CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

Serum zinc, selenium, iron, and copper levels in pregnant women with fetal growth restriction

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Summary

Background: Fetal growth restriction is associated with many adverse effects and increases the risk of perinatal mortality by more than ten-fold. Zinc, selenium, iron, and copper have important roles in cell proliferation, inflammation, and oxidative stress which possibly serve as the basis for development of fetal growth restriction. *Objective:* To compare serum zinc, selenium, iron, and copper plasma levels between normal pregnancies and pregnancies with fetal growth restriction. *Materials and Methods:* The present was a cross-sectional study conducted at Obstetrics Emergency Unit of Cipto Mangunkusumo Hospital Jakarta from February until May 2017. Normal pregnant women and pregnant women with fetal growth restriction were recruited in this study. Maternal blood samples were taken before labor, and serum zinc, selenium, iron, and copper levels measurements were done. *Results:* Thirty normal pregnancies and 30 pregnancies with fetal growth restriction were enrolled in this study. Mean serum zinc, selenium, iron, and copper levels in normal pregnancy were 42.07 µg/dL, 69.80 µg/L, 70.50 µg/dL, and 2177 µg/L, respectively. Meanwhile, mean serum zinc, selenium, iron, and copper levels in pregnancy with fetal growth restriction were 43.53 µg/dL, 80.83 µg/L, 106 µg/dL, and 2,133.5 µg/L, respectively. There were significant differences in serum selenium concentrations ($p = 0.013$) and serum iron concentrations ($p = 0.009$) between the two groups. There were no significant differences in serum zinc and copper levels between both groups. *Conclusion:* Serum selenium and iron levels were higher in pregnancies with fetal growth restriction. *Conclusion:* The present study indicates the significant roles of micronutrients and oxidative stress in the pathophysiology of fetal growth restriction.

Key words: Fetal growth restriction; Zinc; Selenium; Iron; Copper; Micronutrient.

Introduction

The importance of adequate nutrition before and during pregnancy is a well known requirement for maternal and fetal well-being [1, 2]. Pregnancy is a period where metabolic demand increases due to maternal physiological changes and due to growth of the fetus itself [3, 4]. Inadequate essential vitamin and micronutrient intake can cause biological competition between the mother and the fetus, which negatively impacts both the mother and her fetus [5, 6]. Micronutrient deficiency is very prevalent among productive age women [7, 8]. A study about dietary intake and micronutrient deficiency shows that maternal micronutrient deficiency, among which are zinc and iron, is a very common problem and negatively impacts pregnancy outcomes [9]. Recent data shows that iron and zinc play a role in improving pregnancy outcomes, including birth weight [9].

Compared to non-pregnant state, normal pregnancy was associated with low-grade systemic inflammation, which worsens in pathological pregnancy. It is important to understand that inflammation is an integrated, multisystem response [10]. In pathologic conditions, there is imbalance between oxidative stress and protection by antioxidants [2]. Oxidative stress might be the cause and also the effect of inflammation [10]. Deficiency of several micronutrients with antioxidant effect, such as selenium, copper, and zinc is associated with adverse pregnancy outcome, including fetal growth restriction and preeclampsia [11, 12]. Furthermore, iron deficiency is associated with maternal anemia which increases incidence of low birth weight and fetal growth restriction risk [7, 9].

Fetal growth restriction (FGR) and low birth weight (LBW) are associated with various adverse effects. These conditions increase perinatal mortality risk up to more than ten-fold times, and are associated with post-neonatal mortality risk up to four-fold [9, 13]. Other adverse effects include low intelligence, poor school grades, and low competitive ability in workplace [9, 13]. Upon reaching adult age, these infants are more prone to degenerative diseases such as hypertension, atherosclerosis, and diabetes [9, 13, 14]. About 30 million babies in developing countries are born with FGR each year. This number is six times higher compared to developed countries [15]. Asia, especially Southeast Asia, has the highest prevalence of LBW and FGR (75%), followed by Africa and Latin America [15].

Revised manuscript accepted for publication May 21, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 6, 2019
doi: 10.12891/ceog4744.2019

7847050 Canada Inc.
www.irog.net

Published:10 December 2019

Although the etiology of FGR and preeclampsia are multifactorial, there is common pathophysiology which is abnormal placentation [10, 16]. Placentation defect that is firstly described in FGR and preeclampsia is characterized by inadequate or absence of spiral artery remodeling in junctional zone segments [17]. Placental ischemia or hypoxia mechanism due to placentation defect is associated with oxidative stress production and reactive oxygen species (ROS) release to maternal circulation. This process is thought to be the basis of FGR pathogenesis [18, 19].

Various studies show the important role of micronutrient, such as zinc, selenium, iron, and copper since preconception period until fetal growth and development [20, 21]. These micronutrients have important roles in cell proliferation and differentiation, inflammation, and oxidative stress both in normal pregnancy and pathological pregnancy [2, 20].

Due to the possible importance of micronutrients in fetal growth restriction pathogenesis, the authors would like to describe the maternal serum zinc, selenium, iron, and copper levels in pregnancies with FGR compared to normal pregnancies.

Materials and Methods

This research was a cross-sectional study that was conducted for four months from February until May 2017 in Obstetrics Emergency Unit of Cipto Mangunkusumo Hospital Jakarta. Subjects were enrolled through consecutive sampling until a minimal sample of 30 people in each group was achieved. The subjects for normal pregnancy in this research were pregnant women with gestational age of 37-42 weeks and without comorbidities or complication. The subjects for pregnancy with FGR were pregnant women with gestational age of 28 weeks or more that had an estimated fetal weight or abdominal circumference of less than 10th percentile on that gestational age, or have been diagnosed with FGR based on growth curve from previous examination. Exclusion criteria for this research were multiple pregnancy, intrauterine infection, uterine malformation, fetus with major congenital anomaly, and pregnant women with diabetes, kidney disease, cardiopulmonary diseases or uncontrolled autoimmune diseases.

The study received ethical approval from the Research Ethical Committee of the Faculty of Medicine, Universitas Indonesia. Subjects that met the research criteria were involved in the study after signing an informed consent form. Subject data, including clinical and supporting examination were written in the research form. Before labor, 5 cc of venous blood was taken for micronutrient level assessment. Blood samples were centrifuged at the speed of 3,000 rpm, and micronutrient concentration measurement was performed using Inductively coupled plasma mass spectrometry (ICP-MS) technique. Micronutrient level measurement was performed in Prodia Bunda or Prodia Kramat Laboratory Jakarta.

Data was analyzed with SPSS version 20.0. Data with normal distribution were reported in mean and standard deviation, while data with uneven distribution were reported in median with minimum and maximum value. Bivariate analysis was done using unpaired *t*-test if the data distribution was normal, and Mann-Whitney test if the data distribution was uneven. The difference between both groups was considered significant if p value was below 0.05 ($p < 0.05$).

Results

Sixty subjects that met the research criteria were enrolled in this study. Thirty samples were pregnant women with FGR, and 30 samples were normal pregnant women. Out of 30 subjects with FGR, 17 patients had preeclampsia with severe features.

Characteristics of the subjects in this study are shown in Table 1. Mean patient age on both groups were 29 years. There was a significant difference in birth weight between both groups. Mean birth weight of normal pregnancies was 3,153.33 grams, and mean birth weight of pregnancies with FGR was 1,785.83 grams. This result corresponds with the selection criteria. Furthermore, there was a significant difference between median gestational age of both groups. Median gestational age of FGR group was younger than normal group mostly due to clinical decision to terminate the pregnancy in the case of FGR with or without severe preeclampsia.

Maternal serum assessment showed significant differences in iron and selenium levels between normal pregnancy group and FGR group as shown in Table 2. There were no significant differences in zinc and copper levels between both groups.

The following analysis showed that there were no significant differences in micronutrients levels between FGR group with severe preeclampsia and FGR group without severe preeclampsia as shown in Table 3. Therefore, the micronutrients concentrations measured in the FGR group were not influenced by the presence of severe preeclampsia.

Discussion

Zinc

Zinc is an essential component in more than 200 metalloenzymes [2]. WHO estimates that in 2002 suboptimal zinc intake was occurred in almost half of the world population [22, 23]. Zinc requirement in third trimester of pregnancy is estimated to increase by two-fold of normal zinc requirements [2]. A nutritional analysis shows that pregnant women consume less than 50% recommended zinc intake [2, 23]. Maternal serum zinc concentration in third trimester of pregnancy is 40-70 µg/dL [24-26]. Serum zinc concentration in this study was near the lower limit of normal range, which indicates that there were zinc deficiencies in most subjects. In this study, mean serum zinc concentrations in normal pregnancies was 42.07 µg/dL and mean serum zinc concentrations in pregnancies with FGR was 43.53 µg/dL. There was no significant difference between both groups. This result corresponds to a previous study that compared serum zinc concentrations in normal pregnancies and pregnancies with FGR [25]. Slightly higher zinc concentrations in pregnancy with FGR might occur because of younger gestational ages in this group. Serum zinc concentrations decrease as gestational age increases.

Table 1. — *Characteristics of the subjects.*

Characteristic	Normal group (n=30)	Fetal growth restriction group (n=30)	*p*-value
Patient age (years)	29.23 ± 7.05	29.87 ± 7.08	0.730[a]
Gestational age (weeks)	39 (37-41)	36 (30-40)	< 0.01[b]
Birth weight (grams)	3153.33 ± 361.66	1785.83 ± 484.20	< 0.01[a]

Data are presented in mean ± standard deviation or median (minimum-maximum). [a] unpaired t-test. [b] Mann-Whitney test

Table 2. — *Micronutrients measurement result between normal pregnancy group and FGR group.*

Micronutrient	Normal group (n=30)	Fetal growth restriction group (n=30)	*p*-value
Zinc (µg/dL)	42.07 ± 9.46	43.53 ± 10.76	0.577[a]
Selenium (µg/L)	69.80 ± 15.58	80.83 ± 17.84	0.013[a]
Iron (µg/dL)	70.50 (30-292)	106 (35-304)	0.009[b]
Copper (µg/L)	2177 (1310-3768)	2133.5 (1560-3652)	0.888[b]

Data are presented in mean ± standard deviation or median (minimum-maximum). [a] unpaired t-test. [b] Mann-Whitney test.

Table 3. — *Micronutrients measurement result between FGR without severe preeclampsia group and FGR with severe preeclampsia group.*

Micronutrient	FGR without severe preeclampsia (n=13)	FGR with severe preeclampsia (n=17)	*p*-value[a]
Zinc (µg/dL)	41.92 ± 8.72	44.76 ± 12.21	0.483
Selenium (µg/L)	75.15 ± 14.31	85.18 ± 19.42	0.130
Iron (µg/dL)	107.85 ± 69.25	127.88 ± 55.14	0.385
Copper (µg/L)	2349 ± 547.30	2125.29 ± 406.44	0.209

Data are presented in mean ± standard deviation. [a] unpaired t-test

Decrease in maternal zinc level is considered a part of physiological adaptation in pregnancy due to blood volume changes [2]. It plays an important role in FGR cases where zinc supplements are commonly used to improve fetal growth. The limitation in several studies regarding the administration of zinc supplements to reduce FGR incidence is there was not a large enough sample size to obtain significant results. However, studies showed that zinc supplementation was beneficial in developing countries where its deficiency is common [2, 25].

Zinc is transported through the placenta by active transport from the mother to the fetus. Studies show that fetuses have higher zinc concentrations compared to the mother, even in FGR and preeclampsia cases [2, 24, 25]. This result indicates that the fetus can maintain adequate zinc homeostasis by itself [2]. Decreased serum zinc concentration is associated with an increase in lipid peroxidase in a rat study. This result showed the antioxidant role of zinc [2, 27]

Selenium

In the present study, mean serum selenium level in normal pregnancy was 69.8 µg/L, while mean serum selenium level in pregnancy with FGR was higher, that is 80.83 µg/L. There was a statistically significant difference in serum selenium level between normal pregnancy group and pregnancy with FGR group. The mean serum selenium level in the present subjects were within normal limit as normal selenium concentration in pregnant women is above 35 µg/L [28, 29].

Studies about the association between selenium and FGR shows inconsistent results [25, 30, 31]. One study showed that there was no significant difference in maternal serum selenium level between normal pregnancy and pregnancy with FGR, despite higher selenium concentration in the placenta of FGR cases [25].

Adequate selenium concentration is required as antioxidant. Maternal selenium concentration and glutathione peroxidase activity decrease as gestational age increases. Decreased maternal selenium concentration will cause decreased activity of glutathione peroxidase, which subsequently decrease antioxidant protection [2, 28]. The fetus has lower selenium concentrations compared to the mother because selenium is transported across the placenta depending on the concentration gradient [2]. Higher selenium concentration on FGR group in the present study might be caused by the body compensatory mechanism to overcome oxidative stress in FGR condition, thus causing increased selenium level [29].

Iron

Median serum iron concentrations in pregnant woman with FGR in the present study was 106 µg/dL, while the median was 70.5 µg/dL in normal pregnancy group. The recommended iron concentrations for normal women is 72.0-80.6 µg/dL [32]. Iron deficiency has a negative impact

on pregnancy outcome and baby weight. However, excessive iron storage may contribute to increased oxidative stress [33].

In this study, there was a statistically significant difference in maternal iron concentrations between normal pregnancy group compared to pregnancy with FGR group. This finding was different with another study which mentions that there was no significant difference in iron concentrations between both groups [25]. However, some studies show equal result with the present study where there were increases in iron concentrations in pregnancies with FGR [34, 35].

Under normal condition, as the gestational age increases, maternal ferritin concentration decreases as a result of increased consumption by mother and fetus, and also due to hemodilution. Iron is actively transported in accordance to the need of the fetus. In FGR, maternal ferritin level may increase due to decreased iron extraction by the placenta [34]. The study showed low expression of transferritin receptor in FGR and preeclampsia cases. Other than that, placental isoferritin level was also decreased. It caused lower iron uptake from maternal serum by the placenta. Iron deficiency condition in the fetus could increase fetal corticotrophin and cortisol, which will suppress fetal growth [34, 35].

Increased iron concentration in FGR and preeclampsia are also caused by placental hypoxia and ischemia. Iron is released by lysed erythrocyte in the necrotic and hemorrhagic area of the placenta [35, 36].

Copper

In the present study, median copper concentrations in normal group and FGR group were 2177 µg/L and 2133.5 µg/L, respectively. There was no significant difference in copper concentrations between both groups. The copper concentrations observed in the present study was above normal levels (636.94–1,592.36 µg/L) [37].

Copper is an essential cofactor for several enzymes that play a role in anti-oxidative protection, including catalase and superoxide dismutase (SOD). During pregnancy, plasma copper concentrations increase and will return to normal level after giving birth. Copper concentrations increase as gestational age increases due to synthesis of ceruloplasmin, an important protein that binds copper and acts as antioxidant. Ceruloplasmin synthesis in pregnancy is induced by estrogen [2, 38].

Findings in the present study was in accordance with previous study which showed no difference in copper concentrations between normal pregnancy and FGR [25]. Copper is a transitional metal that can participate in a single electron reaction and thus catalyzes free radical formation including unwanted hydroxyl ion. Therefore, copper has an important role in oxidative stress. Copper itself is a pro-oxidant, but when associated with Cu/Zn SOD, it acts as an antioxidant [2]. Therefore, copper has a complex role in conditions with increased oxidative stress such as pregnancy with FGR and preeclampsia [2, 25].

Copper cannot cross the placenta from maternal serum to the fetus through simple diffusion. Copper from maternal serum is deposited in placental tissue, which then will be moved actively to the fetal tissue according to the fetal demand. Copper concentrations in maternal serum is proven to be higher compared to copper concentrations in umbilical cord blood [2, 38].

Conclusion

In the present study, mean serum zinc, selenium, iron, and copper levels in normal pregnancies were 42.07 µg/dL, 69.80 µg/L, 70.50 µg/dL, and 2177 µg/L, respectively. On the other hand, mean serum zinc, selenium, iron, and copper levels in pregnancies with FGR were 43.53 µg/dL, 80.83 µg/L, 106 µg/dL, and 2133.5 µg/L, respectively. There were significant differences in serum selenium concentrations ($p = 0.013$) and iron concentrations ($p = 0.009$) between normal pregnancies and pregnancies with FGR. There were no significant differences in serum zinc and copper levels between both groups. The mean serum zinc levels in the present study were quite low, both in normal pregnancies and in pregnancies with FGR.

The authors found that serum selenium and iron levels were higher in pregnancies with fetal growth restriction. These micronutrients have a significant relation with oxidative stress. Therefore, the present results confirm the vital role of micronutrients and oxidative stress in the pathophysiology of FGR.

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