Effect of folic acid supplementation in pregnancy on preeclampsia - Folic Acid Clinical Trial (FACT)

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Primary ObjectiveThe overall aim is to evaluate a new preeclampsia (PE) prevention strategy: 4.0mg (1.0mg x 4) of folic acid supplementation vs. placebo from early (80/7 to 166/7 weeks of gestation) pregnancy until delivery.Secondary ObjectivesTo...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Maternal complications of pregnancy
Study type	Interventional

Summary

ID

NL-OMON41628

Source
ToetsingOnline

Brief title
FACT

Condition

- Maternal complications of pregnancy

Synonym
preeclampsia, toxemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: de studie wordt gefinancierd door de Canadian Institute of Health Research (CIHR)

Intervention

Keyword: Folic Acid, preeclampsia, pregnancy

Outcome measures

Primary outcome

PE is the primary outcome measure.

PE is defined as blood pressure *d90 mmHg on two occasions *4 hours apart and

proteinuria developed in women greater than 20 weeks of gestation.

Or

HELLP (Haemolysis, Elevated, Liver Enzymes, Low Platelets) syndrome

- Haemolysis (characteristic peripheral blood smear)

- Serum LDH * 600U/L

- Serum AST * 70U/L

- Platelet count <100 x109/L (Audibert A, et al 1996, Saphier C et al. 1998)

Or

Superimposed pre-eclampsia, defined as history of pre-existing hypertension

(diagnosed pre-pregnancy or before 20 weeks* gestation) with new proteinuria.

Proteinuria is defined as:

- urinary protein *300mg in 24 hour urine collection, OR

- in the absence of 24 hour collection, *2+ dipstick proteinuria, OR

- random protein-creatinine ratio *30mg protein/mmol (Diagnosis, Evaluation,

and Management of the Hypertensive Disorders of Pregnancy, JOGC 2008).

Secondary outcome

Secondary outcomes will include:

- Maternal death,
- Severe PE (PE with convulsion or HELLP or delivery <34 weeks),
- Placenta Abruptio
- Preterm delivery,
- Premature rupture of membranes,
- Antenatal inpatient length of stay,
- Intrauterine growth restriction,
- Spontaneous abortion,
- Perinatal mortality,
- Stillbirth
- Neonatal death

Neonatal morbidity such as:

- Retinopathy of prematurity,
- Periventricular leukomalacia,
- Early onset sepsis,
- Necrotising enterocolitis,
- Intraventricular haemorrhage,
- Ventilation,
- Need for O2 at 28 days,
- Length of stay in Neonatal Intensive Care Unit.

Study description

Background summary

Preeclampsia is a complication of pregnancy which affects at least 5% of all pregnancies worldwide and has serious health consequences to these women and their babies. The only effective treatment for preeclampsia is delivery of the baby. Because delivery may be required before the anticipated date of delivery; preeclampsia is also one of the leading causes of preterm delivery and accounts for 25% of very low birth weight infants. Recent research has also shown that women who have had preeclampsia during pregnancy are more likely to be at risk for future cardiovascular events later in life.

Recently some studies have shown that supplementation with multivitamins containing folic acid is associated with a reduced risk of developing preeclampsia. These findings also suggested that for the prevention of preeclampsia, a high dose of folic acid (much higher than the amount of folate received from food intake or what is usually taken during pregnancy) may be needed.

Study objective

Primary Objective
The overall aim is to evaluate a new preeclampsia (PE) prevention strategy: 4.0mg (1.0mg x 4) of folic acid supplementation vs. placebo from early (80/7 to 166/7 weeks of gestation) pregnancy until delivery.

Secondary Objectives
To evaluate whether or not the effect of folic acid on PE risk differs according to:
a) gestational age at intervention (8-13 and 14-16 weeks of gestation),
b) smoking,
c) age,
d) dietary and commercial folic acid consumption at the time of randomization,
e) subject compliance (percent of tablets used), and
f) Canadian and international centers.

Study design

This study is a randomized, double-blind, placebo-controlled, Phase III, international multi-centre study of 4.0 mg of folic acid supplementation in pregnancy for prevention of preeclampsia in women who are at high risk of developing preeclampsia.

Intervention

Folic Acid 1.0 mg or placebo x 4 tablets will be taken daily by oral administration.
The dosage of folic acid is based on the maximum acceptable dose regimens in Canadian centers and data from randomized controlled trials. The majority of women in our study will routinely take 1.0 mg folic acid in a prenatal vitamin supplement as recommended by their primary obstetrical provider, and the study requirements do not require that subjects change their practice. Therefore the actual total daily dose will be up to 5.0 mg of folic acid in the trial arm (4.0 mg from Study Treatment and 1.0 mg from routine supplementation), and up to 1.0 mg of folic acid daily in the placebo arm (from routine supplementation).

Study burden and risks

Women participating in this study will fill out a diary concerning their use of study medication and use of other drugs.

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.

It is possible that there is no direct benefit from study participation. The study treatment (folic acid 4 mg or placebo) might not help prevent preeclampsia in pregnancy. However, while there is no guarantee that participants will benefit, the knowledge gained from their taking part in this research study may help other pregnant women at high-risk for developing preeclampsia in the future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Capability of subject to comprehend and comply with study requirements
2. * 18 years of age at time of consent
3. Subject is taking *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 and 16+6 weeks of pregnancy
(Gestational age of subjectswill be calculated based on the first day of the last menstrual period or ultrasound performed before 126/7. If early ultrasound and LMP dates differ by * 7 days, base GA estimate on LMP date; if > 7 days, use early <126/7 ultrasound)
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):
a) 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)
b) Pre-pregnancy diabetes (documented evidence of Type I or Type II DM)
c) Twin pregnancy
d) Documented evidence of history of PE in a previous pregnancy
e) 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)

Exclusion criteria

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 mg daily for the duration of pregnancy
2. Known major fetal anomaly or fetal demise

3. History of medical complications, including:
a) renal disease with altered renal function,
b) epilepsy,
c) cancer, or
d) 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 presence of:
a) Alcohol abuse (* 2 drinks per day) or alcohol dependence
b) 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

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	300
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	folic acid
Generic name:	folic acid

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-05-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	27-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-001918-42-NL
ISRCTN	ISRCTN23781770
CCMO	NL41914.018.14