RESEARCH PAPER

Impact of Iron-Folic Acid Supplementation on Cognitive Abilities of School Girls in Vadodara

ADITI SEN AND SHUBHADA J KANANI

From Department of Foods and Nutrition, Maharaja Sayajirao University of Baroda, Vadodara, India. Correspondence to: Dr Shubhada Kanani, 14, Anupam Society, Behind Pizza Inn, Jetalpur Road, Vadodara, India. E-mail: skanani28@yahoo.com
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Objectives: To assess impact of daily and intermittent iron-folate (IFA) supplementation on cognition of underprivileged primary schoolgirls in Vadodara.

Design: Experimental-control longitudinal study.

Setting: Municipal primary schools.

Participants: Schoolgirls (*n*=161) in the age group of 9 – 13 years.

Intervention: Participants at three randomly selected schools were given IFA tablets (100 mg elemental iron + 0.5 mg folic acid) either once weekly or twice weekly or daily for one year. The fourth was the control school.

Outcome measures: Digit span, maze test, visual memory test, and clerical task scores.

Results: IFA supplementation given daily and twice-weekly significantly improved cognition in most tests; the effect was not seen in once-weekly or control groups. In daily and twice weekly IFA groups, positive change in cognition test scores was relatively higher in girls with good compliance(>70% dose) vs. poor compliance; in anemic (hemoglobin<11 g/dL) vs non-anemic girls and in those with higher hemoglobin (Hb) gain (>1g/dL) vs. lower Hb gain.

Conclusion: Twice weekly IFA supplementation is comparable to daily IFA in terms of beneficial effects on cognition in young adolescent girls.

Keywords: *Anemia, Cognition, Iron-folate supplementation, School girls.*

Iron deficiency in school age and early adolescence has been primarily studied for its detrimental effect on hematinic status. However, in iron deficiency, decreased brain iron stores may impair the activity of iron-dependent enzymes necessary for the synthesis, function, and degradation of neurotransmitters(1) and produce scholastic under-achievement or behavioral disturbances in school children(2,3). Iron thus plays a vital role in cognitive development of growing children and adolescents. Studies indicate that iron supplementation has positive effects on hemoglobin (Hb) levels and growth(4,5). It may also have beneficial impact on cognitive abilities, in young women(6). It is worthwhile to explore if this impact will be seen with intermittent iron-folate supplements in young adolescents entering puberty. As suggested by the mucosal block theory, weekly or intermittent iron supplementation may show overall similar iron absorption over the week as compared to daily supplements. Further, intermittent doses reduce side effects, increase compliance, and reduce cost. Once weekly (iron-folic acid) IFA has already shown significant impact on Hb levels among adolescent girls, which were comparable to those with daily supplements(7). Since little is known about other non-hematinic benefits of intermittent and daily IFA supplementation, this study was undertaken with the objective of assessing the impact of intermittent (once and twice weekly) and daily IFA supplementation on

cognitive abilities of underprivileged schoolgirls in early adolescence (9-13 years).

METHODS

This was an experimental-control semi-longitudinal study; an efficacy trial to assess impact of iron-folic acid supplements on cognition.

Sampling: Using accepted procedures, desired sample size was calculated(8), which came to 46 per group. Allowing for dropouts, each study group required about 60 subjects of age 9-13 years; which were available in standards V and VI per school. Thus, four schools were randomly sampled from the sampling universe of 17 schools (all municipal primary schools for girls in the morning shift), and all the consenting girls in Standards V-VI were enrolled. The schools were comparable as regards variables which could independently influence cognition; such as home enviromnent (socio-economic background; slum conditions; parents' education) and school environment (government schools with similar syllabi and teaching facilities). Prior permission from the Primary School Board, Vadodara and informed consent from the students and their parents were taken.

Intervention: Three schools were randomly decided as experimental schools (ES) and the fourth was the control school (CS)(n=65). The participants in the three ES schools were given IFA tablets (100 mg elemental iron + 0.5 mg folic acid): either once weekly (E1: IFA-1Wkly) (n=94) or twice weekly (E2: IFA-2Wkly) (n=118) or daily (ED: IFA-Daily) (n=81) for one year. The investigators maintained regular supply of IFA, supervised the distribution and recorded compliance in all the schools. The class monitor/class teacher assisted and maintained compliance registers.

Pre-and post-intervention hemoglobin data were collected on all girls. In view of limited working school days, and the time required to conduct four cognitive tests twice in a year; a random 60% sample (n=240) was selected for the tests of cognition. Of these, data of 161 girls was available pre and post intervention; after also excluding girls who had attained menarche prior to or during the study, though they did receive IFA supplements.

Outcome variables: Hemoglobin levels were measured using cyanmethemoglobin method(9). The cognitive functions of the girls were assessed using two tests (Digit span and Maze test) adapted from the Gujarati version of Wechsler Intelligence Scale for Children (WISC)(10) and two tests earlier used in the department; suitably modified for this group. These tests have been employed in previous studies on school children and adolescents and found to be valid(11). Digit Span assesses shortterm memory for numbers, attention - concentration, and ability to recall the correct sequence of the numbers backward and forward; Maze test assesses visual-motor coordination and speed, and fine motor coordination; Visual Memory test assesses short-term memory; Clerical task assesses the ability to concentrate and discriminate (in this case locating similar looking (but different) letters on a page of Gujarati text). The change in each group for hemoglobin and cognition test scores (means and standard deviations) pre and post-intervention was calculated and compared between study groups. Girls with good compliance were defined as those who consumed ≥70% of the tablets given. All the data were coded, entered and analyzed in Epi Info, Version 6.04-d(12). To compare intervention groups for statistical significance of impact (P<0.05), ANOVA test; and to compare each group with control, students t test was used.

RESULTS

At baseline, all the four groups were statistically similar having comparable cognition test scores and Hb levels (P>0.05) (***Table* I,II**). Overall, the mean hemoglobin (Hb) was 11.3 g/dL at baseline, and more than two-third (68.3%) of the girls were anemic (Hb <12 g/dL).

Impact on hemoglobin levels: Each of the intervention groups showed significant higher (P<0.001) Hb increment vs. the controls (***Table* I**), with the mean Hb increment the highest (1.0 g/dL) in the IFA-2Wkly Group. The mean Hb increments among initially anemic girls in all the supplemented groups were higher than those among initially non-anemic girls, with IFA-Daily group showing highest increment (1.9 g/dL) followed closely by IFA-2Wkly (1.6 g/dL).

TABLE I CHANGE IN MEAN HEMOGLOBIN (g/dL) LEVELS AFTER THE INTERVENTION

Study Groups	N	Initial	Final	Mean change
E1	65	11.5 ± 1.06	12.1 ± 0.44	0.6 ± 0.88
E2	89	11.1 ± 1.47	12.0 ± 0.41	1.0 ± 1.23
ED	59	11.3 ± 1.69	12.2 ± 0.55	0.9 ± 1.38
CS	41	11.5 ± 0.67	11.6 ± 0.63	0.03 ± 0.24

E1: Once weekly IFA supplementation; E2: twice weekly IFA supplementation; ED: daily IFA supplementation; CS: Control, no supplementation. Values are Mean±SD.

Mean compliance with IFA tablets was 72%. Good compliance (≥70% dose consumed) was seen in more than 50% subjects in all 3 groups. Mean increase in Hb was significantly higher in good compliance group (0.9 g/dL to 1.5 g/dL) than in poor compliance group (0.08 g/dL to 0.3 g/dL), with impact better in IFA-Daily and IFA-2Wkly (P<0.001).

Impact on cognitive function: Experimental subjects showed higher increments in test scores than controls (***Table* II**). On comparing each group with control by 't' test, the increments in IFA-Daily and IFA-2Wkly were significantly higher than No-IFA, in all the four cognitive function (CF) tests; whereas IFA-1Wkly was significantly higher, only in two of the four tests. Within the intervened groups, in Digit Span and Clerical Task, IFA-Daily and IFA-2Wkly (p<0.05) had significantly better scores than IFA-1Wkly. Overall, IFA-Daily and IFA-2Wkly showed marked improvement in most tests, while IFA-1Wkly consistently showed less improvement in cognitive test scores.

Girls with good compliance showed better improvement in all four tests compared to those with poor compliance. IFA-2Wkly with good compliance was comparable to IFA-Daily in three of the four tests. In IFA-1wkly, even those with good compliance showed less impact than the comparison groups in 2Wkly and IFA-Daily regimens.

Hemoglobin gain vs cognitive function: ***Fig.*1** reveals that cognitive function scores were higher (though not signficant) among those who gained more than 1 g/dL Hb than those who gained less (P>0.05). Within those who gained higher level of Hb, IFA-2Wkly and IFA-Daily had better improvement in scores than IFA-1Wkly.

***Fig.*2** depicts the mean change in cognitive function test scores in initially anemic girls.

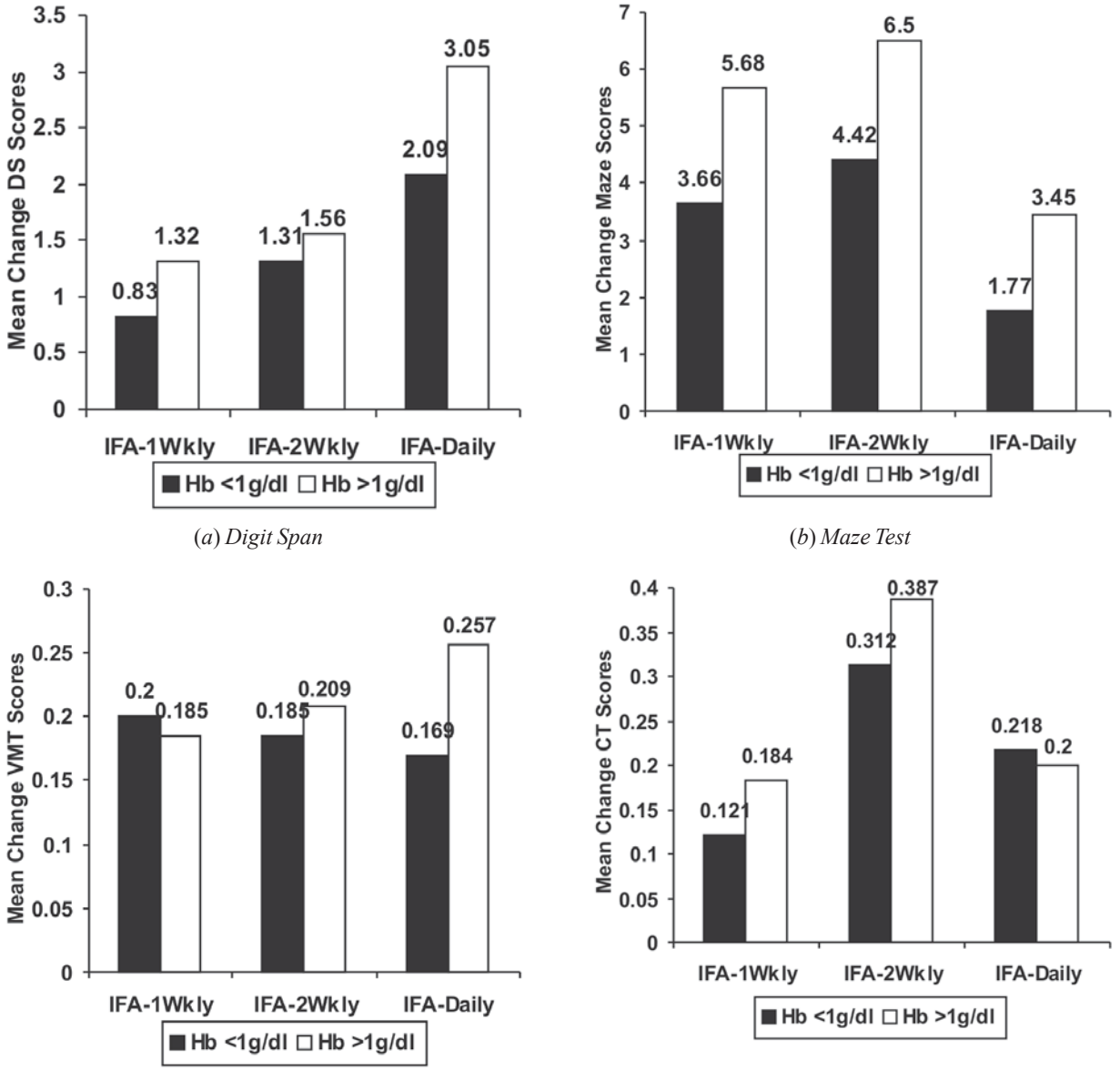
DISCUSSION

The findings of this study indicate that daily and twice weekly iron folate supplementation are comparable as regards significant impact on hemoglobin levels as well as cognitive functions of girls in the pubertal phase of development. The once-weekly IFA group consistently performed less satisfactorily in all the cognitive function tests. Further, those intitially anemic and those showing higher Hb gain (atleast 1 g/dL) showed better impact on cognitive function test scores; again more clearly in the daily and twice-weekly dose regimens; with

TABLE II CHANGE IN MEAN COGNITIVE TEST SCORES AFTER THE INTERVENTION

Study Groups	N	DS Test	Clerical Task	VMT	Maze Test
IFA-1Wkly (E1)	43	1.05 ± 1.47	0.15 ± 0.12	0.19 ± 0.13	3.25 ± 3.39
IFA-2Wkly (E2)	42	1.41 ± 1.28	0.34 ± 0.21	0.20 ± 0.13	4.35 ± 3.16
IFA-Daily (ED)	42	2.56 ± 2.05	0.22 ± 0.14	0.21 ± 0.15	4.07 ± 3.24
No-IFA (CS)	34	0.50 ± 1.23	0.14± 0.16	0.08 ± 0.14	1.47 ± 3.12

IFA-1Wkly (E1): Once weekly IFA supplementation; IFA-2Wkly (E2): twice weekly IFA supplementation; IFA-Daily (ED): daily IFA supplementation; No-IFA (CS): Control, no supplementation
Comparing with control: E2 and ED were highly significant (P<0.001) in all cognition tests except clerical task.
Within experimental group: In 2 of the 4 tests (DS and clerical task), ED significantly better than E2 (P<0.05); E2 significantly better than E1 (P<0.001).



(*a*) *Digit Span* (*b*) *Maze Test*

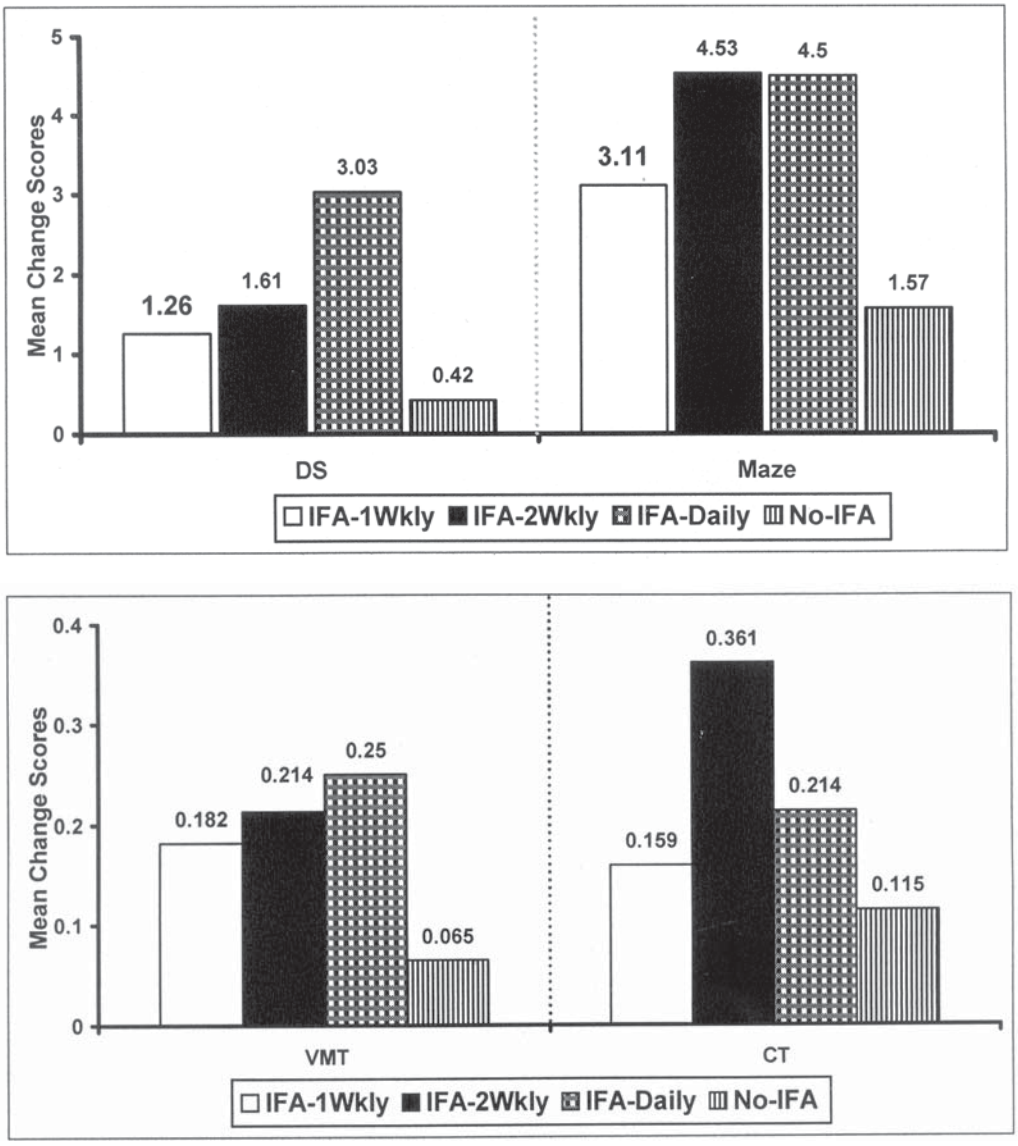
(*c*) *Visual Memory Test* (*d*) *Clerical Task*

IFA-1Wkly: once weekly IFA supplementation; IFA-2Wkly: twice weekly IFA supplementation; IFA-Daily: daily IFA supplementation

FIG. 1 *Mean change in cognition test scores in the school girls who gained ≥1g/dL vs. <1g/dL hemoglobin after the intervention.*

daily showing best impact. This evidence indicates that a higher uptake of iron (more frequent than once-weekly) is needed to lead to cognitive improvements; and the encouraging finding is that twice weekly IFA was consistently comparable to daily IFA in this regard. This finding has important program implications as twice weekly IFA supplement will cost less and be more feasible to deliver to beneficiary girls than daily IFA.

As regards the absorption of iron and reduction of anemia from a physiological perspective, studies reviewed by Hallberg(13) on daily as well as intermittent IFA supplementation reported that six times more iron was absorbed when IFA was given



IFA-1Wkly: Once weekly IFA supplementation; IFA-2Wkly: twice weekly IFA supplementation; IFA-Daily: daily IFA supplementation; No-IFA: Control, no supplementation

FIG. 2 *Mean change in cognitive function test scores in initially anemic girls.*

daily than when given weekly and concluded that there was no mucosal block during oral iron therapy in humans. However, he further stated that, if relatively high iron doses were given for a long time to subjects with low grade anemia, then all the doses of iron, all dosage schedules, and all iron preparations will give a similar Hb response. Thus, in the long run, intermittent iron-folate therapy will perhaps have a satisfactory impact on reducing anemia at lower cost and greater compliance. From our study and from literature reviewed(4,14,15), it appears that a long-term supplementation program, whether once or twice weekly, is likely to be as effective as daily IFA with regard to improvements in hemoglobin levels.

Literature relating to functional benefits of IFA interventions (such as cognitive abilities) among young adolescents is limited. In a double blind, placebo-controlled clinical trial in Baltimore, post

WHAT IS ALREADY KNOWN?

- Daily Iron-folate (IFA) supplementation improves hematinic status and growth among adolescent girls.

WHAT THIS STUDY ADDS?

- Intermittent IFA supplementation (twice-weekly) was comparable to daily IFA as regards significantly improving cognitive functions among school girls (9-13 years) and showed better impact than once-weekly IFA.

intervention, non-anemic iron deficient adolescent girls (N=73) (serum ferritin ≤12 µg/L with normal Hb) receiving oral ferrous sulphate (650 mg twice daily) performed better on a test of verbal learning and memory than the control group (P<0.02)(16). Studies done in Indonesia concluded that daily IFA supplementation to anemic school children significantly improved learning-achievement scores after three months(17-19). In rural Varanasi, 6-8 year olds showed significant improvements in tests such as object assembly and digit span after one year intervention (ferrous gluconate 200 mg)(20). We have also observed earlier a positive impact of IFA on cognitive abilities of school children (9-15 years) in Vadodara, who were supplemented with 60 mg elemental iron + 0.5 mg folic acid for 3 months (unpublished data).

This study underscores the importance of reducing anemia to improve cognition by showing that higher the magnitude of gain in Hb, higher the gain in CF test scores. It further indicates that to improve cognition, twice weekly IFA is superior to once weekly IFA and is likely to show a similar impact as daily IFA supplementation. Supervised supplementation, an important aspect of intermittent dosing, is feasible in school settings with active participation of class monitors and teachers.

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REFERENCES

1. Erikson KM, Jones B, Beard JL. Altered functioning of dopamine D_1 and D_2 receptors in brains of iron deficient rats. Physiol Pharmacol Behav 2001; 69: 409-418.
2. Pollitt E, Liebel RL. Iron deficiency and behaviour. J Pediatr 1976; 88: 372-381.
3. Sen A, Kanani SJ. Deleterious functional impact of anemia on young adolescent school girls. Indian Pediatr 2006; 43 : 219-226.
4. Kanani S, Poojara RM. Supplementation with IFA enhances growth in adolescent Indian girls. J Nutr 2000;130: 452S-455S.
5. Lawless JW, Latham MC, Stephenson LS, Kinoti SN, Pertet AM. Iron supplementation improves appetite and growth in anemic Kenyan primary school children. J Nutr 1994; 124: 645-654.
6. Murray-Kolb L, Beard JL. Iron treatment normalizes cognitive functioning in young women. Am J Clin Nutr 2007; 85: 778-787.
7. Beard JL. Weekly iron intervention: The case from intermittent iron supplementation. Am J Clin Nutr 1998; 68: 209-212.
8. Fisher AA, Laing J, Stoeckel J, Townsend JW. Handbook for Family Planning, Operations Research Design. 2nd edition. New York: The Population Council; 1991.
9. International Nutritional Anemia Consultancy Group. Guidelines for Eradication of Iron Deficiency Anemia. A Report of International Nutritional Anemia Consultancy Group. New York and Washington DC: INACG: The Nutrition Foundation; 1977.
10. Bhatt M. Gujarati adaptation of Wechsler Intelligence Scale for Children. Ahmedabad-India: Jayshree Mudranalaya Press; 1973.
11. Kanani S, Singh P, Zutshi R. The impact of daily iron vs. calcium supplementation on growth, physical work capacity and mental functions of school going adolescent boys and girls (9 to16 yrs) of Vadodara. MD Thesis,Department of Foods and Nutrition, M. S. University of Baroda, Vadodara, India. 1999.

12. Epi Info, Version 6.04-d. Centre for Disease Control and Prevention (CDC). Epidemiology Program Office, Atlanta, Georgia and World Health Organization, Global Programme on AIDS. Geneva: Switzerland; 2001.

13. Hallberg Z. Combating iron deficiency: daily administration of iron is far superior to weekly administration. Am J Clin Nutr 1998; 68: 213-217.

14. Kotecha PV, Patel RZ, Karkar PD, Nirupam S. Impact evaluation of Adolescent Girls' Anemia Reduction Program Vadodara district. Department of Preventive and Social Medicine. Government Medical College, Government of Gujarat and Unicef – Gujarat. 2002.

15. Sharma A, Prasad K, Rao KV. Identification of an appropriate strategy to control anemia in adolescent girls of poor communities. Indian Pediatr 2000; 37: 261-267.

16. Bruner AB, Joffe A, Duggan K, Casella JF, Brandt J. Randomized study of cognitive effects of iron supplementation in non-anemic iron deficient girls. Lancet 1996; 348: 992-996.

17. Soemantri AG, Pollitt E, Kim I. Iron deficiency anemia and educational achievement. Am J Clin Nutr 1985; 42:1221-1228.

18. Soemantri AG. Preliminary findings on iron supplementation and learning achievement of rural Indonesian children. Am J Clin Nutr 1989; 50: 698-702.

19. Soewonda S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. Am J Clin Nutr 1989; 50: 667-674.

20. Agarwal DK, Upadhyay SK, Tripathi AM, Agarwal KN. Nutritional Status, Physical Work Capacity and Mental Function in School Children. New Delhi: Scientific report 6, Nutrition Foundation of India; 1987.