Relationship Between Molecular Mechanism Of Maternal Iron Deficiency And Central Nervous System Function Of Neonatal

Yusrawati MD, Dr, Sp.OG, Defrin MD, Sp.OG, Karmia HR MD, Sp.OG

Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology Faculty of Medicine, Andalas University, Padang, Indonesia

---

Abstract Maternal iron deficiency in pregnancy, labor, and postpartum will provide indirect effect which decrease neonatal growth, neonatal neurotrophine, ferritin, and zinc. This study was conducted to determine the relationship between molecular mechanism of maternal iron deficiency and central nervous system function of neonatal. This is an observational study with cross sectional design to 80 at term pregnant women in Yarsi and BMC Hospital in Padang that examined in August-November 2016. The haemoglobin concentration, leukocytes, and ferritin will be taken from maternal blood. After giving birth, neonatal ferritin, neonatal neurotrophine, and neonatal zinc will be taken from umbilical cord of neonatal by using ELISA method. Statistical analysis was conducted by using independent-t test. The maternal ferritin level then divided into two groups, maternal ferritin <15μg/L and maternal ferritin >15 μg/L. The results showed that neonatal ferritin was lower in subjects with maternal ferritin <15μg/L than those with maternal ferritin >15μg/L (58.59 ± 2.33 vs 134.68 ± 7.44 μg/L, $P<0.01$). Neonatal neurotrophine was lower in subjects with ferritin <15μg/L than those with ferritin >15μg/L (1776.20 ± 3.11 vs 3309.82 ± 1.61μg/L, $P<0.01$). Neonatal zinc was lower in subjects with ferritin <15μg/L than those with ferritin >15μg/L (6.72 ± 8.29 vs 14.96 ±6.40 mmol/L, $P<0.01$). Neonatal ponderal index was lower in subjects with ferritin <15μg/L than those with ferritin >15μg/L (2.05 ± 0.31 vs 2.75 ± 0.27, $P<0.01$). Neonatal head circumference was also lower in subjects with ferritin <15μg/L than those with ferritin >15μg/L (32.80 ± 2.38 vs 33.98 ± 1.49 cm, $P=0.051$). The mean level of neonatal ferritin, neonatal neurotrophine, neonatal zinc, and neonatal ponderal index were lower in maternal with iron deficiency than in maternal with normal iron level.

Keyword : neonatal, neurotrophine, ferritin, maternal, zinc, ponderal index, neonatal head circumference

---

Correspondence address: Dr. Yusrawati MD, Sp.OG(K), Division of Maternal-Fetal Medicine, Department of Obstetrics & Gynecology, Faculty of Medicine, Andalas University Padang, Indonesia.
Fax: +6275139246
Email : yusrawati_65@yahoo.co.id

Introduction

Pregnancy is a condition that increases iron requirement to meet the needs of fetus, placenta, and increased red cell mass. Nutrition plays a role in intellectual development of a child since intra uterine life, hence the slogan "smart babies through prenatal university". The most common nutritional deficiency seen in pregnant women is iron deficiency.[1,2] This is usually caused by insufficient iron stores before pregnancy and inadequate iron intake during pregnancy. Serum ferritin concentration has been used as a standard measurement of iron stores in infants, children, and adults. Serum ferritin directly correlate with the total amount of iron stored in the body. Serum ferritin measurement range from about 15-200 µg/L for women. Although laboratory ranges vary, most are close to these value.[3]

Iron deficiency is associated with decreased intellectual performance or cognitive function. Iron is essential in the for dendritogenesis, synaptogenesis, neurogenesis, myelination, and synthesis of neurotransmitters and neurotrophic factors to facilitate brain growth and development since intra uterine life.[4] Previous study that conducted on animals by Trans et al in 2006 found that animal iron deficiency in early life causes epigenetic changes that alter the structure of chromatin and the expression of neurotrophine.[5,6]

Neonatal zinc level also thought to be related to the maternal iron level. Zinc along with iron have a high concentration in the brain, especially in the hippocampal and have function in neurotransmission. Zinc deficiency induces cognitive deficits, especially in terms of learning and memory. Under normal circumstances, transferrin saturation with iron is usually less than 50%. When the ratio between iron and zinc of more than 2:1, transferrin available for the zinc is reduced, thereby inhibiting zinc absorption. The opposite also occurs if the zinc in high doses can inhibit the absorption of iron.[7]

Low iron status in pregnancy also will affect the size of neonatal anthropometry. Previous research shows that levels of serum iron, TIBC, and transferrin saturation mothers in the third trimester is closely linked with birth weight and body length of time the baby is born.[8] The perinatal period is one of the most critical with respect to nutrition, therefore this study was carried out to estimate a mean difference of neonatal zinc, neonatal neurotrophine, neonatal ferritin, neonatal head circumference, and neonatal ponderal index in two groups of maternal ferritin namely maternal ferritin $<15\mu g/L$ and maternal ferritin $>15\mu g/L$. The mean level of the neonatal ferritin, neonatal zinc, neonatal neurotrophine, neonatal head circumeference, neonatal ponderal index in the two groups were evaluated.

Subjects And Methods

This was an observational study with cross sectional design that conducted on August-November 2016. This study was based on 80 pregnant women with at term pregnancy and their newborn as well. The subject selected were among those admitted in maternity wards in Yarsi and BMC Hospital in Padang, Indonesia. Data were statically analyzed by using comparative independent-t test. The inclusion criterias were mother with at term pregnancy, normal leukosit range (5900-16.900 $10^3/\mu l$)[9], and the neonates live born. All patients were healthy without any signs of infection (fever, leucocytes $\geq$16.900 $10^3/\mu l$)[9], pervaginam hemorrhage or other spontaneus bleeding, history of vascular, kidney, and diabetes mellitus disease. Maternal serum and cord blood was determined by using ELISA.

Ethical Issues

Necessary permissions and approvals were obtained from the Hospital Administration and Ethical Committe prior to starting the study. A well informed and valid concent was obtained from those participating in the study.

Sample Collection

Maternal serum were collected from antecubital vein for analyzed the maternal ferritin, haemoglobin, and leukocytes. For the newborn, cord blood was taken for analyzed the neonatal ferritin, neurotrophine, and zinc. Iron status of pregnant women were evaluated using their ferritin level. The maternal ferritin levels then were divided into two groups, maternal ferritin <15µg/L and maternal ferritin >15µg/L. The birthweight, body length, and head circumference were measured after the delivery.

Results

The Maternal and infant characteristic by the grade of ferritin maternal are presented in table 1. As shown in table 1, the mean values of the maternal leukocytes, neonatal body length, neonatal birthweight in maternal ferritin <15µg/L were lower than the mean values of that variables in maternal ferritin >15µg/L. As the other variables such as Apgar score in the first and the fifth minute, parity, and gestational age didn't show a different between the two groups. As presented in table 2, mean values of neonatal ferritin, neonatal neurotrophine, neonatal zinc, and neonatal ponderal index were lower in the maternal ferritin <15µg/L group than the maternal ferritin >15µg/L group ($P<0{,}05$). In the other side neonatal head circumference didn't showed a significant difference ($P>0.05$).

Table 1. Characteristic of maternal and infant by the level of maternal ferritin

	Ferritin <15 (µg/L)[a]		Ferritin >15 (µg/L)[b]	
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)
Maternal:				
Ferritin (µg/L)	8.6 ± 2.4[1]		31.6± 1.5	
Leukosit (103/µl)	9727.5 ± 4.5[1]		9905 ± 1.9	
Neonatal:				
Body Length (cm)	48.2 ± 1.7[1]		48.3 ± 2.2	
Body Weight (gr)	2329.1 ± 306.6[1]		3097.9 ± 441.6	
Apgar Score 1'		8 (6.0 – 9.0)[2]		8 (5.0-6.0)
Apgar Score 5'		9 (7-10)[2]		9 (7-10)
Paritas		1 (0-3)[2]		2 (0-6)
Gestational Age (week)		38.0 (37.0-42.0)[2]		38.00 (35.0-42.0)

[1] The distribution was normal using Kolmogorov-Smirnov

[2] The distribution didn't normal using Kolmogorov-Smirnov

[a] Maternal iron deficiency

[b] Normal maternal iron level

Table 2. Comparison of neonatal ferritin, neurotrophine, zinc, head circumference , and ponderal index between ferritin maternal <15μg/L and ferritin maternal >15μg/L

	Ferritin <15 μg/L	Ferritin >15 μg/L	*P*
	Mean ± SD	Mean ± SD	
Neonatal Ferritin (μg/L)[1]	58.59 ± 2.33	134.68 ± 7.44	0.000
Neonatal Neurotrophine (pg/ml)[1]	1776.20 ± 3.11	3309.82 ± 1.61	0.000
Ponderal Indeks[1]	2.05 ± 0.31	2.75 ± 0.27	0.000
Neonatal Zinc (mmol/L)[1]	6.72 ± 8.29	14,96 ±6.40	0.000
Neonatal Head Circumference (cm)[2]	32.80 ± 2.38	33.98 ± 1.49	0.051

[1] The mean difference using independent-t test was P<0.01
[2] The mean difference using independent-t test was P>0.05

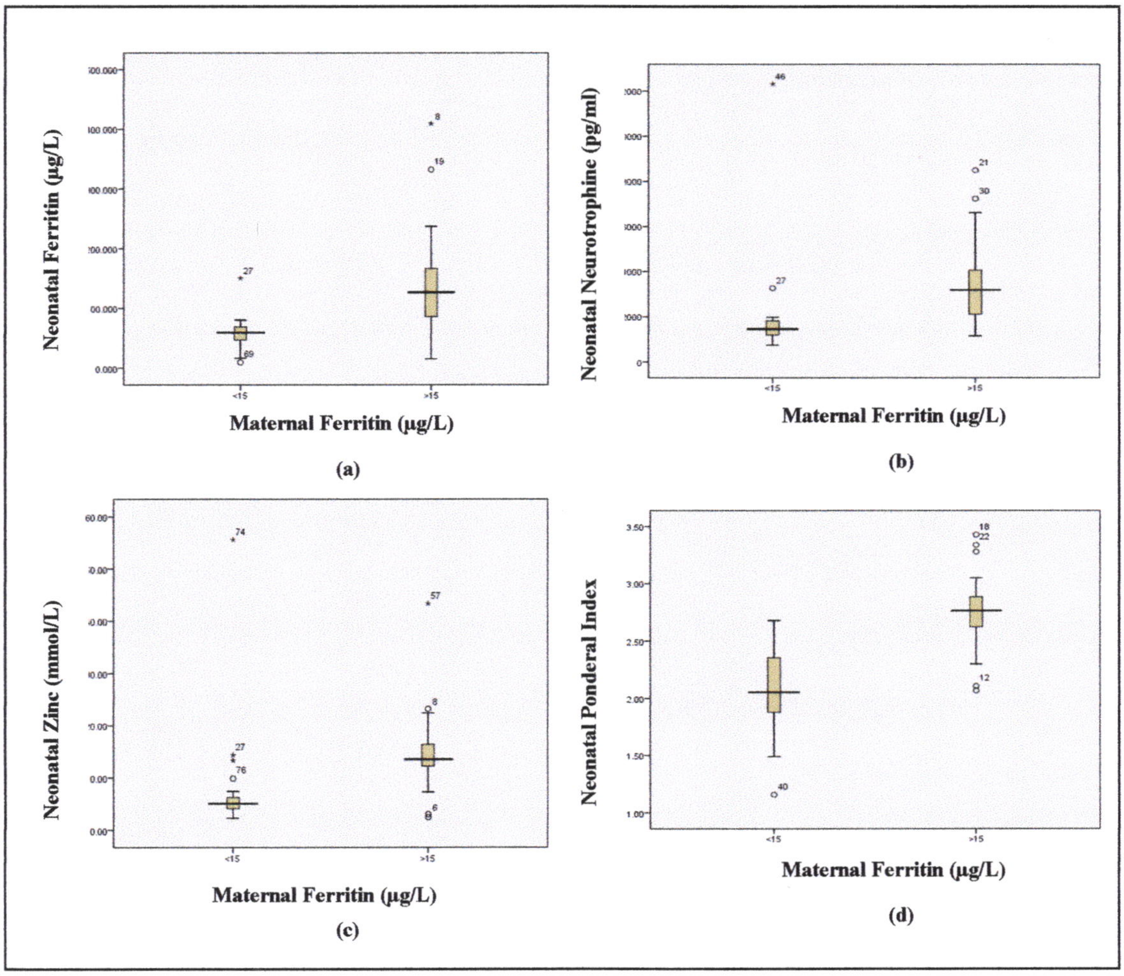

Figure 1. (a) distribution of neonatal ferritinlevel to maternal ferritin concentration, (b) distribution of neonatal neurotrophine level to maternal ferritin concentration, (c) distribution of neonatal zinc level to maternal ferritin concentration, (d) distribution of neonatal ponderal index to maternal ferritin concentration

Discussion

Iron deficiency during fetal and neonatal will affect the structure and function of the hippocampal as the part of the brain that responsible for memory formation and learning. But how exactly cellular mechanism that can cause it is haven't known yet. Several studies have shown that nutritional deficiencies including iron has an impact on the neurotrophine expression in the central nervous system. This Neurotrophine generally have an impact on an area in the brain associated with cognitive and behavioral processes in hippocampal, cortex and amygdala.[4]

In this study, there was found a significant difference between neonatal neurotrophine levels in the maternal ferritin <15μg/L group and maternal ferritin >15μg/L group (P<0,01). This is consistent with the other study by Tran et al in 2008 which found that the pups born from rats that experience iron deficiency showed a decreased activity of neurotrophine that will damage the differentiation of neuron development in the hippocampal.[5] The study then conclude that iron homeostasis is critical for proper neurotrophic factor expression during early life and this provide a possible molecular basis for the neuro-morphologic and behavioral deficits in perinatal iron deficiency. Another study by Lazoff et al in 2006 also showed that iron deficiency during prenatal and postnatal reduce neurotrophine levels and decrease neurogenesis in the dentate gyrus of the in mice. This finding indicates that the iron balance is very important for the expression of neurotrophine that will help the development of the brain. It can also explain how the deficiency of iron in perinatal can cause behavioral deficits in children.[1]

It is known that iron deficiency in the mother also reduce the iron storage in the fetus that would eventually lead to neonatal iron deficiency.[6] It was found that newborns of mothers with low serum ferritin would have low serum ferritin as well. This suggests that the ability of the fetus in the process of iron storage is influenced by maternal iron storage.[6] Jariwala et al in 2014 found that there was a positive correlation between maternal serum iron and neonatal cord serum iron (P=0.004, r=0.386).[10] In this study we found a significant difference between neonatal ferritin levels in the two groups (p <0.01). This finding is consistent with the study by Gaspar et al in 1997 that reported a serum ferritin level of umbilical cord blood of neonates who were born to mothers with low ferritin levels (<12 μg /l) was lower than that of neonates who were born to mothers with normal serum ferritin levels. A study by Peres in 2005 reported that a babies born to mothers with low serum ferritin levels tend to have low serum ferritin levels also.[3]

This study also consistent with a study by Udaphyaya et al in 2004 found that neonatal haemoglobin and iron levels were significantly higher than the mother despite the iron deffeciency that the mother suffered. This is indicate selective uptake of Iron by the fetus but the ferritin levels were low as compared to newborns of non-anemic mothers. In that study they found a significant difference between neonatal ferritin in anemic and non anemic mother (P< 0.01), suggesting that the maternal Iron status influences the Iron level of newborn and therefore mother with adequate Iron status tend to produce newborns with correspondingly adequate Iron levels.[11]

Micronutrient interactions are particularly important during pregnancy, when the developing fetus is very vulnerable to inappropriate micronutrient status. Study of Guo Ma et al in 2004 found that mean serum zinc in the anemic group was much lower than those in the non-anemic group.[12] In this study we found a significant difference between neonatal zinc level in maternal ferritin <15μg/L and maternal ferritin >15μg/L (p

<0.01). This is consistent with study by Udaphyaya et al in 2004 that found iron deficiency anemia in maternal affected maternal zinc and interestingly their newborn also had significantly lower levels of zinc as compared to those with non-anemic mothers.[10]

In our study we found mean difference of ponderal index in the two groups (2.05 ± 0.31 vs 2.75 ± 0.27, $P<0.001$). Study by Hou J et al in 2000 found that neonatal with small ponderal index had lower ferritin serum than neonates with higher ponderal index.[13] Our study also found the mean value of neonatal head circumference was lower in the maternal ferritin <15μg/L than maternal ferritin levels >15μg/L, but we didn't found any significant diffrence (P>0.05). Study by Dalal et al in 2009 also found that mean value of head cicumference were lower in the anemic group mother than head circumference in non-anemic group mother (31.08 vs 32.27 cm).[8]

Conclusions

In this study we have evaluated 80 mothers and their neonates to study the relationship between materal serum ferritin and neonatal neurotrophine, zinc, ferritin, head circumference, and ponderal index. The data in our study are consistent with earlier literature reports. Data in our study suggested that neonatal neurotrophine, zinc, ferritin, head circumference, and ponderal index were lower in maternaliron deffeciency. So there is a relationship between molecular mechanism of maternal iron deficiency and central nervous function of neonatal.

Acknowledgement

We sincerely thank BOPTN dan PNBP FK Unand for the fund to our study. We also grateful to all subjects that give their concent and have participate in our study.

REFERENCES

1. Lozoff B, Georgieff MK. Iron deficiency and brain development. Semin Pediatr Neurol. 2006;13:158–65.
2. Georgieff MK. The role of iron in neurodevelopment: fetal iron deficiency and the developing. Biochemsoc trans. 2008; 36:1267-71.
3. Siddappa AM, Rao R, Long JD, Widness JA, Georgieff MK. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. Neonatology. 2010;92(2):73-82.
4. Estrada J A, Contreras I, Rivero F,Bernardo P, Otero GA. Review Molecular mechanisms of cognitive impairment in iron deficiency: Alterations in brain derived neurotrophic factor and insulin like growth factor expression and function in the central nervous system. Nutritional Neuroscience. 2014;17:193-206.
5. Tran PV, Carlson ES, Freetham SJ, Georgieff MK. Early-life iron deficiency anemiaa alters neurotrophic factor expression and hippocampal neuron differentiation in male rats. The journal of nutrition ingestive behavior and neurosciences. 2008;138:2495-501.
6. Rdlowski EC, Johnson RW. Perinatal iron deficiency and neurocognitive development. Frontiers in Human Neuroscience. 2012; 595(7):1-11.

7. Jaime-Perez JC, Herrera-Garza JL, Gomez-Almaquer D. Sub optimal fetal iron acquisition under a maternal environment. Arch Med Res. 2005;36:598–602.
8. Dalal E, Shah J. A comparative study on outcome of neonates born to aemic mothers versus no anemic mothers. National Journal of Medical Research. 2014;4(4)270-273.
9. Cunningham FG, Leveno KJ, Bloom SL. Obstetri Wiliam. Edisi ke-24. Jakarta: EGC; 2014.
10. Jariwala M, Suvarna S, Kumar GK, Amin A, Udas AC. Study of the concetration of trace elements Fe, Zn, Cu, Se and their correlation in materal serum, cord serum and colostrum. Ind J Cli Biochem. 2013; 29(2):181–8
11. Udaphyaya C, Mishra S, Ajmera P, Sharma P. Serum iron, copper, ad zinc status in maternal and cord blood. Indian Journal of clinical biochemsitri. 2004;19(2):48-52
12. Ma AG, Chen XC, Xu RX, Zheng MC, Wang Y, Li JS. Compariso of serum levels of iron, zinc, and copper in anaemic ad non-aaemic pregnant women in China. Asia Pac J Clin Nutr. 2004;13(4)348-52.
13. Hou J, Cliver SP, Tamura T, Johnston KE, Goldenberg R. Maternal serum ferritin and fetal growth. Obstet Gyenecol. 2000;95(3):447-52

COGI

Certificate of Attendance

This is to certify that

Yusrawati Wati

Presenter of the Oral presentation

The relationship between molecular mechanism of maternal iron deficiency and central nervous system function of neonatal

has attended

The 24th World Congress on
Controversies in Obstetrics, Gynecology & Infertility (COGI)

Amsterdam, The Netherlands, **November 10-13, 2016**

Organizing Committee