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High Dose Folic Acid Supplementation Throughout Pregnancy for Preeclampsia Prevention

Submission date
14/01/2010

Recruitment status
No longer recruiting

Registration date
31/03/2010

Overall study status
Completed

Last Edited
26/04/2023

Condition category
Pregnancy and Childbirth

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Pre-eclampsia (PE) is a complication of pregnancy that affects at least 5% of all pregnancies worldwide. Early signs of pre-eclampsia include having high blood pressure and protein in your urine. It has profound health implications to women and infants in both the short and long term, and has significant economic consequences on society. Recent research has shown that women who have PE during pregnancy are more likely to be at risk for future cardiovascular events later in life. Presently, the only effective treatment for PE is for a woman to deliver her unborn baby. Because delivery may be required earlier than the expected date, PE is also one of the leading causes of preterm birth, which puts these babies at increased risk of serious health problems. A successful preventative therapy, such as folic acid supplementation, could have a significant impact on the disease burden in this population. Studies on folic acid supplementation suggest that a high dose of folic acid may be needed for the prevention of PE. The aim of this study is to find out whether high-dose supplementation of folic acid throughout pregnancy is an effective preventative strategy in women who are at high risk of developing PE.

Who can participate?
Pregnant women (8 0/7 and 16 6/7 weeks of gestation) aged 18 or over, taking 1.1 mg or less of folic acid supplementation who fulfil at least one of the following risk factors for PE:
1. Pre-existing high blood pressure
2. Pre-pregnancy diabetes
3. Twin pregnancy
4. History of PE in a previous pregnancy
5. BMI 35 kg/m2 or over within 3 months prior to current pregnancy or up to joining the study

What does the study involve?
Eligible women will be randomly allocated to take four tablets of folic acid daily or to take placebo (dummy) tablets. There are four visits during the study and one telephone call 6 weeks after delivery.

What are the possible benefits and risks of participating?
Folic acid is relatively nontoxic in humans; however, in rare instances it can cause allergic reactions or hypersensitivity including redness of the skin, skin rash and itching. While there is no guarantee that women will benefit from the study, the knowledge gained from this study may help other pregnant women at high risk for developing PE in the future.

Where is the study run from?
The study is run from Ottawa Hospital Research Institute (Canada) and is recruiting women from Canada, Australia, Argentina, Jamaica and the United Kingdom.

When is the study starting and how long is it expected to run for?
The study started in March 2011 and will run until December 2015.

Who is funding the study?
Canadian Institute of Health Research (CIHR).

Who is the main contact?
Dr Shi Wu Wen
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01355159

Secondary identifying numbers
MCT-98030

Study information

Scientific Title
Effect of folic acid supplementation in pregnancy on preeclampsia - Folic Acid Clinical Trial

Acronym
FACT

Study objectives
High dose (4.0 mg per day) supplementation for pregnant women at high risk of developing preeclampsia starting in early pregnancy and continued throughout the entire pregnancy lower the incidence of preeclampsia.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ottawa Hospital Research Ethics Board, 14/10/2010

Study design
Randomised double-blind placebo-controlled phase III international multicentre trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

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

Health condition(s) or problem(s) studied
Prevention of pre-eclampsia

Interventions
Current interventions as of 13/03/2012:
Drug name: Folic Acid /Placebo
Dosage form: Tablet
Dosage: 4 mg
Frequency: 4 tablets of 1 mg folic acid daily

Study Treatment will be administered from randomization until delivery.

Follow up visits:
Visit 2 at 24 0/7 - 26 6/7 weeks in pregnancy
Visit 3 at 34 0/7 - 36 6/7 weeks in pregnancy

Visit 4 Postpartum
Visit 5 Telephone interview at 42 days (±3 days) post-partum

Secondary investigator:
Dr. Mark Walker
(Same address as Dr. Shi Wu Wen in contact details below)

Previous interventions:
Drug name: Folic Acid /Placebo
Dosage form: Tablet
Dosage: 4 mg
Frequency: 4 tablets of 1 mg folic acid daily

Study Treatment will be administered from randomization until delivery.

Follow up visits:
Visit 2 at 24 0/7 - 26 6/7 weeks in pregnancy
Visit 3 at 34 0/7 - 36 6/7 weeks in pregnancy
Visit 4 Postpartum (within 8 - 24 hours post-partum)
Visit 5 Telephone interview at 42 days (±3 days) post-partum

Secondary investigator:
Dr. Mark Walker
(Same address as Dr. Shi Wu Wen in contact details below)

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Folic acid

Primary outcome measure
Preeclampsia is measured by chart reviews (medical tests) in women greater than 20+0 weeks of gestation.

Secondary outcome measures
Current secondary outcome measures:
1. Maternal death is measured by chart reviews from randomization until 42 days postpartum (after delivery)
2. Severe preeclampsia is measured by chart reviews (medical tests) from 20+0 weeks of gestation until delivery
3. Placenta abruption is measured by chart reviews (medical tests) from 20+0 weeks of gestation until delivery
4. Preterm birth is measured by chart reviews from 20+0 weeks to 36+6 weeks of gestation
5. Premature rupture of membranes. is measured by chart reviews (medical tests) from randomization until the onset of labor
6. Antenatal inpatient length of stay is measured by chart reviews from randomization until admission for delivery

7. Intrauterine growth restriction is measured by chart reviews (medical tests) from 20+0 weeks of gestation until delivery
8. Spontaneous abortion is measured by chart reviews from randomization until 20+0 weeks of gestation
9. Perinatal mortality is measured by chart reviews from 20+0 weeks of gestation until 28 days of life
10. Stillbirth is measured by chart reviews from a birth of infant to 20+0 weeks of gestation
11. Neonatal death is measured by chart reviews from birth of infant until 28 days of life

Neonatal Morbidity:
12. Retinopathy of prematurity is measured by chart reviews (medical tests) for the duration of the hospital stay, or up to 6 weeks
13. Intraventricular hemorrhage (IVH) is measured by chart reviews (medical tests) for the duration of the hospital stay, or up to 6 weeks
14. Early onset sepsis is measured by chart reviews (medical tests) from birth to 48 hours of life.
15. Necrotising enterocolitis is measured by chart reviews (medical tests) for the duration of the hospital stay, or up to 6 weeks
16. Ventilation is measured by chart reviews (medical tests) for the duration of the hospital stay, or up to 6 weeks
17. Need for oxygen at 28 days is measured by chart reviews (medical tests) from birth of infant until 28 days of life.
18. Length of stay in 'high level' neonatal care unit is measured by chart reviews (medical tests) for the duration of the hospital stay, or up to 6 weeks

Previous secondary outcome measures:
1. Maternal death
2. Severe PE (PE with convulsion or haemolytic anaemia, elevated liver enzymes and low platelet count [HELLP] or delivery less than 32 weeks)
3. Preterm delivery, premature rupture of membranes, antenatal inpatient days, intrauterine growth restriction (less than 3rd centile)
4. Perinatal mortality, spontaneous abortion, neonatal morbidity, retinopathy of prematurity, leukomalacia, thrombocytopenia, neutropenia, early onset sepsis, necrotising enterocolitis, intraventricular haemorrhage, ventilation, need for O2 at 28 days, length of stay in neonatal Intensive Care Unit (NICU)

Overall study start date
01/09/2008

Completion date
30/07/2016

Eligibility

Key inclusion criteria
Current inclusion criteria as of 28/04/2014:
1. Capability of subject to comprehend and comply with study requirements
2. At least 18 years of age at time of consent
3. Subject is taking less than or equal to 1.1 mg of folic acid daily at the time of randomization
4. Live fetus (documented positive fetal heart prior to randomization)
5. Gestational Age between 8 0/7 and 16 6/7 weeks of pregnancy
6. Subject plans to give birth in a participating hospital site

7. Pregnant subjects must fulfill at least one of the following identified risk factors for pre-eclampsia (PE):
7.1 Pre-existing hypertension (documented evidence of diastolic blood pressure ≥90 mmHg on two separate occasions or at least 4 hours apart prior to randomization, or use of antihypertensive medication during this pregnancy specifically for the treatment of hypertension prior to randomization)
7.2 Pre-pregnancy diabetes (documented evidence of Type I or Type II DM)
7.3 Twin pregnancy
7.4 Documented evidence of history of PE in a previous pregnancy
7.5 BMI > 35 kg/m2 within 3 months prior to this pregnancy or up to randomization of this pregnancy (documented evidence of height and weight to calculate BMI is required)

Inclusion criteria from 13/03/2012 to 28/04/2014:
1. Capability of subject to comprehend and comply with study requirements
2. At least 18 years of age at time of consent
3. Subject is taking less than or equal to 1.1 mg of folic acid daily at the time of randomization
4. Live fetus (documented positive fetal heart prior to randomization)
5. Gestational Age between 8 0/7 and 16 6/7 weeks of pregnancy
6. Subject plans to give birth in a participating hospital site
7. Pregnant subjects must fulfill at least one of the following identified risk factors for pre-eclampsia (PE):
7.1 Pre-existing hypertension (documented evidence of diastolic blood pressure ≥90 mmHg on two separate occasions or at least 4 hours apart prior to randomization, or use of antihypertensive medication during this pregnancy specifically for the treatment of hypertension prior to randomization)
7.2 Pre-pregnancy diabetes (documented evidence of Type I or Type II DM)
7.3 Twin pregnancy
7.4 Documented evidence of history of PE in a previous pregnancy
7.5 BMI > 35 kg/m2 within 3 months prior to this pregnancy or during the first trimester of this pregnancy (documented evidence of height and weight to calculate BMI is required)

Inclusion criteria from 14/07/2011 to 13/03/2012:
1. Capability of subject to comprehend and comply with study requirements
2. At least 18 years of age at time of consent
3. Subject is taking less than or equal to 1 mg of folic acid daily at the time of randomization
4. Live fetus (documented positive fetal heart prior to randomization)
5. Gestational Age between 8 0/7 and 16 6/7 weeks of pregnancy
6. Subject plans to give birth in a participating hospital site
7. Pregnant subjects must fulfill at least one of the following identified risk factors for pre-eclampsia (PE):
7.1 Pre-existing hypertension (documented evidence of diastolic blood pressure ≥90 mmHg on two separate occasions or at least 4 hours apart prior to randomization, or use of antihypertensive medication during this pregnancy specifically for the treatment of hypertension prior to randomization)
7.2 Pre-pregnancy diabetes (documented evidence of Type I or Type II DM)
7.3 Twin pregnancy
7.4 Documented evidence of history of PE in a previous pregnancy
7.5 BMI > 35 kg/m2 within 3 months prior to this pregnancy or during the first trimester of this pregnancy (documented evidence of height and weight to calculate BMI is required)

Original inclusion criteria until 14/07/2011:
1. Women at least 18 years of age at time of consent

2. Taking less than or equal to 1 mg of folic acid at the time of randomisation
3. Between 8 and 16 weeks of pregnancy. Gestational age of patients will be based on the first day of the last menstrual period and confirmed by ultrasound examination completed between 80/7 and 166/7 weeks of pregnancy.
4. Pregnant women with body mass index (BMI) less than 40 kg/m^2 prior to her pregnancy or prior to her first trimester. Previous BMI (height and weight) record or measurement is required.
5. Pregnant subjects (nulliparous, primaparous or multiparous) must fulfill at least one of the following identified risk factors for pre-eclampsia (PE)
6. Pre-pregnancy or current chronic hypertension (or diastolic blood pressure greater than or equal to 90 mmHg before 20 gestational weeks or use of antihypertensive medication)
7. Pre-pregnancy or current diabetes (insulin-dependent or use of hypoglycaemic agents)
8. History of PE in the previous pregnancy

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
3,656

Total final enrolment
1198

Key exclusion criteria
Current exclusion criteria as of 14/07/2011:
1. Known history or presence of any clinically significant disease or condition which would be a contraindication to folic acid supplementation of up to 5.1 mg daily for the duration of pregnancy
2. Known major fetal anomaly or fetal demise
3. History of medical complications, including:
3.1 Renal disease with altered renal function
3.2 Epilepsy
3.3 Cancer, or
3.4 Use of folic acid antagonists such as valproic acid
4. Individual who is currently enrolled or has participated in another clinical trial or who received an investigational drug within 3 months of the date of randomization (unless approved by the Trial Coordinating Centre)
5. Known history or presence of:
5.1 Alcohol abuse (≥ 2 drinks per day) or alcohol dependence
5.2 Illicit drug/substance use and/or dependence
6. Known hypersensitivity to folic acid
7. Multiple Pregnancy (triplets or more)
8. Participation in this study in a previous pregnancy

Previous exclusion criteria:
1. Known history or presence of any clinically significant disease or condition, as determine by the Principal Investigator which he/she believes would be a contraindication to folic acid supplementation of up to 5 mg daily for the pregnancy duration
2. Women who have known abnormalities (e.g. hydatidiform mole) or known foetal chromosomal or major malformations in the current pregnancy
3. Women who have a history of medical complications, including:
3.1. Untreated hypo/hyper thyroidism
3.2. Renal disease with altered renal function
3.3. Epilepsy
3.4. Any collagen disease such as lupus erythromatosus and scleroderma
3.5. Active and chronic liver disease (hepatitis)
3.6. Cancer
3.7. Use of folic acid antagonists such as valproic acid
4. Threatened abortion. Women with a previous bleeding in the first trimester, can be included if the site documents a viable foetus at the time of recruitment through ultrasound.
5. Women who are using illicit drug or alcohol abuse (greater than or equal to 2 drinks per day) during current pregnancy
6. Known history or presence of:
6.1. Alcoholism
6.2. Drug dependence and/or substance abuse
6.3. Hypersensitivity or idiosyncratic reaction to folic acid
7. Previously been enrolled in this study

Date of first enrolment
31/03/2011

Date of final enrolment
31/12/2015

Locations

Countries of recruitment
Argentina

Australia

Canada

Jamaica

United Kingdom

Study participating centre
501 Smyth Road
Ottawa
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Sponsor information

Organisation
Ottawa Hospital Research Institute (OHRI) (Canada)

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Sponsor type
Research organisation

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ROR
https://ror.org/03c62dg59

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research (CIHR) (Canada) - http://www.cihr-irsc.gc.ca (ref: MCT-98030)

Results and Publications

Publication and dissemination plan
Planned publication of study results in a high-impact peer reviewed journal.

Intention to publish date
01/07/2018

Individual participant data (IPD) sharing plan
The current data sharing plans for the 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?
Protocol article	protocol	01/05/2013		Yes	No
Results article	results	12/09/2018		Yes	No
Results article		01/07/2021	15/04/2021	Yes	No
Results article	results of a secondary analysis	18/04/2023	26/04/2023	Yes	No