Effect of High Dose Folic Acid Supplementation in Pregnancy on Pre-eclampsia (FACT): Double Blind, Phase III, Randomised Controlled, International, Multicentre Trial

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BMJ 2018;362:k3478

ABSTRACT

Preeclampsia is a serious medical condition, affecting approximately 3% to 5% of pregnancies, accounting for more than 35,000 maternal deaths annually worldwide and an important factor in maternal morbidity. Preeclampsia affects multiple organ systems and leads to an increased risk of other serious maternal and neonatal complications in pregnancy. Since delivery of the placenta is the only known cure, preeclampsia is a leading cause of preterm delivery, perinatal morbidity, mortality, and long term disability. Epidemiological studies of the association between folic acid supplementation and the incidence of preeclampsia show promise, although findings have been inconsistent. The current study, the Folic Acid Clinical Trial, was designed and conducted to evaluate the effect of daily supplementation with 4.0 mg folic acid beyond the first trimester on the risk of developing preeclampsia among pregnant women at high risk of this condition.

The researchers performed a randomized, double-blind, placebo-controlled, phase III international multicenter trial carried out at 70 high-risk obstetric referral centers covering diverse populations in Canada, Argentina, Australia, Jamaica, and the United Kingdom. Pregnant women eligible for participation in the trial included those between 8 and 16 completed weeks of gestation with a confirmed viable fetus and at least one of the following risk factors for preeclampsia: preexisting hypertension, prepregnancy diabetes (type 1 or 2), twin pregnancy, preeclampsia in a previous pregnancy, or body mass index greater than 35 kg/m². Documentation of body mass index measured (height and weight) between 3 months before pregnancy and up to the time of randomization was required as part of study eligibility. We excluded women if they had a known fetal anomaly or fetal death, a history of maternal medical complications (including renal disease with altered renal function),
epilepsy, cancer, or current use of folic acid antagonists, illicit drug or alcohol misuse (>2 drinks daily) during current pregnancy, known hypersensitivity to folic acid, multiple pregnancy, previous participation in this trial, or a history or presence of any important disease or condition that would preclude the use of high-dose (up to 5.1 mg daily) folic acid.

The primary outcome was preeclampsia, defined as hypertension presenting after 20 weeks’ gestation with major proteinuria or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). There were 2464 pregnant women with at least 1 high-risk factor for preeclampsia randomized between 2011 and 2015 (1144 to the folic acid group and 1157 to the placebo group); 2301 were included in the intention-to-treat analyses. Preeclampsia occurred in 169/1144 (14.8%) women in the folic acid group and 156/1157 (13.5%) in the placebo group (relative risk [RR], 1.10; 95% confidence interval [CI], 0.90–1.34; \( P = 0.37 \)). There was no evidence of differences between the groups for any other adverse maternal or neonatal outcomes.

The researchers concluded that supplementation with 4.0 mg/d folic acid beyond the first trimester does not prevent preeclampsia in women at high risk of this condition.

**EDITORIAL COMMENT**

(In the United States, where the large majority of women receive prenatal care, particularly in the third trimester, preeclampsia continues to play a role in maternal mortality but has an even larger impact on neonatal morbidity and mortality, primarily through the need for preterm delivery. Worldwide, preeclampsia continues to be one of the largest contributors to both maternal and neonatal morbidity and mortality. Thus, prevention of preeclampsia is a public health issue that has large morbidity, mortality, and cost implications both in the United States and across the globe. This need has led to a number of prospective randomized trials with a focus on prevention.

One nutritional intervention that may be of benefit is calcium. There have been several prospective, randomized trials that do find benefit with a decreased risk of preeclampsia when collected together in a systematic review: RR, 0.48; 95% CI, 0.33–0.69 (Cochrane Database Syst Rev 2006;3:CD001059). However, the benefit of calcium appears to be confined to settings that have a low calcium diet and the developing world: RR, 0.36; 95% CI, 0.18–0.70. Another dietary approach focused on supplementation with antioxidants. While early studies suggested that there might be a reduction in preeclampsia (Cochrane Database Syst Rev 2005;4:CD004227), subsequent, large studies did not find benefit from vitamin C and E supplementation on the risk of preeclampsia, RR, 0.97; 95% CI, 0.82–1.13 (N Engl J Med 2006;354:1796–1806; Lancet 2006;367:1145–1154). One always wonders whether earlier supplementation or larger doses would have made a difference, but thus far, these approaches have not been found to be of benefit in the United States. In other approaches, there have been 2 small trials examining bed rest, but there has been no statistically significant data to support bed rest as a modality to prevent preeclampsia; the same was true for exercise in pregnancy (Cochrane Database Syst Rev 2006;2:CD005939). In a small trial of garlic supplementation, while there was a slight reduction in the risk of preeclampsia, it was not statistically significant: RR, 0.78; 95% CI, 0.31–1.93 (Cochrane Database Syst Rev 2006;3:CD006065).

In the study abstracted above, the authors examined the potential impact of a higher dose of folic acid, 4.0 mg/d, as opposed to the lower 400 μg/d commonly used for all pregnant women. The authors randomized more than 2000 women to the higher folic acid dose versus placebo. Upon follow-up, there was absolutely no difference in preeclampsia, about 14%, in the 2 groups.

Thus, despite a large number of prospective trials of a wide range of interventions including the current one, an obvious medication or intervention to prevent preeclampsia has not been clearly identified, other than the antiplatelet medications, in particular low-dose aspirin. In a Cochrane meta-analysis, low-dose aspirin was associated with a reduction in the risk of preeclampsia overall and even a greater risk reduction in high-risk women (Cochrane Database Syst Rev 2007;2:CD004659). Because of the modest effect and the infrequency of the disease, the number needed to treat to prevent 1 case of preeclampsia was 72 overall, although this was reduced to 19 in the high-risk population. Of note, criticisms of some of the prospective, randomized trials have included that a number of the trials recruited patients up to 20 or 24 weeks’ gestation, long past any potential effect that the low-dose aspirin could have on placentation.
or early placental function thought to be at the root of preeclampsia. Thus, in meta-analyses that have examined dosage and timing of starting, there appears to be a larger and more consistent reduction in preeclampsia with a greater than 100-mg dose started by 16 weeks' gestation \( (Am \ J \ Obstet \ Gynecol \ 2018;218:287–293) \).

Thus, despite our best efforts, it appears that the best intervention we have at this time to reduce the risk of preeclampsia is aspirin. Historically, we have used the low-dose aspirin of 81 mg/d; it appears likely that a higher dose should be used and that probably the best way to do that is to simply double the dose to 162 mg/d. Further, this medication should be started right at the end of the first trimester and prior to 16 weeks' gestation. These efforts will reduce the risk of preeclampsia, but we need to do better. We continue to await the groundbreaking basic, translational, and clinical studies that will lead to better understanding of the pathophysiology of preeclampsia and its prevention and treatment.—ABC

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**Rare Autosomal Trisomies: Important and Not So Rare**

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Prenat Diagn 2018;38(10):765–771

**ABSTRACT**

Noninvasive prenatal testing (NIPT) analyzes cell-free DNA (cfDNA) in maternal plasma, which is a combination of DNA from maternal cells and from placental cytotrophoblast. The technique of massively parallel sequencing (MPS) sequences and counts large numbers of unique, single-locus DNA fragments and assigns them to the chromosome of origin. It is possible to assess all chromosomes, but most platforms have only been validated for nonmosaic trisomies of chromosomes 13, 18, and 21 and for sex chromosome aneuploidies. The phenotypic variability of sex chromosome aneuploidy and their lower positive predictive values and higher false-negative rates have raised questions regarding their suitability for use in routine NIPT. Similar arguments have been used in relation to microdeletion syndromes by organizations such as the American College of Obstetrics and Gynecology but could also apply to the analysis of trisomies involving the other autosomal chromosomes not currently validated for NIPT. There is scant literature regarding rare autosomal trisomies (RATs) identified at NIPT.

The authors performed a prospective case series of RATs and their genetic and obstetric outcomes and reviewed the available data regarding the clinical utility of NIPT using the Illumina sequencing platform, assessing all chromosomes that were reported for further management. Prospective data were collected on consecutive blood samples from patients receiving routine prenatal care through both private and public clinics from March 2015 to August 2017. Eligibility of patients was based on a singleton pregnancy, with no obvious abnormality, at a minimum of 10 weeks' gestation at sample collection with no other exclusion criteria. Samples were rejected if the gestation was less than 10 weeks, there was insufficient sample volume, or more than 5 days had elapsed between sample collection and receipt in the laboratory. Repeat sample collection was sought in these scenarios. Detection of a fetal abnormality was seen as an indication for invasive testing and not for NIPT.

There were 28 RATs identified in 23,388 samples (one in 835), the most common being trisomy 7 (n = 6), followed by trisomy 16 (n = 4) and trisomy 22 (n = 3). Abnormal outcomes occurred in 16 cases: miscarriage (n = 6), true fetal mosaicism (n = 5), and fetal structural anomaly on ultrasound (n = 5). Growth restriction was seen in 8 cases and correlated with very low pregnancy-associated plasma protein A levels. Two of the 17 live-born babies had a structural anomaly, and 1 had a phenotype similar to mosaic trisomy 16 despite a normal microarray result.