metabolic bottlenecks, high folic acid exposure could create a mismatch between circulating folate and intracellular utilization, amplifying epigenetic perturbations in the developing brain.

Against this backdrop, leucovorin offers a mechanistically attractive alternative: it directly feeds into reduced folate pools, can bypass certain transport and metabolic constraints, and has not been associated with the same pattern of adverse preclinical neurodevelopmental changes at comparable doses. The convergence of preclinical data on excess folic acid with clinical observations of leucovorin's benefits in ASD, FRAA-positive pregnancies, and infertility underscores that the choice of folate form may help avoid iatrogenic risk while maximizing neuroprotection.

TOWARD PRECISION FOLATE STRATEGIES IN PREGNANCY

The Giorlandino trial raises important translational questions for obstetrics, neurology, and nutrition regarding screening and targeted supplementation. FRAA are present in 60–70% of mothers of ASD children according to prior studies and in 17% of women planning pregnancy in this trial, suggesting that FRAA testing could function as a feasible biomarker for stratifying neurodevelopmental risk and guiding folate formulation.[22]

In FRAA-positive pregnancies, leucovorin was associated with lower ASD incidence, reduced ASD symptom severity, and improved cognitive outcomes, while folic acid failed to provide comparable protection. Leucovorin already carries a favorable safety profile in pregnancy when used for hematologic indications. Combined with the infertility case series and preclinical folic acid data, these results support a broader re-examination of folate policy that differentiates by immune status, genotype, and metabolic context rather than relying solely on generic folic acid dosing targets.[22]

Current guidelines, built primarily around neural tube defect prevention, remain anchored to folic acid and do not address the implications of FRAA, *MTHFR* polymorphisms, or potential neurodevelopmental effects of excess folic acid. A next-generation framework would integrate FRAA screening, selected genetic testing, and careful consideration of folate form, favoring leucovorin or other reduced folates in defined high-risk groups, while larger multicenter trials extend and validate the promising pilot signal observed by Giorlandino *et al.* (2026).[22]

INTEGRATING IMMUNOLOGY, GENETICS, AND NUTRITION

Perhaps the most significant conceptual advance from this set of findings is the integration of maternal autoimmunity and genetic variation into prenatal nutrition and ASD prevention paradigms. FRAA-mediated cerebral folate deficiency bridges immunology, metabolism, and neurodevelopment, and the infertility and preclinical folic acid data add genetic and epigenetic dimensions, together defining a multi-layered folate biology that is not addressed by one-size-fits-all folic acid supplementation.

Future work should expand FRAA research beyond ASD to include language delay, learning disorders, and ADHD; harmonize FRAA assays, thresholds, and reporting standards to enable clinical laboratory implementation; and systematically explore timing, dosing, and co-nutrient strategies for leucovorin, including preconception initiation. Additionally, since folinic acid (and methylfolate) are chiral, future tests using levoleucovorin are advised, as this would permit using a dosage half that seen in this trial, by eliminating the inactive isomer. Against this evolving evidence base, the question "Is leucovorin a better folate source for pregnancy?" becomes not merely speculative but empirically grounded, with early data suggesting that, for specific immunologic and genetic subgroups, the answer may well be yes.

Conclusion

Leucovorin, rather than folic acid, appears to be the more biologically effective prenatal folate strategy in pregnancies complicated by folate receptor alpha autoantibodies, because it can bypass the impairment to receptor-mediated transport caused by FRAA and may better support fetal neurodevelopment. The emerging clinical literature supports the possibility that leucovorin could reduce forestall neurodevelopmental risk more effectively than the current standard of folic acid,

while also aligning with evidence that folate pathway abnormalities are relevant to autism susceptibility.

Taken together, these findings strengthen the argument for moving beyond a one-size-fits-all model of perinatal folate supplementation and toward biomarker-informed care. For pregnancies with documented folate receptor alpha autoantibodies, leucovorin may represent the most rational choice, although larger prospective trials are still needed to define efficacy, safety, dosing, and who benefits most.

The accumulated mechanistic, epidemiologic, and early clinical evidence suggests that folate supplementation should be tailored to maternal folate biology rather than applied uniformly. In pregnancies complicated by FRAA, leucovorin offers a compelling targeted approach that may better preserve folate availability to the fetus and result in neurotypical developmental outcomes. Given that these data support the promise of leucovorin as the preferred folate form in this FRAA-positive subgroup, and the absence of any deleterious follow-on effects due to leucovorin use, it may be beneficial to recommend this option to at-risk women planning pregnancy while looking to confirmation from larger controlled trials prior to routine clinical adoption.

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Conflict of Interest:

The author has no conflicts of interest to declare.

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