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Pilot study of folinic acid vs folic acid supplementation in pregnant women with folate receptor alpha autoantibodies to lower the risk of autism and learning disorders in their children

Submission date 22/05/2025	**Recruitment status** No longer recruiting	[ ] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [X] Record updated in last year
Registration date 23/05/2025	**Overall study status** Completed	
Last Edited 22/05/2025	**Condition category** Mental and Behavioural Disorders	

Plain English summary of protocol

Background and study aims

Autism spectrum disorder (ASD) is a condition that affects how people communicate, interact socially, and process information. While its exact causes are still being studied, researchers have found that problems with folate (vitamin B9) metabolism during pregnancy may play a role in brain development and the risk of ASD in children. Some pregnant women produce specific autoantibodies, called folate receptor alpha autoantibodies (FRAAs), which can block the transport of folate to the baby's brain. This may lead to a condition called cerebral folate deficiency, which has been linked to a higher risk of autism and learning difficulties.

This study aims to find out whether giving these women a more active form of folate, called folinic acid, instead of standard folic acid, during pregnancy can help reduce the risk of autism and developmental problems in their children.

Who can participate?

The study is open to healthy pregnant women between the ages of 18 and 42 years, in their first trimester, who are expecting one baby and have tested positive for FRAAs. Women with diabetes, epilepsy, genetic conditions in the fetus, or who are taking certain medications are not eligible to participate.

What does the study involve?

Participants are randomly placed into two groups. One group receives folinic acid (0.5 mg twice daily) and the other receives folic acid (0.4 mg once daily) from early pregnancy until delivery. The tablets look the same, and neither the participants nor the doctors know which treatment each woman receives (this is called "double-blind").

After birth, the children will be followed for 24 to 30 months. At the end of this period, doctors will assess their development, learning ability, and signs of autism, using internationally recognised tools.

What are the possible benefits and risks of participating?
There is no guaranteed personal benefit, but taking part may help discover whether folinic acid can protect children from autism and learning problems. This could lead to better care in future pregnancies.
Both folinic acid and folic acid are safe and commonly used in pregnancy. No significant side effects are expected at the doses used in this study. Participants will be monitored regularly to ensure safety.

Where is the study run from?
The study is being conducted at the Altamedica Medical Institute, a prenatal and research centre based in Rome, Italy.

When is the study starting and how long is it expected to run for?
The study began in April 2022 and is expected to finish in June 2025.

Who is funding the study?
The study is funded by the Altamedica Medical Institute, which also conducts the research.

Who is the main contact?
Prof. Claudio Giorlandino, claudio.giorlandino@altamedica.it

Contact information

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
FRAA-FOL-INT001

Study information

Scientific Title
Folate receptor alpha antibody-positive pregnancies: a randomized controlled trial comparing folinic acid vs folic acid supplementation and risk of autism spectrum and learning disorders in offspring – pilot study

Acronym
FRAA-FOL

Study objectives
Folinic acid supplementation in pregnant women positive for folate receptor alpha antibodies reduces the incidence of autism spectrum disorders in their offspring compared to supplementation with standard folic acid.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 21/09/2022, Artemisia SPA (Viale Liegi, 41, Rome, 00198, Italy; +39 (0)685059773; comitato.etico@artemisia.it), ref: 2022_57389

Study design
Single-centre randomized double-blind placebo-controlled parallel-group pilot trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital, Laboratory

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Neurodevelopmental disorders, specifically autism spectrum disorder and early learning disabilities in offspring of pregnant women with folate receptor alpha autoantibodies

Interventions
Participants will be randomly assigned in a 1:1 ratio using a computer-generated randomisation list. Allocation concealment will be ensured through the use of sealed, opaque envelopes. Both participants and clinical assessors will be blinded to group allocation.

Intervention arm (Group A): Participants will receive folinic acid 0.5 mg, administered orally twice daily from enrolment (in the first trimester) until delivery.

Control arm (Group B): Participants will receive folic acid 0.4 mg, administered orally once daily from enrolment until delivery.

All participants' children will be followed up from birth to 24 months of age, at which point they will undergo developmental and neuropsychiatric evaluations to assess for autism spectrum disorder and early learning disabilities.

Intervention Type
Supplement

Primary outcome measure
Neurodevelopmental benefit is measured as a reduction in the incidence of autism spectrum disorder (ASD), using the M-CHAT-R/F screening tool followed by DSM-5 confirmation, at 24–30 months of age in children of FRAA-positive pregnant women receiving folinic acid versus folic acid

Secondary outcome measures

1. ASD severity measured using Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) and Autism Diagnostic Interview – Revised (ADI-R) at 24–30 months of age
2. ASD subtype classification measured using ADOS-2 and ADI-R at 24–30 months of age
3. Cognitive development measured using the Bayley Scales of Infant and Toddler Development, Fourth Edition (Bayley-4) at 24–30 months of age
4. Early learning ability measured using the Mullen Scales of Early Learning at 24–30 months of age
5. Adaptive behavior measured using the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) at 24–30 months of age

Overall study start date
01/04/2022

Completion date
01/06/2025

Eligibility

Key inclusion criteria
1. Pregnant women in the first trimester of gestation
2. Singleton pregnancy (no multiple gestation)
3. Age between 18 and 42 years
4. Positive for folate receptor alpha autoantibodies (FRAA) — either blocking or binding type
5. Nulliparous (no previous pregnancies beyond 20 weeks)
6. Willing and able to provide written informed consent
7. Willing to comply with the intervention and follow-up schedule until 24–30 months postpartum

Participant type(s)
Healthy volunteer, Patient, Population

Age group
Adult

Lower age limit
18 Years

Upper age limit
42 Years

Sex
Female

Target number of participants
18

Total final enrolment
29

Key exclusion criteria

1. Multiple pregnancy (e.g., twins or more)
2. Presence of genetic or structural fetal abnormalities detected at baseline
3. Maternal epilepsy or current use of antiepileptic drugs
4. Maternal diabetes mellitus (pre-gestational or gestational)
5. Chronic use of antifolate medications (e.g., methotrexate, sulfasalazine)
6. Any serious maternal medical condition that could interfere with participation or outcome assessment
7. Inability or unwillingness to comply with the treatment or follow-up schedule

Date of first enrolment
01/04/2023

Date of final enrolment
23/10/2023

Locations

Countries of recruitment
Italy

Study participating centre
Altamedica
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Sponsor information

Organisation
Altamedica

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Sponsor type
Hospital/treatment centre

Website
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Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
Planned publication in a peer-reviewed journal; the manuscript is currently being finalised for submission . Study findings will also be presented at relevant conferences in maternal-fetal medicine and neurodevelopment.

Intention to publish date
01/07/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be available upon request from Dr Claudio Giorlandino (email: claudio.giorlandino@altamedica.it). The shared data will include individual participant data (IPD) related to clinical outcomes, laboratory measurements, and neurodevelopmental assessments. Data will become available after publication of the main results and will be accessible for research purposes only. Access will be granted upon reasonable request and subject to approval by the study's data access committee to ensure confidentiality and compliance with ethical regulations. Participant consent for data sharing was obtained, and all data will be anonymised to protect participant privacy. Any legal or ethical restrictions related to data privacy and consent will be strictly respected.

IPD sharing plan summary
Available on request