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Leucovorin as a Perinatal Intervention to Lower Autism Risk in Offspring

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ABSTRACT

Background: *Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with limited effective medical treatments targeting core symptoms. Leucovorin (folinic acid), a bioactive form of vitamin B9, has demonstrated efficacy in improving communication and behavioral outcomes in children with ASD, particularly those with cerebral folate deficiency or folate receptor alpha autoantibodies (FRAA). Critically, therapeutic benefit diminishes as children age, underscoring the value of earlier intervention.*

Observation: *A case study of two FRAA-positive women who supplemented with leucovorin beginning pre-conception yielded neurotypical development in both offspring through age three. A subsequent randomized pilot trial by Giorlandino et al. (2026) screened 220 women planning pregnancy and enrolled 18 FRAA-positive participants. Children born to mothers receiving leucovorin showed a markedly lower rate of ASD diagnosis at 30 months (10%) compared to those receiving standard folic acid (62.5%).*

Conclusion: *The accumulating evidence supports leucovorin as a safe, evidence-based prenatal intervention for mothers at elevated risk of bearing an ASD child. FRAA positivity is an actionable biomarker for identifying high-risk pregnancies. This commentary discusses the relevant biological mechanisms, reviews current clinical evidence, and offers guidance for psychiatrists who counsel or co-manage patients in perinatal or preconception contexts.*

Keywords

Autism spectrum disorder, Cerebral folate deficiency, Folate receptor autoantibody, Leucovorin, Neurodevelopmental disorder prevention.

Abbreviations

ASD: Autism Spectrum Disorder, CARS: Childhood Autism Rating Scale, CFD: Cerebral Folate Deficiency, FRAA: Folate Receptor Alpha Autoantibody, FRα: Folate Receptor Alpha, RCT: Randomized Clinical Trial, UMFA: Unmetabolized Folic Acid.

Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication, restricted interests, and repetitive behaviors. Despite decades of research, effective pharmacological treatments targeting the core symptoms of ASD remain elusive, and behavioral therapies, while beneficial, are resource-intensive and dependent on early identification. Prevalence estimates continue to rise, with the U.S. Centers for Disease Control and Prevention reporting approximately 1 in 36 children meeting ASD diagnostic criteria. This trajectory imposes considerable burden on affected individuals, families, and mental health systems.

Psychiatrists occupy a critical position in the ASD landscape: evaluating children and adults for diagnosis, co-managing psychiatric comorbidities such as anxiety and attention-deficit/hyperactivity disorder, and increasingly counseling patients of childbearing age. As evidence accumulates linking folate pathway dysfunction to ASD pathogenesis, a practical and biologically plausible intervention has emerged: substituting leucovorin (folinic acid, the bioactive form of vitamin B9) for standard folic acid in at-risk pregnancies.

This commentary synthesizes the current evidence on leucovorin as a pediatric treatment for ASD, reviews the newly published prenatal data documenting reduced numbers of ASD in at-risk pregnancies treated with leucovorin in place of folic acid, including a 2026 randomized pilot trial, and provides clinically oriented guidance for identifying candidates for prenatal leucovorin supplementation. The goal is to equip psychiatrists with actionable knowledge as the field moves toward earlier, biomarker-guided prevention.

Leucovorin as a Treatment for ASD in Children

Biological Rationale

Leucovorin is a bioactive derivative of folate that bypasses the dihydrofolate reductase conversion step required by folic acid, entering folate-dependent metabolic pathways directly. These pathways are essential for DNA synthesis, methylation reactions, and neurochemical homeostasis. Of particular relevance to ASD, leucovorin can cross the blood-brain barrier via the reduced folate carrier, a route that remains accessible even when the primary transporter, folate receptor alpha (FRα), is functionally impaired [1,2].

The folate receptor alpha autoantibody (FRAA) blocks FRα, preventing folic acid from entering the central nervous system while leaving the reduced folate carrier intact. This selective barrier results in cerebral folate deficiency (CFD) despite normal or even elevated serum folate levels. CFD has been identified as a contributing mechanism in ASD, and FRAA has been detected at substantially elevated rates in ASD-affected children relative to neurotypical controls [2].

Randomized Clinical Trial Evidence

Several double-blind, placebo-controlled randomized clinical trials (RCTs) have established leucovorin's efficacy in pediatric ASD. A landmark U.S. trial demonstrated that oral leucovorin supplementation (2 mg/kg/day, maximum 50 mg/day) for 12 weeks significantly improved standardized verbal communication scores compared to placebo, with the most robust gains observed in children who were FRAA-positive [1]. Subsequent RCTs conducted across five countries have corroborated these findings, reporting improvements in Childhood Autism Rating Scale (CARS) scores and behavioral checklists with no significant adverse events [3-5]. Meta-analytic data support leucovorin's safety and efficacy across these populations, and children with high FRAA titers consistently demonstrate the greatest response, establishing FRAA as a clinically meaningful predictive biomarker [5].

A key limitation of the pediatric literature is the observation that treatment efficacy declines as children age. This dose-response relationship with developmental timing implies that maximal benefit is achieved when the folate pathway is corrected at the earliest vulnerable period, ideally during neural development itself. This observation logically motivates investigation of prenatal intervention.

Extending the Evidence to Pregnancy

Case Study: Proof of Concept

The first direct evidence of prenatal leucovorin benefit came from a 2025 case study by Giorlandino et al., in which two women with previous neurodivergent children and confirmed FRAA positivity initiated supplementation with 7.5 mg leucovorin per day prior to

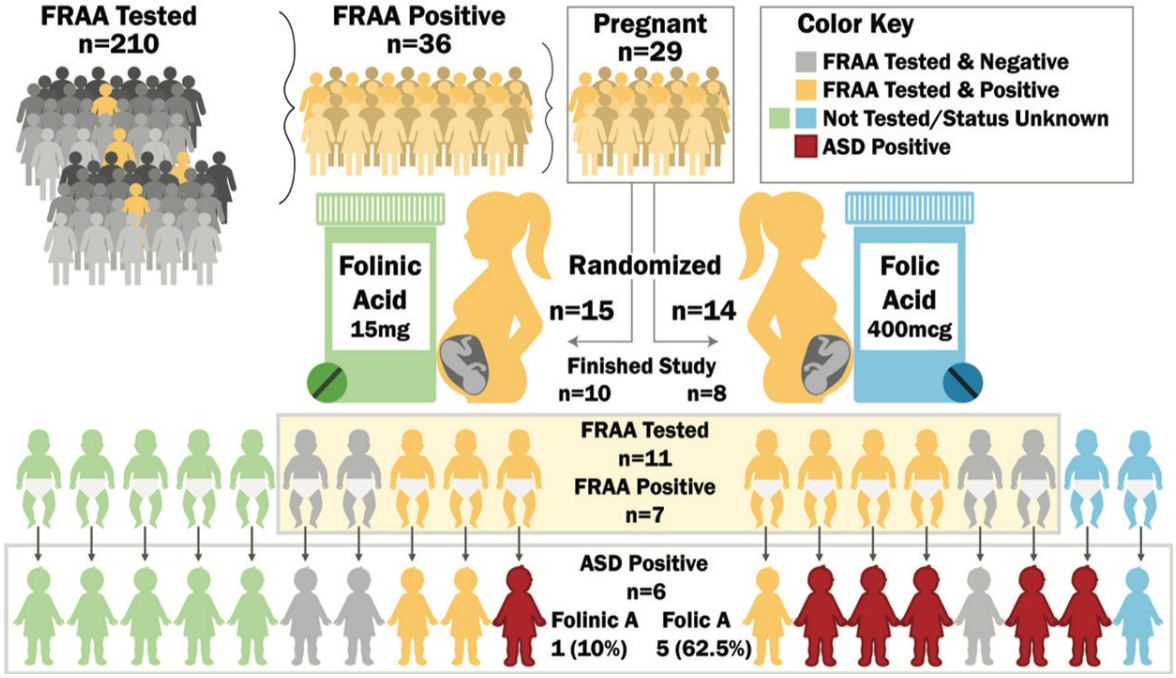

Figure 1: Overview of the Giorlandino et al. randomized pilot trial. Of 220 women planning pregnancy, 36 (17%) tested positive for folate receptor alpha autoantibodies (FRAA). Twenty-nine became pregnant and entered the study, randomized to leucovorin (calcium folinate) or standard folic acid supplementation. Eighteen women completed the trial (n = 10 leucovorin, n = 8 folic acid). Children were assessed for ASD at 30 months. ASD prevalence: leucovorin arm, 10% (1/10); folic acid arm, 62.5% (5/8).

conception and continued throughout pregnancy [6]. This work followed the previous Giolandino et al. report that FRAA positivity in pregnancy correlated with increased nuchal translucency and later ASD diagnosis of offspring [7]. Both offspring in the case study were followed to age three and demonstrated neurotypical developmental trajectories with no signs of ASD. While a two-patient case study cannot establish causation, it provided the first clinical signal that prenatal leucovorin intervention is feasible, well-tolerated, and potentially effective.

Giorlandino et al.: Randomized Pilot Trial

Building on this case, the Giorlandino group conducted a randomized pilot trial specifically designed to evaluate leucovorin as a substitute for folic acid in FRAA-positive pregnancies [8]. Among 220 women planning a pregnancy who were screened for FRAA, 17% tested positive (36 women). Those who subsequently became pregnant were randomized to receive either standard folic acid supplementation or leucovorin throughout pregnancy. Eighteen women completed the study: ten in the leucovorin arm and eight in the folic acid arm. All children were assessed for ASD at 30 months of age using validated instruments. Figure 1 is a schematic diagram of the trial process.

The results were striking. In the folic acid arm, five of eight children (62.5%) received an ASD diagnosis at 30 months. In the leucovorin arm, only one of ten children (10%) was diagnosed with ASD, representing a six-fold reduction in prevalence, and of note, that one ASD child carried the *SHANK2* gene [8]. Although the sample size was small, the magnitude of the difference is clinically meaningful and statistically suggestive, and the study provides the strongest evidence to date that prenatal leucovorin supplementation can substantially reduce ASD incidence in FRAA-positive pregnancies.

Importantly, this trial also established a practical and scalable screening framework. FRAA testing of women planning pregnancy via an ELISA blood test, identified the high-risk subpopulation. The 17% FRAA positivity rate in the general planning-pregnancy cohort suggests that a meaningful proportion of prospective mothers may benefit from this targeted intervention.

Safety Profile of Leucovorin in Pregnancy

Leucovorin has been an approved pharmaceutical agent since the early 1980s, initially indicated for reduction of toxicity from methotrexate and other anti-folate chemotherapeutic agents. It has a well-characterized adverse effect profile developed over four decades of clinical use across diverse populations. Regulatory agencies and major clinical guidelines consistently affirm its safety during pregnancy and lactation [9].

Human data show no evidence of fetal harm attributable to leucovorin at the doses studied. Across multiple pediatric ASD trials, leucovorin was well tolerated with adverse event rates comparable to placebo [1,3]. The safety of folic acid, the parent compound, is extensively documented, and leucovorin's direct metabolic availability avoids the conversion bottleneck that can lead to accumulation of unmetabolized folic acid (UMFA). UMFA has emerged as a concern in its own right, with evidence suggesting that elevated UMFA may paradoxically impair cerebral folate availability in susceptible individuals. Substituting leucovorin avoids this problem while preserving the established benefits of folate supplementation in preventing neural tube defects [9].

Clinical Guidance for Psychiatric Practitioners

The accumulated evidence supports two interrelated clinical contexts in which psychiatrists may encounter leucovorin as a relevant intervention: (1) evaluation and management of ASD children with co-occurring psychiatric conditions, and (2) preconception and perinatal counseling of adults at elevated risk for bearing an ASD child. Tables 1 and 2 summarize current guidance for each context.

Identifying High-Risk Pregnancies

The Giorlandino trials and earlier case literature identify FRAA positivity as the primary biomarker for high-risk pregnancy. Testing for FRAA is commercially available and requires only a blood draw. The 2026 trial found 17% of a general planning-pregnancy cohort to be FRAA-positive, suggesting that systematic screening could identify a substantial group who would benefit from intervention. Family history of ASD, learning disability, or communication disorder in a first-degree relative should trigger FRAA screening in both prospective parents [11,12]. Additional considerations include documented genetic variants in folate metabolism pathways and the presence of maternal autoimmune conditions, which may amplify FRAA titers and inflammatory risk to the fetus [6-8,13,14].

Table 1: Leucovorin recommendations for ASD children [1,3-5,10].

Table 1. Clinical Guidance for Leucovorin Use in ASD Children	
Domain	**Recommendation**
Diagnosis-Guided Treatment	Screen ASD children for cerebral folate deficiency, FRAA status, metabolic blocks, and relevant genetic polymorphisms to identify those most likely to benefit from leucovorin supplementation.
Dosage and Monitoring	Evidence supports leucovorin at 0.5–2 mg/kg/day (maximum 50 mg/day). Monitor clinical response and FRAA titers over time; long-term tolerability is well established.
Safety Counseling	Clinicians may confidently advise families on the safety of leucovorin for children and pregnant women based on robust clinical and regulatory data spanning four decades.
Early Intervention	Given declining efficacy with age, initiation should not await definitive ASD diagnosis when FRAA positivity or CFD is confirmed. Consider prophylactic supplementation in high-risk settings.
UMFA Concern	Unmetabolized folic acid (UMFA) may impair cerebral folate bioavailability. Substituting leucovorin for folic acid eliminates UMFA accumulation risk while maintaining folate sufficiency.

Table 2: Leucovorin guidance for at-risk pregnancies [6,8].

Table 2. Clinical Guidance for Leucovorin Use in At-Risk Pregnancies	
Risk Criterion	**Clinical Guidance**
Family History	Immediate family member with ASD, serious learning disability, or communication disorder warrants FRAA screening of both prospective parents prior to or at the start of pregnancy.
FRAA Positivity	FRAA positivity in either parent is the primary biomarker for high-risk pregnancy. FRAA-positive mothers should substitute leucovorin (7.5 mg/day) for standard folic acid, ideally beginning pre-conception.
Genetic Variants	Documented variants affecting folate metabolism or transport (e.g., MTHFR, DHFR, RFC1 polymorphisms) increase risk of CFD in offspring and support leucovorin supplementation.
Maternal Autoimmune Conditions	Autoimmune disorders increase the likelihood of FRAA and heightened inflammatory milieu during gestation, representing an independent indication to consider leucovorin.
Timing	Supplementation should begin pre-conception and continue throughout pregnancy to encompass all critical windows of fetal neurodevelopment.
Paternal FRAA	Whether paternal FRAA contributes to offspring risk is not yet established. Testing both parents is a reasonable precautionary measure given the low cost and non-invasive nature of FRAA testing.

Role of the Psychiatrist

Psychiatrists are particularly well positioned to initiate this clinical pathway. They commonly evaluate adults with subclinical or undiagnosed autism traits, treat parents of autistic children who present with anxiety or mood disorders related to caregiving stress, and counsel women of reproductive age managing psychiatric conditions. Any of these encounters represents an opportunity to inquire about ASD family history and, where indicated, to recommend FRAA testing and appropriate folate supplementation in coordination with obstetrics or primary care.

It is also worth noting that many women of childbearing age with psychiatric conditions are already managed with medications that can interact with folate metabolism. Psychiatrists ordering or co-managing these treatments may wish to incorporate routine folate pathway assessment into preconception planning discussions.

Conclusion

The evidence base for leucovorin as an intervention in ASD has matured from pediatric RCT data into a compelling prenatal prevention paradigm. The 2026 randomized pilot trial by Giorlandino et al. provides the first controlled data indicating that prenatal leucovorin supplementation in FRAA-positive women dramatically reduces ASD incidence in offspring compared to standard folic acid. Combined with the well-established safety profile of leucovorin, the availability of a simple screening test for FRAA, and the biological coherence of the cerebral folate deficiency hypothesis, a clear rationale now exists for incorporating this intervention into preconception counseling for at-risk populations.

As personalized medicine approaches continue to reshape neurodevelopmental care, leucovorin stands out as a targeted, mechanistically grounded, and clinically actionable tool. Psychiatrists who engage with patients at reproductive age, ASD-affected families, or prenatal populations are encouraged to familiarize themselves with FRAA screening and the emerging leucovorin literature. Future research should evaluate optimal dosing regimens, paternal FRAA contributions, and long-term neurodevelopmental outcomes in leucovorin-exposed cohorts to further refine clinical recommendations.

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