A randomized controlled trial on the effects of periconceptional and prenatal folic acid supplementation on congenital anomalies and preterm birth

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Ethical review	Approved WMO
Status	Completed
Health condition type	Neurological disorders congenital
Study type	Interventional

Summary

ID

NL-OMON39036

Source
ToetsingOnline

Brief title
Folic acid Extra

Condition

- Neurological disorders congenital
- Pregnancy, labour, delivery and postpartum conditions

Synonym
spina bifida/myelomeningocele; preterm birth

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: congenital anomalies, Folic Acid (vitamin B11), pregnancy complications, randomised controlled trial

Outcome measures

Primary outcome

Primary

The primary outcome measures are: FA related congenital anomalies and preterm birth.

Information on all congenital anomalies of live births, stillbirths and terminations of pregnancy following prenatal diagnosis will be derived from the database of EUROCAT, where virtually all congenital anomalies are registered. Data about the diagnosis and the medical history are collected in a standardized procedure of high quality (37). FA related congenital anomalies are neural tube defects, heart anomalies, limb defects, urinary tract malformations, oral cleft and Down syndrome. The congenital anomalies will be classified according to the guidelines for case classification by Rasmussen et al (2003) (38).

Preterm birth is defined as a gestational age < 37 weeks. Gestational age will be assessed from the medical records. Medical terminations will also be included, to avoid bias toward the null hypothesis (39).

Secondary outcome

Secondary outcome measures are:

- Birth weight, obtained from medical records

- preeclampsia (defined as a systolic blood pressure >= 140 mmHg and/or

diastolic blood pressure >= 90 mmHg after 20 weeks of gestation among women with

previously normal blood pressure, combined with proteinuria (>= 300 mg/24

hours)), obtained from medical records

- compliance with intervention.

Study description

Background summary

Approximately one in 44 babies is affected with a congenital anomaly (CA) in Europe (1). About 10% of these CA affect the nervous system (1). The beneficial effects of periconceptional folic acid (FA, vitamin B11) supplementation on neural tube defects (NTD) are evident from randomised controlled trials (RCTs) in high and low risk populations (2;3).

Risk factors for congenital anomalies

Some (groups of) women have a higher risk for having a baby with a congenital anomaly. Mothers of previous children with NTDs have an increased risk of having another child with an NTD. In the Netherlands, these women are prescribed a higher dose of FA (4.0 mg) periconceptional and during the first trimester of pregnancy (3).
Besides genetic predisposition, some gene-environment interactions are known. An example is the interaction between the maternal MTHFR 677C>T polymorphism and FA. Mothers with MTHFR 677TT genotype (homozygous for the polymorphism) who did not use folate supplementation periconceptionally, have a twofold increased risk of having a child with a congenital heart defect (4).

The effects of folic acid

The beneficial effects of periconceptional folic acid (FA) supplementation on neural tube defects (NTD) are evident. Numerous studies have shown that FA supplementation reduces the risk of NTD considerably (5;6). Internationally, a dose of 0.4 mg FA periconceptionally has been agreed upon as the recommended dose (7). But although 0.4 mg is recommended, there is still great uncertainty

about the optimal dose of FA supplementation. Wald et al (8) studied the dose-response relationship in a large study, and showed that with higher doses of FA supplementation, more NTDs were prevented. They concluded that the current recommended daily dose of FA will render only partial protection against NTDs. According to Wald et al*s analysis, 5 mg of FA would be necessary to render 90% protection within the populations.

In addition to these larger effects in the prevention of NTD with a higher dose, FA very probably also has a preventive effect on the birth prevalence of congenital anomalies other than NTD. Case-control studies have yielded strong evidence for a preventive effect on the prevalence of congenital heart defects (9), and reasonable evidence exists for a preventive effect on limb defects and urinary tract malformations (11;12). One case-control study showed a possible effect on Down syndrome (13). Ambiguous results were found with regards to the prevention of clefts (10). All effects on congenital anomalies are achieved by FA supplementation before conception and in the first trimester of pregnancy. Another effect of FA supplementation during pregnancy, with a probably completely independent causal pathway, is the effect on preeclampsia and on preterm birth. From case-control studies, strong evidence is found that FA supplementation (dosages from 0.4 mg to 3.0 mg or more) in the 2nd and/or 3rd trimester, reduces the risk of preeclampsia and preterm birth (14-16). However the level of that evidence is insufficient to draw final conclusions. An RCT is needed to assess whether e.g. 0.8 mg of FA supplementation in 2nd and 3rd trimester has a protective effect on preterm birth compared with the current Recommended Daily Average of 0.4 mg Food Folate Equivalents (FFE), (17) for which only a 0.1 to 0.2 mg FA supplementation would be needed.

Studies on folic acid antagonists show similar effects on congenital anomalies. The use of these kinds of medication during the first trimester of pregnancy is associated with an increased risk for congenital anomalies such as NTDs, urinary tract defects and cardiovascular defects (18-20), but not with pregnancy complications such as preterm delivery perinatal mortality, low birth weight and low Apgar scores (20).
Side-effects of folic acid

The safety of (high doses of) FA supplementation has been topic of debate. Concerns were mostly that FA supplementation would mask pernicious anaemia due to B12 deficiency and would increase the risk of cancer. Several studies were unable to detect the effect of masking pernicious anaemia (21). Furthermore, FA might be related to the risk of certain cancers, as shown by Ebbing et al (22), although other population-based studies have shown FA-use to be associated with a decline in cancer incidence (21). It might be that FA increases the risk of cancer for individuals with a history of or predisposition to cancer, or influenced growth of cancers that were silent. However, this is likely only the result of long-term exposure, and not when only using FA supplementation for less than a year around conception and during pregnancy. Recently the UK food agency reaffirmed its advice for compulsory fortification based on the latest

evidence from published and not yet published studies (23). Other concerns stem from a possible relation between childhood asthma and FA consumption during pregnancy (24). The strength of the evidence is however not such, that this has implications on recommendations of FA consumption during pregnancy at this time. However, it is important to critically follow all new evidence on this (and other topics) as well.

Because of a very low response rate, and termination of funding of the project, recruitment of participants stopped November 1st, 2013. Women who were pregnant before that date will be followed up, until a year after giving birth, in order to obtain data about pregnancy and birth outcome, and the presence of congenital anomalies. This follow up will be approximately till June 2015.

Study objective

In the proposed study, two main issues will be addressed: first, it will be studied whether a high dose (4.0 mg) of FA supplementation periconceptional has an added value over the now recommended low dose of 0.4 mg in the prevention of congenital anomalies (CA). Such a study requires a very large number of participants in order to have sufficient power to detect differences. It is virtually impossible to recruit this number of participants in one country, and therefore several international studies will be combined. The lead for this combined study is the International Clearinghouse for Birth Defects Surveillance and Research in Italy, where a FA supplementation trial is currently being conducted. Each of the two trials aims at recruiting 5000 women. A total of 10.000 women is sufficient to assess differences in congenital anomalies. Hopefully, more countries can and will participate in these combined analyses, so that differences in specific congenital anomalies can be detected as well.
The second main issue that will be addressed in the proposed study is whether 0.8 mg FA supplementation in later pregnancy (2nd and 3rd trimester), compared to 0.2 mg FA (RDA), has a preventive effect on preeclampsia and preterm birth.

Research questions:
1. What is the effect of a high (4.0 mg) versus low (0.4 mg) dose of folic acid supplementation from 4 weeks before conception to 12 weeks of gestation on the prevalence of folic acid related congenital anomalies?
2. What is the effect of 0.8 mg folic acid supplementation versus 0,2 folic acid supplementation from 12 weeks of gestation to the end of pregnancy on the prevalence of preterm birth and preeclampsia?

Secondary research questions:
3. Which side effects of periconceptional and prenatal folic acid use are reported by trail participants?
4. What associations between study groups and the incidence, severity and types of side effects reported, can be identified?
a. During the first period (until 12 weeks of gestation);

b. During the second period (from 12 weeks of gestation until the end of the pregnancy).

Study design

The Dutch study will be designed as a randomised controlled trial, with four intervention arms:
1) low dose (0.4 mg) of FA from 4 weeks preconception to 12 weeks of gestation, and RDA (0,2 mg) FA supplementation after 12 weeks of gestation;
2) low dose (0.4 mg) of FA from 4 weeks preconception to 12 weeks of gestation, and 0.8 mg FA supplementation after 12 weeks of gestation;
3) high dose (4.0 mg) of FA from 4 weeks preconception to 12 weeks of gestation, and RDA (0,2) mg FA supplementation after 12 weeks of gestation;
4) high dose (4.0 mg) of FA from 4 weeks preconception to 12 weeks of gestation, and 0.8 mg FA supplementation after 12 weeks of gestation.

Randomisation is double blind: participants, pharmacists and researchers are blind for the doses. Independent researchers of MediClara, AHZ and VUmc datamanagement have the randomisation code.

Intervention

Women in all intervention groups will receive identical pills, containing two different doses of folic acid (0.4 or 4.0 mg). Women will start taking the pills after randomisation, but at least 4 weeks before conception, and will receive new pills from their pharmacy every 16 weeks.
At 12 weeks of gestation, all women will receive a new set of pills, half of them will receive 0.2 mg supplements and half will receive 0.8 mg of FA.

Follow-up:
After randomisation, women will receive new pills every 16 weeks at the pharmacy, until a period of 12 months has gone by without them getting pregnant or until the end of their pregnancy (live birth, stillbirth, spontaneous abortion, or termination).

Study burden and risks

Intervention

Participants have to take one pill each day, starting at least one month before conception, until the end of pregnancy. This is largely consistent with the current advice given to women in the Netherlands who want to become pregnant or are pregnant. The difference between the current advice and the study intervention is in the duration of the usage of FA supplementation pills, respectively until 12 weeks of gestation and until the end of pregnancy. However, many pregnant women choose to use multivitamin supplements during the

whole pregnancy period and even afterwards, during breast feeding period. Therefore, for most participants participation will not differ much from their normal behaviour.

Measurements

Most measurements will be completed without involvement of the participant. These data will be retrieved from medical records and EUROCAT after consent. Additional information will be retrieved from small questionnaires, which can take several minutes to fill in, for example when picking up the pills at the CP.
It is possible that the GP, gynaecologist, midwife or other involved medical specialists take additional measurements which would not always be completed in usual care (but are optional in usual care), to make sure the medical records are sufficient for this study. These possible additional measures will not include invasive measurements.

Benefits

There are no direct health benefits for the participants. However, FA is shown to be effective in the prevention of NTDs, so participants profit from this risk reduction (6;48).
Additionally, FA supplements are administered for free to participants, therefore there is a financial benefit to those who would have used FA supplements on their own initiatives when not in the study.

Risks
With a high dose of 5.0 mg FA, some hypersensitivity reactions (rash, fever) have been reported, but these occur rarely.

Contacts

Public
Vrije Universiteit Medisch Centrum

van der Boechorststraat 7
Amsterdam 1081 BT
NL
Scientific
Vrije Universiteit Medisch Centrum

van der Boechorststraat 7
Amsterdam 1081 BT
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All women living in the Northern region of the Netherlands of 18 to 45 years old who want to become pregnant within 12 months are eligible for participation in the study.

Exclusion criteria

Women who had previous offspring with NTD and other women who take high doses of FA for any other reason and women who use FA-antagonists will be excluded from the study.
Further exclusion criteria are:
a) no informed consent given
b) not understanding Dutch
c) already pregnant at time of inclusion or within 4 weeks after start intervention
d) planning to move to an area where the study is not implemented
e) recently or at present using folic acid antagonists or antifolates or other drugs influencing the folic acid metabolism (methotrexaat, pyrimethamine, trimethoprim)
f) being affected by diabetes, megaloblastic anaemia and/or cancer (previous cancer or abnormal PAP smears)
g) being allergic to folic acid or any other ingredient of the pills used in this study
h) take defined dosages of folic acid for directions other than those listed in the above exclusion criteria.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	19-04-2012
Enrollment:	5000
Type:	Actual

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:	06-02-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-12-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2014
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	EUCTR2011-003325-10-NL
CCMO	NL37586.029.11