THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.13546 J. Obstet. Gynaecol. Res. 2017

Randomized control trial comparing effectiveness of weekly versus daily antenatal oral iron supplementation in preventing anemia during pregnancy

Indra Malik R. Goonewardene and Diluk I. Senadheera

Academic Obstetrics and Gynaecology Unit, Teaching Hospital, Galle, Sri Lanka

Abstract

Aim: This study was conducted to determine whether weekly antenatal oral iron and folate supplementation is an effective alternative to a daily regimen in non-anemic pregnant women to prevent anemia and iron deficiency during the third trimester.

Methods: From December 2014 to April 2015, non-anemic pregnant women (n = 292) who presented to the Academic Obstetric Unit, Teaching Hospital Mahamodera Galle, Sri Lanka, at 14–22 weeks gestation and who had been treated with mebendazole 100 mg twice daily for three days were randomly allocated to receive 120 mg elemental iron, 3 mg folic acid and 100 mg vitamin C weekly (n = 149) or 60 mg elemental iron, 1 mg folic acid and 100 mg vitamin C daily (n = 143). Side effects were assessed at four weekly intervals and hemoglobin concentration (Hb), hematocrit and serum ferritin (SF) were measured at 32–36 weeks gestation.

Results: Only 106 participants in each group completed the study. There were no significant differences between the groups in mean duration of supplementation; presupplementation and post-supplementation mean Hb, hematocrit or SF levels; risk of developing anemia, ID or high Hb levels by an intension to treat analysis; and in those who completed the trial. Significantly greater side effects occurred in the daily compared to the weekly supplementation group.

Conclusion: In non-anemic pregnant women, a weekly regimen is an effective alternative to a daily regimen for antenatal oral iron and folate supplementation for preventing anemia and iron deficiency during the third trimester.

Key words: antenatal oral iron and folate, intermittent, non-anemic pregnant women, Sri Lanka, weekly versus daily.

Introduction

As the prevalence of anemia during pregnancy in Sri Lanka was estimated at > 40%, antenatal oral iron and folate supplementation commencing from the second trimester has been implemented for all pregnant women in Sri Lanka for several decades. During the last few years, the dose has been 60 mg of elemental iron and 1 mg of folate, as recommended by the World Health Organisation (WHO).[1] Currently, WHO recommends an intermittent regimen (e.g. weekly 120 mg of elemental iron and 2.8 mg of folate) for non-anemic pregnant women in communities where the prevalence of anemia is < 20%, as an effective alternative to a daily regimen for prevention of anemia during pregnancy.[2] It is thought that an intestinal

Received: March 30 2017.
Accepted: October 9 2017.
Correspondence: Professor Malik Goonewardene, Department of Obstetrics and Gynaecology, IMU Clinical Campus, Seremban, Malaysia. Email: malikg@eureka.lk
Former Senior Professor and Chair, Department of Obstetrics and Gynaecology, Faculty of Medicine, University of Ruhuna, P.O. Box 70, Galle, Sri Lanka.

epithelial cell becomes saturated with a single oral dose of iron, resulting in reduced iron absorption thereafter. Therefore, as intestinal cell turnover occurs every five to six days, if oral supplements are administered weekly, new intestinal epithelial cells would be exposed to each subsequent dose, resulting in improved iron absorption.[3–5] Weekly supplements have been shown to produce similar maternal and infant outcomes as daily supplements and to reduce the risk of the undesirable high levels of hemoglobin (Hb) in mid and late pregnancy.[2,6,7] However the quality of evidence available to support this is poor, thus further research on this subject has been recommended.[2,7] Intermittent oral iron supplementation may also reduce peroxidase and free radical mediated oxidative stress that damages the intestinal mucosa resulting in the unpleasant gastrointestinal side effects associated with daily oral iron supplements.[8–10] Therefore, weekly regimens may be more acceptable to women and therefore increase their compliance.[2,6,7] However, intermittent supplementation programs have been shown to increase the risk of mild anemia at term, especially in communities where the prevalence of anemia and iron deficiency (ID) is relatively high.[7,11–13] Furthermore, the reduction of gastrointestinal side effects per se may not improve compliance, and other strategies may be required to improve compliance in addition to the effectiveness of antenatal oral iron supplementation programs.[14–17]

In 2001, a randomized control trial (RCT) conducted at the Academic Unit of the Teaching Hospital Mahamodera Galle (THMG), Sri Lanka demonstrated that a daily regimen of antenatal oral iron supplementation was markedly better than weekly or thrice weekly regimens for preventing anemia during the third trimester of pregnancy.[11] This finding was most probably a result of the high prevalence of anemia and ID in the women presenting for antenatal care to the unit at that time.[18]

There is some evidence to suggest that the prevalence of anemia during pregnancy in Sri Lanka is probably < 20% currently, at least in certain regions of the country.[19,20] Although in 2009 the national prevalence of anemia in pregnancy was estimated to be approximately 16.7%, with wide regional variations from 7% to 29%, only 228 pregnant women were sampled and the estimates of anemia in non-pregnant women were as high as 35% in some regions.[19] In contrast, the national estimate of overall anemia in Sri Lanka in 2007 was 34%.[21] As Sri Lanka has a good healthcare system and it is possible to confirm the non- anemic status of pregnant women at the booking visit, as well as to monitor their hematological status and change to a therapeutic regimen if anemia is detected during pregnancy, weekly antenatal oral iron supplementation may be suitable for non-anemic pregnant women in areas where the prevalence of anemia is < 20%. Therefore it has been suggested that the current practice to routinely administer daily supplements of 60 mg of elemental iron to all pregnant women in Sri Lanka should be reviewed.

Prior to the commencement of the current RCT, a cross-sectional study of women presenting for antenatal care to the unit demonstrated that only 16.6% were anemic, defined as a Hb concentration of < 11 g/dL, and that the rate of ID was 36.9%, based on a cutoff serum ferritin (SF) value of < 30 μg/L, which was found to be the best SF cutoff level for the detection of anemia in the study population (Senadheera and Goonewardene, unpublished observation). Therefore, the objective of the current RCT was to evaluate whether a daily regimen of antenatal oral iron and folate supplementation could be replaced with a weekly regimen in non-anemic women presenting for antenatal care to the unit to prevent anemia, without causing a significant reduction in Hb concentration during the third trimester of pregnancy.

Methods

As the mean Hb in women who presented for antenatal care to the unit was 11.6 g/dL ± 0.6 (mean ± standard deviation [SD]) (Senadheera and Goonewardene, unpublished observation), a minimum clinically relevant difference of Hb was considered to be 0.3 g/dL. Therefore, to detect a non-inferiority level of -0.3 g/dL with a significance of 0.01 and a power of 90% for weekly compared to daily oral iron and folate supplementation, the minimum sample size for a two arm non inferiority RCT was calculated to be 105 participants for each arm.[22] Allowing for a post randomization dropout rate of 40%, a total sample of 294 was targeted. Using computer-generated random numbers and sequentially numbered, sealed, opaque envelopes, the parallel random allocation sequence in a 1:1 ratio was prepared.

Consecutive pregnant women (n = 350) at 12–20 weeks gestation, presenting to the antenatal clinic from November 2014 to January 2015, were enrolled in the study. When venous blood was drawn for routine antenatal investigations including the full

blood count (FBC) at the THMG, an additional 5 mL of blood was obtained for the cross-sectional study carried out to assess the rate of anemia and ID in these women. As SF assessment facilities were not available at THMG, this second sample of blood was sent to Durdan's Hospital Laboratory, Galle (DHLG) where the hematological indices were measured by flow cytometry and hydrodynamic focusing methods using a Sysmex-XS-500i System and SF was measured by electrochemiluminescence using a Cobas-e411 Analyzer. Details of any previous iron supplementation were documented.

All women were advised to take 100 mg of mebendazole twice daily for three days and then 200 mg daily tablets of ferrous sulfate (elemental iron 60 mg), 1 mg folic acid and 100 mg vitamin C supplementation at approximately 11.00 hours or 07.00 hours (i.e. approximately 1 h before lunch or dinner and at least 3.5 h after a previous meal or tea). They were also advised to take 300 mg calcium lactate pentahydrate tablets twice a day after lunch and dinner, according to Sri Lankan national guidelines.

Two weeks later, at the next clinic visit, when the FBC and SF reports were available, women with Hb levels < 11 g/dL were identified as anemic and irrespective of their Hb level, women who were diagnosed with hematological disorders and chronic diseases (e.g. thalasemia, rheumatoid arthritis, chronic renal disease) were excluded from the study. From December 2014 to April 2015, a total of 292 non-anemic pregnant women at 14–22 weeks gestation were assigned to the two arms of the RCT using the predetermined random allocation sequence. The participants were assigned to either continue with their daily supplements as described above (n = 143) or to take a weekly supplement of 120 mg elemental iron and 3 mg of folic acid (n = 149). The use of the WHO recommendation of a weekly dose of 2.8 mg of folic acid was not possible as the folic acid tablets available in Sri Lanka contain 1 mg each. In the weekly supplementation group, the vitamin C and calcium supplements were also administered weekly. The participants were given the number of tablets required for six weeks of supplementation to enable them to take the stipulated number of tablets even if they missed the next scheduled clinic visit in four weeks.

All participants were assessed for side effects using a structured questionnaire at four weekly intervals administered by the second author who was blinded to the type of intervention. Their Hb, hematocrit and SF levels were measured again at 32–36 weeks gestation at the DHLG, which was also blinded to the type of intervention.

Anemia was defined as Hb < 11 g/dL and ID was defined as SF < 30 μg/L (Senadheera and Goonewardene, unpublished observation). Continuous variables with normal distributions are presented as means with 95% confidence intervals (CIs) and were compared using the t-test. Discrete numerical variables are presented as medians with interquartile ranges. Categorical variables are presented as percentages. The mean Hb, hematocrit and SF levels and the relative risks (RR) for the development of anemia and ID of participants who were reviewed at 32–36 weeks gestation were compared between the two groups. An intension to treat analysis was also carried out by including the participants who did not return for reassessment with those who became anemic or developed ID. The RR for the development of anemia and ID in the participants in the two supplementation groups were then compared. SPSS version 20 was used for data analysis.

Approval for the study was obtained from the Ethical Review Committee, Faculty of Medicine, University of Ruhuna (Ref 19/18/2014, 3.5) and the Director of the THMG. Informed written consent was obtained from all participants. The trial was registered in the Sri Lanka Clinical Trials Registry (SLCTR 2014/32, Universal Trial No. U1111-1158-6008 on November 21, 2014), and participants were enrolled from November 24, 2014.[23]

Results

Although 149 and 143 participants were assigned to the weekly and daily supplementation groups, respectively, only 106 participants in each group presented for repeat hematological assessments at 32–36 weeks gestation (Fig. 1). There were no significant differences in characteristics between the groups (n = 292) (Table 1). Forty-three and 37 participants did not present for repeat hematological assessments between 32 and 36 weeks in the weekly and daily supplementation groups, respectively. There were no significant differences in the mean duration of supplementation during the study (range 14–22 weeks in both groups, mean 18.2 weeks SD 2.6 in the daily vs mean 17.9 weeks SD 2.5 in the weekly group; P = 0.470). There were also no significant differences in the mean Hb, hematocrit and SF levels between the groups

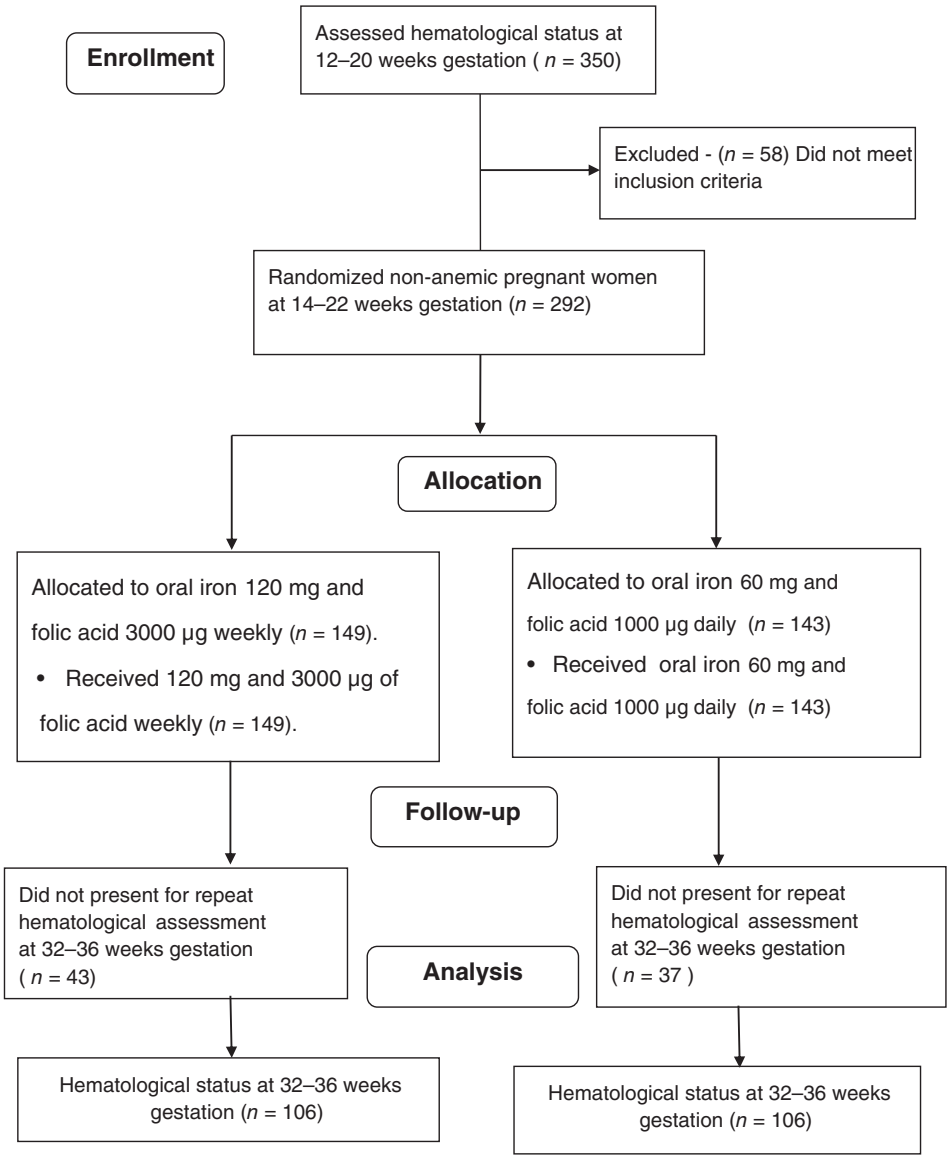

Figure 1 Flow chart of the method.

prior to and after oral iron supplementation in the participants who completed the RCT (n = 212) (Table 2). Although there was a significant reduction in SF levels in both groups, from 45.2 (95% CI 41.8–48.6) to 33.5 (95% CI 31.4–35.6) in the daily group and 48.6 (95% CI 45.1–52.1) to 34.6 (95% CI 31.6–37.6) in the weekly group ($P < 0.001$), the mean SF levels remained > 30 µg/L in both groups after supplementation (Table 2). Of the 57 non-anemic participants who had ID, 49% (15 in the daily and 13 in the weekly group) became anemic by the end of the trial, while only 6% (9) of the participants without prior ID became anemic by the end of the trial. The number of participants with ID increased from 28 (26.4%) in both study groups to 53 (50%) in the daily and 49 (46.2%) in the weekly group. However, there was no significant difference between the groups in the proportion of participants who became anemic or developed ID by the end of the trial (P = 0.561) (Table 3).

In the participants that completed the RCT, there was no increased risk of developing anemia or ID when administered weekly compared to daily antenatal oral supplements. Furthermore, there was no increased risk of developing Hb > 13 g/dL in the daily supplementation group (Table 4). The Hb,

Table 1 Characteristics of non-anemic women prior to antenatal oral iron supplementation (n = 292)

Characteristics	Daily group (n = 143)	Weekly group (n = 149)	P
Age in years			
Mean (95% CI)	27.6 (16.2–38.9)	27.5 (15.5–39.4)	0.410
Range	16–41	13–42	
Gestational age			
Mean (95% CI)	15.8 (11.1–20.5)	15.9 (11.3–20.4)	0.372
Range	12–20	12–20	
Parity			
Median (IQR)	1 (1–2)	1 (1–2)	-
Range	1–4	1–6	
Gestational age at registration 12–16 weeks	89 (62.6%)	87 (58.3%)	0.372
Received iron supplements before registration between 12–16 weeks	11 (7.7%)	10 (6.7%)	0.781
Gestational age at registration 17–20 weeks	55 (38.7%)	62 (40.9%)	0.122
Received iron supplements before registration between 17–20 weeks	9 (6.3%)	16(10.7%)	0.073

95% CI, 95% confidence interval; IQR, interquartile range.

Table 2 Presupplementation and post-supplementation hematological status in women who completed the randomized control trial (n = 212)

Hematological Parameters	Presupplementation			Post-supplementation		
	Daily group (n = 106)	Weekly group (n = 106)	$P^{\dagger}$	Daily group (n = 106)	Weekly group (n = 106)	$P^{\dagger}$
Hb g/dl						
Mean	11.9	11.8	0.239	11.8	11.7	0.731
95% CI	11.8–12.0	11.0–11.9		11.7–11.9	11.6–11.8	
Hct %						
Mean	34.8	34.4	0.360	35.2	35.2	0.913
95% CI	34.5–35.1	34.1–34.70		34.8–35.6	34.9–35.5	
SF µg/L						
Mean	45.2	48.6	0.692	33.5	34.6	0.663
95% CI	41.8–48.6	45.1–52.1		31.4–35.6	31.6–37.6	

†By t test. and CI, confidence interval; Hb, hemoglobin; Hct, hematocrit; SF, serum ferritin.

hematocrit and SF levels of the intention to treat analysis were similar to those of participants who completed the RCT (Table 5). The proportion of participants complaining of side effects was significantly greater in the daily compared to the weekly supplementation group, and nausea was the most common side effect reported (Table 6).

Discussion

A weekly regimen of antenatal oral iron supplementation was comparable to a daily regimen for preventing anemia or ID during the third trimester of pregnancy in non-anemic pregnant women. This was observed even after intention to treat analysis was

Table 3 Distribution of participants who completed the randomized controlled trial according to their presupplementation and post-supplementation serum ferritin and hemoglobin levels (n = 212)

Serum ferritin (µg/L)	Presupplementation		Post-supplementation			
	Hemoglobin ≥ 11 g/dL n = 212		Hemoglobin < 11 g/dL n = 37		Hemoglobin ≥ 11 g/dL n = 175	
	Daily group n = 106	Weekly group n = 106	Daily group n = 20	Weekly group n = 17	Daily group n = 86	Weekly group n = 89
<30	29	28	15	13	38	37
≥30	77	78	5	4	48	52

Table 4 Relative risk of developing anemia, iron deficiency and high hemoglobin concentrations after weekly compared to daily supplementation (n = 212)

Hemoglobin and Serum Ferritin categories	Daily supplement (n = 106)	Weekly supplement (n = 106)	Relative Risk (95% CI)	P
Hb < 11 g/dL	20	17	0.85	0.588
Hb ≥ 11 g/dL	86	89	(0.47–1.53)	
SF < 30 μg/L	53	50	0.94	0.680
SF ≥ 30 μg/L	53	56	(0.71–1.24)	
Hb < 13 g/dL	97	97	1.0	1.000
Hb ≥ 13 g/dL	9	9	(0.35–2.89)	

CI, confidence interval; Hb, hemoglobin; SF, serum ferritin.

Table 5 Relative risk of developing anemia, iron deficiency and high hemoglobin concentrations after weekly compared to daily supplementation: An intention to treat analysis (n = 292)

Hemoglobin and Serum Ferritin categories	Daily supplement (n = 143)	Weekly supplement (n = 149)	Relative risk (95% CI)	P
Hb < 11 g/dL	57	60	1.010	0.943
Hb ≥11 g/dL	86	89	(0.76–1.34)	
SF < 30 μg/L	90	93	0.991	0.927
SF ≥ 30 μg/L	53	56	(0.83–1.18)	
Hb < 13 g/dL	134	140	1.04	0.928
Hb ≥13 g/dL	9	9	(0.37–2.97)	

CI, confidence interval; Hb, hemoglobin; SF, serum ferritin.

Table 6 Side effects of antenatal oral iron supplementation (n = 292)

Side effect	Daily group (n = 143)	Weekly (n = 149)	$P^{\dagger}$
Nausea	56 (39%)	25 (17%)	< 0.001
Dyspeptic symptoms	40 (28%)	28 (19%)	0.031
Vomiting	27 (19%)	17 (9%)	0.039
Constipation	20 (14%)	10 (7%)	0.017

†By chi square test.

conducted, considering that the women who did not present for repeat hematological assessments between 32 and 36 weeks possibly developed anemia and ID, although it is unlikely that all of would have developed anemia and ID. A significantly larger proportion of women in the daily supplementation group reported side effects, with nausea being the most frequent; although the participants were not blinded to the type of intervention, weekly supplementation would have been more acceptable to them. Therefore, weekly antenatal oral iron supplementation appears to be appropriate for non-anemic pregnant women, although it was not suitable more than a decade ago.[10] This is probably because of improvements in the nutritional status of women as a result of the improved socioeconomic status in Sri Lanka. Although an increased risk of high Hb (> 13 g/dL) has been reported with daily supplements, this was not observed in the current study.[6]

Although this trial was carried out in a state hospital (99.9% of women in Sri Lanka deliver in hospitals and only approximately 10% of deliveries in Galle occur in private hospitals), the results of this study may be generalizable to the district of Galle, Sri Lanka. However, before recommending weekly antenatal oral iron supplementation for non-anemic pregnant women nationally, regional community-based studies need to be conducted in each district of Sri Lanka to gather national data. Similarly, before embarking on weekly antenatal supplementation programs for non-anemic pregnant women, it would be prudent to carry out regional community-based studies in other countries and settings to confirm the generalizability of this concept at present, even if earlier studies have shown that intermittent supplements were inadequate in a particular community.

The need to improve the effectiveness of antenatal oral iron supplementation programs, irrespective of

daily or weekly administration, needs to be stressed. All pregnant women attending the antenatal clinic in the unit are routinely counseled on how to store the supplements as well as the optimum method of intake, and the same procedure was adopted during the current study. A formal assessment of compliance would have enabled a better quantification of the amount of iron and folate received by the participants and provided a better idea of patient perceptions regarding the two regimens. It may also have also enabled greater compliance by motivating the women to comply with the advice given. However, as a pragmatic approach was adopted in the current trial, our results probably reflect the potential effectiveness of these regimens in the community. The administration of daily supplements for two weeks to all the participants prior to randomization to the weekly and daily supplementation groups was unavoidable as hematological reports were not available before the antenatal clinic ended for a particular day, and it was considered unethical to request an additional visit to the hospital to obtain the reports or withhold the standard (daily) supplementation for two weeks. The larger proportion of participants in the weekly compared to the daily group (10.7% vs 6.3%; $P = 0.073$) who registered for the trial between 17 and 20 weeks gestation and had received oral iron supplementation is unlikely to have significantly affected the results because the primary outcome measures were quite similar between the two groups.

The main limitation of the trial was the high proportion of women who did not present for repeat hematological assessment between 32 and 36 weeks gestation. This reflects a common practice seen in the unit, with pregnant women defaulting scheduled clinic appointments and presenting at term in labor. However, the randomization of more than 40% of women in excess of the minimum required sample size resulted in greater than the minimum required number of women presenting for the repeat hematological assessments. The intention to treat analysis also addressed this limitation. The strength of this study is that SF assays were also carried out, while most of the studies conducted in Sri Lanka with similar objectives have not studied SF levels, probably as a result of the higher cost.

In conclusion, in non-anemic pregnant women presenting to the unit for antenatal care, weekly antenatal oral iron supplements were comparable to daily supplements for preventing anemia and ID during the third trimester. Side effects were observed more frequently in the daily compared to the weekly supplementation group, with nausea the most common. Therefore, weekly antenatal oral iron and folate supplementation could be more acceptable to non-anemic pregnant women.

Disclosure

The cost of the FBC and SF assays were met by funds from the Department of Obstetrics and Gynaecology, University of Ruhuna.

The authors have no conflict of interest.

Author contributions

All authors have read and approved the final version of the manuscript.

References

1. World Health Organization. *Guideline: Daily Iron and Folic Acid Supplementation in Non-anaemic Pregnant Women*. Geneva: WHO, 2012.
2. World Health Organization. *Guideline: Intermittent Iron and Folic Acid Supplementation in Non-anaemic Pregnant Women*. Geneva: WHO, 2012.
3. Anderson GJ, Frazer DM, McKie AT, Vulpe CD, Smith A. Mechanisms of haem and non-haem iron absorption: Lessons from inherited disorders of iron metabolism. *Biometals* 2005; **18**: 339–348.
4. Frazer DM, Anderson GJ. The orchestration of body iron intake: How and where do enterocytes receive their cues? *Blood Cells Mol Dis* 2003; **30**: 288–297.
5. Frazer DM, Wilkins SJ, Becker EM *et al*. A rapid decrease in the expression of DMT1 and Dcytb but not Ireg1 or hephaestin explains the mucosal block phenomenon of iron absorption. *Gut* 2003; **52**: 340–346.
6. Casanueva E, Viteri FE, Mares-Galindo M *et al*. Weekly iron as a safe alternative to daily supplementation for nonanemic pregnant women. *Arch Med Res* 2006; **37**: 674–682.
7. Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2015: (10): CD009997.
8. Casanueva E, Viteri FE. Iron and oxidative stress in pregnancy. *J Nutr* 2003; **133** (Suppl 2): 1700S–1708S.
9. King SM, Donangelo CM, Knutson MD *et al*. Daily supplementation with iron increases lipid peroxidation in young women with low iron stores. *Exp Biol Med* 2008; **233**: 701–707.
10. Viteri FE, Casanueva E, Tolentino MC, Diaz-Francés J, Erazo AB. Antenatal iron supplements consumed daily produce oxidative stress in contrast to weekly supplementation in Mexican non-anemic women. *Reprod Toxicol* 2012; **34**: 125–132.
11. Goonewardene M, Liyanage C, Fernando R. Intermittent oral iron supplementation during pregnancy. *Ceylon Med J* 2001; **46**: 132–135.

12. Mumtaz Z, Shahab S, Butt N, Rab MA, DeMuynck A. Daily iron supplementation is more effective than twice weekly iron supplementation in pregnant women in Pakistan in a randomized double-blind clinical trial. *J Nutr* 2000; **130**: 2697–2702.
13. Young MW, Lupafya E, Kapenda E, Bobrow EA. The effectiveness of weekly iron supplementation in pregnant women of rural northern Malawi. *Trop Doct* 2000; **30**: 84–88.
14. Goonewardene M, Shehata M, Hamad A. Anaemia in pregnancy. *Best Pract Res Clin Obstet Gynaecol* 2012; **26**: 3–24.
15. Hyder SM, Persson LA, Chowdhury AM, Ekström EC. Do side-effects reduce compliance to iron supplementation? A study of daily- and weekly-dose regimens in pregnancy. *J Health Popul Nutr* 2002; **2**: 175–179.
16. Goonewardene IMR, Liyanage C. Efficacy of the current antenatal oral iron supplementation programme. *Sri Lanka J Obstet Gynaecol* 1996; **18**: 14–17.
17. Senanayake HM, Premaratne SP, Palihawadana T, Wijeratne S. Simple educational intervention will improve the efficacy of routine antenatal iron supplementation. *J Obstet Gynaecol Res* 2010; **36**: 646–650.
18. Goonewardene M, Seekkuge J, Liyanage C. Iron stores and its correlation to haemoglobin levels in pregnant women attending an antenatal clinic. *Ceylon Med J* 1995; **40**: 67–69.
19. Jayatissa R, Moazzem Hossain SM. *Nutrition and Food Security Assessment in Sri Lanka - 2009. Kurunegala District*. Sri Lanka: Medical Research Institute, 2010.
20. Chathurani U, Dharshika I, Galgamuwa D, Wickramasinghe ND, Agampodi TC, Agampodi SB. Anaemia in pregnancy in the district of Anuradhapura, Sri Lanka – need for updating prevalence data and screening strategies. *Ceylon Med J* 2012; **57**: 101–106.
21. Department of Census and Statistics. *Demographic and Health Survey 2006/7: Prevalence of Anaemia among Children and Women*. Sri Lanka: Health Sector Development Project, Ministry of Healthcare and Nutrition, 2009.
22. Julious SA. Sample sizes for clinical trials with Normal data. *Stat Med* 2004; **23**: 1921–1986 and the Sealed Envelope Ltd. 2012. Power calculator for continuous outcome non-inferiority trial. [Cited 05 June 2014]. Available from URL: https://www.sealedenvelope.com/power/continuous-noninferior/.
23. Senadheera D, Goonewardene M. Randomised control trial comparing effectiveness of weekly versus daily antenatal oral iron supplementation in preventing anemia during pregnancy. Sri Lanka Clinical Trials Registry No. SLCTR/2014/032. [Cited 23 Aug 2016]. Available from URL: http://trials.slctr.lk/trials/252. 2014.