

Preventing preeclampsia

Drs Mark Walker and Shi Wu Wen discuss their clinical investigation of a potential new treatment for one of the world's leading causes of maternal deaths



To begin, could you outline the aims and objectives of the Folic Acid Clinical Trial (FACT)?

The purpose of FACT is to study the effect of the supplementation of 4.0 mg of folic acid throughout pregnancy. Based on our results, we are aiming to definitively establish whether or not a high-dose supplementation of folic acid throughout pregnancy is an effective preventative strategy in women who are deemed to be at high risk of developing preeclampsia (PE). The overall aim of our randomised controlled trial is to evaluate a new PE prevention strategy of high-dose folic acid supplementation from early pregnancy – that is, 8^{0/7} to 16^{6/7} weeks of gestation – until the delivery of the baby.

What is the scientific rationale behind using folic acid as a supplementation in pregnancy on PE?

Increased folic acid supplementation may work to reduce blood vessel inflammation and injury which in turn improves the health of maternal blood vessels and facilitates healthy formation of the placenta, thereby reducing the risk of PE. Indeed, some epidemiologic studies have shown the potential preventative effect of folic acid on PE. For example, in our Ottawa and Kingston (OAK) Birth Cohort of 2,951 mother-baby pairs, we established that supplementation with ≥ 1.0 mg folic



acid or multivitamins containing ≥ 1.0 mg folic acid in the early second trimester was associated with increased serum folate, lowered plasma homocysteine and reduced the risk of PE by 63 per cent. In another study, the occurrence of PE in pregnant women exposed to folic acid antagonists was compared to those who were not exposed. Interestingly, it was found that the risks of PE and severe PE were increased in the mothers with folic acid antagonist exposure.

Could you explain how FACT developed and why you decided to conduct it as a randomised controlled trial?

FACT developed as a result of cohort studies conducted by us and other research groups that suggested folic acid supplementation is associated with a decreased risk of PE. However, because observational studies are more subject to bias we recognised the need to conduct a randomised controlled trial to determine for certain if high-dose folic acid is an effective treatment strategy.

At what stage is FACT presently? Can you outline progress so far and explain the importance of the trial's international focus?

As of 9 June 2014, 975 study participants have been randomised into FACT. It is a truly international trial with 771 Canadian,

108 Australian, 59 Argentinean, 11 Jamaican and 26 UK study participants. With all of these countries now in the recruitment phase of the trial, we anticipate completing recruitment in January 2016. A large and concerted international effort is required to complete FACT in a timely fashion. Given the worldwide disease burden of PE, global outreach is paramount; we believe it is important to make sure the trial's results have global impact and can be applied to countries beyond Canada.

What do you hope will be the far-reaching effects of the trial following completion?

Ultimately, we hope we will be able to find a preventative strategy that will decrease the incidence, intensity and impact of PE. We are currently collaborating with Health Canada in a pilot study on FACT biomarkers to measure the polymorphisms of Methylene tetrahydrofolate reductase (MTHFR), methionine synthase (MTR) and other related lipid profile markers.

The knowledge gained from FACT biomarkers may offer the promise of new diagnostic and treatment avenues and may be helpful in designing new treatments and preventative strategies for all women of childbearing age at risk for developing PE.

What future research projects related to FACT are you exploring?

Our team of researchers believes that the women and children who participated in FACT are an invaluable cohort that can help support future research or the next generation of FACT. Clinical and basic scientific research such as further evaluating if high-dose folic acid supplementation in pregnancy is beneficial as a preventive strategy for social impairments associated with autism and other child developmental disorders. Furthermore, we would also like to explore the cardiovascular risks of postpartum women, and the interrelationship of folic acid with PE and intrauterine growth restriction (IUGR).



Facing the **facts**

Funded by the **Canadian Institutes of Health Research**, an international clinical trial is investigating the effect of folic acid supplementation in pregnancy on preeclampsia

PREECLAMPSIA (PE) AFFECTS 5 per cent of pregnant women worldwide. Signs of the condition include hypertension (high blood pressure) and proteinuria, a condition that causes the kidneys to spill a large amount of protein into the urine. Although most cases of PE are mild, if not diagnosed and monitored it can pose a serious threat to the health of women and their babies. Indeed, this and other hypertensive disorders of pregnancy are a leading global cause of maternal and infant illness, and even death. PE is responsible for approximately one-third of maternal deaths worldwide and the second most common cause of pregnancy-associated deaths in industrialised countries.

At present, the only way to cure PE is for the baby to be delivered. Because delivery is often required weeks before the projected birth date, PE is one of the leading causes of preterm delivery, accounting for 25 per cent of very low birth-weight infants. Additionally, recent studies have suggested that women who have suffered from PE are more likely to develop cardiovascular problems later in life. Given the disease burden of PE, novel therapies must undergo proper scientific investigation.

AN INNOVATIVE INVESTIGATION

Two eminent researchers, Drs Shi Wu Wen and Mark Walker, both based at the Ottawa Hospital Research Institute (OHRI) in Ottawa, Canada, are conducting an investigator-led, international, multi-centre, randomised, double-blind, placebo-controlled, phase III trial of 3,656 women. Funded by the Canadian Institutes of Health Research (CIHR), the team is aiming to discover whether 4.0 mg of folic acid supplementation from early pregnancy (8^{0/7} to 16^{6/7} weeks of gestation) until delivery is a beneficial prevention strategy for women at risk of developing PE.

Entitled the Folic Acid Clinical Trial (FACT), the study arose from the need to provide a scientific basis for supplementing pregnant women at risk of developing PE with high-dose folic acid. Indeed, recent studies suggest that successful prevention of PE may require a higher dose of

folic acid than the amount of folate derived from food intake or what is usually taken during pregnancy. Additionally, the Society of Obstetricians and Gynaecologists of Canada (SOGC) currently recommends that pregnant women who fall within specific risk categories for birth defects take 4.0 mg of folic acid before and during the first trimester of pregnancy. However, while there seems to be a connection between intake of folic acid and prevention of PE, there is a lack of conclusive evidence about the preventative effect of high-dose folic acid supplementation. With the weighty disease burden of PE, it is paramount that novel therapies such as folic acid supplementation undergo thorough scientific investigation – and this is where FACT comes in.

MAPPING THE METHODS

In FACT, pregnant women at high risk of developing PE will be randomised in a 1:1 ratio to 4.0 mg of folic acid or a placebo. Although the 4.0 mg folic acid supplementation is the same as the current recommended dosage in women with a family or personal history of neural tube defects, it will be taken throughout the entire course of the pregnancy rather than only during the first trimester. Women who are taking up to 1.1 mg of folic acid are eligible for the trial; therefore, since the researchers will not ask women to change their current practices, the total folic acid dose may be 5.1 mg in the trial arm and up to 1.1 mg in the placebo arm. The 4.0 mg folic acid or the placebo will be taken daily by oral administration from randomisation (8^{0/7} to 16^{6/7} weeks) until delivery of the baby.

The folic acid and placebo tablets both have identical appearances, preventing the study participants and researchers from knowing which the participant is taking. While the researchers expect that the effects of folic acid obtained from food and routine supplementation will be balanced through randomisation, they intend to collect information on additional dietary sources of folic acid through the use of a food questionnaire.

INTELLIGENCE

EFFECT OF FOLIC ACID SUPPLEMENTATION IN PREGNANCY ON PREECLAMPSIA – FOLIC ACID CLINICAL TRIAL (FACT)

OBJECTIVE

To evaluate a new preeclampsia (PE) prevention strategy: 4.0 mg (1.0 mg x 4) of folic acid supplementation versus placebo from early (8^{0/7} to 16^{6/7} weeks of gestation) pregnancy until delivery.

SPONSOR

Ottawa Hospital Research Institute (OHRI)

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DR SHI WU WEN is a Senior Scientist in the Clinical Epidemiology Program at the OHRI, Professor in the Department of Obstetrics and Gynecology and in the Department of Epidemiology and Community Medicine, member of the Faculty of Graduate Studies at the University of Ottawa, and Visiting Professor of Anhui Medical University and Central-South University in China. He has published over 200 peer-reviewed articles in numerous top tier medical journals.



Folic Acid Clinical Trial



Study participants will have three visits: the first will be at the time of recruitment, between 8^{0/7} and 16^{6/7} weeks of gestation, the second between 24^{0/7} and 26^{6/7} weeks of gestation and the third between 34^{0/7} and 36^{6/7} weeks of gestation. During these three visits, systolic and diastolic blood pressure measurements will be taken, the study participants' weight will be obtained and the presence of protein in their urine will be assessed by dipstick. At the time of delivery of the baby, further data is collected, including blood pressure measurements, and then a telephone interview 42 days after the birth will complete the data collection.

The Folic Acid Clinical Trial will inform clinical decisions about preventing preeclampsia, providing solid scientific rationale for offering or withholding high-dose folic acid supplementation

DATA ANALYSIS

The researchers will analyse the differences between prognostic variables and intake of folic acid from other sources in both the intervention and placebo groups. Chi-square tests will be used in the comparison of incidences of PE and occurrences of secondary outcome measures (such as maternal death, spontaneous abortion, stillbirth and neonatal death) between the intervention and placebo groups. Additionally, multiple logistic regression analysis will be used to account for potential confounding factors.

To ensure safety, an independent Data and Safety Monitoring Board (DSMB) will

periodically review and evaluate accumulated trial data for study participant safety, conduct and progress. Furthermore, any adverse medical occurrences reported or observed during the study, regardless of their relationship to the treatment, will be collected, documented and reviewed.

FUTURE DIRECTIONS

Looking ahead, Wen and Walker are confident that FACT will provide much-needed answers about the effects of high-dose folic acid supplementation. At present, lack of conclusive evidence could result in two unfavourable outcomes: folic acid treatment may not be offered, denying women and their offspring a potentially beneficial therapy, or clinicians may use high-dose folic acid simply because there are no other effective therapies to offer, potentially causing needless suffering if folic acid supplementation is found to be harmful.

The researchers believe the results from FACT will inform clinical decisions about preventing PE, providing solid scientific rationale for offering or withholding high-dose folic acid supplementation. Additionally, they are eager to conduct follow-up studies with the study participants in order to explore whether folic acid supplementation during pregnancy has any long-term impacts on the health of the women and their babies.

PREECLAMPSIA: THE RISK FACTORS

Women between 8^{0/7} to 16^{6/7} weeks of gestation are eligible to participate in FACT if they have been diagnosed with high blood pressure, pre-pregnancy diabetes, are obese, expecting twins, or suffered from PE in a previous pregnancy.