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Correlation of fetal femur length, birth length between IFA and MMN since preconception period⁶

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MMN;
Femur length;
Birth length

Abstract

Objective: A short femur length (FL) could be a marker early onset fetal growth restriction. The objective of this study is to know the correlation of fetal femur length and birth length between iron folic acid (IFA) and multimicronutrient (MMN) since preconception period.

Methods: This randomized double-blind study provided IFA and MMN from preconception period in Banggai District Central Sulawesi. 19 preconception women were followed in their pregnancy to the childbirth. Measurements of fetal size to report are FL (cm) between 22--24 weeks and 37--38 weeks gestation.

Results: The results showed in 2nd trimester of pregnancy mean fetal FL in IFA group = $3.70 \pm SD 0.20$ in MMN group mean fetal FL = $4.18 \pm SD 0.29$. In the 3rd trimester of pregnancy in IFA group, mean fetal FL = $6.53 \pm SD 0.45$ in MMN group mean fetal FL = $6.61 \pm SD 0.30$. The average length of infants born in IFA group was $47.86 \text{ cm} \pm 2.41$ and in MMN group was $49.5 \text{ cm} \pm 2.51$. There is no significant correlation of fetal FL in the 2nd and 3rd trimester of pregnancy with the birth length in each group ($p > 0.05$).

Conclusion: Women who get IFA intervention has a short FL compared to MMN group. The availability of the nutrients required for optimal fetal growth.

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Fetal growth restriction is associated with metabolic derangements in the newborn, impaired functioning in childhood and chronic diseases in adulthood. The evaluation of growth parameters at birth is undertaken to identify newborns who have suffered growth restriction in utero and therefore may have been exposed to adverse conditions with implications for the immediate neonatal period. Intrauterine growth restriction (IUGR) is the common end result of maternal, placental, fetal, or genetic factors, and can also result due to a combination of any of these factors. 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. A final classification of neonatal growth outcome depends on how this development is defined. Most obstetricians rely on uterine fundal height, fetal abdominal circumference (AC) measurement and or a sonographic estimate of fetal weight for the detection of IUGR.¹ Femur length (FL) is a fetal biometric parameter reflects the longitudinal growth of the fetus. A short FL also may indicate inaccurate pregnancy dating or could be a marker early onset fetal growth restriction.²

Preconception Women's Service (bridal and newlywed) is a comprehensive service to preconception women to improve women's health and nutritional status, to prevent and treat anemia and monitor pregnancy complications, identifying and managing maternal conditions and behaviors during pregnancy which may pose a risk to both mother and newborn. In this service, preconception women are one month before the conception until 2---3 months after the conception³ and receive health and nutritional guidance, multivitamin and mineral, and early pregnancy monitoring. The target of the program is all prospective brides and groom and newly wedding women and their husbands who are preparing for their pregnancies and child bearing.

UNICEF/WHO/UNU proposed a MMN prenatal supplement to replace the existing IFA supplement, which has been recommended for decades as a means of preventing maternal anemia.⁴ One of the content in MMN is vitamin D, a steroid prohormone which plays an important role in calcium absorption by regulating calcium absorption in the small intestine.⁵ There are 6 vitamins and minerals involved in heme synthesis, namely Cu, vitamin B2, folic acid, vitamin B12, Fe and vitamin B6 which are the main components in the formation of red blood cells and ensure the availability of oxygenation supply in the tissues. There are 6 vitamins and minerals involved in implantation and placenta, namely vitamin C, vitamin E, selenium, vitamin B1, vitamin B3 and vitamin D. There are 3 vitamins and minerals that work in overactivation of the regulatory growth pathways of the mother, Mammalian Target of Rapamycin (mTOR) namely zinc, iodine and vitamin A which will stimulate placental expression and regulate GLUT-1 in the tissue so that the affinity for glucose increases.⁶⁻⁻⁻⁸

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.⁵ The main objective of this

study was to assess correlation of fetal femur length and birth length between IFA and MMN supplementation since preconception period.

Method

Study design

We conducted a randomized, double blind controlled trial in which the effect on birth length, providing IFA and MMN supplementation with RDA of 15 multimicronutrients were compared with the conventional IFA supplement containing ferro sulfate and 0.25 mg folic acid for women from preconception period followed until pregnancy and look at the pregnancy outcomes.

The research was conducted in three sub-districts of Banggai district, namely, Luwuk, North Luwuk, and South Luwuk in Central Sulawesi, Indonesia. Total sample 19 preconception women, in IFA group ($n=7$) and MMN group ($n=12$) were enrolled from September 2016 to January 2018.

The inclusion criteria include preconception women, never pregnant, being married, age 18--35 years, willing to participate the study. Exclusion criteria were preconception women with hyperglycemia (diabetes mellitus), renal failure, hypertension, and tuberculosis, not permanent resident in the region, (stay <6 months), not living with their husband, pregnancy twins, obesity (body mass index >30), severe anemia (<7 g/L), mid upper arm circumference <23.5 cm, proteinuria positive (++) for 6 months following the intervention program but not pregnant, has married >6 years but not pregnant and do not consumed vitamins and or minerals from other sources.

Variables

The observed dependent variables were birth length and femur length (FL). Independent variable was IFA and MMN supplementation group which is delivered since preconception period as much as 1 (one) times a week and 1 (one) time a day during menstruation and when they got pregnant, we followed up delivering daily during the whole of their pregnancy or at least 90 (ninety) tablets.⁹ IFA contain 0.25 mg of folic acid and 200 mg elemental iron, while MMN consists of 15 multivitamins and minerals as shown in Table 1.

Data collection

All women received an anti-helminths prophylaxis with albendazole (400 mg base) before receiving the supplementation. To fulfill a double-blind requirement, MMN from UNICEF in the form of tablets was processed into capsules. The MMN tablet and IFA tablet are crushed and then put into a combination of pink and white capsules. Both IFA and MMN capsules providing the same capsule-shape, color, and packaging. However, each capsule still has no code on the label to ensure the respondent will receive the same type during the implementation of the study. Subject and researchers did not know whether the capsules contain MMN or IFA, the capsules code is known by the promoter only, and is kept strictly confidential until completion of data analysis. Both IFA and

Table 1 Composition of the UNICEF international multiple micronutrient preparation (UNIMMAP) and the iron-folic acid (IFA) supplement.

Nutrient	IFA concentration	UNIMMAP concentration	Unit
Vitamin A	–	80	RE
Vitamin D	–	200	IU
Vitamin E	–	10	mg
Vitamin B1	–	1.4	mg
Vitamin B2	–	1.4	mg
Vitamin B3	–	18	mg
Folic acid	0.25 mg	400	mcg
Vitamin B6	–	1.9	mg
Vitamin B12	–	2.6	mcg
Vitamin C	–	70	mg
Zinc	–	15	mg
Iron	200 mg	30	mg
Copper	–	2	mg
Selenium	–	65	mg
Iodine	–	150	mcg

MMN capsule distribution are performed by researchers. All respondents in one group will receive the same type of capsule, but they will not know the type of capsule received by the respondent in another group.

The measurements of fetal size to report are FL (cm) between 22--24 weeks and 37--38 weeks gestation. Ultrasound examination has done at the Maternity Clinic by obstetric and gynecologic expert using ultrasound brand VOLUSON. At this stage of pregnancy, an ultrasound can be used as both a screening and a diagnostic test. Gestational age at birth for each newborn was derived from the date of the last menstrual period (LMP). Measurement of birth length was completed immediately after the baby was born. To measure the infant's body length using a length board, and all measurements were made in the health centers. To ensure reliability, birth length was 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.

Data analysis

The average different birth length and FL on the IFA and MMN groups using *t* test. The correlation FL with the birth length was tested using Spearman correlation. All variables both IFA and MMN groups were homogeneous with *p* value >0.005 by testing the homogeneity of variance with ANOVA test.

Ethical aspect

All participants provided informed consent. The study was approved by the Ethics Committee of Hasanuddin Makassar University, South Sulawesi, Indonesia (reference number: 1578/H.4.8.4.5.31/PP36-KOMITE/2016).

Table 4 Comparison of femur length (FL) at 2nd and 3rd trimester pregnancy between IFA and MMN supplementation group.

Mean	IFA group	MMN group
<i>2nd trimester pregnancy</i>		
FL	3.70 ± SD 0.20	4.18 ± SD 0.29
<i>3rd trimester pregnancy</i>		
FL	6.53 ± SD 0.45	6.61 ± SD 0.30

**t* test.

Result

Data show the location of respondents lived, characteristics of age, occupation and education between IFA and MMN groups (Table 2).

Table 3 shows the average length of infants born to pregnant women in IFA group was 47.86 cm ± 2.41 and in MMN group was longer, 49.5 cm ± 2.51. The difference birth length of the IFA and MMN supplementation group amounted to 1.64 cm. There is no significant correlation of fetal FL in the 2nd and 3rd trimester of pregnancy with the birth length in each group (*p* > 0.05).

Table 4 shows in 2nd trimester of pregnancy the mean fetal FL in IFA group = 3.70 ± SD 0.20 in MMN group mean fetal FL = 4.18 ± SD 0.29. In the 3rd trimester of pregnancy in IFA group, mean fetal FL = 6.53 ± SD 0.45 in MMN group mean fetal FL = 6.61 ± SD 0.30.

Table 5 shows that there is no significant correlation of fetal FL in the 2nd and 3rd trimester of pregnancy with the birth length in each group (*p* > 0.05).

Discussion

Femur length (FL) is a fetal biometric parameter reflects the longitudinal growth the longest bone of the fetus and similar to the biparietal diameter (BPD). It increases from about 1.5 cm at 14 weeks to about 7.8 cm at term.

Table 2 Characteristics of age, education and occupation between IFA and MMN supplementation group.

No.	Description	IFA supplementation group		MMN supplementation group	
		n = 7	%	n = 12	%
1	<i>Location</i>				
	Luwuk	3	42.9	5	41.7
	North Luwuk	1	14.3	3	25
	South Luwuk	3	42.9	4	33.3
	<i>n</i>	7	100	12	100
2	<i>Age of mothers</i>				
	20--35 years	6	85.7	9	75.0
	<20 to >35 years	1	14.3	3	25.0
3	<i>Occupation of mothers</i>				
	Housewife	5	71.4	5	41.7
	Self employed	1	14.3	2	16.7
	Private personnel	1	14.3	3	25
	Others	0	0	2	16.7
	<i>n</i>	7	100	12	100
4	<i>Education of mothers</i>				
	Junior high school	0	0	1	8.3
	Senior high school	4	57.1	5	41.7
	Diploma	1	14.3	1	8.3
	University degree	2	28.6	5	41.7
	<i>n</i>	7	100	12	100

Table 3 Comparison of birth length between IFA and MMN supplementation group.

Birth length	IFA group supplementation (n = 7)			MMN group supplementation (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 ± 2.41	49 cm	55 cm ± 46 cm
<i>Birth length difference between IFA and MMN group</i>						
Difference	1.64 cm					
95% CI	47.66--50.13					
p value	0.001					

*t test.

Table 5 Correlation of femur length (FL) and birth length at 2nd and 3rd trimester pregnancy between IFA and MMN supplementation group.

Variable	Birth length (p value)	
	IFA group	MMN group
FL 2nd trimester pregnancy	0.545	0.225
FL 3rd trimester pregnancy	0.255	0.221

*Spearman correlation.

From human error to outdated ultrasound equipment to normal variation, femur length is only one variable among many that should be used to make determinations about the future of a pregnancy.²

Addition of height occurs because of increasing number of cells in growth plate. Synchronously, the diameter

of the long bone diaphysis increases by osteoblastic deposition of cortical bone beneath the periosteum, and the marrow cavity expands by osteoclastic bone resorption at the endosteal surface. Vitamin D affects bone and muscle growth by stimulating the differentiation and proliferation of chondrocytes.⁵ Recent research states that there is a direct role of vitamin D in the regulation of Hoxa-10 in human endometrial stromal cells¹⁰ which plays an important role in controlling uterine reception, implantation, and decidualization¹¹ and will further influence the increase in fetoplacental blood flow. Vitamin D deficiency causes a decrease in calcium absorption which causes the release of calcium from the bone to maintain circulating calcium concentration.¹² Our findings indicate that good nutrition before and during pregnancy is important for fetal development and growth. Vitamins and minerals are needed in very small amounts but are important in all the body's functions.

Although there is no significant correlation in each group, women who get IFA intervention has a short FL compared to MMN group. Multimicronutrient supplementation since preconception period is considered a feasible public health strategy and can potentially benefit for mothers and their fetal development. Good nutrition should flow throughout the life cycle and across generations.

Conflict of interest

The authors declare no conflict of interest.

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