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To determine whether taking folic acid during the later stages of pregnancy has any beneficial effects of the cognitive development and growth of the offspring

Submission date
13/02/2013

Recruitment status
No longer recruiting

Registration date
15/05/2013

Overall study status
Completed

Last Edited
18/05/2022

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
It is well established that folic acid supplementation in the early stages of pregnancy can reduce the risk of neural tube defects and some other birth defects. Observational research also suggests that maternal folic acid (folate) intake may have a long-term effect on the central nervous system development of the offspring; however, the evidence so far is inconclusive. The aim of this study is to investigate the effect of folic acid supplementation during pregnancy, on growth, nervous system development and behaviour of the offspring aged 6 and 10.

Who can participate?
Mother-child pairs will be recruited from a previously conducted randomized controlled trial which investigated the effect of folic acid supplementation (400µg/d) in the second and third trimester of pregnancy (FASSTT) study (REC reference number: 05/Q2008/21).

What does the study involve?
In the FASSTT trial in pregnancy, participants were randomised to receive either folic acid supplement (400µg/d) or placebo in the second and third trimesters of pregnancy. A nonfasting blood sample was collected from each mother participant at the time of recruitment (14th gestational week) and again at the end of pregnancy (36th gestational week) and a cord blood sample was collected at birth. In all cases, the blood samples collected were analysed for B-vitamin concentrations, DNA methylation of targeted genes and genome-wide analysis; the results were compared for the two intervention groups. The children of these women were followed up at ages 6-7y and 10-11y for data on their growth and cognitive function. They also provided DNA samples via cheek swab and blood sample. The DNA samples from the children were collected for DNA methylation of targeted genes and genome-wide analysis to see if maternal folate status during pregnancy influenced DNA methylation in early life. In addition, blood samples collected at follow-up were analysed for B-vitamin concentrations.

What are the possible benefits and risks of participating?
There is no direct proven benefit; this study will lead to a greater understanding of the impact of folate in pregnancy on child development. By taking part in the study the mother will find out how their child performs on the cognitive assessment. The results of this study will help to generate specific recommendations for folate intake and supplement usage in pregnancy for better health of the mother and the child. In the unlikely event that the child shows results outside the normal range, the mothers permission will be asked to refer the child to the consultant paediatrician involved in this study.

Where is the study run from?
The study will be run from Ulster University, Coleraine.

When is the study starting and how long is it expected to run for?
Original FASSTT trial: June 2005 to October 2007.
Follow-up study: January 2013 to March 2019.
The recruitment of 6 year old children started in January 2013 and concluded in February 2014. The follow-up of the children at age 10 has already begun in February 2016 and is expected to run until March 2019.

Who is funding the study?
1. Biotechnology and Biological Sciences Research Council (BBSRC) (UK)
2. Economic and Social Research Council (ESRC) (UK)
3. HSC Research and Development Division of the Public Health Agency, Northern Ireland (Enabling Research Award).

Who is the main contact?
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
The effect of folic acid supplementation during pregnancy on the growth, cognitive development and behaviour of 6 and 10 year old children: a follow-up investigation of children of FASSTT study participants

Acronym
EpiFASSTT

Study objectives
It is hypothesised that folic acid supplementation during the second and third trimesters of pregnancy may have significant effects on the cognitive development, behaviour and growth. This is a follow up study on the participants of a previous randomised controlled trial and their offspring. This previous trial took place in 2005-2007 as part of an ongoing collaborative research project between the University of Ulster and the Causeway Hospital, Northern Health and Social Services Trust. It investigated the effect of 'Folic Acid Supplementation in the Second and Third Trimester' and the health outcomes of the mother and newborn (FASSTT study: REC reference number: 05/Q2008/21). A total of 125 women completed the FASSTT study.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Current ethical approvals as of 27/07/2017:
1. Salisbury & South Wiltshire NHS Research Ethics Committee, 20/06/2005, Ref: 05/Q2008/21
2. Office of Research Ethics Committees in Northern Ireland (ORECNI), 16/08/2012, Ref: 12/NI /0077
3. Northern Health and Social Care Trust, 28/12/2012, Ref: NRP12-0305-05

Previous ethics approvals:
1. Office of Research Ethics Committees in Northern Ireland (ORECNI), 02/09/2016
2. Northern Health and Social Care Trust, 05/09/2016

Study design
Follow-up study on the participants of a previous randomised controlled trial and their offspring

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Folic acid supplementation in pregnancy

Interventions

Current interventions as of 10/10/2017:
In 2005/2007 a randomised controlled trial investigating the effect of Folic Acid Supplementation during the Second and Third Trimester (FASSTT) and the health outcomes of the mother and newborn was conducted. Healthy pregnant women aged 18-35 years, who have taken folic acid supplementation during their first trimester of pregnancy, were recruited from antenatal clinics of the Causeway Hospital, Coleraine. At the end of the first trimester, women willing to take part were randomly assigned to take placebo or 400ug/d of folic acid until the end of the pregnancy. Blood samples were collected from the mother participant before the start of the intervention (14th gestational week), at the 36th gestational week (representative of post-intervention) and a cord blood sample was collected at birth. In all cases, the blood samples collected were analysed for B-vitamin concentrations, DNA methylation of targeted genes and genome-wide analysis; the results were compared for the two intervention groups.
For the purpose of the follow-up investigation, children who were born to mothers who took part in the FASSTT trial will be asked to take part in the FASSTT Offspring study where they will attend an appointment at the Human Intervention Studies Unit (HISU) at Ulster University, Coleraine. The study will be explained to the participants and any queries answered. Informed consent will be obtained from both the mother and assent will be obtained from the child. The child will be asked to complete a cognitive assessment at approximately 6 years of age using the Wechsler Preschool and Primary Scale of Intelligence test, 3d UK edition (WPPSI) and at the age of 10 years by the Wechsler Intelligence Scale for Children, 4th UK edition (WISC-IV). The psychological tests: Trait Emotional Intelligence Questionnaire (TEIque), Attachment Style Questionnaire and Resilience Questionnaire (RASP) will be used at age 10. The mother will be asked to complete a Health & Lifestyle and Parenting Style Questionnaire. Anthropometric measurements of the child will be taken using standard equipment; weight (digital weighing scales), height (stadiometer), waist circumference (non-stretchable tape) and body fat (portable bioelectrical impedance scales). In addition, a buccal swab (obtained by gently rubbing the mucosa inside the cheek) and whole venous blood sample (collected by venepuncture) will be collected for B-vitamin concentrations, DNA methylation of targeted genes and genome-wide analysis; the results were compared for the two intervention groups.
In a random selection of children, brain activity assessments will be carried out using magnetoencephalography (MEG). The MEG machine will be used to assess brain function by passively measuring the magnetic fields produced by neurons in the brain. The current study will be the first of its kind to report the use of MEG neuro-imaging in a nutritional investigation of children. Ulster University, Magee has one of the few MEG machines in the UK (and the only one on the Island of Ireland) and the expertise to apply this safe and unintimidating procedure in children.

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Intervention Type
Supplement

Primary outcome(s)
To determine the effect of folic acid supplementation during pregnancy on cognitive development of the offspring aged 6 and 10 years. Each child will undergo a cognitive assessment at approximately 6 years of age using the Wechsler Preschool and Primary Scale of Intelligence test, 3rd edition (WPPSI) and at the age of 10 years using the Wechsler Intelligence Scale for Children, 4th UK edition (WISC-IV). The cognitive assessments are composed of a battery of subtests, sampling a broad spectrum of behaviour.

Key secondary outcome(s))
To investigate the effect of folic acid supplementation during pregnancy on the offspring's growth, behaviour, brain activity and DNA methylation.
Anthropometric measurements of the child will be taken by using standard equipment; weight (digital weighing scales), height (stadiometer), waist circumference (non-stretchable tape) and body fat (portable bioelectrical impedance scales). In addition, a buccal swab and blood sample (age 10 years only) of each child will be taken for DNA methylation and B-vitamin analysis.
In a random selection of FASSTT children age 10 years old, brain activity assessments will be

carried out by magnetoencephalography (MEG). The MEG machine will be used to assess brain function by passively measuring the magnetic fields produced by neurons in the brain. The current study will be the first of its kind to report the use of MEG neuro-imaging in a nutritional investigation of children. Ulster University, Magee has one of the few MEG machines in the UK (and the only one on the Island of Ireland) and the expertise to apply this safe and unintimidating procedure in children.

Completion date
31/12/2019

Eligibility

Key inclusion criteria
Current inclusion criteria as of 27/07/2017:
1. The FASSTT trial involved healthy women in the first trimester of pregnancy with singleton pregnancies, without current pregnancy complications, and aged between 18 and 35y.
2. Women who participated in a previous randomized controlled trial (FASSTT study, REC ref: 05 /Q2008/21) and their healthy children aged 6-7y and 10-11y who were born as singleton live births to mothers who completed the trial in the 2nd and 3rd trimesters of pregnancy.
3. Parents who consented and children who assented to their participation in follow-up studies in which cognitive development and growth were measured.

Previous inclusion criteria:
Woman who participanted in a previous randomised controlled trial (FASSTT study, REC reference: 05/Q2008/21) and their children

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Sex
All

Total final enrolment
119

Key exclusion criteria
Current exclusion criteria as of 27/07/2017:
1. The FASSTT trial excluded women from participation if during the first trimester of pregnancy they had taken folic acid supplements at a dose above 400µg/d, if they had gastrointestinal, hepatic, renal, or vascular disease, hematologic disorders, epilepsy, a previous pregnancy with an NTD or were the first degree relative of a woman who had a pregnancy with an NTD, or were themselves a sufferer of an NTD. Participants who were taking a medication known to interfere with B vitamin metabolism or those who had undergone in vitro fertilization treatment were also excluded.

2. Any child who has a severe current health problem or disability with impact on cognitive development (primary outcome measure)
3. Any child whose informed written consent cannot be obtained from the parent/guardian
4. Any child who refuses to have the measurements taken

Previous exclusion criteria:
1. Any child who has a severe current health problem or disability with impact on cognitive development (primary outcome measure)
2. Any child whose informed written consent cannot be obtained from the parent/guardian
3. Any child who refuses to have the measurements taken

Date of first enrolment
01/11/2016

Date of final enrolment
31/03/2019

Locations

Countries of recruitment
United Kingdom

Northern Ireland

Study participating centre
University of Ulster
Coleraine
United Kingdom
BT52 1SA

Sponsor information

Organisation
University of Ulster (UK)

ROR
https://ror.org/01yp9g959

Funder(s)

Funder type
Government

Funder Name
Northern Ireland Centre for Food and Health (NICHE) (UK)

Funder Name
Department of Education and Learning, Northern Ireland

Alternative Name(s)
DELNI

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Funder Name
Biotechnology and Biological Sciences Research Council

Alternative Name(s)
UKRI - Biotechnology And Biological Sciences Research Council, BBSRC UK, Biotechnology and Biological Sciences Research Council (BBSRC), BBSRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Economic and Social Research Council

Alternative Name(s)
Economic and Social Research Council (ESRC), ESRC

Funding Body Type
Government organisation

Funding Body Subtype

National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/04/2018		Yes	No
Results article	results	18/02/2019		Yes	No
Results article	follow-up results	31/10/2019	04/11/2019	Yes	No
Results article		10/03/2021	23/03/2021	Yes	No
Results article		16/05/2022	18/05/2022	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes