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Effects of Multimicronutrient and IFA Supplementation in Preconception Period Against Birth Length and Birth Weight: A Randomized, Double Blind Controlled Trial in Banggai Regency, Central Sulawesi

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ABSTRACT

Background: The beneficial effects of MMN and Iron Folic Acid (IFA) supplementation on pregnancy outcomes is still debatable. The objective of this study is to know the effect of IFA and MMN supplementation since preconception period on pregnancy outcomes. Multimicronutrient deficiencies may contribute to low birth weight and birth length which is associated with increased risk of infant morbidity and mortality in developing countries.

Method: The research was conducted in three sub-districts of Banggai district, namely, Luwuk, North Luwuk, and South Luwuk. This was a double blind study, randomized controlled trial, providing multimicronutrient for women from preconception period using prospective design with saturated sampling technique. A total of 19 preconception women followed until pregnancy and look at the pregnancy outcomes were enrolled from September 2016 to Januari 2018.

Results: The mean birth weight of infants born to pregnant women in the MMN group was heavier at 3142.5 g with a value (p= 0.001). LBW percentage of pregnant women MMN group was smaller, equal to 8.3% with value (p=0,863). The average length of infant born to pregnant women in MMN group was longer, 49,5 cm with value (p=0,001). Short birth length (<48 cm) of pregnant mother MMN group smaller, equal to 41,7% with value (p=0,515).

Conclusions: Pregnant women who get MMN intervention produce better pregnancy outcomes.The nutritional status of women before pregnancy is very important to achieve mother and fetal welfare and also considered as the most important thing for governing fetal growth.

Keywords: *Preconception period, multimicronutrient, birth weight, birth length*

INTRODUCTION

Low birth weight (LBW) is associated with the increasing risk of infant morbidity and mortality in developing countries[1]. It has been estimated that infants weighing 2000–2500 and 2500–3000 g at birth are four- and two-times higher risk of post neonatal mortality than those weighing 3000–3500 g, respectively. Through its impact on fetal growth and micronutrient stores, nutrition of the pregnant woman contributes to infant morbidity and mortality[2,3,4].

Epidemiological studies suggest that the interaction between maternal nutritional intake, hormonal disorders, and placental development is a determinant of stunting. Stunting events begin in the womb and continue until at least 24 months of age; so that the preconception period

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up to 2 years is a critical period for the occurrence of stunting and a priority for intervention. Babies born less than 2500 grams are classified as premature and small during pregnancy (small for gestational age) a high risk for stunting.

Maternal Mortality Rate in Banggai district in 2014 is relatively high, (279/100.000) compare to the national target 2015 (102/100.000). To overcome these problems, innovative efforts as a breakthrough to accelerate improvement of the nutritional and health status of Preconception Women (PcW) has been started in Integrated Health Post (Posyandu) for PcW. The services to pregnant women or antenatal care have been hampered by the delay of first contact (K1) of pregnant women, and the big number of cases of anemia in pre-pregnant women (preconception). Therefore, preconception women services supposed to be a very important action, which is part of Maternal and Child Health Service (MCH) in Banggai District. Preconception health services are health services for women of reproductive age, before the first pregnancy which is a public health strategy to improve women's health and reduce maternal and child mortality. By following the preconception health service, the mother to-be are able to get early identification of pregnancy risk factors such as anemia before pregnancy, identifying and managing maternal conditions and behaviors during pregnancy which may pose a risk to both mother and newborn.

UNICEF/WHO/UNU proposed a multimicronutrient (MMN) prenatal supplement to replace the existing iron folic acid (IFA) supplement, which has been recommended for decades as a means of preventing maternal anaemia[5,6]. Multimicronutrient supplementation since preconcepcetion period is considered a feasible public health strategy in areas with micronutrient deficiencies and can potentially benefit both mothers and their infants[7,8]. Still, the evidence for benefits of MMN supplementation on pregnancy outcome is sparse[1]. We conducted a randomised, double blind controlled trial in which the effects on birth weight and birth length multimicronutrient supplementation with RDA of 15 multimicronutrients were compared with the conventional iron folic acid (IFA) supplement containing ferro sulfate / ferro fumarate or ferro gluconate and 0.25 mg folic acid.

Multimicronutrient (MMN) supplementation

Maternal micronutrients deficiency during pregnancy is an outstanding public health issue worldwide. Due to the increased nutritional requirement, pregnant women are vulnerable to micronutrients deficiency. However, the beneficial effect of MMN supplementation on preconception women and during pregnancy and on postnatal growth of children are still unclear. There has been a scarse studied on the prevention of MMN deficiencies as a strategy to reduce the risk of prenatal anaemia and attention has tended to focus instead on iron supplementation during pregnancy, with conflicting results.

MMN supplementation should be considered as a strategy for improving the micronutrient and haematological status of preconception women of reproductive age. MMN supplementation using the United Nations International Multiple Micronutrient Preparation (UNIMMAP) is a balanced preparation of 15 vitamins and minerals formulated by an Expert Committee of the United Nations Children's Fund, primarily for using by pregnant and lactating women. The MMN tablet consist of vitamin A (retinyl acetat) 800 RE, vitamin E 10 mg, selenium 65 microgram, vitamin D3 (Colecalciferol) 200 IU, vitamin B1 (Thiamin) 1.4 mg, vitamin B2 (Riboflavin) 1.4 mg, vitamin B3 (Niacin) 18 mg, vitamin B6 1.9 mg, vitamin B12 (cyanocobalamin) 2.6 microgram, asam folat 400 microgram, vitamin C 70 mg, iron 30 mg *(iron sulphate),* zinc 15 mg *(zinc sulphate)*, iodium 150 microgram and cuprum *(cooper sulfat)* 2 mg.

MATERIAL AND METHOD

A randomized, double blind controlled Trial

To fulfill a double-blind requirement, MMN from UNICEF in the form of tablets was processed into capsules. The MMN tablet and IFA tablet is crushed and then put into a combination of pink and white capsules. MMN capsules and control capsules are both made with similar weight and color. Subjects, data collectors and researchers did not know whether the capsules contained MMN or iron folate, so the parties involved in the field did not know whether the subjects were in the MMN group or iron folate group.

Randomisation and intervention

The women enrolled in the study were individually randomized with iron folic acid and multimicronutrient supplements. MMN supplementation using the United

Nations International Multiple Micronutrient Preparation (UNIMMAP) is a balanced preparation of 15 vitamins and minerals formulated by an Expert Committee of the United Nations Children's Fund, primarily for using by pregnant and lactating women. One group received a daily multimicronutrient tablet containing of 15 micronutrients as recommended in the future prenatal supplement. The control group received the conventional prenatal iron folic acid (IFA) supplement. Preconception women were instructed to take one tablet weekly if not in menstruating period, and to take one tablet daily if in menstruating periode and during pregnancy preferably together with breakfast.

The manufacturer provided the tablets in containers with a colour code for each intervention group. This code was kept secret from study participants, study personnel, and data analysts until data cleaning and preliminary data analysis had been carried out. For managing of administration in the field, randomization by excel randomization six block program AABB, ABAB, ABBA, BBAA, BABA, and BAAB was done. However, the health workers who collected outcome data after delivery did not have any knowledge of intervention group of the women.

Android gate way

There has been conducted a 24-hour consultation and monitoring of capsules consumption through android. The team of the first 1000 days of life provides 24-hour consultation services through android to ensure the consumption of capsule and question – answer of daily emerging issues during preconception period–positive pregnancy test up to the delivery.

Study area and population

The study was carried out from September 2016 to Januari 2018 in three sub-districts of Banggai district, namely, Luwuk, North Luwuk, and South Luwuk Central Sulawesi.

Infant Measurements

Newborn weight were measured to the nearest 1 mm with a TANITA digital scale. To measure the infant's body length using a length board. All measurements were made in the health centers. To ensure reliability, all anthropometric variables were measured twice, by regional public hospital or clinic staff who have been trained and under the supervision of researcher. The average of the 2 measures was used for analysis. The weighing scales were calibrated monthly.

Statistical analyses

The type of statistical test used is adjusted to the type of variable being tested, if there is a test of the relationship between categorical data and categorical data then using the chi-square test, the average difference test depends on the normality of the data (Anova or Kruskal Wallis) when testing the relationship of categorical data and numerical data. Meanwhile the confidence interval used was 95% with p-values < 0.05 were considered significant. All statistical analyses were performed with SPSS 23.0 (SPSS® Inc.)

RESULTS

Homogeneity Test

Homogeneity between groups before treatment is very important in an experimental study, to ensure that differences in conditions after treatment between groups is indeed an effect of treatment (Meneinert, 1986). In table 1 it can be seen that in both IFA and MMN supplementation groups all variables were homogeneous with p value> 0.005 by testing the homogeneity of variance with Anova test.

Table 1. Homogeneity Test for Preconception Women in IFA Supplementation Group and MMN Supplementation Group

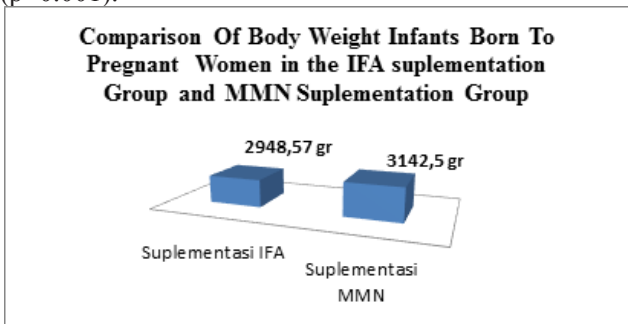
No	Variable	P value*
1	Residential area	0,633
2	Mother's age	0,989
3	Education mother	0,321
4	Father's education	0,648
5	Mother's work	0,499
6	Father's work	0,102
7	Systolic blood pressure at preconception periode	0,079
8	Diastolic blood pressure at preconception periode	0,189
9	Maternal weight at preconception periode	0,086
10	Maternal height at preconception periode	0,848
11	Body mass index at preconception periode	0,818

Cont... **Table 1. Homogeneity Test for Preconception Women in IFA Supplementation Group and MMN Supplementation Group**

12	Mid Upper Arm Circumference at preconception periode	0,601
13	Maternal Haemoglobin level at preconception periode	0,467
14	Maternal Sflt-1 value at preconception periode	0,661
15	Maternal VEGF value at preconception periode	0,766

**Anova test (test homogenity of variance)*

From graph 1, it can be seen that the comparison of the average body weight of infants born in the IFA Suplementation group was lower (2948 g ± SD 344.40) compared to the average body weight of infants born in the MMN supplementation group (3142.5 g±SD 464.48) and the results of statistical tests showed that there were significant differences in the average of body weight infants born to pregnant women in both groups (p=0.001).



Graph 1. Comparison Of Body Weight Infants Born To Pregnant Women in the IFA Supplementation Group and MMN Supplementation Group

Table 2. Comparison of Body length Infants Born To Pregnant Women in the IFA and MMN Suplementation Group

Body length of Infant Born	**IFA Suplementation Group (n=7)**			**MMN Suplementation Group (n=12)**		
	Mean ± SD	**Median**	**Min± Max**	**Mean ± SD**	**Median**	**Min± Max**
	47,86 cm ± 2,41	**48 cm**	**50 cm ± 43 cm**	**49,5 cm ± 2,54**	**49 cm**	**55 cm ± 46 cm**
Mean difference body length of Infant Born To Pregnant Women in the IFA and MMN supplementation group						
Difference	1,64 cm					
95% CI	47,66 – 50,13					
P value	0,001					

From table 2 shows that in the IFA supplementation group the average body length of infants born to pregnant women was 47.86 cm±2.41 median value of 48 cm and the average body length of infants born to pregnant women in MMN supplementation group was 49.5 cm±2.54 and median value was 49 cm. The difference in body length of the IFA and MMN supplementation groups was 1.64 cm. The mean birth weight of infants born to pregnant women in the MMN group was heavier at 3142.5 g with a value (p = 0.001). The average length of infant born to pregnant women in MMN group was longer, 49,5 cm with value (p = 0,001).

Table 3. Category Body Length of Infant Born to Pregnant Women in the IFA and MMN Supplementation Group

Supplementation Group	Short birth length (<48 cm)		Normal birth length (≥48 cm)		Total		P value
	n	%	n	%	n	%	
IFA	4	57,1	3	42,9	7	100	0,515
MMN	5	41,7	7	58,3	12	100	
Total	**2**	**47,4**	**17**	**52,6**	**19**	**100**	

**Chi Square Test*

From table 3 shows that short birth length (<48 cm) of pregnant mother MMN group smaller, equal to 41,7% with value (p = 0,515).

DISCUSSION

The effect of MMN supplementation on infants' birth weight

Birth weight is a simultaneous effect of energy and protein intake factors that play a dominant role, as well as the role of MMN in determining nutritional status since the preconception period. The meta-analysis of MMN administration and pregnancy outcomes conducted[9] explains that the exact mechanism of how MMN supplementation can affect pregnancy outcomes is not yet understood, but MMN can improve immune function thereby reducing the risk of infection in the mother, improving maternal energy metabolism, improve response to stress, and increase the volume of plasma and erythrocytes circulating in the body.

The effect of MMN supplementation on infants' birth length

Between the metaphysics and epiphyses lies the growth plate, where bone growth occurs, so that the bones can become long. The increase in height occurs because of the increasing number of cells in the modified growth plate by MMN supplementation, wherein the content of vitamin D which is a steroid prohormon plays an important role in calcium absorption by regulating calcium absorption in the small intestine. Vitamin D stimulates the synthesis of calcium binding proteins and phosphorus binding proteins in the small intestinal mucosa.

Bone mineralization is positively associated with bone mineral density (BMD). Vitamin D deficiency causes a decrease in calcium absorption which causes the release of calcium from the bone to maintain circulating calcium concentration[10]. Vitamin D also plays a role in stimulating the differentiation and proliferation of chondrocytes so that the growth of the bone growth plate is better, resulting in more body length addition compared to the IFA supplementation group. The more nutrient content, the better absorption of vitamins so that its utilization is more effective for bone growth.

There are a number of biological pathways that explain the role of vitamin D that can affect maternal health, placental and fetal growth during pregnancy. In vitro research shows that vitamin D plays an important role in the metabolism of glucose and insulin which can affect the availability of energy for the fetus.

Vitamin D modulates the immune system that can help shape the right maternal immune response to the placenta which also regulates the key target genes associated with proper placental implantation. Vitamin D plays a direct role in the production of antimicrobial peptides such as katelicidin, which are produced after activation regulated by vitamin D receptors where the production requires 25 (OH)-D which plays an important role in preventing infection during pregnancy. Vitamin D also affects bone and muscle growth[11].

Recent studies have suggested a direct role of vitamin D in the regulation of Hoxa-10 in human endometrial stromal cells. Overall, the study shows that endometrial expression of Hoxa-10 plays an important role in controlling uterine reception, implantation, and desidualization[12] and will further influence fetoplacental

blood flow.

CONCLUSION

Pregnant women who get multimicronutrien (MMN) intervention since preconception period produce better pregnancy outcomes. Posyandu for PcW in Banggai District has became an innovative intervention to increase the health status of PcW starting from preconception period. Preconception period is the best time for women to modify their dietary habits and select healthy nutritional patterns that associated with better birth outcomes.

Ethical Clarance: The study was approved by the Hasanuddin University with the number 1578/ H4.8.4.5.31/31/PP.36-Kometik/2016. All women received an anti-helminthes prophylaxis with albendazole (400 mg base) before receiving the supplementation.

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Conflict of Interest: Nil

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