CME LIVE OPEN ACCESS

Journal of
Gynecology and Reproductive Health

Mini Review Article

ISSN: 2574-2728

Perinatal Leucovorin Offers a Precision Folate Strategy for at Risk Pregnancies

George Ayoub*

Department of Psychology, Santa Barbara City College, Santa Barbara, CA 93109, USA.

Corresponding Author: George Ayoub, Department of Psychology, Santa Barbara City College, Santa Barbara, CA 93109, USA. neuro@sbcc.edu.

Received: 2026 Mar 06 **Accepted:** 2026 Mar 27 **Published:** 2026 Apr 10

Abstract

Autism spectrum disorder (ASD) arises from converging genetic, immune, and metabolic perturbations, and current medical treatments for core symptoms remain both limited and largely postnatal. Folate receptor-alpha autoantibodies (FRAA) and folate-pathway polymorphisms create cerebral folate deficiency despite adequate systemic folate, and FRAA are enriched in ASD children and their mothers, defining a mechanistically coherent, testable risk subgroup. Randomized trials in ASD children demonstrate that folinic acid (leucovorin), a reduced and bioactive folate that bypasses FRAA-blocked folate receptor alpha via alternative transporters, improves communication and global symptom scores, with greatest efficacy at younger ages, and it has a favorable safety profile. Translating this finding upstream, a pilot randomized trial in FRAA-positive pregnancies found that perinatal leucovorin, compared with standard folic acid, was associated with markedly lower ASD incidence, lower ADOS-2 scores, and higher Bayley-4 cognitive indices in offspring, while a case series of two FRAA-positive mothers with prior neurodivergent children reported neurotypical development to age three after preconception and gestational leucovorin. Additional case series in women with MTHFR polymorphisms and infertility suggest that replacing folic acid with reduced folates can restore fertility without increasing total folate dose, underscoring folate form as a modifiable determinant of reproductive and neurodevelopmental outcome. In parallel, preclinical and epidemiologic data raise concern that high-dose synthetic folic acid remains unmetabolized and may perturb neurodevelopmental trajectories in susceptible subgroups. Together, these converging lines of evidence support a precision perinatal folate paradigm in which leucovorin replaces folic acid for FRAA-positive and folate-pathway impaired women, warranting systematic screening and multicenter trials to test leucovorin as a viable prenatal strategy for reducing ASD incidence.

Keywords: Perinatal Leucovorin, Precision Folate Strategy, Pregnancies, Epidemiologic, Neurodevelopmental

1. Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous neurodevelopmental condition in which converging genetic, immune, and metabolic perturbations alter early brain development, yet current medical treatments for core symptoms are largely postnatal and only partially effective. Periconceptional folic acid and multivitamin supplementation consistently reduce neural tube defect risk and have been associated with modest reductions in ASD risk, but these population-level policies do not account for substantial variation in folate transport, metabolism, genetic variations, and immune interference [1-3]. Among the most compelling biological modifiers of folate bioavailability are folate receptor-alpha autoantibodies (FRAA), which block folate receptor-mediated transport across placenta and choroid plexus, leading to cerebral folate deficiency despite normal serum folate and increasing ASD risk in offspring. FRAA are enriched in ASD children and in mothers of ASD-affected children, defining an immune-mediated endophenotype within the broader spectrum. In parallel, polymorphisms in folate-pathway genes such as MTHFR, and the accumulation of unmetabolized folic acid (UMFA) with high-dose synthetic folic acid, further constrain effective reduced folate delivery to the developing brain and may perturb epigenetic programming during critical periods [4-6].

Folinic acid (leucovorin) is a reduced, bioactive folate that enters cells via alternative transporters and bypasses FRAA-blocked folate receptor-alpha, thereby directly supporting nucleotide synthesis and methylation reactions crucial for neurogenesis and synaptogenesis. It has been used for decades to recover patients from depleted vitamin B9 following chemotherapy and has an excellent safety profile [7,8].

Randomized controlled trials in ASD children, particularly those with cerebral folate deficiency or FRAA, show that leucovorin improves communication and global symptom measures, with the greatest efficacy at younger ages and no reported detrimental effects [9,10]. These findings raise the pivotal translational question of whether shifting folate formulation from folic acid to leucovorin during the periconceptional and gestational periods can reduce ASD incidence in biologically defined high-risk pregnancies. Emerging clinical data now provide a prevention signal. A pilot randomized study in FRAA-positive pregnancies reported markedly lower ASD incidence, reduced ASD symptom severity, and higher cognitive scores among offspring of mothers receiving leucovorin compared with folic acid [11]. While a FRAA-positive case series with preconception leucovorin documented neurotypical development in offspring to age three [12]. Complementary case reports of infertility associated with MTHFR polymorphisms indicate that switching from folic acid to reduced folates restores fertility without increasing total folate dose, underscoring folate form as a modifiable determinant of reproductive and neurodevelopmental outcomes[13] Against this backdrop, preclinical and epidemiologic data linking excess folic acid and UMFA to adverse neurodevelopmental signatures in susceptible subgroups suggest that folic acid may not be universally benign [14].

We argue that, given the mechanistic, clinical, and translational evidence, perinatal leucovorin is a promising precision folate strategy to reduce ASD risk in FRAA-positive and folate pathway-impaired pregnancies. Folate immunobiology, genetic variation, and emerging concerns about excess folic acid lead us to propose a targeted framework for screening, supplementation, and future trials that move ASD prevention upstream into the periconceptional window.

2. Autism Folate Biology and Unmet Prevention Needs

ASD emerges from interactions among genetic variants, maternal immune activation, metabolic constraints, and environmental factors that converge on early neurodevelopmental pathways [15]. Folate-dependent one-carbon metabolism is central to DNA synthesis, repair, and methylation, and thus represents a key biological axis through which perinatal nutrition can shape fetal brain development. Yet current folic-acid–based policies, while effective against neural tube defects, do not distinguish between different folate forms or individual vulnerabilities that may modulate ASD risk [16].

3. Folate Receptor Alpha Autoantibodies and Cerebral Folate Deficiency

Folate receptor-alpha autoantibodies (FRAA) impair receptor-mediated transport of 5-methyltetrahydrofolate into the central nervous system, causing cerebral folate deficiency despite normal or elevated systemic folate. FRAA are substantially more prevalent in ASD children and in mothers of ASD-affected children than in the general population, defining an immune-mediated folate transport disorder relevant to neurodevelopment. Experimental models and clinical observations indicate that FRAA-mediated folate deprivation can alter behavior, and that restoring reduced folate availability can partially reverse these effects [17–19].

4. Leucovorin Versus Folic Acid: Pharmacology and Transport Pathways

Leucovorin is already in a reduced, metabolically active form and utilizes the reduced folate carrier and proton-coupled folate transporter to enter cells, thereby bypassing blocked folate receptor-alpha in FRAA-positive individuals. In contrast, folic acid is a synthetic oxidized vitamin that depends on both receptor-mediated transport and enzymatic reduction, processes that can be saturated or impaired in the presence of FRAA, MTHFR polymorphisms, or high background folic acid exposure. These pharmacologic distinctions mean that leucovorin and folic acid are not interchangeable with respect to cerebral folate delivery, particularly in high-risk biological subgroups.

5. Clinical Evidence for Leucovorin in ASD Children

Randomized controlled trials in ASD children and language impairment show that leucovorin improves verbal communication and global ASD symptom scores, with particularly robust effects in subgroups positive for FRAA or other folate-pathway abnormalities. Open-label series and meta-analytic syntheses further support benefits on irritability, adaptive function, and other core domains, while confirming an acceptable safety profile across doses used in pediatric practice [1,9,10,20,21]. These data provide proof-of-principle that correcting reduced folate bioavailability can meaningfully modify neurobehavioral outcomes even after birth.

6. Perinatal Leucovorin in FRAA-Positive Pregnancies Pilot Randomized Trial

A pilot randomized trial in FRAA-positive women planning pregnancy provided the first controlled evidence that folate formulation during gestation can modulate early ASD risk markers. In this study, perinatal leucovorin, compared with folic acid, was associated with substantially lower ASD incidence at 24–30 months postnatal, lower ADOS-2 scores, and higher Bayley-4 cognitive indices despite the small sample size [11]. These results suggest that bypassing FRAA-blocked transport with leucovorin during pregnancy may confer neuroprotection that standard folic acid fails to deliver in this subgroup. Figure 1 provides a visual schematic of the study protocol and findings.

7. FRAA-Positive Case Report with Preconception Leucovorin

Complementing the randomized pilot, a case series of two FRAA-positive mothers with prior neurodivergent offspring examined leucovorin initiated before conception and continued throughout pregnancy. Both subsequent children developed neurotypically to age three, with no

ASD symptoms detected, providing the earliest direct suggestion that restoring effective folate delivery during fetal life may prevent ASD in high-risk contexts [12]. Although uncontrolled and small, these cases underscore the importance of timing and support the rationale for preconception initiation of leucovorin in FRAA-positive women.

8. Infertility MTHFR Polymorphisms and the Role of Reduced Folates

Case series in women with infertility and MTHFR polymorphisms suggest that replacing folic acid with reduced folates such as leucovorin or 5-methyltetrahydrofolate can restore fertility and result in successful pregnancies without altering total folate dose. These observations indicate that folic acid is not universally effective across genotypes and that folate form can be a critical determinant of reproductive success [13]. When considered alongside FRAA-positive pregnancy data, they support a broader view in which reduced folates may be preferable for multiple folate-pathway-impaired reproductive phenotypes.

9. Excess Folic Acid UMFA and Emerging Neurodevelopmental Concerns

Preclinical work shows that high-dose prenatal folic acid can alter cortical DNA methylation and gene expression networks, suggesting that supraphysiologic exposure to synthetic folic acid may not be benign during vulnerable developmental windows [14,22]. Observational human data link extended second-trimester folic acid supplementation and higher UMFA burden with adverse behavioral and cognitive outcomes in early childhood, particularly in specific subgroups [11]. These findings challenge the assumption that "more folic acid is always better" and strengthen the case for physiologic folate forms and individualized dosing.

10. Integrating Immunology Genetics and Nutrition in Perinatal Folate Strategy

Taken together, FRAA, folate-pathway polymorphisms, and UMFA define a multilayered biology in which immune, genetic, and metabolic factors interact to shape cerebral folate availability and ASD risk. This integrative perspective moves beyond generic folic acid supplementation toward a stratified approach that aligns folate form and timing with underlying biology. Within this framework, perinatal leucovorin becomes a logical candidate for intervention in high-risk women rather than a universal replacement for folic acid.

11. A Precision Framework for Perinatal Leucovorin Use

A precision perinatal leucovorin framework would prioritize FRAA-positive women, those with prior ASD-affected children, documented folate-pathway polymorphisms, or infertility responsive to reduced folates. For such women, substituting leucovorin for folic acid starting with preconception and continuing through pregnancy may optimize cerebral folate delivery while avoiding excessive synthetic folic acid exposure. Implementation will require harmonized assays, clear thresholds, and integration with existing antenatal care pathways.

12. Practical Considerations for Screening and Implementation

Operationalizing this strategy entails practical decisions about whom to screen, which biomarkers to use, and how to counsel patients on folate formulations. FRAA testing in women with prior neurodevelopmentally affected offspring, unexplained infertility, or strong family history of ASD may offer a high-yield starting point, while selected genetic testing can refine risk stratification. Clinicians will also need guidance on dosing, monitoring, and how to integrate leucovorin into or alongside established neural tube defect-prevention guidelines.

13. Research Priorities and Trial Design Considerations

Given the promising but preliminary nature of existing evidence, adequately powered multicenter trials are needed to test periconceptional leucovorin versus standard folic acid in FRAA-positive and folate-pathway–impaired pregnancies, with ASD and cognitive outcomes tracked into early childhood. Key design issues include timing of initiation, dose selection, choice of co-nutrients, and incorporation of mechanistic biomarkers such as FRAA titers, UMFA levels, and methylation signatures. Parallel observational cohorts can help refine risk stratification and identify additional subgroups likely to benefit from precision folate strategies.

14. Conclusions

Current folic-acid-centered perinatal policies, while successful for neural tube defects, do not accommodate biologically defined subgroups in whom synthetic folic acid may be insufficient or potentially harmful for neurodevelopmental outcomes. The convergence of mechanistic data on FRAA and cerebral folate deficiency, pediatric ASD trials of leucovorin, perinatal prevention signals, and emerging concerns about excess folic acid supports evaluation of perinatal leucovorin as a targeted strategy to reduce ASD risk in high-risk pregnancies. Further rigorous clinical trials and implementation research are now needed to translate this precision folate paradigm into practice.

Acknowledgements

We thank Shana Anderson for producing the visual schematic of the clinical trial depicted in Figure 1.

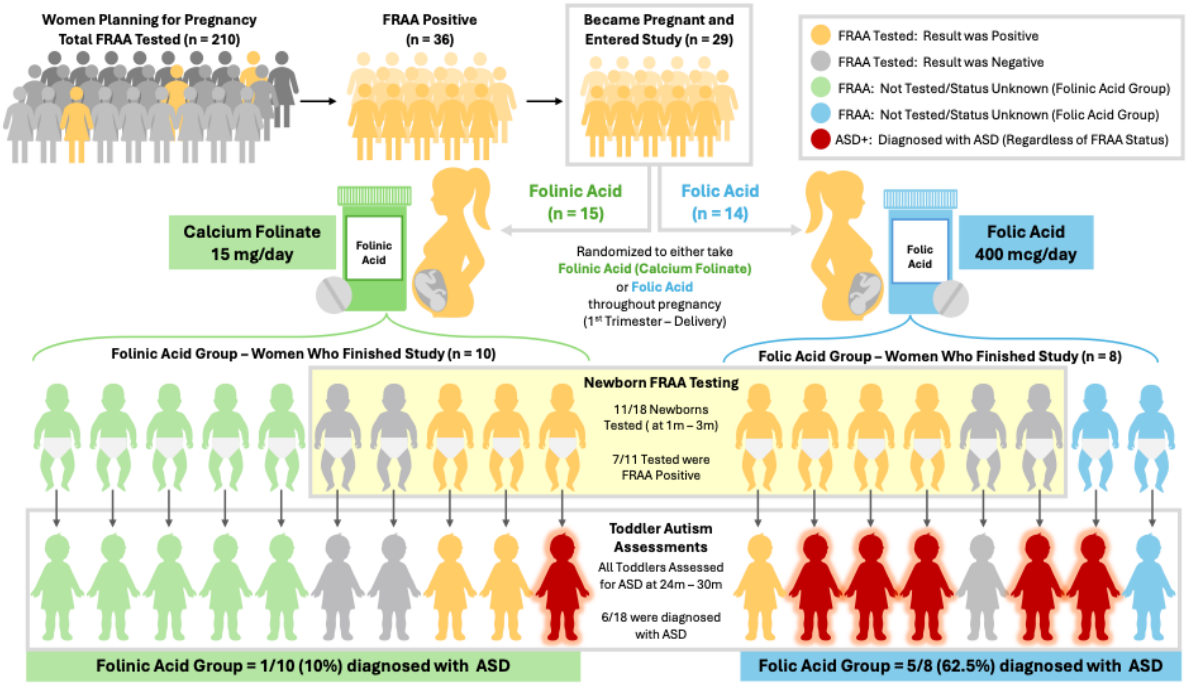

Figure 1: Visual schematic of leucovorin/folic acid trial [11]. 210 women planning pregnancy were recruited and tested for FRAA, with 36 found to be positive. Of these, 29 became pregnant and entered the study, with half receiving standard folic acid supplementation and half receiving leucovorin. Ten leucovorin and eight folic acid arm women completed the study, and their children were assessed at 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.

Funding
The author received no funding for this work.

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