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Iron versus Iron and Vitamin B6 Supplementation in Treatment of Iron Deficiency Anemia during Second Trimester of Pregnancy: Quasi Experimental Trial

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Abstract

Background: Anemia is one of the most prevalent complications during pregnancy. It is commonly considered a risk factor for poor pregnancy outcomes and can result in complications that threaten the life of both mother and fetus, such as preterm birth, and low birth weight. There is clear evidence to support prompt treatment in all patients with iron deficiency anemia because it is known that treatment improves quality of life and physical condition as well as alleviates fatigue and cognitive deficits. **Objective:** The aim of the study was to evaluate the value of addition of vitamin B6 to iron in treatment of iron deficiency anemia in pregnant women during the second trimester. **Patients and Methods:** The study was done by giving anemia pregnant women iron therapy and vitamin B6 which represent group A and iron therapy alone which represents group B. For each pregnant woman, age, parity and gestational history were taken before treatment. All pregnant women took their allocated treatment regularly for three weeks after diagnosis of iron deficiency anemia with complete blood picture and followed up after three weeks. **Results:** Results of the study revealed that there was no statistically significant difference between the two groups of therapy according to the hemoglobin level before treatment (p-value = 0.734), statistically significant higher mean value in after treatment than before treatment (p-value = 0.048), there was a significant difference in the rate of change of hemoglobin (p-value = 0.011) and body mass index (p-value < 0.001). **Conclusion:** Iron and vitamin B6 seems to increase hemoglobin level more than iron only. Thus, in pregnant women with iron deficiency anemia iron plus vitamin B6 may be

considered as a more effective alternative treatment than iron only.

Keywords

Vitamin B6, Iron Deficiency Anemia, Second Trimester, Hemoglobin

1. Introduction

All over the world, anemia is one of the public health problems and continued as a universal top cause of serious global health issues. Current suggestion from World Health Organization (WHO) document showed that about 38% (32 million) of pregnant women are anemic in the world. Out of this, 46.3% (9.2 Million of them are in Africa). Anemia is a condition in which the number of red blood cells and consequently their oxygen-carrying capacity is insufficient to meet the body's physiologic needs [1].

Iron deficiency anemia is common during pregnancy but can have serious consequences for the mother and child increasing the risk of miscarriages, stillbirths, prematurity, low birth weight, and severe neonatal complications that needs admission to intensive care units [1].

Iron deficiency is the most widespread nutritional deficiency in the world and it accounts for 75% of all types of anemia in pregnancy. It is due to the fact that diet during pregnancy is insufficient to supply iron requirements. It has a high prevalence in developing countries [2].

Oral iron is the usual treatment, but some cases may require intravenous iron. Iron deficiency anemia patients are associated with long hospitalization and many adverse events. [3].

A study indicates that vitamin B6 deficiency is one of the common causes of nutritional anemia in pregnancy, and a prospective study was conducted on pregnant women during each trimester that measures serum levels of iron, ferritin, vitamin B6, vitamin B12 folate and total protein/albumin. They observed that several pregnant women with anemia who were non-responsive to iron supplementation also had vitamin B6 deficiency, and that anemia in these cases improved with the administration of vitamin B6 [4].

A prospective study in healthy pregnant women showed that blood levels of iron, ferritin and vitamin B6, in particular, fell to the lower limit of the non-pregnant reference range by the third trimester. They conclude that it is important to take into account the deficiency of vitamin B6 besides iron in the evaluation of anemia during pregnancy [4].

Pyridoxal phosphate functions as a coenzyme of 5-aminolevulinic acid synthase, which is involved in the synthesis of heme, an iron-containing component of hemoglobin. Hemoglobin is found in red blood cells and is crucial for transport of oxygen throughout the body. Both pyridoxal and Pyridoxal phosphate are able to bind to the hemoglobin molecule and affect its ability to bind and re-

lease oxygen. However, the impact of this on normal oxygen delivery to tissues is not known. Vitamin B6 deficiency may impair hemoglobin synthesis and lead to microcytic anemia [5].

The effect of vitamin B6 and iron in treatment of iron deficiency anemia in pregnancy is still unknown, therefore, this study aimed to evaluate the effect of vitamin B6 and iron in treatment of iron deficiency anemia in second trimester women [6].

The aim of the study was to evaluate the value of addition of vitamin B6 to iron in treatment of iron deficiency anemia in pregnant women during the second trimester.

2. Patients and Methods

This is a quasi experimental study was conducted at outpatient Clinic, Ain Shams University Maternity Hospital, over a period of one year from May 2021 to May 2022. One hundred twelve pregnant women were recruited according to inclusion criteria from outpatient clinic, Ain Shams Maternity Hospital.

This study is looking for pregnant women between the ages of 18 and 45 who are between 13 and 26 weeks gestation and have iron deficiency anemia with a hemoglobin level between 8 and 10.5 gm%. Additionally, participants should be healthy and mentally competent.

Excluded those with anemia caused by conditions other than iron deficiency, autoimmune disease, Malabsorption disease, chronic inflammatory conditions, gastritis, women with renal disease or liver disease or bleeding tendency, malignancy, allergy to iron, women with persistent vomiting and pregnant women with placenta previa or other cause of persistent bleeding.

All patients attended Ain Shams Maternity University Hospital outpatient clinic with inclusion criteria for antenatal care subjected to: A. Complete history was taken: Personal history, obstetric history, menstrual history, medical history and past history. B. Investigations: Routine investigations including: CBC, liver function, kidney function tests, random blood sugar, coagulation profile (prothrombin time and partial thromboplastin time) and serum iron and ferritin and obstetric ultrasound study: For assessment of gestational age, fetal life, implantation site of placenta and fetal weight. C. By using non-equivalent Quasi Experimental Study, Patients were divided into two groups as follows:

Group A: received 120 mg elemental iron in form of ferrous fumarate 350 mg (one tablet once daily P.O) according to who guidelines and 75 mg vitamin B6 (pyridoxine one tablet once daily P.O) daily.

Group B: received 120 mg elemental iron in form of ferrous fumarate 350mg (one tablet once daily P.O) per day only.

They took their allocated treatment regularly for 3 weeks after diagnosis of iron deficiency anemia (8-10.5 gm %) with complete blood count. Then hemoglobin level of pregnant women in both groups was assessed after three weeks.

Primary outcome: hemoglobin level measured (3 weeks after the onset of therapy).

Secondary outcome: Side effects of treatment (nausea, vomiting, constipation), compliance of patient, maternal morbidity; e.g. Preeclampsia, preterm labor and fetal morbidities: LBW, IUGR.

Statistical analysis: ***Sample Size and sample size justification*****:** Using G power 3.1 software for sample size calculation, setting power at 80%, alpha error at 0.05 and assuming medium effect size difference (d = 0.5) between two study groups regarding mean hemoglobin level 3 weeks after onset of therapy, sample size of 102 women will be needed (51 women/group) to detect difference between two groups using two sided two-independent samples t test, assuming 10% drop out rate, sample will be increased to 56 women per group (total 112 women) and sample size calculated using assumption (no reference paper) pilot study.

Ethical consideration: A written informed consent was obtained from all participants before screening and enrollment. Participants participated voluntarily in the research and their confidentiality was respected. Benefits and risks from participation in the research were explained to all participants after approval of research ethical committee.

3. Results

The following table (Table 1) shows that there was no statistically significant difference between group A and group B regarding age and gestational age with p-value ($p > 0.05$).

The following table (Table 2) shows that there was statistically significant difference between group A and group B regarding body mass index in which

Table 1. Comparison between the two studied groups according to age and gestational age.

	Group A (n = 58)	Group B (n = 58)	p
Age (years)			
Min. - Max.	18.0 - 45.0	19.0 - 42.0	0.875
Mean ± SD.	29.56 ± 6.79	29.41 ± 6.14	
Gestational age (weeks)			
Min. - Max.	13.0 - 26.0	13.0 - 26.0	0.652
Mean ± SD.	18.93 ± 4.33	19.29 ± 4.29	

Student t-test.

Table 2. Comparison between the two studied groups according to body mass index.

BMI (kg/m^2)	Group A (n = 58)	Group B (n = 58)	p
Min. - Max.	19.0 - 28.0	19.0 - 31.0	<0.001
Mean ± SD.	22.75 ± 2.33	25.20 ± 2.89	

Student t-test. BMI = Body mass index.

group B is higher than group A. with p-value ($p < 0.05$).

The following table (Table 3) shows no statistically significant difference between groups according to hemoglobin level before treatment, with p-value ($p > 0.05$), while, statistically significant higher mean improvement in group A than group B according to hemoglobin level after treatment, with p-value ($p < 0.05$) and additionally, a highly statistically significant higher mean value in after treatment than before treatment according to hemoglobin level in each group, with p-value ($p < 0.001$).

The following table (Table 4) shows that there was a statistically significant higher amount change of hemoglobin level in group A than group B, with p-value ($p < 0.05$).

The following table (Table 5) shows that there was no statistically significant difference between group A and group B regarding side effects and compliance, with p-value ($p > 0.05$).

The following table (Table 6) shows that there is no statistically significant difference between groups according to maternal morbidities and fetal morbidities, with p-value ($p > 0.05$).

4. Discussion

Anemia is the most frequent physiological disturbance in the world throughout the life of a woman. It is a serious condition in industrialized and semi-industrialized countries and it becomes a very serious condition in poor resources

Table 3. Comparison between the two studied groups according to hemoglobin.

Hemoglobin level (g/dL)	Group A (n = 58)	Group B (n = 58)	p
Before treatment			
Min. - Max.	8.20 - 10.50	8.10 - 10.50	0.734
Mean ± SD.	9.77 ± 0.64	9.73 ± 0.67	
After treatment			
Min. - Max.	9.4 - 13.1	8.4 - 13.3	0.048*
Mean ± SD.	11.18±1.03	10.79±1.07	
p-value	<0.001*	<0.001*	

Student t-test. *: Statistically significant at $p \leq 0.05$.

Table 4. Comparison between the two studied groups according to change of hemoglobin.

Amount change of hemoglobin level (g/dL)	Group A (n = 58)	Group B (n = 58)	p
Mean ± SD.	1.41 ± 0.63	1.06 ± 0.81	0.011*
Min. - Max.	0.4 - 2.8	−0.7 - 3.3	

Student t-test. *: Statistically significant at $p \leq 0.05$.

Table 5. Comparison between the two studied groups according to side effects and compliance of patients.

Side effect	Group A (n = 58)	Group B (n = 58)	p
No	56 (96.6%)	53 (91.4%)	0.438
Yes	**2 (3.4%)**	**5 (8.6%)**	
Constipation	2 (3.4%)	3 (5.2%)	1.000
Gastritis	1 (1.7%)	2 (3.4%)	1.000
Heart burn	1 (1.7%)	1 (1.7%)	1.000
Compliance	58 (100%)	58 (100%)	1

Chi-square test.

Table 6. Comparison between the two studied groups according to Maternal Morbidities & Fetal Morbidities.

Morbidities	Group A (n = 58)	Group B (n = 58)	p
Maternal Morbidities			
PPH	1 (1.7%)	2 (3.4%)	0.563
PPROM	1 (1.7%)	0 (0.0%)	0.321
Preterm labor	0 (0.0%)	1 (1.7%)	0.321
IUGR	0 (0.0%)	0 (0.0%)	1
IUFD	0 (0.0%)	0 (0.0%)	1
Fetal Morbidities			
NICU admission (sepsis)	1 (1.7%)	0 (0.0%)	0.321
NN Death	0 (0.0%)	0 (0.0%)	1

Chi-square test. PPH = Post-partum hemorrhage; PPROM = Preterm premature rupture of membranes; IUGR = Intrauterine growth restriction; IUFD = Intrauterine fetal demise; NICU = Neonatal intensive care unit; NN = Neonatal.

countries. Anemia is a major public health problem, causing adverse outcomes in pregnancy. Among fertile, non-pregnant women, approximately 40% have low iron reserves [7].

Anemia has a significant impact on the health of the fetus and that of the mother. It affects the oxygen delivery through the placenta to the fetus and interferes with the normal intrauterine growth, leading to fetal loss, perinatal deaths, and increased preterm labors. There is also evidence that less severe anemia is associated with poor pregnancy outcome [8].

Iron supplementation is usually recommended during pregnancy to correct or prevent iron deficiency because dietary intake of iron is unlikely to meet the daily dietary requirements of 30 mg [2].

A study indicates that vitamin B6 deficiency is one of the common causes of nutritional anemia in pregnancy, and a prospective study was conducted on

pregnant women during each trimester measures serum levels of iron, ferritin, vitamin B6, vitamin B12 folate and total protein/albumin. They observed that several pregnant women with anemia who were non-responsive to iron supplementation also had vitamin B6 deficiency, and that anemia in these cases improved with the administration of vitamin B6 [4].

As the effect of vitamin B6 and iron for treatment of iron deficiency anemia in pregnancy is still unknown, this study aimed to evaluate the effect of vitamin B6 and iron in treatment of iron deficiency anemia in second trimesteric women.

Therefore, our study was conducted at Ain Shams Maternity Hospital in the period between September 2021 and May 2022 to evaluate the value of addition of vitamin B6 to iron in treatment of iron deficiency anemia in pregnant women in the second trimester.

Cases enrolled in the study with no statistically significant differences between study groups regarding basic demographic data as age, gestational age but showed statistically significant difference between group A (iron and vitamin B6) and group B (iron only) regarding body mass index in which group B is higher than group A.

The statistical analysis of current study results showed that there was statistically significant higher mean improvement in group A than group B according to hemoglobin level after treatment and highly statistically significant higher mean value in after treatment than before treatment according to hemoglobin level in each group.

And there was a statistically significant higher amount change of hemoglobin level in group A than group B. On the other hand, regarding side effects and compliance there was no statistically significant difference between group A and group B. Also there is no statistically significant differences between group A and group B regarding maternal and fetal morbidities as NICU admission, PPROM, preterm labor, IUGR, IUFD, NN Death and PPH.

Current study disagreed with a randomized controlled study that conducted by *Ramakrishnan & Neufeld* [9] to compare the efficacy of a multiple micronutrient (MM) supplement containing iron compared to iron-only (FE) during pregnancy to improve birth outcomes in Mexico. The MM supplement was designed to provide 100% - 150% of the recommended dietary allowance of key vitamins (700 g retinol, 2 g vitamin B-12, 66.5 mg vitamin C) and minerals (15 mg Zn) and was similar to supplements that are commercially available. The control group received only iron. Both supplements contained 60 mg of iron in the form of ferrous sulfate. Hemoglobin concentrations were measured at 32 weeks of gestation and one month postpartum. They concluded that mean hemoglobin concentrations were significantly higher in the FE group compared to the MM group at 32 weeks of gestation and no differences in any of the outcomes at one month postpartum and this differs from the current study, they didn't study vitamin B6 with Fe supplements and included pregnant women in third trimester.

Compared with control supplementation that was usually iron plus folic acid

in most studies, MM supplementation resulted in a significant reduction in the incidence of low birth weight [pooled risk ratio (RR) 0.86; 95% confidence interval (CI) 0.81, 0.91] and SGA (pooled RR 0.83 [95% CI 0.73, 0.95]) and an increase in mean birth weight (weighted mean difference (WMD) 52.6 g [95% CI 43.2 g, 62.0 g]). There was no significant difference in the overall risk of preterm birth, stillbirth, and maternal or neonatal mortality, but we found an increased risk of neonatal death for the MM group compared with iron folate in the subgroup of five trials that began the intervention after the first trimester (RR 1.38 [95% CI 1.05, 1.81]).

On the other hand, Makola *et al.* [10] conducted a study to test the effect of a micronutrient-fortified beverage (prepared by Procter and Gamble Company) containing 11 micronutrients (iron, iodine, zinc, vitamin A, vitamin C, niacin, riboflavin, folate, vitamin B-12, vitamin B-6 and vitamin E) on the hemoglobin, iron and vitamin A status of pregnant women. A group of 259 pregnant women with gestational ages of 12 to 34 weeks was enrolled in a randomized double-blind controlled trial in which study women received 8 weeks of supplementation. Each group was supplied with an iron/folic acid supplement that contained 60 mg of elemental iron and 500 micro grams of folic acid to be taken on a daily basis plus the micronutrient-fortified beverage (experimental) group or the non-fortified (control) group. They agreed with the current study that both groups experienced a significant increase in hemoglobin concentrations, but pregnant women in the fortified-beverage group had a higher mean increase of 8.62 g/L, whereas mothers in the placebo group had a mean increase of only 4.46 g/L, they studied pregnant women in second and third trimester with different doses of Fe and more micronutrients used in this study than ours.

Also Ronnenberg *et al.* [11] assessed non fasting plasma concentrations of folic acid, vitamin B-12, vitamin B-6 (as pyridoxal-59-phosphate), hemoglobin (Hb), ferritin and transferrin receptor (TfR) in 563 non pregnant textile workers aged 21 - 34 y from China. All women had obtained permission to become pregnant and were participating in a prospective study of pregnancy outcomes. By comparing nutritional status across three strata of Hb concentration: 100, 100 - 119, and ≥120 g/L, mean concentrations of all three vitamins (folate, vitamin B12, vitamin B6) were significantly lower among women with hemoglobin of, 100 g/L than among non-anemic women. Moreover, the prevalence of vitamin deficiencies decreased across Hb strata, with the prevalence of vitamin B-6 deficiency, for instance, nearly 250% greater among women in the lowest Hb group than among non-anemic women. Among women with Hemoglobin of,100 g/L, 54% were deficient in one or more vitamins compared with 31% of non-anemic women (χ^2 p = 0.002) and this supports our study regarding the role of vitamin B6 in improving anemia. They also observed distinct seasonal trends were observed in the prevalence of moderate anemia (Hb, 100 g/L) and deficiencies of folic acid and vitamin B-6, with significantly lower concentrations of folate and Hemoglobin occurring in summer and lower concentrations of vitamin B-6 oc-

curring in winter and spring than in other seasons. They concluded that deficiencies of folic acid, vitamin B-6 and iron were relatively common in this sample of Chinese women of childbearing age and were contributing to the high prevalence of anemia.

They also stated that maternal vitamin B deficiencies may contribute to more common adverse pregnancy complications, such as spontaneous abortion, preeclampsia, preterm birth and low birth weight. And the high prevalence of vitamin B deficiencies that they observed may increase the risk of adverse pregnancy outcomes.

Allen *et al.* [12] disagreed with us, a meta-analysis to compare the effects of multiple-micronutrients with those of iron supplements alone or iron with folic acid, on hemoglobin and micronutrient status of pregnant women. The five treatment groups received the following micronutrients: C, control (vitamin A, 1000 g RE as retinol acetate); FA, folic acid (400 microgram); FA Fe, FA plus iron (ferrous fumarate, 60 mg); FA Fe Zn, FA Fe plus zinc (zinc sulfate, 30 mg); MN, FA Fe Zn plus other micronutrients. They found that multiple micronutrients supplemented group had no statistical significance difference on hemoglobin concentration between multiple micronutrient supplemented group and the other four groups, also they didn't include vitamin B6 as our study.

A study was designed by Risonar *et al.* [13] to determine the effectiveness of a redesigned Fe supplementation delivery system (ISDS) in improving Hemoglobin concentrations and compliance among pregnant women by training health workers on reliable monitoring and evaluation systems. Hemoglobin measurements were conducted at baseline and after 6 months in total, 1180 pregnant women given Fe/folic acid tablets daily through the redesigned ISDS in the experimental areas and the existing ISDS (neither reliable monitoring nor evaluation systems) in the control areas. The intervention consisted of providing UNICEF tablets (Lomapharm, Germany) containing 60 mg elemental Fe and 0.40 mg folic acid to all pregnant women to be taken once daily in both treatment areas. Although there were significantly more anemic pregnant women in the experimental than in the control area at baseline (50.7 versus 37.3 %; $p = 0.001$). The mean Hemoglobin concentration increased significantly in the experimental area by 0.5 g/dl ($p = 0.002$). In contrast to the current study, the experimental group was significantly higher in the reporting side effects from iron intake than the control group (34.7 versus 23.8%; $p = 0.019$).

We were in line with Hyder *et al.* [14] compared side-effects of iron supplementation and their impact on compliance among pregnant women. These women were assigned to receive either weekly doses of 2×60 mg iron (one tablet each Friday morning and evening) or a daily dose of 1×60 mg iron. Fifty antenatal care centers were randomly assigned to prescribe either a weekly- or a daily-supplementation regimen (86 women in each group). Side-effects were assessed by recall after one month of supplementation and used for predicting compliance in the second and third months of supplementation. Of five gastrointestinal side-effects (heartburn, nausea, vomiting, diarrhea, or constipation) assessed,

vomiting occurred more frequently in the weekly group (21%) than in the daily group (11%, $p < 0.05$). Compliance (ratio between observed and recommended tablet intake) was significantly higher in the weekly-supplementation regimen (93%) than in the daily-supplementation regimen (61%, $p < 0.05$). Overall, gastrointestinal side-effects were not significantly associated with compliance.

Limitations of the study: the mean body mass index of our study sample was 22.75 kg/m^2 in group A and 25.20 kg/m^2 in group B. no study for obese or morbid obese women, measuring serum vitamin B6 would be more accurate but this was not available due to unavailable kits and limited resources and Covid 19 Pandemic limits recruitment of anemic pregnant women.

Points of strength of the study: assessment of the study outcomes was done by the same observer, study targeting specific group of pregnant anemic women as regards gestational age (2nd trimester) and hemoglobin range (8 - 10.5) g/dl, specifically no studies done before in this area.

5. Conclusion

Iron and vitamin B6 seems to increase hemoglobin level more than iron only. Thus, in pregnant women with iron deficiency anemia iron plus vitamin B6 may be considered as a more effective alternative treatment than iron only.

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Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with ethical standards of the ethical committee of the department of obstetrics and gynaecology faculty of medicine, Ain Shams University.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Al-Khaffaf, A., Frattini, F., Gaiardoni, R., Mimiola, E., Sissa, C. and Franchini, M. (2020) Diagnosis of Anemia in Pregnancy. *Journal of Laboratory and Precision Medicine*, **5**, 1-5. https://doi.org/10.21037/jlpm.2019.12.03

[2] Stoltzfus, R. and Dreyfuss, M. (1998) Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anemia (Vol. 2). ILSI Press, Washington.

[3] Long, B. and Koyfman, A. (2018) Emergency Medicine Evaluation and Management of Anemia. *Emergency Medicine Clinics*, **36**, 609-630. https://doi.org/10.1016/j.emc.2018.04.009

[4] Hisano, M., Suzuki, R., Sago, H., Murashima, A. and Yamaguchi, K. (2010) Vitamin B6 Deficiency and Anemia in Pregnancy. *European Journal of Clinical Nutrition*, **64**, 221-223. https://doi.org/10.1038/ejcn.2009.125

[5] Merrill Jr., A.H. and McCormick, D.B. (2020) Riboflavin. In: Marriott, B.P., Birt, D.F., Stallings, V.A. and Yates, A.A., Eds., *Present Knowledge in Nutrition* (*Eleventh Edition*), Elsevier, Amsterdam, 189-207. https://doi.org/10.1016/B978-0-323-66162-1.00011-1

[6] Fite, M.B., Assefa, N. and Mengiste, B. (2021) Prevalence and Determinants of Anemia among Pregnant Women in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. *Archives of Public Health*, **79**, Article No. 219. https://doi.org/10.1186/s13690-021-00711-3

[7] Milman, N. (2008) Prepartum anaemia: Prevention and Treatment. *Annals of Hematology*, **87**, 949-959. https://doi.org/10.1007/s00277-008-0518-4

[8] Saha, L., Pandhi, P., Gopalan, S., Malhotra, S. and Kumar, S. (2007) Comparison of Efficacy, Tolerability, and Cost of Iron Polymaltose Complex with Ferrous Sulphate in the Treatment of Iron Deficiency Anemia in Pregnant Women. *Medscape General Medicine*, **9**, 1.

[9] Ramakrishnan, U. and Neufeld, L.M. (2004) Multiple Micronutrient Supplements during Pregnancy Do Not Reduce Anemia or Improve Iron Status Compared to Iron-Only Supplements in Semirural Mexico. *The Journal of Nutrition*, **134**, 898-903. https://doi.org/10.1093/jn/134.4.898

[10] Makola, D., Ash, D. and Tatala, S. (2003) A Micronutrient-Fortified Beverage Prevents Iron Deficiency, Reduces Anemia and Improves the Hemoglobin Concentration of Pregnant Tanzanian Women. *The Journal of Nutrition*, **133**, 1339-1346. https://doi.org/10.1093/jn/133.5.1339

[11] Ronnenberg, A.G., Goldman, M.B., Aitken, I.W. and Xu, X.P. (2000) Anemia and Deficiencies of Folate and Vitamin B-6 Are Common and Vary with Season in Chinese Women of Childbearing Age. *The Journal of Nutrition*, **130**, 2703-2710. https://doi.org/10.1093/jn/130.11.2703

[12] Allen, L.H., Peerson, J.M. and Bulletin, N. (2009) Impact of Multiple Micronutrient versus Iron-Folic Acid Supplements on Maternal Anemia and Micronutrient Status in Pregnancy. *Food and Nutrition Bulletin*, **30**, S527-S532. https://doi.org/10.1177/15648265090304S407

[13] Risonar, M.G.D., Rayco-Solon, P., Tengco, L.W., Sarol, J.N., Paulino, L.S. and Solon, F.S. (2009) Effectiveness of a Redesigned Iron Supplementation Delivery System for Pregnant Women in Negros Occidental, Philippines. *Public Health Nutrition*, **12**, 932-940. https://doi.org/10.1017/S1368980008003418

[14] Hyder, S.M.Z., Persson, L.Å., Chowdhury, A.M.R. and Ekström, E.-C. (2002) Do Side-Effects Reduce Compliance to Iron Supplementation? A Study of Daily- and Weekly-Dose Regimens in Pregnancy. *Journal of Health, Population and Nutrition*, **20**, 175-179.