WEEKLY IRON FOLIC ACID SUPPLEMENTATION FOLATE DOSE RESPONSE STUDY

ASSESSING THE POTENTIAL TO PREVENT NEURAL TUBE DEFECTS

OCTOBER 2019

SAHMRI South Australian Health & Medical Research Institute

UBC

UPM UNIVERSITI PUTRA MALAYSIA

NUTRITION INTERNATIONAL Nourish Life

ANAEMIA GLOBALLY

Globally, in 2016, it was estimated that one third (33%) of women of reproductive age (WRA; aged 15-49 years) were affected by anaemia.[1] While there are many causes of anaemia, it is thought that approximately 50% of cases are attributable to a deficiency in the essential trace mineral, iron.[2–4] Iron deficiency anaemia can have severe consequences as it impairs motor and cognitive function, resulting in fatigue and low productivity.[4–6] If iron deficiency anaemia occurs during pregnancy, there is an increased risk of an infant being born low birth weight, in addition to an increased risk of maternal and perinatal mortality.[7,8] This is especially important as 16 million adolescent girls aged 15-19 years old give birth each year in developing regions and pregnant adolescents are at a higher risk of becoming stunted, [9–12] as well as adverse infant birth outcomes such as: low birth weight, preterm birth, and anaemia.[13,14]

ROLE OF FOLIC ACID

Iron is not the only micronutrient implicated in anaemia, the B-vitamin folate also plays a role in red blood cell (RBC) formation.[15] Not only does folate play a role in the formation of RBCs, but it also plays a crucial role in the prevention of neural tube defects (NTDs).[16] NTDs occur early in pregnancy, before 28-days post-conception, a period in which many women do not know they are pregnant.[17] In 2015, it was estimated that there were 260,100 NTD-affected birth outcomes worldwide, resulting in approximately 117,900 under-5 deaths and varying levels of disability for those infants who survived.[18]

WHO GUIDELINES FOR WEEKLY IRON FOLIC ACID SUPPLEMENTATION

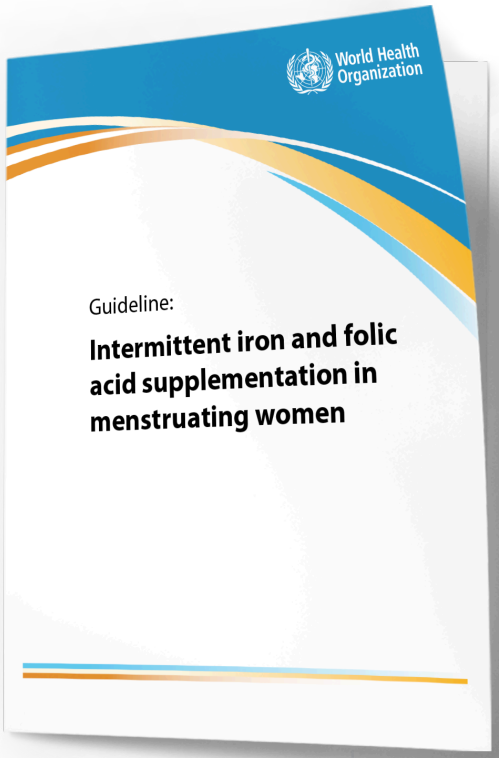
In 2011, the World Health Organization released guidelines for Intermittent iron and folic acid (IFA) supplementation in menstruating women.[19] This guideline recommends once weekly iron folic acid supplementation as a preventative public health measure for all menstruating adolescent girls and adult women in areas where the prevalence of anaemia is >20%.[19] The aim of this guideline is to improve haemoglobin concentrations and iron stores and reduce the risk of anaemia in WRA. Here, women are recommended to take supplements containing 60 mg of elemental iron and 2.8 mg of folic acid for a period of three months, followed by three months of no supplementation, after which supplementation should resume.[19] Alternatively, when appropriate, supplements can be given throughout the school or calendar year.

Table 1

Suggested scheme for intermittent iron and folic acid supplementation in menstruating women

Supplement composition	Iron: 60 mg of elemental iron[a] Folic acid: 2800 µg (2.8 mg)
Frequency	One supplement per week
Duration and time interval between periods of supplementation	3 months of supplementation followed by 3 months of no supplementation after which the provision of supplements should restart. If feasible, intermittent supplements could be given throughout the school or calendar year
Target group	All menstruating adolescent girls and adult women
Settings	Populations where the prevalence of anaemia among nonpregnant women of reproductive age is 20% or higher

[a] 60 mg of elemental iron equals 300 mg of ferrous sulfate heptahydrate, 180 mg of ferrous fumarate or 500 mg of ferrous gluconate.



The current WHO guidelines were informed by an evidence review that found intermittent iron supplementation (with or without other vitamins or micronutrients), compared with no supplementation, resulted in a 27% reduced risk of anaemia.[19] This was later confirmed by a 2014 Cochrane review found that intermittent iron supplementation (with or without other vitamins or micronutrients), compared with no supplementation, was able to significantly improve haemoglobin and ferritin concentrations and reduce the risk of anaemia.[20] However, in comparison to daily supplementation, intermittent regimes produced an increased prevalence of anaemia, despite similar haemoglobin concentrations. The authors of this review noted that intermittent supplementation is a feasible intervention in areas where daily supplementation is unlikely to be successful or not possible.[20] In the review conducted for this guideline, the evidence for the role of weekly folic acid in preventing NTDs was not assessed. The dose of folic acid present in this supplement was recommended as it is seven times the daily dose (0.4 mg) found to be effective in reducing NTDs in randomised control trials.[21]

Although studies examining weekly folic acid have found that it is effective at increasing red blood cell folate (RBC folate) and plasma folate concentrations,[16] a rigorous dose finding trial has not yet been conducted to know if 2.8 mg of folic acid per week is an optimal dose to reduce the risk of NTDs, as it is unethical to conduct trials with NTDs as an outcome. Thus, further research is needed to determine the most effective and safe weekly dose, if any, of folic acid needed to improve folate status to a level that would be associated with prevention of NTDs.[19]

PURPOSE OF WEEKLY FOLIC ACID DOSE RESPONSE STUDY

This study, supported by Nutrition International, will assess whether current WHO guidelines for the weekly supplementation of IFA with 2.8 mg of folic acid is sufficient for raising red blood cell folate (RBC folate and plasma folate) to concentrations associated with a reduced risk of a NTD.

METHODS

In 2019, a dose-finding trial is being conducted in order to provide evidence for the guideline on weekly folic acid supplementation in menstruating women. This study is a three-arm, parallel-group, randomised, placebo controlled trial with a 16 week intervention period followed by a 4 week washout period. This trial will take place in Selangor, Malaysia where a total of 300 women (18-45 years of age) will be recruited from the community surrounding Universiti Putra Malaysia. In Malaysia, the prevalence of anaemia among females was 35.5%.22 Ethical approval was received from Universiti Putra Malaysia (JKEUPM-2018-255) and the University of British Columbia (H18-00768).

To participate in this study, women must be: non-pregnant (self-reported), not planning on becoming pregnant, not currently taking micronutrient supplements containing folic acid or participating in another nutritional intervention, apparently healthy, not taking any medication known to inhibit folate status, and in the community during the time of the scheduled blood draws. Those women with severe anaemia (defined as haemoglobin <80 g/L) will be contacted within 3 days and referred to a local health centre for follow-up, but will not be excluded from the study unless their medical practitioner recommends withdrawal.[23]

Women will be randomized at the individual level to one of three treatment groups. Each supplement will contain 60 mg of iron as ferrous sulfate and either 0 mg, 0.4 mg, or 2.8 mg of folic acid. The current Recommended Dietary Allowance (RDA) for folic acid for WRA is 0.4 mg/day,[24] and it is also the daily dose recommended to decrease the risk of a NTD-affected pregnancy.[21] The dose of 0.4 mg was chosen as it is a formulation that is commonly available on the market and is used as the current standard of care for WRA.[19] The dose of 2.8 mg (7 d x 0.4 mg/d) folic acid per week was chosen because it is the current recommended

WHO formulation for weekly IFA supplementation. The tablet containing 0 mg of folic acid will act as the control. Supplements will be taken once weekly during a pre-specified day for 16 weeks.

Fasting, venous blood will be collected at 0, 16, and 20 weeks. From this, the primary outcome measure will be RBC folate at 16 weeks. Secondary outcomes will include: RBC folate concentrations at 20 weeks (after a 4 week washout period) as well as plasma folate concentrations at 16 and 20 weeks. The percentage of women with a RBC folate concentration ≥906 nmol/L (the level associated with the lowest risk of a NTD) following 16 weeks of treatment and 4 weeks of washout will also be determined.[25]

IMPLICATIONS OF THE RESULTS OF THE STUDY

This study will assess whether WHO guidelines for the weekly supplementation of IFA with 2.8 mg of folic acid are sufficient for raising RBC folate to the level needed to prevent NTDs. This research is needed by policy makers across the globe and will inform WHO guidelines on the optimal weekly dose of folic acid needed, if any, to effectively prevent NTD-affected pregnancies. Weekly IFA supplements that contain 2.8 mg folic acid are currently less accessible, and countries need to know if the additional costs and efforts to procure WHO recommended weekly IFA is a good investment. Cost-benefit analyses need to be made based on a country's context, considering factors such as: anaemia rates, adolescent pregnancy rates, and the prevalence of folate deficiencies and NTDs. Policymakers are demanding this information to justify the continued global recommendation of weekly folic acid in the weekly IFA formulation. The results of this trial will initially be shared with Malaysian stakeholders in early 2020, following this the results will be disseminated to the broader nutrition and health community in 2020.

Currently, Nutrition International reaches over 3 million adolescent girls with weekly iron and folic acid supplementation (WIFAS) programs. For more information about this study contact Dr. Tim Green (**Tim.Green@sahmri.com**) and for more information about Nutrition International's Adolescent Nutrition Programs contact Dr. Marion Roche (**mroche@nutritionintl.org**).

REFERENCES

1. World Health Organization. Prevalence of anaemia in women of reproductive age. Estimates by WHO region. [Internet]. Global Health Observatory data repository. 2017 [cited 2018 Oct 11]. Available from: http://apps.who.int/gho/data/view.main.ANAEMIAWOMENPREVANEMIAREG?lang=en
2. Stevens, GA, MM F, De-Regil L, Paciorek C, Flaxman S, Branca F et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995–2011: a systematic analysis of population-representative data. Lancet Glob Heal. 2013;1:E16–E25.
3. United Nations Children's Fund. Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers. Geneva; 2001.
4. Stoltzfus R, Mullany L, Black R. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. In: Ezzati M, Lopez A, Rodgers A, Murray C, editors. Iron deficiency anaemia. Geneva: World Health Organization; p. 163–210.
5. Balarajan Y, Ramakrishnan U, Ozaltin E, Shankar A, Subramanian S. Anaemia in low-income and middle-income countries. Lancet. 2011;378:2123–35.
6. Haas J, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. J Nutr. 2001;131:676S–688S.
7. Kozuki N, Lee AC, Katz J. Moderate to Severe, but Not Mild, Maternal Anemia Is Associated with Increased Risk of Small-for-Gestational-Age Outcomes. J Nutr [Internet]. 2012;142(2):358–62. Available from: http://jn.nutrition.org/cgi/doi/10.3945/jn.111.149237
8. Steer P. Maternal hemoglobin concentration and birth weight. Am J Cinical Nutr. 2000;71 (5 Supp:1285S–1287S.
9. Neal S, Matthews Z, Frost M, Fogstad H, Camacho A V., Laski L. Childbearing in adolescents aged 12-15 years in low resource countries: A neglected issue. new estimates from demographic and household surveys in 42 countries. Acta Obstet Gynecol Scand. 2012;91(9):1114.
10. UNFPA. Girlhood, not motherhood: Preventing adolescent pregnancy. New York; 2015.
11. Gigante DP, Rasmussen KM, Victora CG. Pregnancy increases BMI in adolescents of a population-based birth cohort. J Nutr. 2005;135:74–80.
12. Rah JH, Christian P, Shamim AA, Arju UT, Labrique AB, Rashid M. Pregnancy and lactation hinder growth and nutritional status of adolescent girls in rural Bangladesh. J Nutr. 2008;138:1505–11.
13. Hediger ML, Scholl TO, Schall JI. Implications of the Camden Study of adolescent pregnancy: interactions among maternal growth, nutritional status, and body composition. Ann N Y Acad Sci. 1997;817:281–91.

14. Strobino DM, Ensminger ME, Kim YJ, Nanda J. Mechanisms for maternal age differences in birth weight. Am J Epidemiol. 1995;142:504–14.
15. Gropper S, Smith J. Advanced Human Nutrition and Metabolism. 6th Editio. Belmont, CA, USA: Wadsworth, Cengage Learning; 2013. 500-509 p.
16. De-Regil L, Pena-Rosas J, Fernandez-Gaxiola A, Rayco-Solon P. Effects and safety of periconceptional folate supplementaion for preventing birth defects (Review). Cochrane Database Syst Rev [Internet]. 2014;35(12):1–254. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007950.pub3/full
17. Botto L, Moore C, Khoury M, Erickson J. Neural-tube Defects. N Engl J Med. 1999;341(20):1509–19.
18. Blencowe H, Kancherla V, Moorthie S, Darlison MW, Modell B. Estimates of global and regional prevalence of neural tube defects for 2015: A systematic analysis. Ann N Y Acad Sci. 2018;1414:31–46.
19. World Health Organization. Guideline: Intermittent iron and folic acid supplementation in menstruating women. World Heal Organ. 2011;1–30.
20. Fernández-Gaxiola AC, De-Regil LM. Intermittent iron supplementation for reducing anaemia and its associated impairments in menstruating women. Cochrane Database Syst Rev. 2011;2011(12).
21. Berry R, Li Z, Erickson J, Li S, Moore C, Wang H. Prevention of Neural-Tube Defects with Folic Acid in China. N Engl J Med. 1999;341(20):1485–90.
22. Institute for Public Health. National Health and Morbidity Survey 2015 (NHMS 2015). Vol. II: Non-Communicable Diseases, Risk Factors & Other Health Problems. Vol. II, Ministry of health. 2015. 1-291 p.
23. World Health Organization, Chan M. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva, Switz World Heal Organ [Internet]. 2011;1–6. Available from: http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Haemoglobin+concentrations+for+the+diagnosis+of+anaemia+and+assessment+of+severity#1
24. IOM. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. A Report of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline and Subcommittee on Upper Reference Levels of Nutrients, Food and Nutrition Board, Institute of Medicine. Washington, DC: National Academy Press; 1998.
25. Daly LE, Kirke PN, Molloy A et al. Folate levels and neural tube defects. Implications for prevention. JAMA. 1995;274:1698–702.

NUTRITION INTERNATIONAL

Nourish Life

Weekly Iron Folic Acid Supplementation Folate Dose Response Study

WWW.NUTRITIONINTL.ORG

2019

This study was made possible thanks to financial support from the Government of Canada through Global Affairs Canada.