

# Leucovorin, and not Folic Acid, Supports Fertility and Reduces Autism Risk in Pregnancy

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## Abstract

Recent studies urge a reconsideration of folate supplementation in prenatal vitamins, especially for women with MTHFR genetic polymorphisms. The prevailing policy recommends folic acid for all women of childbearing age to prevent neural tube defects and support healthy fetal development. However, folic acid may be a suboptimal option for many, with leucovorin proving to satisfy the folate necessity for a wider group of patients. Two new studies have shown that for women presenting with MTHFR biomarkers, leucovorin and not folic acid was able to reverse infertility, and leucovorin and not folic acid prevented the development of autism in pregnancies. This evidence, along with multiple clinical trials showing some remission of autism symptoms in children using leucovorin, suggests substituting leucovorin as the folate source for fertility and pregnancy.

**Keywords:** Autism; Leucovorin; Mthfr; Fertility; Pregnancy

## Introduction

Traditional prenatal care universally recommends folic acid supplementation to women seeking pregnancy and during gestation, aiming to protect against neural tube defects and foster optimal fetal development. Yet, recent studies advocate for the replacement of folic acid with leucovorin (folinic acid), a bioactive folate form, in prenatal supplements, both to enhance fertility and to reduce autism risk in progeny.

### Fertility Benefits

Recent clinical reports, including an Australian case series, have revealed important limitations with folic acid supplementation in women with MTHFR (methylenetetrahydrofolate reductase) genetic variants. In these women, the conversion of folic acid to biologically active forms is hindered, which can compromise fertility outcomes. The case series included twelve women with infertility and MTHFR variants, who were prescribed folinic acid and/or 5-MTHF (the natural circulatory folate) at higher doses, with folic acid discontinued. Eleven out of twelve women conceived

after making this change, and ten delivered healthy babies. This clinical success underscored the superiority of bioactive folate forms over standard folic acid for such cases [1].

### Autism Risk Reduction

Multiple clinical trials have shown folinic acid supplementation in children displaying autism spectrum disorder (ASD) leads to substantial improvements in communication and behavioral outcomes, particularly in those with cerebral folate deficiency or autoantibodies to folate receptors [2–6]. The effect is strongest for younger children, with a lesser impact for teens. This suggests folinic acid's critical role in neurodevelopment, extending the therapeutic window to the earliest developmental stages, should include pregnancy.

A pivotal recent Italian case study indicated that insufficient bioavailable folate during fetal development may be a modifiable risk factor for autism in offspring. In this study, two women who each had previous neurodivergent children and tested positive for

the folate receptor alpha autoantibody (FRAA) began intervention with 7.5 mg folinic acid/day prior to conception and continued throughout the pregnancy. In both cases, the offspring exhibited no signs of ASD and showed neurotypical development through to the conclusion of the study at age three [7].

As a whole, this new study suggests folinic acid supplementation be earlier than the published clinical trials have used, beginning pre-conception and continuing through pregnancy, to maximize

neurodevelopmental protection and minimize ASD risk [7].

**Leucovorin is Superior to Folic Acid**

Leucovorin supplementation has several benefits over folic acid, especially for individuals with MTHFR polymorphisms or presenting with FRAA. The advantages of leucovorin over folic acid are as follows, and the categories of women who specifically benefit from leucovorin use are identified in Table 1.

**Table 1:** Women who benefit from substituting leucovorin (folinic acid) for folic acid [1,7,8].

Group	Rationale
Women with MTHFR Gene Variants, or positive for FRAA	Cannot efficiently activate or access folic acid; folinic acid bypasses this metabolic bottleneck
Women with Previous Infertility or Pregnancy Loss	Direct evidence of increased conception and live births with folinic acid/5-MTHF
Women at Elevated Risk for ASD or Neurodevelopmental Disorders in Progeny	Maximizes early neurodevelopment, reduces autism risk
All women planning pregnancy	Prevalence of MTHFR variants and potential subclinical folate deficiency justify universal use
Women with family history of neural tube defects, miscarriage, or developmental delay	Increased folate requirement and benefit from active forms

**Boosts Fertility**

Acts as an immediately usable form of folate [1,8].

Circumvents impaired metabolism present in MTHFR variants, directly supporting DNA synthesis, cell division, and reproductive health [8].

Improves conception rates, as demonstrated by case series [1].

**Reduces Autism Risk**

Ensures optimal fetal brain and neural tube development by directly supplying the form of folate required for neurogenesis [9].

Counteracts the risk posed by genetic or acquired blocks to folate activity [10].

Early supplementation (pre-pregnancy and during gestation) is now advised to provide continual neurodevelopmental protection, providing a proactive strategy in reducing ASD incidence [7].

**Universal Safety and Efficacy**

Folinic acid is well-tolerated, safe in pregnancy, and effective for at-risk women and the general population alike [8].

**Circumvents UMFA**

Excess folic acid in the diet beyond what can be metabolized to active folate can remain in the system as unmetabolized folic acid (UMFA). UMFA interferes with bioavailable folate. Folinic acid substitution can reduce this problem [11].

**Leucovorin in Pre-Pregnancy and Pregnancy**

**Key recommendations:**

Substitute folic acid with leucovorin and/or 5-MTHF in

prenatal vitamins. Note, in the absence of availability of such prenatal vitamins, it is advised to continue to use those available and prescribe leucovorin (folinic acid) in addition. In this case, the leucovorin levels should be well above the estimated folic acid daily levels due to a blocking effect from unmetabolized folic acid on folate absorption.

Begin supplementation at least 2-3 months before conception, and continue throughout pregnancy.

Screen for MTHFR polymorphisms and/or FRAA where feasible. Consider universal adoption due to safety record.

Early leucovorin intervention not only paves the way for higher fertility and successful conception in genetically diverse populations, it may also protect fetal brain development, thus helping prevent ASD, a major public health advance. Policymakers and practitioners should consider updating guidelines to prioritize bioactive folate forms in reproductive health protocols.

Shifting to leucovorin (folinic acid) and/or 5-MTHF supplementation for pre-pregnancy and pregnancy care represents a critical evidence-based advancement. It addresses both impaired fertility and the rising prevalence of autism, benefiting women with known genetic risk factors and the wider population due to its safety, efficacy, and broad neurodevelopmental protection. Endorsing folinic acid for all women planning pregnancy is a medically robust preventative strategy both for fertility and for autism risk reduction.

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