

# The effect of multi-micronutrient and protein supplementation on iron and micronutrients status in pregnant women

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## ABSTRAK

**Latar belakang:** Keuntungan suplementasi multi mikronutrien semakin mendapat perhatian melihat banyaknya ibu hamil dengan status nutrisi yang suboptimal, namun rendahnya kepatuhan mengurangi efektivitas dari program suplementasi besi-asam folat yang dicanangkan pemerintah. Tujuan studi ini adalah untuk menilai efektivitas suplementasi multi-mikronutrien dan protein pada status besi dan mikronutrien wanita hamil.

**Metode:** Studi eksploratif dilakukan pada 100 wanita hamil selama  $\leq 12$  minggu yang melakukan asuhan antenatal di Rumah Sakit Budi Kemuliaan, Jakarta. Susu formula yang mengandung multi-mikronutrien dan protein diberikan setiap bulan hingga persalinan. Pemeriksaan antropometri, darah maternal dan tali pusat, ultrasonografi (USG), dan dietary recall merupakan variabel yang dinilai. Data dianalisis menggunakan uji korelasi. Korelasi antar variabel diuji menggunakan uji Pearson atau Spearman.

**Hasil:** Kadar hemoglobin mengalami penurunan secara signifikan ( $p < 0,001$ ), dengan kadar terendah pada trimester 2. Kadar pada tiap trimester secara berurut adalah  $12,16 \pm 1,03$  g/dL; 12 menderita anemia, dan 17 memiliki kadar feritin yang rendah,  $10,85 \pm 0,95$  g/dL; 58 menderita anemia, dan 69 memiliki kadar feritin yang rendah, dan  $11,02 \pm 0,35$  g/dL; 50 menderita anemia dan 51 memiliki kadar feritin yang rendah. Kadar feritin dan besi serum juga turun pada trimester satu dan dua ( $p < 0,001$ ). Kadar seng dan vitamin D juga mengalami penurunan. Anemia tidak mempengaruhi luaran kehamilan seperti persalinan preterm, preeklamsia, atau berat badan lahir rendah.

**Kesimpulan:** Kadar hemoglobin, feritin, besi, seng, dan vitamin D maternal selama kehamilan tidak dapat dipertahankan atau ditingkatkan dengan suplementasi multi-mikronutrien dan protein.

## ABSTRACT

**Background:** Potential benefits of multiple micronutrient supplements has become an increasing interest seeing as the high rate of pregnant women with suboptimal nutritional status, but low compliance often reduces effectiveness of large-scale iron and folic acid supplementation program. The aim of this study was to investigate the efficacy of multi-micronutrient and protein supplementation on iron and micronutrients status in pregnant women.

**Methods:** An exploratory study was conducted to 100 pregnant women  $\leq 12$  weeks, who underwent antenatal care in Budi Kemuliaan Hospital, Jakarta. The subjects received formulated powder milk containing multi-micronutrient and protein supplement monthly until delivery. Anthropometric measurement, maternal and cord blood exam, ultrasound and dietary recall were done. The data was analyzed by correlation test. Correlation between variables was tested using Pearson or Spearman correlation test.

**Results:** The mean maternal hemoglobin level significantly decreased during study ( $p < 0.001$ ), being the lowest in second trimester. The levels on the first, second, and third trimester respectively was  $12.16 \pm 1.03$  g/d; 12 anemic subjects and 17 had low ferritin level,  $10.85 \pm 0.95$  g/dL; 58 anemic subjects and 69 had low ferritin level, and  $11.02 \pm 0.35$  g/dL; 50 anemic subjects and 51 had low level of ferritin). Ferritin and serum iron levels were decreased at trimester one and two ( $p < 0.001$ ), also the zinc and vitamin D level declined. Anemia did not correlate with pregnancy outcomes such as preterm delivery, preeclampsia, or low birth weight.

**Conclusion:** The levels of maternal hemoglobin, ferritin, iron, zinc, and vitamin D during pregnancy could not be maintained or increased by multi-micronutrient and protein supplementation.

**Keywords:** anemia, iron status, micronutrients, vitamin

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Many women have suboptimal nutritional status and insufficient intake during pregnancy, which leads to an increased risk to develop anemia and micronutrients deficiency. The World Health Organization (WHO) estimates from 35-75% of pregnant women in developing countries, including 37.1% in Indonesia, are anemic.<sup>1-4</sup> Current knowledge indicates that iron deficiency anemia and micronutrients deficiency in pregnancy are risk factors for miscarriage, congenital anomaly, preeclampsia, gestational diabetes, preterm delivery and subsequent intrauterine growth restriction or low birth weight, and possibly correlated with neonatal health with its long-term outcome.<sup>4-6</sup> There has been an increasing interest in the potential benefits of multiple micronutrient supplements. Low compliance often reduces the effectiveness of large-scale iron and folic acid supplementation program. Milk powder consists of multi-micronutrient and protein supplementation is expected to give better compliance hence, will be more effective. The aim of this study was to investigate the efficacy of multi-micronutrient and protein supplementation on iron and micronutrients status in pregnant women.

## METHODS

This is an exploratory study with open single group. The study was conducted at Budi Kemuliaan Hospital, Jakarta, to 100 pregnant women  $\leq$  12 weeks pregnancy who underwent antenatal care. The inclusion criteria were women with  $\leq$  12 weeks of pregnancy and no congenital anomaly (confirmed by ultrasound examination), willing to participate, not on other pregnancy milk/multi-micronutrient supplementation, and was not enrolled in any other interventional study. The exclusion criteria were subjects with hyperemesis gravidarum, women with intrauterine fetal death, abortion, or did not consume the product within a week.

This study was conducted between February 2012 until April 2013. The protocol used in this study was approved by the Ethical Committee For Research In Human from the Faculty of Medicine, Universitas Indonesia (No. 480/PT02. FK/ETIK/2012).

Subjects were asked to fill out a questionnaire to obtain data on their general and family characteristics, current illnesses, and dietary intake upon their first visit. Anthropometric measurement, ultrasound examination, and blood exam were done. Products were given to subjects monthly, and the compliance was monitored by trained field assistants randomly by phone. The product used in this study was formulated powder milk, adapted to the additional need of Indonesian pregnant women. It was packed in 150 g alufoil in a folding box. Spoon was provided in each pack/box to ensure accurate dilution of the product. Its ingredients per 200 ml serving were folic acid 471 mg, Fe 15.9 mg, Ca 360 mg, P 186 mg, Mg 36 mg, Na 78 mg, K 240 mg, Cl 139.5 mg, Zn 4.1 mg, vitamin A 1545 IU, vitamin D 105 IU, Vitamin E 1.8 IU, thiamin 750 mg, riboflavin 750 IU, pyridoxine 1650 mg, cobalamin 1.56 mg, vitamin C 48 mg, biotin 5.7 mg, niacinamide 2.4 mg, pantothenic acid 1.05 mg, choline 26.7 mg and docosahexaenoic acid (DHA) 15 mg. Study parameters were anthropometric status, maternal hemoglobin, erythrocyte, hematocrit, mean corpuscular volume (MCV), serum iron, ferritin, high sensitivity c-reactive protein (hsCRP), vitamin D, A, B12, E, zinc, folic acid, and albumin level, dietary intake, pregnancy complication (preterm and preeclampsia), babies' birth weight, and appearance, pulse, grimace, activity and respiration (APGAR) score, and iron, micronutrients and status of the cord blood.

Blood test and ultrasound examination data were collected three times; at baseline, three months after supplementation and before delivery. Immediately after birth, the cord blood was collected. The dietary recall was recorded twice; at baseline and three months after supplementation using 24-hours food recall by trained nutritionists.

The data was analyzed by SPSS version 20 program. Each dependent variable was tested for homogeneity variance using the Kolmogorov-Smirnov test. Baseline data were described and summarized either by means and standard deviations for the normally distributed variables, and medians or interquartile ranges for the non-normally distributed variables. Correlation between variables was tested using Pearson or Spearman correlation test.

## RESULTS

A total of 100 of 124 subjects completed the study. Of those who dropped out, 14 subjects refused to complete the study, 10 subjects did not consume the product within a week consecutively. There were 89, 84, and 72 subjects who consumed the products once daily in trimesters one, two, and three, respectively. As many as five, seven and 21 subjects did not consume the products less than three times in trimesters one, two, and three. The subjects who did not consume the products 3-7 times/week were six, nine and seven subjects in trimesters one, two and three.

The characteristics of the subjects and pregnancy outcomes are shown in tables 1 and 2. The mean age of the subjects was 29 year old. Sixty percent of subjects had normal body mass index, and 81% had mid-upper arm circumference  $\leq$  23.5 cm. Normal weight gain during pregnancy was found in 46% subjects.

Most of subjects delivered their babies in  $\leq$  37 weeks (98%), 95% with birth weight  $\leq$  2,500 g (95%), and APGAR score  $\leq$  7 (98%). Only one subject had gestational hypertension.

### Maternal anemia, iron, micronutrient and vitamin status

The mean maternal hemoglobin level in the first trimester was  $12.16 \pm 1.03$  g/dL, 12 subjects had anemia, and 17 subjects had low ferritin level ( $<20$  g/dL). In the second trimester, the mean maternal hemoglobin level was  $10.85 \pm 0.95$  g/dL. Fifty-eight subjects had anemia and 69 subjects had low ferritin level. We found maternal hemoglobin level in the third trimester was  $11.02 \pm 0.35$  g/dL, 50 subjects had anemia and 51 subjects had low level of ferritin. Subjects who were anemic and/or had low ferritin level, were given additional ferrous fumarate 360 mg supplementation. The number of subjects who consumed additional iron supplementation was 19, 79, and 93 subjects in trimesters one, two and three. Respectively the maternal iron, micronutrient and vitamin status are shown in tables 3 and 4.

Significant correlation was found between hemoglobin and vitamin B12 level in trimester two ( $r = 0.157$ ;  $p = 0.042$ ). However, no correlation was found between hemoglobin level with folic

acid, vitamin B12, and zinc in trimesters one and three, as well as folic acid and zinc in trimester two ( $p > 0.05$ ).

**Table 1.** Characteristics of the subjects (n=100)

Characteristics of the subjects	n (%)
<b>Education</b>	
Elementary school	4
Junior high school	7
Senior high school	59
Diploma	18
University	12
<b>Occupation</b>	
Housewives	42
Working	58
<b>Body mass index (kg/m<sup>2</sup>)</b>	
Underweight ( $<18.5$ )	12
Normal (18.5-24.9)	60
Overweight (25-29.9)	25
Obese ( $\geq 30$ )	3
<b>Maternal weight gain during pregnancy</b>	
Low	36
Normal	46
Over	18
<b>Gravida</b>	
Primi	38
Multi	62

**Table 2.** Pregnancy outcome

Pregnancy outcome	Number of subjects
<b>Gestational age at delivery (weeks)</b>	
$< 37$	2
$\geq 37$	98
<b>Gestational hypertension/preeclampsia</b>	
No	99
Yes (third trimester)	1
<b>Mode of delivery</b>	
Spontaneous delivery	48
Vacuum extraction	6
Caesarean section	46
<b>Birth weight (grams)</b>	
$< 2500$	5
$\geq 2500$	95
<b>APGAR Score (minute-1)</b>	
$< 7$	2
$\geq 7$	98

**Table 3.** Maternal iron status

Iron Status	Trimester 1		Trimester 2		Trimester 3	
	Mean ± SD/ Median (min-max)	%	Mean ± SD/ Median (min-max)	%	Mean ± SD/ Median (min-max)	%
Hemoglobin (g/dL)	12.2 ± 1.0		10.9 ± 1		11.0 ± 0.4	
Anemia		12		58		50
Normal		88		42		50
Ferritin(µg/L)	65.2 (4-410.4)		12.5 (3.9-216)		16.1(4-312)	
Deficiency		17		69		51
Insufficiency		15		14		30
Normal		68		17		19
MCV(fL)	85.2 (65.1-94.4)		88.6 (69.7-98.2)		85.8 (61.9-93.2)	
Low		13		6		15
Normal		87		94		85
Erythrocyte (x10 <sup>6</sup> /µL)	4.3 (± 0.4)		3.73 (± 0.3)		4.01 (± 0.4)	
Low		7		61		32
Normal		93		39		68
Serum iron (µg/L)	167.2 (39-3772)		137.5 (22-2231)		222.0 (21-3042)	
Low		53		55		56
Normal		37		42		40
High		10		3		4

**Table 4.** Maternal micronutrient and vitamin status

Maternal micronutrients	Trimester 1		Trimester 2		Trimester 3	
	Mean± SD/ Median (min-max)	%	Mean± SD/ Median (min-max)	%	Mean± SD/ Median (min-max)	%
Zinc (µg/L)	51.5 (± 13.0)		42.9 (± 9.9)		42.3 (± 10.2)	
Low		75		97		97
Normal		25		3		3
Folic acid (ng/mL)	21.2 (10.9-40)		22.2 (10.2-33.9)		20.3 (9.2-40)	
Normal		15		10		13
High		85		90		87
Vitamin D (ng/mL)	12.8 (± 5)		14.1 (± 5.5)		13.6 (± 5.4)	
Low		99		99		100
Normal		1		1		0
Vitamin B12 (pg/mL)	386 (145-848)		287 (122-816)		248 (125-1285)	
Low		4		21		30
Normal		96		79		69
High		0		0		1
Vitamin A (µg/L)	0.44 (0.2-7.3)		0.4 (0.2-1.7)		0.4 (0.1-3.1)	
Low		3		4		3
Normal		91		88		95
High		6		8		2
Vitamin E (mg/L)	11.9 (5.1-24.4)		14.1 (3-27.1)		15.8 (3.6-27.9)	
Low		0		1		0
Normal		69		49		37
High		31		50		63

**Table 5.** Maternal nutrient intake during the study

Nutrient intake	Trimester		Trimester 2	
	Mean± SD/ Median (min-max)	%	Mean± SD/ Median (min-max)	%
Energy (Kcal)	1256.8 (653-3864)		1559 (± 319.1)	
Low		86		69
Normal		10		23
High		4		8
Protein (mg)	47.1 (21-146)		56.11 (± 15.1)	
Low		73		59
Normal		23		36
High		4		5
Calcium (mg)	497.2 (57-3458)		874 (84-4159)	
Low		85		68
Normal		13		31
High		2		1
Iron (mg)	18.5 (3-186)		23.4 (3-250)	
Low		70		51
Normal		19		33
High		11		16
Zinc (mg)	5.4 (2-19)		9.6 (± 2.6)	
Low		96		87
Normal		4		13
High		0		0
Folic Acid (µg)	8.3 (0.6-465)		10.8 (1-247)	
Low		43		32
Normal		22		37
High		35		31
Vitamin A (µg)	2521 (185-13129)		4406 (1023-16734)	
Low		4		0
Normal		4		0
High		92		100

**Nutrition intake and albumin level**

Food frequency questionnaire (FFQ) showed many subjects had low nutrition intake including energy, protein, calcium, iron, and zinc intake. There was negative correlation between iron serum in second trimester with iron intake in first trimester ( $p = 0.353$ ), and hemoglobin level in third trimester with iron intake in second trimester ( $p = 0.067$ ;  $r =$

**Table 6.** Cord blood iron status

Cord Blood	Mean(± SD)/ Median (min-max)	%
Hemoglobin (g/dL)	13.24 ± 1.93	
Anemia		56
Normal		44
Hematocrit (%)	36 (16.7-52.5)	
Low		76
Normal		24
Ferritin (µg/L)	153.45 (40-1050)	
Deficiency		0
Insufficiency		0
Normal		100
Erythrocyte (x10 <sup>6</sup> /µL)		
Low	3.89 (1.89-4.75)	51
Normal		49
MCV (fL)	99.65 (69-118.2)	
Low		28
Normal		72
Serum Iron (ug/L)	523 (32-32714)	
Low		14
Normal		31
High		35

-0.151). Maternal nutrients intake during study are shown in table 5.

The mean albumin levels were  $3.90 \pm 0.27$ ;  $3.43 \pm 0.24$ , and  $3.37 \pm 0.28$  g/dL, in trimesters one, two, and three. Respectively the total number of subjects who had low albumin level was significantly increased during study. The subjects number 3, 46, and 62 had low albumin levels in trimesters one, two, and three. Significant correlation was found between hemoglobin and albumin level in trimester two ( $r = 0.259$ ;  $p = 0.007$ ) and trimester three ( $r = 0.240$ ;  $p = 0.011$ ), but no significant correlation was found between hemoglobin and albumin level in trimester one.

**Cord blood iron status and maternal iron status**

The mean cord blood hemoglobin level was  $13.24 \pm 1.93$  g/dL and 56% had low hemoglobin level. No correlation was found between cord blood hemoglobin level and maternal hemoglobin level in trimesters one, two, and three ( $p > 0.05$ ).

No correlation was found between cord blood and maternal hemoglobin level in first trimester

( $p = 0.862$ ), second trimester ( $p = 0.304$ ), and third trimester ( $p = 0.204$ ).

## DISCUSSION

Anemia and multi-micronutrients deficiency is a worldwide problem particularly in developing countries including Indonesia. WHO estimates 35% to 75% (56% on average) of pregnant women in developing countries, and 18% of women from industrialized countries are anemic.<sup>1,2</sup> On 2013, 37% Indonesian pregnant women were found to be anemic.<sup>3</sup> Criteria of anemia, based on WHO criteria, which is hemoglobin level  $< 11$  g/dL during pregnancy, was used to diagnose anemia in this study.<sup>2</sup>

From our study we found hemoglobin level was significantly decreased, during pregnancy being the lowest in second trimester. Ferritin and serum iron levels were also decreased during trimesters one and two.

Decrease of hemoglobin, ferritin and serum iron levels can be caused by many factors. One of the factors is the physiologic changes during pregnancy. Plasma volume increases (40%) disproportionately to the increase in red blood cell mass (20-30%). Physiologic hemodilution and anemia occur, especially in the middle of the third trimester.<sup>7</sup> The lowest hemoglobin and ferritin level were found in second trimester, even though there were no significant changes between second and third trimester. The level was slightly increased in the third trimester. It might be because of additional iron therapy, Fe fumarate 360 mg twice daily, were given for anemic subjects or low ferritin level from first and second trimester.

The increase of iron requirements in pregnancy may also cause the decreased levels. Iron requirements increase approximately to 1,000 mg during pregnancy for iron loss, expansion of red blood cell mass, fetal, placenta and blood loss at delivery.<sup>1,7</sup> When available iron stores are insufficient to meet the demand during pregnancy, iron deficiency will occur. These mechanisms may explain the decrease of hemoglobin and ferritin levels in second and third trimesters, as shown in current study.

Low iron intake could also effect the decrease in the levels. Seventy subjects on first study intake,

**Table 7.** Cord blood micronutrient status

Micronutrient status (normal range)	Mean( $\pm$ SD)/ Median (min-max)
Folic acid (7-14.9 ng/mL)	27.5 (0-40.0)
Vitamin B12 (211-911pg/mL)	405 ( $\pm$ 131.63)
Vitamin D (30-100 ng/mL)	15.5 (6.70-41.30)
Vitamin A (0.2-0.8 ug/L)	0.39 ( $\pm$ 0.184)
Vitamin E (3-14 mg/L)	11.23 (0.82-35.6)
Zinc (60-130 ug/L)	54.8(26.4-3321)

and 51 subjects in second trimester had low iron intake, and most of the subjects consumed vegetables as source of iron, which has low absorption. FFQ most of the subjects also had low dietary intake for other micronutrients, except vitamin A. The amount of elemental iron in the products may have been insufficient to maintain iron status on each individual. Each glass of the product only contained 15.9 mg, whereas the daily recommendation of iron supplementation for pregnant women is 27-30 mg. Additional oral iron supplementation (ferrous fumarate 360 mg~105 mg elemental iron) was given to subjects who had anemia or low ferritin level ( $< 20$  g/dL). Those combinations could maintain the levels of hemoglobin, ferritin and serum iron during third trimester, but no significant changes were found on the particular subjects, and also the increment of the hemoglobin and ferritin level. Factors influencing iron absorption were not assessed in this study, such as coffee, tea, milk, and calcium. The product consumed only contains 50 mg of vitamin C, which can increase iron absorption; and 360 mg calcium, which can decrease iron absorption.<sup>8</sup>

Nutritional status might also contribute to the result. Twelve subjects were found underweight and 19 subjects had mid upper arm circumference (MUAC)  $\leq 23.5$  cm which represents low protein and energy, but 36 subjects also had low maternal weight gain during their pregnancy based on their body mass index (BMI). Recommendation from Institute of Medicine for maternal weight gain during pregnancy based on BMI before pregnancy is 12.5-18 kg for underweight, 11.5-16 kg and 7-11.5 kg for normal and overweight respectively, whereas the maximum weight gain for obese pregnant women is 6 kg.<sup>9</sup> Low energy and protein intake were observed in 86 and 73 subjects on first trimester; 69 and 59 subjects on

second trimester. Our findings showed significant correlation between hemoglobin and albumin levels in second trimester and third trimester. Our findings support the previous study showing iron deficiency anemia to be related to low energy and iron intake.<sup>9</sup> In addition to iron, protein, vitamin B6, B12, folic acid and zinc are needed for hemoglobin synthesis.<sup>10</sup> Low vitamin B12 level was found in 4, 21, and 30 subjects in first, second, and third trimester. Significant correlation was found between hemoglobin and vitamin B12 level in second trimester.

Previous clinical trial showed iron supplementation did not increase maternal serum ferritin or hemoglobin, reduce risk of maternal anemia, or reduce any other measures of maternal iron status, but the proportions of women with absent iron stores and iron deficiency anemia at 28 weeks of gestation were significantly lower. The gestation duration was also significantly longer, and there was an increase of infant birth weight.<sup>11</sup>

Anemia during pregnancy may lead to several conditions, such as reduced immunity, increase the risk of preeclampsia, postpartum hemorrhage, preterm delivery, low APGAR score, and low birth weight or intrauterine growth restriction.<sup>1,12,13</sup>

In our study, 69 and 50 subjects had anemia in second and third trimester, but only two subjects had preterm delivery and five subjects had infant birth weight < 2,500 g, and another subject had gestational hypertension. There is a substantial amount of evidence showing that low birth weight and preterm delivery are consequences of maternal iron deficiency anemia in early and second trimester pregnancy, but not in third trimester. Iron supplementation and therapy could also minimize adverse pregnancy outcome in our study.<sup>1</sup>

Cord blood iron status was also measured in our study. Fifty six percent had low hemoglobin level, but all subjects had normal ferritin level. No correlation was found between maternal hemoglobin first, second, and third trimester with cord blood hemoglobin level ( $p > 0.05$ ). However, the levels of iron, vitamin A, vitamin B12, vitamin D, and folic acid are higher in cord blood than in third trimester maternal serum. Our findings differ with previous studies, showing anemia and low ferritin level during pregnancy were related to low cord blood

ferritin level, but not low hemoglobin level. In addition to an iron stores reflection, ferritin is also an acute-phase reactant that is elevated in the setting of inflammation. The normal cord blood ferritin level could be a result of high iron stores or inflammatory state.<sup>10,14</sup>

The strength of our study is that the measurements were not only from maternal status every trimester during pregnancy, but also from parameters in the cord blood. The weakness of the study is that there is no control group to compare our findings.

In conclusion, the levels of hemoglobin, iron, zinc, and vitamin D maternal during pregnancy could not be maintained or increased by multi-micronutrient and protein supplementation. One of the factors that can aggravate these findings was maternal low nutritional intake during the study.

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#### **Conflicts of Interest**

The authors affirm no conflict of interest in this study.

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