The Effect Of Multi-Micronutrient Supplementation Since Preconception On Levels Of Malondialdehyde (Mda) For Pregnant Women

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ABSTRACT
The nutritional status of a mother before and during pregnancy is important for a healthy pregnancy outcome. The preconception period is a critical time for improving the nutritional status of pregnant women and preventing pregnancy complications. (MMN) compared to iron folate (IFA). Methodology: A double-blind randomized cohort study was carried out in three districts of Luwuk, South Luwuk, and North Luwuk, Banggai Regency with a total sample of 19 pregnant women given MMN supplementation and IFA supplementation. See the effect of multi-micronutrient supplementation during pregnancy on MDA levels measured several times (preconception, trimester 1, trimester 2, trimester 3). Results: MMN supplementation group MDA levels from preconception (144.43) decreased in trimester 1 (127.60) to trimester 2 (130.94) again until trimester 3 (96.03), while the average IFA supplementation group MDA from preconception (110.54), increased in trimester 1 (153.87) increased again in trimester 2 (172.50) then decreased in trimester 3 (81.75), a decrease in MDA levels was better in the MMN supplementation group.

INTRODUCTION
Malnutrition before and during pregnancy can cause adverse perinatal results. Nutritional deficiencies in pregnant women can cause maternal deaths associated with iron deficiency anemia due to bleeding after childbirth (SDKI, 2012). Malnutrition in pregnant women can interfere with fetal development and contribute to the low birth weight which results in stunting (UNICEF, 2013). Nutritional deficiencies during pregnancy permanently cause non-communicable diseases such as coronary heart disease, cancer, and diabetes. Micronutrient deficiencies in reproductive women and pregnant women, according to Cochran review and the Lancet series recommend the use of iron, folic acid, and multi micronutrient supplementation to reduce anemia and low birth weight as a form of specific interventions. Micronutrients are vitamins and minerals that are needed for the body's normal functioning, growth, and development. Mothers in low-income countries often consume inadequate micronutrients due to limited intake of animal products, fruits, and vegetables. Lack of micronutrients in pregnancy can worsen conditions that lead to potential side effects in the mother such as anemia and even death. Mineral and vitamin deficiencies have no clinical symptoms; can damage intellectual development, cause illness and death of pregnant women, and weak immune system. (Unicef, 2013).

Preconception nutritional status plays an important role in optimizing pregnancy outcomes, maternal health and producing a good generation. Maternal nutrition affects fetal and maternal perceptual nutrition is needed for long-term children's health. Suboptimal outcomes are related to maternal preconception nutrition for example stunting.

Reactive Oxygen Species (ROS) increase due to the absence of antioxidants such as vitamin A, vitamin C and vitamin E. ROS, for example hydroxyl radicals, hydrogen peroxide, and oxygen singlets, result from aerobic metabolism and phagocytic processes. During respiration in the mitochondria, producing superoxide radicals, converted to hydrogen peroxide by superoxide dismutase producing hydroxyl radicals can cause fat peroxidation, with the end produce of malondialdehyde (MDA) genotoxic and mutagenic.

Lipids are an essential component of cell membranes that maintain cell structure and function. Lipids are the main target of ROS attacks such as oxygen free radicals and lipid oxidation is associated with various pathologies. Polar lipids are components of the structure of cell membranes, participating in the formation of cell barriers. Most of these are lipid bilayers, in almost all membranes they are lipids based on glycerol. Lipid membranes are important in controlling the physiological state of the membrane by modifying its biophysical aspects, such as polarity and permeability. Vitamin C (ascorbic acid) plays a role in removing unrestricted radicals and inhibiting lipid peroxidation. Vitamin E and vitamin C are antioxidants to protect against biological membrane damage by their ability to eliminate free radicals. Based on the above background it is necessary to research multimicronutrient supplementation and IFA with markers of membrane damage (MDA) for pregnant women.

MATERIAL AND METHODS
This study gave multi-micronutrient tablets to mothers from preconception to delivery, from September 2016 to
January 2018, as many as 19 preconception mothers, followed by pregnancy until delivery and examination of membrane damage (MDA) every trimester. The study was carried out in 3 districts namely Luwuk, North Luwuk and South Luwuk, in Banggai Regency, Indonesia. A prospective cohort study design with a double-blind randomized controlled trial study design.

The Content of Multi Micronutrient Capsules
Multi-micronutrient capsules are produced by Loma Pharm Germany, which contains Se 65 mcg, Retinol (vitamin A) 800 ug, Vitamin E 10 IU, Vitamin D 200 IU, Vitamin B1 1.4 mg, Vitamin B2 1.4 mg, Vitamin B2 18 mg, Vitamin B6 1.9 mg, Vitamin B12 2.6 mcg, Folic Acid 400 mcg, Vitamin C 70 mg, Iron 30 mcg (iron sulfate), zinc 15 mg (zinc sulfate), copper (Copper) 2 mg, Iodine 150 micrograms. Given during the preconception as much as 1 time a week and once a day during menopause and for the period of pregnancy are given every day during pregnancy.

The Content of Iron Capsules + Folic Acid
A capsule containing 60 mg Fe and 400 micrograms of folic acid is given at the time of preconception as much as 1 time a week and 1 time a day during menopause and for pregnancy given every day during pregnancy.

BIOCHEMICAL METHODS
Blood is collected in the morning after overnight fasting, using a Vacutainer blood collection tube and transported to the local laboratory location for processing within 1 hour after blood is drawn. Blood is immediately processed for the separation of plasma and red blood cells by centrifugation at 2000 rpm for 10 minutes. Plasma samples are stored at 80°C then transported to the Laboratory for MDA measurement. Measuring MDA concentration is a lipid peroxidation product, MDA measurements are determined using commercially available sandwich-ELISA kit (Elabscience, Wuhan, China), adduct obtained with thioarbituric acid (TBA).

Measuring Compliance

<table>
<thead>
<tr>
<th>MDA</th>
<th>IFA supplementation group</th>
<th>MMN supplementation group</th>
<th>P1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Median</td>
<td>Min - Max</td>
</tr>
<tr>
<td>Preconception</td>
<td>110.54 ± 80.82</td>
<td>63.20</td>
<td>54.5 - 274.7</td>
</tr>
<tr>
<td>Trimester 1</td>
<td>153.87 ± 63.27</td>
<td>130.20</td>
<td>82.3 - 245.3</td>
</tr>
<tr>
<td>Trimester 2</td>
<td>172.50 ± 93.53</td>
<td>120.60</td>
<td>93.4 - 349.2</td>
</tr>
<tr>
<td>Trimester 3</td>
<td>81.75 ± 30.08</td>
<td>92.40</td>
<td>38.7 - 121.9</td>
</tr>
</tbody>
</table>

1 Mann Whitney Test

In the Table 1 shows an average increase in MDA levels from preconception (110.54), trimester 1 (153.87) to trimester 2 (172.50) and then decrease in trimester 3 (81.75) of the IFA supplementation group. While the MMN supplementation group MDA levels from preconception (144.43) decreased in trimester 1 (127.60), until trimester 2 (130.94) decreased again until trimester 3 (96.03), a decrease in MDA levels was better in the MMN supplementation group.
in the placenta\(^9\). Environments with low oxygen levels produce ROS which not only have a direct effect on cells but is also active as second messengers for the regulation of transcription factors that alter gene expression in embryos. Hypoxia-inducible factor (HIF-1) regulates transcription genes related to energy metabolism such as \textit{erythropoiesis}, angiogenesis. HIF-1 is activated during hypoxia, regulating vascular development through regulation of vascular endothelial growth factor (VEGF), NF-kB transcription factors, cytokine regulators and antiapoptotic gene expression. Changes in NF-kB are indicated by changes in cellular proliferation and apoptosis through the regulation of the BCL gene\(^10\).

Increased activity of antioxidant enzymes causes inactive ROS and a decrease in lipid peroxidation. A balance between the production of ROS and antioxidants will protect the tissue from damage. MDA is a metabolite of lipid peroxidation production detected in plasma and used as an indicator of lipid peroxidation. Catalase, superoxide dismutase (SOD) and glutathione peroxidase are components of the antioxidant defense system that controls free radicals in cells. lipids in trimester 3. In trimester 2 and trimester 3, there is an increase in glutathione peroxidase. Increased glutathione peroxidase activity is a form of fetal protection against the effects of hydrogen peroxidase. Increased glutathione peroxidase can reduce MDA levels in trimester 3\(^11\).

Research Chatziralli IP et al, 2017 states the provision of \(300\) mg of vitamin E every day for 3 months in diabetics can reduce levels of MDA.\(^14\) Vitamin C \(100\) mg, given daily during the 2nd trimester of normal pregnancy, can significantly reduce MDA levels. Giving vitamin C \(500\) mg for 2 months can reduce MDA, as well as giving vitamin E \(400\) IU for 2 months can reduce MDA\(^15\).

Research Basu J et al, 2015 states the highest levels of placental MDA in trimester 1 and then decreased in trimester 2 and trimester 3 in normal pregnancy.\(^17\) Hypoxia occurs in trimester 1 when the invasion of trophoblast extravillous in the spiral arteries clogs the maternal spiral arteries so that hypoxia occurs this condition cause oxygen pressure in the placenta is lower than in the endometrium. ROS in early pregnancy can affect the remodeling of the spiral arteries and the proliferation of cytotrophoblast cells. as a determination of the pathological state in pregnancy.Oghagbon SE et al. 2016 study state pregnancy is a condition that requires...
high metabolism with high oxygen requirements, resulting in increased oxidative stress. MDA levels increase progressively during pregnancy, increase in trimester 2 and trimester 3. Uncontrolled production of MDA due to an increase in oxidative stress can significantly impair cell integrity. An increase in SOD antioxidants in several studies but there are also antioxidants that may decrease in response to lipid peroxidation as a pathological form. In this study, an increase in SOD whiles the catalase and glutathione peroxidase levels decreased. A study from Bassi R et al., 2017 states that pregnancy is a state of physiological stress in the body and signals to respond by increasing the formation of antioxidants to protect tissues. The accumulation of antioxidants in the placenta prevents the detrimental effects of superoxide. In this study MDA levels increased significantly in trimester 2 and trimester 3. An increase in MDA levels corresponds to an increase in pregnancy and correlates with an increase in lipid peroxidation. MDA is the final product of lipid peroxidation.

Hasan IS Research, Laylani LAS, 2017. An increase in MDA levels in trimester 2 and trimester 3 during normal pregnancy. As a slight increase in oxidative stress even though the levels of catalase, glutathione peroxides and vitamin C MDA are antioxidants such as increase with gestational age. Increased oxidative stress during pregnancy can harm the health of mother and fetus.

**CONCLUSION**

MMN supplementation group MDA levels from preconception (144.43) decreased in trimester 1 (127.60) to trimester 2 (130.94) again until trimester 3 (96.03), while the average IFA supplementation group MDA from preconception (110.54), increased in trimester 1 (153.87) increased again in trimester 2 (172.50) then decreased in trimester 3 (81.75), a decrease in MDA levels was better in the MMN supplementation group.

**REFERENCES**

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