BMJ 2018;362:k3536 doi: 10.1136/bmj.k3536

EDITORIALS

Why is the search for pre-eclampsia prevention so elusive?

High dose folic acid fails to work for high risk women

Jenny E Myers *clinical senior lecturer*[1], Marcus Green *chief executive*[2], Lucy C Chappell *NIHR research professor in obstetrics*[3]

[1]University of Manchester, UK; [2]Action on Pre-eclampsia, UK; [3]School of Life Course Sciences, King's College London, UK

Pre-eclampsia remains a leading cause of maternal and perinatal mortality and morbidity globally. A recent World Health Organization analysis estimated that hypertensive disorders of pregnancy account for 14% of maternal deaths worldwide.[1] These stark facts drive the search for effective, safe, and affordable treatment to prevent pre-eclampsia. Although low dose aspirin reduces the risk of pre-eclampsia by 17%,[2] the remaining burden of disease is considerable and additional prophylactic treatments are still needed.

In a linked paper, Wen and colleagues (doi:10.1136/bmj.k3478) report the results of FACT, a double blinded, multinational randomised controlled trial that aimed to determine whether daily supplementation with 4 mg folic acid from the first trimester reduced pre-eclampsia in women with risk factors for the condition.[3] Pre-eclampsia occurred in a similar proportion in the placebo and intervention groups and the authors concluded that high dose folic acid does not prevent pre-eclampsia in high risk women. All secondary outcomes (including proportions of small for gestational age infants) did not differ between treatment and placebo groups.

For many years folic acid, at doses of around 0.4-0.5 mg daily, has been recommended to women before and during early pregnancy for the prevention of neural tube defects in offspring. These global recommendations follow consistent findings from epidemiological studies and trials,[4] which reported a reduction in prevalence of neural tube defects with folic acid supplementation.

More recently, observational studies have suggested an association between folic acid supplementation and a lower risk of other pregnancy complications such as pre-eclampsia.[5] The persistent problem of confounding by other dietary and lifestyle factors made firm conclusions difficult, but Wen and colleagues' adequately powered trial now provides definitive evidence that folic acid does not prevent pre-eclampsia.

It is important to maintain a clear distinction between the use of folic acid to prevent neural tube defects—which has substantial supporting evidence—and folic acid for the prevention of pre-eclampsia. The lack of benefit reported by Wen and colleagues must not detract in any way from the importance of folic acid supplements for the prevention of neural tube defects. For most women, this means low dose folic acid 0.4-0.5 mg daily, but some women, such as those taking antiepileptic drugs that interfere with folic acid metabolism,[6] or women with a previous baby with a neural tube defect, should take the higher recommended dose of 5 mg daily.

The new trial was designed and performed to a high standard and the findings are widely generalisable given the inclusion of women from Canada, the United Kingdom, Jamaica, Argentina, and Australia. The participants had established risk factors for pre-eclampsia, reflected in a 13-15% prevalence.

Optimal timing of folic acid supplements for pre-eclampsia prevention is debated, since the proposed mechanism of action could be either improvement of early (ie, first trimester) placentation or promotion of endothelial function (across all trimesters). Mean gestation at recruitment in the linked trial was 14 weeks. This likely represents real world supplementation, particularly in resource poor settings, where few women have contact with healthcare professionals before this time. Use of aspirin in these higher risk women was surprisingly low, given that most participants had a clear indication for aspirin prophylaxis.

These findings are another disappointment in the long search for a more effective measure to prevent pre-eclampsia. Other treatments, such as antioxidant supplements, have been equally biologically plausible but failed to translate into clinical benefits.[7] This may reflect the heterogeneity of a syndrome that ranges from early onset pre-eclampsia, with impaired placental function and poor fetal growth, through to predominantly maternal multi-organ manifestations with no fetal growth restriction.

The concept of a one size fits all prophylactic against pre-eclampsia is as unlikely as a single treatment for all diabetes regardless of the underlying cause. Even aspirin has different effects on pre-eclampsia risk in different subgroups, according

Correspondence to: LC Chappell lucy.chappell@kcl.ac.uk

to recent studies.[8] The proposal that pre-eclampsia phenotypes should be differentiated by the degree of placental involvement[9] needs further exploration to help inform new options for both prevention and treatment.

Where next for pre-eclampsia prevention? Bidirectional translational research between laboratory and clinic, robust pre-eclampsia phenotyping, and recognition of the needs of women in low and middle income countries where access to expensive therapeutic treatments is limited are essential. Meanwhile a global reduction in pre-eclampsia related deaths will require implementation of the evidence base that already exists for aspirin prophylaxis, prompt recognition and treatment of hypertension, use of magnesium sulfate (for prevention of eclamptic seizures), and timely delivery.

Recommendation of low dose folic acid supplementation before pregnancy and in the first trimester must continue for prevention of neural tube defects. But Wen and colleagues' trial does not support higher dose folic acid supplements for the prevention of pre-eclampsia. All pregnant women and their families hope for a healthy pregnancy and a happy outcome; until we find additional ways to prevent pre-eclampsia, thousands of women each year will not achieve this goal.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following: none.

Provenance and peer review: Commissioned; not peer reviewed.

1 Say L, Chou D, Gemmill A, etal . Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health* 2014;2:e323-33. 10.1016/S2214-109X(14)70227-X. 25103301
2 Duley L, Henderson-Smart DJ, Meher S, King JF. Antiplatelet agents for preventing pre-eclampsia and its complications. *Cochrane Database Syst Rev* 2007;(2):CD004659. 10.1002/14651858.CD004659.pub2. 17443552
3 Wen SW, White RR, Rybk N, etal . Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. *BMJ* 2018;362:k3478.
4 De-Regil LM, Peña-Rosas JP, Fernández-Gaxiola AC, Rayco-Solon P. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. *Cochrane Database Syst Rev* 2015;(12):CD007950. 10.1002/14651858.CD007950.pub3. 26662928
5 Bulloch RE, Lovell AL, Jordan VMB, McCowan LME, Thompson JMD, Wall CR. Maternal folic acid supplementation for the prevention of preeclampsia: A systematic review and meta-analysis. *Paediatr Perinat Epidemiol* 2018; published online 8 Jun. 10.1111/ppe.12476. 29882975
6 Royal College of Obstetricians and Gynaecologists. Epilepsy in Pregnancy: Green-top Guideline No. 68. 2016. https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg68_epilepsy.pdf.
7 Rumbold A, Duley L, Crowther CA, Haslam RR. Antioxidants for preventing pre-eclampsia. *Cochrane Database Syst Rev* 2008;(1):CD004227. 10.1002/14651858.CD004227.pub3. 18254042
8 Poon LC, Wright D, Rolnik DL, etal . Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history. *Am J Obstet Gynecol* 2017;217:585.e1-5. 10.1016/j.ajog.2017.07.038. 28784417
9 Staff AC, Benton SJ, von Dadelszen P, etal . Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* 2013;61:932-42. 10.1161/HYPERTENSIONAHA.111.00250. 23460278