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Micronutrients Supplementation during Preconception Period Improves Fetal Survival and Cord Blood Insulin-Like Growth Factor 1

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ABSTRACT

The objective of this study was to evaluate the efficacy of multi-micronutrients (MMN) supplementation during preconception period on improving fetal survival and concentration of umbilical cord Insulin-like Growth Factor 1 (IGF-1). A randomized double blind community based trial had been conducted. Study subjects were randomly assigned into two groups (n = 210 in each group), namely multi-micronutrient group (MMN group) and placebo-iron folic acid group (Placebo-IFA group). The MMN group received capsule of multi-micronutrients containing 15 micronutrients every 2 days during preconception period (2-6 months before pregnancy) and to be continued with daily dose during pregnancy. Placebo-IFA group received placebo capsule every 2 days during preconception period (2-6 months before pregnancy) and to be continued with daily dose of iron and folic acid during pregnancy. Four hundred twenty eligible subjects were enrolled to meet approximately 115 babies born. The outcome variables were fetal survival and concentration of serum umbilical cord IGF-1. Data were analyzed using independent t-test to compare mean difference between MMN group and Placebo-IFA group and chi-square was used for dichotomous data to analyzed odd ratio. Results demonstrated significant difference of fetal survival (gestation age >37 weeks) between MMN group and Placebo-IFA group (p = 0.003). Fetuses in MMN group were more likely to survive than those in Placebo-IFA group (OR = 6,099; 95% CI: 0.934-39.847). Despite IGF-1 concentration of umbilical cord of neonates in MMN group was higher (23.6±16.2 ng mL^{-1}) compare to those in Placebo-IFA group (15.8±17.3 ng mL^{-1}) but it was not different significantly (p = 0.070). Furthermore, IGF-1 concentration of umbilical cord of male neonates (18.3±12.2 ng mL^{-1}) was lower than that of female neonates (21.5±19.9 ng mL^{-1}). These findings imply that MMN supplementation prior to pregnancy is very important to support intra uterine environment in early pregnancy for successful complete gestation period.

Key words: Multi-micronutrients, preconception nutrition, early pregnancy, fetal survival, IGF-1

INTRODUCTION

The period of intrauterine growth and development is the most vulnerable in human life cycle. Many studies revealed that most of the adverse pregnancy outcomes such as fetal loss, preterm delivery and intrauterine growth restriction (IUGR) appeared as a result of the unsuccessful fetal-maternal communication in early pregnancy, particularly during implantation period (Van Nieuwenhoven *et al*., 2003; Imakawa *et al*., 2004).

The probability of conception during one menstrual cycle is approximately 30% and only 50-60% of all conceptions survive beyond 20 weeks of gestation. Of the pregnancy that are lost, 75% are due to failure of implantation, before the women becomes aware that they might have been pregnant (Wilcox *et al*., 1988; Macklon *et al*., 2002). It means that to survive during pregnancy is a hard effort for a human conceptus, because most of conceptie loss in early pregnancy.

Miscarriage or spontaneous abortion and preterm delivery are the common adverse pregnancy outcomes. Miscarriage occurs from 31 (Wilcox *et al*., 1988) up to 50% (El-Sayed *et al*., 2009; Hure *et al*., 2012). The incidence of preterm delivery worldwide is about 9.6% globally. This rates are various across regions from 6.2% in Europe to 9.1% in Asia, 10.6% in North America and 11.9% in Africa (Beck *et al*., 2010).

Despite many epidemiological evidences have been compiled extensively, the mechanism underlying early embryonic loss and those contribute to several adverse pregnancy outcomes are poorly understood. Maternal nutrition plays a critical role in fetal growth and development (Fall *et al*., 2003; Wu *et al*., 2004), particularly micronutrient deficiencies have been associated with significant high risk of pregnancy complication which are contributing to adverse pregnancy outcomes (Hirschi and Keen, 2000; Keen *et al*., 2003).

The role of nutritional intervention during pregnancy to improve pregnancy outcomes has been well documented (Villar *et al*., 2003) but maternal multi micronutrients supplementation had no significant effect on cord hormone concentration (Roberfroid *et al*., 2010). Considering the critical period of early pregnancy, particularly during implantation period, we intervention with micronutrients only during pregnancy might be too late to prevent the adverse pregnancy outcomes. Several studies provide evidences on the association between preconception multivitamin use and preterm delivery (Vahratian *et al*., 2004; Catov *et al*., 2007) or preeclampsia (Bodnar *et al*., 2006).

Those evidences ensure the plausibility that micronutrients supplementation pre-conceptually may be more important than during pregnancy itself (Shah and Sachdev, 2004) and also in periconceptional period (Cetin *et al*., 2010). Based on such evidences, we investigated the efficacy of multi-micronutrients (MMN) supplementation during preconception period on fetal survival and fetal growth hormone, particularly Insulin-like Growth Factor 1 (IGF-1).

MATERIALS AND METHODS

A randomized double blind community-based trial had been conducted at district of Probolinggo, East Java province. The study protocol was approved by Ethical Committee, Faculty of Medicine Gajah Mada University with register No. KE/FK/202/EC. The study was also registered with register trials number TCTR20150614001. Beginning on March 2011 until July 2012, we enrolled 420 eligible subjects from physical screening of 1603 newly married women at catchment area of 9 selected health centers. The eligible subjects were newly married women who desired to be pregnant in the 1st year of marriage, 16-35 years age and apparently healthy. They were randomly assigned to received either multi micronutrient from United Nations International Multiple Micronutrients Preparation (UNIMMAP) formulation containing 15 micronutrients, every 2 days (1 day intermittent) during preconception period and to be continued with daily dose during pregnancy (MMN group) or placebo during preconception period and to be continued with daily dose of iron and folate, 60 mg iron and 250 µg, respectively only during pregnancy (Placebo-IFA group). Randomization had been carried out by using a random permuted blocks method with block size of 10 and allocation ratio 1:1, then we had equal subjects of 210 in each group (Meinert and Tonascia, 1986).

Supplements for two groups were prepared in similar physical appearance of capsules in size and color to blind both researcher and subjects. Furthermore, MMN used the UNICEF-derived formulation containing 15 micronutrients: 30 mg iron, 400 µg folic acid, 800 µg retinol, 200 IU vitamin D, 10 mg vitamin E, 70 mg vitamin C, 1.4 mg vitamin B1, 1.4 mg vitamin B2, 18 mg vitamin B3, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 15 mg zinc, 2 mg copper, 65 µg selenium and 150 µg iodine. Package of supplement was delivered to subjects monthly in dark color bottles, each bottle contains 16 capsules and 30 capsules for preconception and pregnancy period respectively. Field workers were responsible to distribute supplement and monitor the adherence of supplement consumption by home visit regularly. To monitor the adherence of supplement consumption, all subjects received a simple monitoring card and checked the monitoring card as well as validated by counting the remaining capsules in each bottle.

At enrollment, all newly married women who fulfilled the inclusion criteria were recruited and signed an informed consent. Pregnancy detection was done by urinary human Chorionic Gonadotrophin (hCG) and blood glucose test was done using rapid test kit Nesco® for diabetic screening. Physical test was also carried out by medical doctor at women and child services unit of health center. Women who were detected pregnant or suspect of diabetes (blood glucose >200 g dL^{-1}) and apparently unhealthy were excluded. Subjects who fulfilled the inclusion criteria received Albendazole tablet to eliminate worm infection, before they received supplement. The Albendazole tablet was consumed in front of field workers or midwives, during enrollment.

The primary outcome variables were fetal survival and cord blood Insulin-like Growth Factor 1 (IGF-1). Fetal survival was reflected by gestation age and categorized as dichotomous data using single cut off point gestation age of 37 weeks (survive if gestation age ≥37 weeks). Gestation age was calculated on the basis of the last menstrual period which was noted monthly in monitoring card. Concentration IGF-1 was assessed from venous umbilical cord blood serum. Midwives or laboratory workers collected venous blood of umbilical cord immediately after delivery at hospital or health center, as well as delivery at home. About 8 mL of blood was extracted from the clamped cord with syringe, then transferred gently into a polypropylene 10 mL dry tube without preservative and allowed it to clot at room temperature for 30-45 min. Blood sample then centrifugated at 3000 rpm for 10 min and serum was frozen immediately at -20°C. If babies were born at village health center or midwive's home, cord blood was immediately delivered by a carrier to local hospital using cold chain equipment, then centrifugated and frozen storage according to standard procedure. The frozen serum samples were then delivered to Biomaterial Laboratory, Dr. Soetomo General Hospital Surabaya to be stored at -80°C until ready for analysis.

Concentration of sera IGF-1 were analyzed at Clinical Pathology Laboratory Dr. Soetomo General Hospital Surabaya, using Enzyme-linked Immunosorbent Assay (ELISA) and commercial kit Quantikine® for human IGF-1 immunoassay, from R and D System, USA. Social economic background, nutritional status including body mass index and mid Upper Arms Circumferences (MUAC) were also assessed at baseline. Body weight was measured by using digital body weight scale Seca® type 803. Height or stature was measured by using microtoise, MUAC was measured by using fiber tape (Unicef). The overall data set was completely compiled on July 2014.

Baseline data was statistically analyzed by using independent t-test and Mann-withney U-test to compare mean difference between MMN group and Placebo-IFA group. Chi-square test was done to examine the different of fetal survival between MMN group and Placebo-IFA group, as well as to analyzed odd ratio. Independent t-test was also used to examine effect of treatment on concentration of IGF-1 in cord blood serum.

RESULTS

Subject enrollment: We carried out physical screening of 1603 newly married women from 9 selected sub districts. First of all, we excluded 851 subjects since they did not desire to be pregnant in the 1st year of marriage, and/or used contraception. Then 752 subjects who desired to have a child in the 1st year of marriage continued the next step screening. In the early selection by midwives, 201 married women were not eligible for the next screening due to various reasons, such as 126 subjects were pregnant based on rapid test for urinary human chorionic gonadotropin and 75 subjects moved out from study areas. Further step, 551 subjects got physical examination and pregnancy test. Among them, 131 subjects were not eligible since three subjects had tuberculosis (TB) infection, two subjects were suspected of diabetes mellitus and 126 subjects were already pregnant. The TB infection was detected base on sputum test and subjects who suspected diabetes were detected base on twice non fasting blood glucose test with glucose level>200 g dL^{-1}. Subjects who were detected getting pregnant at enrollment were not eligible because we had missed their preconception period. Base on the screening process, we fulfilled 420 eligible subjects to be enrolled the study (Fig. 1).

All eligible subjects were assigned randomly into two groups (MMN group and Placebo-IFA group). In MMN group there were 95 pregnant subjects, which were 38 subjects were pregnant before 2 months of intervention and 57 subjects were pregnant after 2 months intervention. Total pregnant subjects in Placebo-IFA group were 106, 48 subjects getting pregnant before 2 months intervention and 58 subjects were pregnant after 2 months intervention. Subjects who pregnant before 2 months of intervention were not intensively followed up, because they did not received 2 months intervention prior to pregnancy. Only subjects who pregnant after received 2 months of intervention were intensively followed up until birth. There were 56 births and 36 cord blood samples in MMN group and 50 births and 28 cord blood samples in Placebo-IFA group. Figure 1 shows the flow chart of entire eligible subjects enrolled and randomized into two groups.

Baseline data of treatment (MMN) group and control (Placebo-IFA) group

Social economic status: The social economic status was recorded such as age, education level, occupation, income and marital status. The data were presented descriptively and compared between MMN group and Placebo-IFA group.

Table 1 revealed that subjects within MMN group were relatively younger than Placebo-IFA group. The average of age within treatment group was 20.9±3.3 years, compared to 22.4±3.9 years within control group. Subjects within MMN group were mostly younger than 20 years and in arrange of 20-25 years with percentage of 43.9% in each age category. More than a half of subjects within Placebo-IFA group were in 20-25 years (51.7%). Percentage of subject age younger than 20 years in MMN group was higher (43.9%) than in Placebo-IFA group (25.9%).

Education level of Placebo-IFA group was relatively higher compare to MMN group. Subjects who graduated from university or college were higher in Placebo-IFA group (24.1%) than treatment group (10.5%). Most of subjects in two groups had no occupation (housewives), with

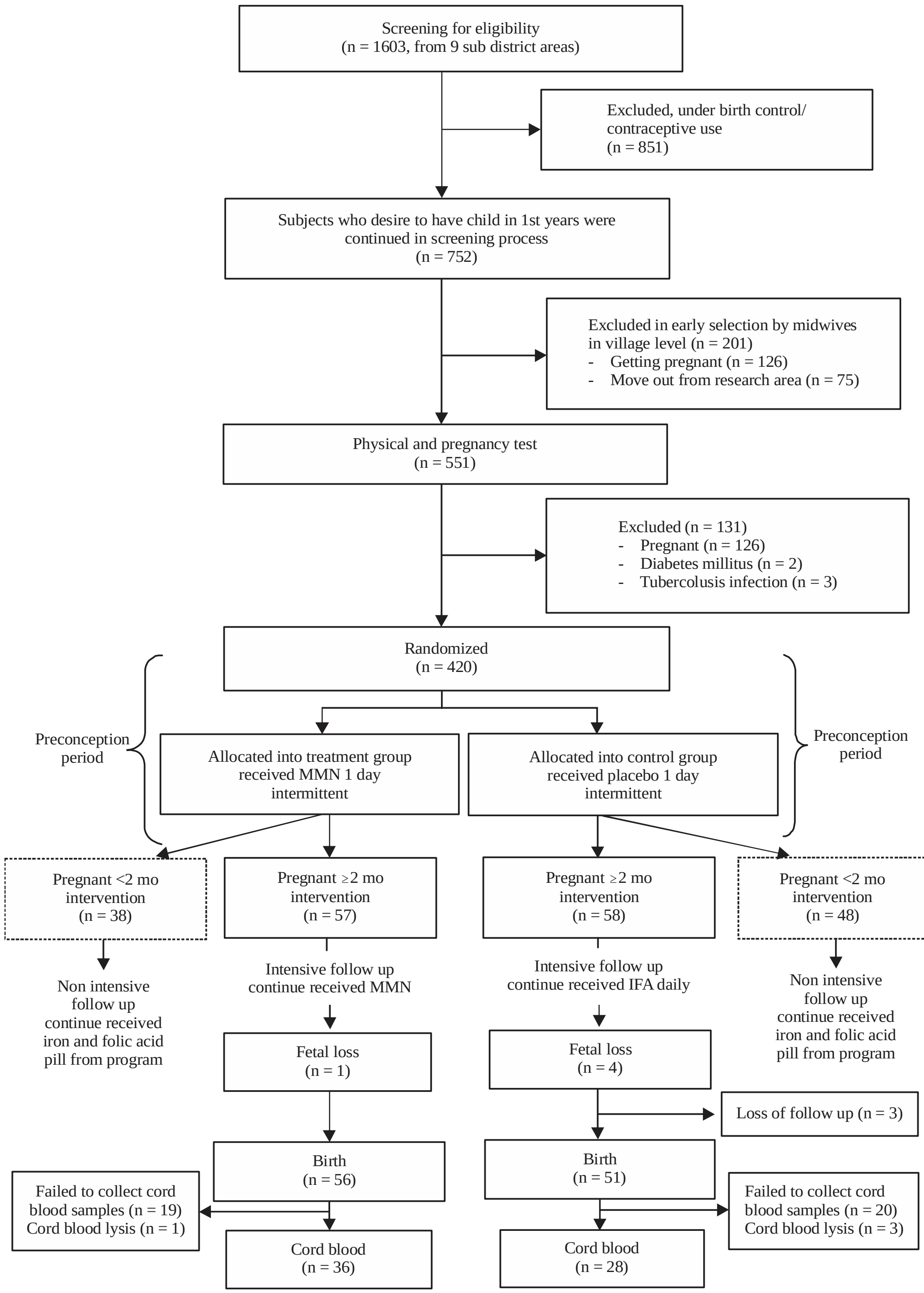

Fig. 1: Flow chart of research work

percentage of 68.4% within MMN group and 63.8% within Placebo-IFA group. Teacher and industrial workers were other type of occupation with high percentage than other categories. Less than 40% of subjects had income and more than half of subjects within two groups had income

Table 1: Social economic status of subjects within multi-micronutrients and Placebo-IFA group

Variables	MMN group (n = 57) No.	%	Placebo-IFA group (n = 58) No.	%	Statistical analysis
Age (years)					
<20	25	43.9	15	25.9	
20-25	25	43.9	30	51.7	p = 0.026
>25	7	12.3	13	22.4	
Education level					
No schooling at all	1	1.8	0	0.0	
Elementary school	8	14.0	9	15.5	
Junior high school	13	22.8	16	27.6	p = 0.598
Senior high school	29	50.9	19	32.8	
Graduate of university/collage	6	10.5	14	24.1	
Occupation					
No occupation	39	68.4	37	63.8	
Teacher	4	7.0	12	20.7	
Health practices	2	3.5	1	1.7	
Civil servant	1	1.8	0	0.0	p = 0.362
Industrial worker	8	14.0	5	8.6	
Others	3	5.4	3	5.1	
Income					
<500,000	9	50.0	13	61.9	
500,000-1,000,000	5	27.8	8	38.1	p = 0.138
>1,000,000-2,000,000	3	16.7	0	0.0	
>2,000,000	1	5.6	0	0.0	
Marital status					
1st marriage	57	1005.0	57	98.3	p = 0.322
2nd marriage	0		1	1.7	

*Statistical analysis using Mann-Whitney U-test for categorical data (education, occupation and marital status), independent t-test for age and income (α = 0.05), MMN: Multi-micronutrients

below Rp 500,000. The income level was more likely greater within MMN group rather than Placebo-IFA group, whereas no subject within Placebo-IFA group had income up to Rp 1000,000.

All subjects in MMN group were in the 1st marriage and 98.3% of subjects in Placebo-IFA group also in their first marriage but only 1.7% was in second marriage.

Statistical analysis was carried out to compare the mean value between MMN group and Placebo-IFA group to ensure the homogeneity by using independent t-test and Mann-withney U-test for continuous data and categorical data respectively. Table 1 shows, all statistical tests revealed that there were no significant difference of socio-economic characteristic between two groups (p>0.05), unless for age (p = 0.026).

Anthropometric measurement: The baseline data between MMN group and Placebo-IFA group were compared descriptively. Some variables discussed were nutritional status including body size such as body weight, height, as well as mid Upper Arms Circumference (MUAC). All anthropometric data were shown in Table 2.

The preconceptional body size and nutritional status of pregnant subjects in two groups look like similar. Table 2 shows that underweight subjects were 22.8 and 24.1% in MMN group and Placebo-IFA group, respectively. Percentage of overweight and obese subjects was twice higher in Placebo-IFA group (15.5%) compared to MMN group (8.8%). Subjects within Placebo-IFA group were slightly shorter than those in MMN group. Percentage of subjects with short stature (<145 cm) was slightly higher within Placebo-IFA groups (17.2%) than MMN group (14%). Moreover, MUAC variable revealed that percentage of subjects with risk for chronic energy deficiency (<23.5 cm) was more than 30% in both groups.

Univariate analysis for mean comparison between MMN group and Placebo-IFA group was done using independent sample t-test for homogeneity testing. All baseline anthropometric data which reflected the initial condition or preconception data between two groups were tested, as shown in Table 3. Results showed that no significant differences of means between two groups (p>0.05) for all anthropometric measurement including body weight, height, MUAC, as well as Body Mass Index (BMI). All data were comparable between two groups.

Effect of treatment on fetal survival: Among pregnant women who were intensively followed until delivery, there were 3 subjects loss of follow up due to they moved out from study area. Therefore, we had 112 data of fetal survival. Table 4 shows the distribution of fetal survival data and fetal age based on treatment group. Babies born before 37 weeks of gestation were categorized as not-survive, consist of abortion (fetal loss before 20 weeks of gestation) and preterm delivery (birth before 37 weeks of gestation). Either fetal loss (miscarriage) or preterm delivery more likely

Table 2: Baseline of anthropometric status in multi-micronutrients and Placebo-IFA group as preconception data

	MMN group (n = 57)		Placebo-IFA group (n = 58)	
Variables	No.	%	No.	%
BMI				
Under weight	13	22.8	14	24.1
Normal weight	39	68.4	35	60.3
Over weight	4	7.0	7	12.1
Obese	1	1.8	2	3.4
Body weight (kg)				
<40	11	19.3	10	17.2
≥40	46	80.7	48	82.8
Height (cm)				
<145	8	14.0	10	17.2
≥145	49	86.0	48	82.8
MUAC (cm)				
<23.5	18	31.6	19	32.8
≥23.5	39	68.4	39	67.2

MMN: Multi-micronutrients, BMI: Body mass index, MUAC: Mid upper arms circumference

Table 3: Univariate analysis to compare the means value of several preconception data between MMN group and Placebo-IFA group

Variables	MMN group (n = 57)	Placebo-IFA group (n = 58)	p-value*
Body weight	47.4±8.1	47.3±9.2	0.920
Height	150.9±5.6	149.9±5.7	0.308
MUAC	25.2±3.3	25.3±3.8	0.833
BMI	20.8±3.5	21.0±3.8	0.805

*Statistical analysis using independent t test (α = 0.05), MMN: Multi-micronutrients, BMI: Body mass index, MUAC: Mid upper arms circumference

Table 4: Distribution of fetal survival and fetal age within multi-micronutrients and Placebo-IFA group

	MMN group (n = 57)		Placebo-IFA group (n = 55)		Total (n = 112)	
Gestation age	No.	%	No.	%	No.	%
Fetal survival*						
Survival (≥37 weeks)	56	98.2	45	81.8	101	90.2
Not survive (<37 weeks)	1	1.8	10	18.2	11	9.8
Fetal age						
Miscarriage (<28 week)	1	1.8	4	7.4	5	4.5
Early preterm (28-35 weeks)	0	0.0	4	7.4	4	3.6
Late preterm (35-37 weeks)	2	3.5	2	3.7	4	3.6
At term (>37 weeks)	54	94.7	45	81.5	99	88.4

*Chi-square test: Contingency coefficient: 0.266, p = 0.003 (OR: 6,099, 95% CI: 0.934-39.847), MMN: Multi-micronutrients, BMI: Body mass index, MUAC: Mid upper arms circumference occurred in Placebo-IFA group than in MMN group. Percentage of not-survive fetal was higher in Placebo-IFA group (18.2%) than MMN group (1.8%). In MMN group there was only one case of miscarriage, whereas in Placebo-IFA group there were miscarriage as well as early preterm (born in 28-35 weeks) 4 (7.4%) in cases each. The detailed data regarding fetal loss and preterm delivery both of early preterm and late preterm between MMN group and Placebo-IFA group was shown in Table 4.

Based on statistical analysis for dichotomous data using chi-square test, it revealed that there was significant difference of fetal survival between MMN group and Placebo-IFA group, 98.2% and 81.8% respectively (p = 0.003). Fetuses in MMN group showed higher survival rate compared to Placebo-IFA group (OR = 6,099; 95% CI: 0.934-39.847). From the Odd Ratio (OR) value, it implies that fetuses in MMN group had six times to be survive compare to fetuses in Placebo-IFA group.

Effect treatment on cord blood IGF-1: Out of 112 of pregnant subjects who followed up until complete gestation, there were 107 subjects delivered their babies, with only 64 cord blood samples collected (36 samples and 28 samples in MMN group and Placebo-IFA group, respectively). Descriptive data of concentration of cord blood IGF-1 including mean value, standard deviation as well as range value was shown in Table 5. Mean value of serum cord blood IGF-1 concentration was higher in MMN group (23.6±16.2 ng mL^{-1}) than that in Placebo-IFA group (15.8±17.3 ng mL^{-1}). Otherwise, statistical analysis using independent t-test revealed that there was no significant difference of IGF-1 concentration between two groups (p = 0.070). Furthermore, IGF-1 concentration of umbilical cord of male neonates (18.3±12.2 ng mL^{-1}) was lower than that of female neonates (21.5±19.9 ng mL^{-1}) but it was not significantly different (p = 0.387). Data plot of IGF-1 concentration between MMN group and Placebo-IFA group or between male and female neonates were performed in Fig. 2 and 3, respectively.

Table 5: Comparison of mean value of IGF-1 concentration (ng mL^{-1}) between multi-micronutrients and Placebo-IFA group

Descriptive value	MMN group (n = 36)	Placebo-IFA group (n = 28)	Total (n = 64)
Mean*	23.6±16.2	15.8±17.3	20.1±17.0
Range	3.3-63.7	1.5-87.1	1.5-87.1

*Independent t test : t = 1.844, df = 61, p = 0.070, mean difference = 7.806, MMN: Multi-micronutrients, IGF-1: Insulin-like growth factor 1

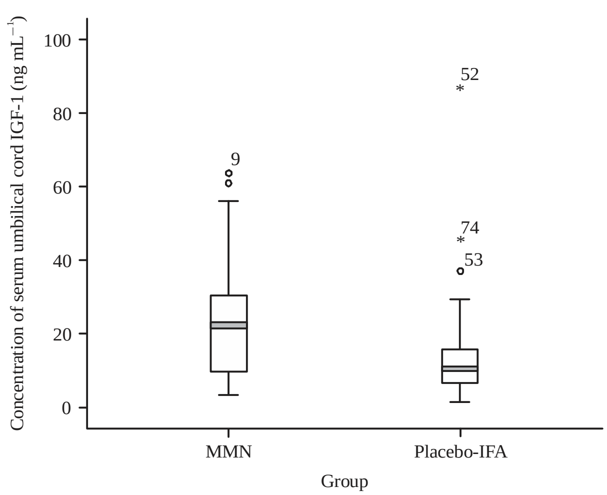

Fig. 2: Mean comparison of serum umbilical cord IGF-1 concentration between MMN group and Placebo-IFA group (p = 0.070)

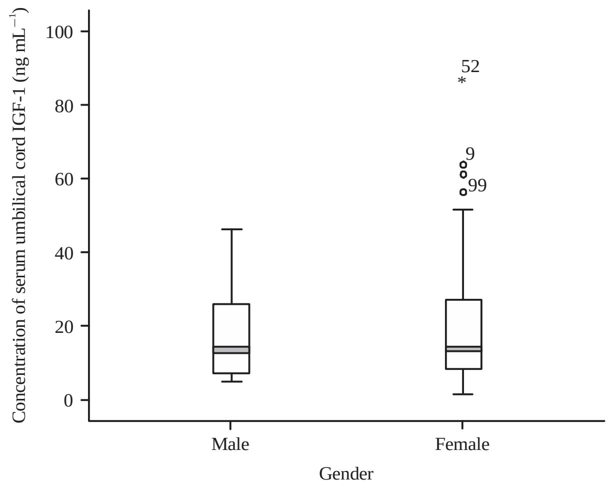

Fig. 3: Mean comparison of serum umbilical cord IGF-1 concentration between male and female neonates (p = 0.387)

DISCUSSION

Fetal survival is defined as the ability of fetus to survive in uterine until delivery in complete gestation period or at term delivery (birth >37 weeks). Un-survive fetus is fetus loss before 20 weeks of gestation (miscarriage) or preterm delivery. Based on data which were described previously, it is known that miscarriage or fetal loss and early preterm were more frequent in Placebo-IFA group rather than in MMN group. Gestational age was in a range of 10-42 and 8-43 weeks in MMN group and Placebo-IFA group, respectively, with averages of 38.9 and 36.6 weeks, respectively. The wide mean difference of gestational age between two groups was due to high percentage of miscarriage (7.4%) and early preterm (7.4%) in Placebo-IFA group.

Supplementation of MMN might prolong the gestational age of subjects within group, since several micronutrients such as selenium, zinc and vitamin D play an important role in implantation phase. Selenium influence progesterone production (Kamada and Hodate, 1998), furthermore, this hormone activates the receptors, exerting a tubular relaxing effect that allows entry of the ovum into the uterus (Guyton and Hall, 2006). Zinc and its protein transport ZIP8 (SLC39A8) stimulate IFNγ expression (Aydemir *et al*., 2009), which plays important role in initiation and modification of uterine vessel and make the integrity of decidual tissue (Ashkar *et al*., 2000). Remodeling of spiral artery is influenced by Zinc as well, since zinc is required by matrix metalloproteinase (Smith *et al*., 2009). Vitamin D 1.25(OH)2D also aids in the transformation of endometrial cells into decidual cells and increases expression of HOXA10, a gene important for embryo implantation in early pregnancy (Shin *et al*., 2010).

Vitamin C and E in MMN play important role on prevention of preterm delivery. Woods *et al*. (2001) provide detailed explanation about the role of vitamin C and E to prevent premature rupture of chorionic membrane and prolong gestational age and prevent preterm delivery. Body iron store also plays an important role in determining the gestation period via the role of corticotropin-releasing hormone (Allen, 2001).

Because of maternal growth hormone is not transferred across the placenta, the fetus is entirely depending on its pituitary gland for growth hormones production. Insulin-like growth factor-1 (IGF-1) is the main important hormone that regulates the fetal growth. Fetal IGF-1 concentration is positively correlated with gestational age (Pirazzoli *et al*., 1997). Moreover, IGF-1 was regulated by glucose level, which is concentration of serum IGF-1 in fasting rat was lower than those in non fasting rat was demonstrated in animal study conducted by Davenport *et al*. (1990).

There was no significant difference in mean value of IGF-1 concentration in serum cord blood between the two groups but the mean of IGF-1concetration in MMN group tend to be higher than that in Placebo-IFA group. This finding was in agreement with another study conducted by Roberfroid *et al*. (2010). This condition is possible since several micronutrients play important role in synthesis of IGF-1. Besides zinc and vitamin A play an important role in cell proliferation, thus micronutrients also stimulate synthesis of IGF-1. In animal study, it was demonstrated that vitamin A deficiency caused decrease of plasma IGF-1 concentration and it was suggested that possible physiologic role of the IGF system to support growth was mediated by vitamin A (Fu *et al*., 2001). Furthermore, IGF-1 was also affected by zinc status and the influence of zinc status on circulating IGF-1 concentration was independent on total energy intake (Cossack, 1986).

Such previous findings explained the detailed mechanisms how micronutrients able to influence fetal growth and development in early pregnancy clearly support our recent finding. It imply that our data provide the importance evidence that fetuses of women who received micronutrients supplement prior to pregnancy have six times more probable to be survive compare to fetuses of women who received iron folic acid only during pregnancy.

CONCLUSION

These findings reveal that MMN supplementation prior to pregnancy is very important to support intra uterine environment in early pregnancy for successful complete gestational age. Fetal survival rate in MMN group was significantly higher than those in Placebo-IFA group. Moreover, MMN supplementation prior to pregnancy also tends to increase umbilical cord serum IGF-1.

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