

# Neonatal Growth, Neurotrophine, Zinc, and Ferritin Concentration in Normal and Iron Deficiency Pregnancy: An Observational Analytic Study

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## Abstract

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**BACKGROUND:** Anemia in pregnancy was one of the national problems. Insufficient iron deposits before pregnancy and inadequate iron intake during pregnancy could lead to iron deficiency anaemia in pregnancy, followed by iron deficiency in neonates.

**AIM:** This study aimed to assess the molecular relationship of maternal iron deficiency with the function of the neonatal central nervous system to know the cognitive aspects of learning ability of children.

**METHODS:** This study was an observational analytic study with cross-sectional design underwent in RSUP Dr M. Djamil Padang, RSI Ibnu Sina Padang, and RSU BMC Padang. The sample size was 80 pregnant women at term. After a maternal and neonatal physical examination, maternal and umbilical blood samples were obtained to assess maternal ferritin levels and neonates ferritin, neurotrophin and zinc levels using the Enzyme-Linked Immunosorbent Assay (ELISA). Data were analysed using the IBM SPSS Statistics for Windows. The independent sample t-test was performed to assess the relationship for normally distributed data and Mann-Whitney test for abnormal data distribution with significance level  $p < 0.05$ .

**RESULTS:** There were differences in mean neonatal ferritin ( $p < 0.001$ ), neonatal neurotrophin ( $p < 0.001$ ), and neonatal zinc ( $p < 0.001$ ) to normal maternal ferritin levels ( $\geq 15 \mu\text{g/ml}$ ) and low maternal ferritin levels ( $< 15 \mu\text{g/ml}$ ). The difference in mean neonatal head circumference (0.92; CI95% -0.79-0.98) was associated with neonatal ferritin levels.

**CONCLUSIONS:** The mean neonatal ferritin, neurotrophin, and zinc levels were found lower in iron deficiency maternal. Maternal iron deficiency correlates with neonate growth, iron deficiency, and neurotrophin expression that affected neonate cognition.

## Introduction

Anaemia in pregnancy was one of the national problems because it reflected the socio-economic well-being of the community and greatly affected the quality of human resources. Anaemia in pregnant women was called "potential danger to mother and child" (potentially harmful to mother and child). Therefore, serious attention was needed from all parties to anaemia related to healthcare services [1]. The highest prevalence of anaemia in pregnancy in the world was found in countries of Southeast Asia, Western Mediterranean and Africa. The target of

"Global Nutrition Targets 2025" among of which was for mother, infant and child was expected to reduce anaemia by 50% infertile women [2].

Iron plays a role in neurocognitive and neurobehavioral development in the last two-thirds of pregnancy. Research on humans and animals showed that iron deficiency anaemia occurred since intrauterine was associated with the developmental disorders of behavioral development and nerve changes that produce irreversible effects on fetal neurochemistry and neurobiology [3]. Iron is important in the process of erythropoiesis, the formation of hemoglobin, myoglobin, gene transcription, cellular enzyme reactions, and oxidation-reduction reactions.

Iron also plays a role in the process of dendritogenesis, synaptogenesis, neurogenesis, myelination and synthesis of brain neurotransmitters. All of these iron functions are important for the brain to perform its functions, so iron deficiency could lead to behavioural impairment, decreased learning function, and memory [4].

Neurotrophin is a growth factor that plays a role in learning, memory, and behaviour in the hippocampus. Synthesis of neurotrophin requires enzyme and iron. Animal studies had found that iron deficiency early in life caused epigenetic changes that alter chromatin structures and expression of neurotrophin genes, leading to a decrease in the differentiation of the hippocampus neurons and causing behavioural and cognition abnormalities, including decreased memory capacity and increased anxiety. Abnormal behaviour and cognition will persist until adulthood despite adequate treatment [4], [5].

Zinc along with iron is a high concentration in the brain especially the hippocampus and is included in the neurotransmission. Zinc deficiency induces cognitive deficits especially in the process of learning and memory. Some of the zinc is a transferrin transport device, which is also an iron transport vehicle. Under normal circumstances, transferrin saturation is usually less than 50% of iron. When the ratio of iron and zinc is more than 2:1, transferrin available for zinc is reduced, thus inhibiting zinc absorption. The opposite also occurs where high concentrated zinc can inhibit the absorption of iron [6]. Therefore, zinc supplementation was recommended in pregnant women who were given iron supplementation [7]. Low iron status in pregnancy will affect the anthropometric size of newborns. Maternal iron status and pregnancy outcomes showed that serum iron, TIBC, and maternal transferrin saturation levels in third-trimester pregnancies were closely related to birth weight and infant length. The presence of a link between iron deficiency (maternal and neonatal), zinc, and neurotrophin with the central nervous system and neonatal anthropometry had caused authors interest to investigate differences in neonatal growth rates, ferritin levels, neurotrophin, and zinc in pregnancies with normal and low ferritin levels.

This study aimed to assess the molecular relationship of maternal iron deficiency with the function of the neonatal central nervous system to know the cognitive aspects of learning ability of children.

## Methods

This was an observational analytic study with a cross-sectional study design. This study was

conducted at RSUP. Dr M. Djamil Padang, RSI. Ibnu Sina Padang, RSU. BMC Padang as well as sample examination conducted in Biomedical Laboratory FK Unand in August 2016-November 2016. A sample size of 80 pregnant women at term consisted of 40 samples with normal ferritin ( $> 15 \mu\text{g/L}$ ) and 40 samples with low ferritin ( $< 15 \mu\text{g/L}$ ). Sampling was done using consecutive sampling which came antenatal care at RSUP. Dr M. Djamil Padang, RSI. Ibnu Sina Padang, and RSU. BMC Padang.

The population of this study were all pregnant women with at term pregnancy who performed antenatal care on obstetricians' practice at RSUP Dr M. Djamil, RSI. Ibnu Sina Padang and RSU. BMC Padang. The inclusion criteria in this study were term pregnancies, neonates born alive, maternal leukocytes within normal limits, and willing to participate in the study.

After signing informed consent, history, clinical examination and obstetric examination, and ultrasound were performed. Mother's blood sample was taken for haemoglobin (Hb), leukocyte and ferritin examination. After the child was born either pervaginam or Caesarea section, cord blood collection was done to check the levels of ferritin, neurotrophin, and zinc. Neonatal anthropometry was measured after birth, i.e. body weight, body length and head circumference. The maternal serum and neonatal cord serum samples obtained were analysed using the Enzyme-Linked Immunosorbent Assay (ELISA) method.

Data were analysed using the IBM SPSS Statistics for Windows (version 23.0; SPSS, Inc., Chicago, IL, USA). The independent sample t-test was performed to assess the association for normally distributed data and Mann-Whitney test for abnormal data distribution with significance level  $p < 0.05$ .

## Results

Mean of ferritin, neurotrophin, and neonatal zinc levels in normal and low maternal ferritin are presented in Table 1.

**Table 1: Mean of Ferritin, Neurotrophin, and Neonatal Zinc Levels in Normal and Low Maternal Ferritin**

|                                               | Low Maternal Ferritin ( $< 15 \mu\text{g/ml}$ )<br>Mean $\pm$ SD | Normal Maternal Ferritin ( $\geq 15 \mu\text{g/ml}$ )<br>Mean $\pm$ SD | CI95%          | p value   |
|-----------------------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------|----------------|-----------|
| Neonates Ferritin Levels ( $\mu\text{g/ml}$ ) | 58.59 $\pm$ 2.33                                                 | 134.68 $\pm$ 7.44                                                      | 53.33-103.07   | $< 0.001$ |
| Neonates Neurotrophin Levels (pg/mL)          | 1776.20 $\pm$ 1.764                                              | 3309.82 $\pm$ 1.614                                                    | 780.88-2286.36 | $< 0.001$ |
| Neonates Zinc Levels (mmol/L)                 | 6.72 $\pm$ 8.29                                                  | 14.96 $\pm$ 6.40                                                       | 4.94-11.53     | $< 0.001$ |

\* Distribution of data was normal, the mean difference was analysed using Independent samples t-test; \*\* Distribution of data was abnormal, the mean difference was analysed using Mann-Whitney Test.

As shown in Table 1, there was a difference of mean ferritin, neutrophil, and zinc of term newborn between normal maternal ferritin ( $\geq 15 \mu\text{g/mL}$ ) with low maternal ferritin ( $< 15 \mu\text{g/ml}$ ) of  $78.20 \mu\text{g/mL}$ ,  $1533.62 \text{ pg/mL}$ , and  $8.23 \text{ mmol/mL}$ , respectively, with  $p < 0.05$ .

**Table 2: Mean of Head Circumference, Body Length, and Neonatal Weight on Normal Neonatal Ferritin and Low Neonatal Ferritin**

|                                 | Low Neonates<br>Ferritin ( $< 75\mu\text{g/ml}$ )<br>Mean $\pm$ SD | Normal Neonates<br>Ferritin ( $\geq 75\mu\text{g/ml}$ )<br>Mean $\pm$ SD | CI95%      | p value     |
|---------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------|------------|-------------|
| Neonates<br>Circumferences (cm) | 34 (28-35)                                                         | 34 (29-36)                                                               | -0.79-0.98 | 0.004**     |
| Neonates Length (cm)            | 48.22 $\pm$ 1.90                                                   | 48.31 $\pm$ 2.06                                                         | -07.9-0.98 | 0.837**     |
| Neonates Weight (gram)          | 2426 $\pm$ 405                                                     | 3083 $\pm$ 464                                                           |            | $< 0.001^*$ |

\* Distribution of data was normal, the mean difference was analysed using Independent samples t-test; \*\* Distribution of data was abnormal, the mean difference was analysed using Mann-Whitney Test.

In Table 2, shown there was a difference in mean of head circumference, body length, and neonatal weight between normal neonatal ferritin ( $\geq 75 \mu\text{g/mL}$ ) with low neonatal ferritin ( $< 75 \mu\text{g/mL}$ ) with  $p < 0.05$ .

**Table 3: Mean Head Circumference, Body Length, and Neonatal Weight in Neonatal Neurotrophin Normal and Neonatal Neurotrophin Low**

|                                     | Low Neonates<br>Neurotrophin ( $< 2000$<br>pg/ml) Mean $\pm$ SD | Normal Neonates<br>Neurotrophin ( $\geq 2000$<br>pg/ml) Mean $\pm$ SD | CI95%      | p value        |
|-------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------|------------|----------------|
| Neonates<br>Circumference<br>s (cm) | 34 (28-35)                                                      | 34.3 (32-36)                                                          | 0.68-2.43  | $< 0.001^{**}$ |
| Neonates<br>Length (cm)             | 48.11 $\pm$ 1.72                                                | 48.48 $\pm$ 2.27                                                      | -0.51-1.26 | 0.400**        |
| Neonates<br>Weight (gram)           | 2412 $\pm$ 357                                                  | 3142 $\pm$ 463                                                        | 0.68-2.43  | $< 0.001^*$    |

\* Distribution of data was normal, the mean difference was analysed using Independent samples t-test; \*\* Distribution of data was abnormal, the mean difference was analysed using Mann-Whitney Test.

Table 3, shown there were differences in mean head circumference and weight of term newborn between normal neonatal neurotrophin levels (neurotrophin  $\geq 2000 \text{ pg/mL}$ ) with low neonatal neurotrophin (neurotrophin  $< 2000 \text{ pg/mL}$ ) with  $p < 0.05$ .

## Discussion

This study shows a significant difference between low maternal ferritin group ( $< 15 \mu\text{g/L}$ ) with normal maternal ferritin group ( $> 15 \mu\text{g/L}$ ). Iron deficiency in the mother reduces iron deposits of the fetus which eventually leads to neonatal iron deficiency [4]. Several previous studies had found that iron deficiency in the fetus and neonate affected neurotrophin expression in the CNS. Neurotrophin has some impacts on areas of the brain that are associated with cognition and behavioural processes in hippocampus, cortex and amygdala areas [3].

Iron deficiency during prenatal and postnatal

periods caused decreased levels of neurotrophin and neurogenesis in the dentate hippocampus. This suggested that iron balance is important for the expression of neurotrophin which will help the development of the brain. It may also explain how an iron deficiency in perinatal periods could lead to deficits of behaviour in children [8].

Concentrations of serum ferritin had been used as a standard measure of iron storage in infants, children, and adults. In adults,  $1 \mu\text{g/l}$  serum ferritin is equivalent to  $8\text{-}10 \text{ mg}$  iron stores. In neonates, the ratio between serum ferritin and non-heme iron in the liver is close to  $1:2.7$  [9]. Perez et al., (2005) found that babies born to mothers with low serum ferritin would tend to have low levels of ferritin as well [10].

The interaction between micronutrients in pregnancy is crucial, where developing fetuses are particularly vulnerable to inappropriate micronutrient status. Excessive and uncontrolled administration of micronutrient supplements during pregnancy may adversely affect other micronutrients because of the competition between each of these micronutrients [11].

Several previous studies had reported that iron supplementation might cause impaired absorption of zinc in the gut. This is due to the barrier of zinc uptake in the intestinal wall. In the state of zinc deficiency, iron metabolism will be disrupted and will lead to iron deficiency anaemia [3]. Therefore, many studies suggested giving zinc along with iron supplementation.

In this study, infants born to mothers with low levels of ferritin had lower zinc levels than infants born to mothers with normal ferritin levels. Research conducted by Jariwala et al., in pregnant women who gave birth at Babha Atomic Research Center Hospital India found a significant correlation between maternal iron levels and maternal zinc levels. Maternal zinc levels would also affect neonatal zinc levels [12].

In this study, it was found that infants with low levels of ferritin had lower zinc levels than infants with normal ferritin levels. Research conducted by Jariwala et al. showed a significant positive correlation between iron levels in neonatal and zinc levels in the neonatal ( $p = 0.001$ ,  $r = 0.54$ ) [11]. Knowing that iron deposits in neonates could be affected by maternal iron status, and with the difference in mean rates of newborn zinc in normal maternal ferritin and low maternal ferritin, it could be concluded that there was an indirect relationship between neonatal zinc levels and neonatal ferritin levels.

Iron deficiency while in the womb and at neonates could disrupt the brain structure, cognitive function, and could result in long-term irreversible motoric and cognitive disorders that cannot be treated with iron supplementation [9]. Neurotrophin plays an important role in neuron protection systems and lowers the risk of neuronal apoptosis. Also,

neurotrophin also plays a role in the growth of axons during development, enhancement of neuron function, neuronal morphological differentiation, and neurotransmitter expression [13]. In this study, there was a significant difference in mean neonatal head circumference between infants with low ferritin levels compared with infants with normal ferritin levels.

Severe deficiency anaemia is associated with poor outcomes such as abortion, preterm delivery, and poor neonatal anthropometry. Previous studies had focused more on the relationship between maternal ferritin levels and anthropometry of newborns. Research conducted by Dalal et al., 2014 had found a significant relationship between the length of the newborn's body and the maternal ferritin level [14]. It is just that the mean difference between maternal ferritin and the length of the newborn's body was not studied in this study

In this study, a significant difference in mean birth weight between infants with normal ferritin levels and infants with low ferritin levels were found. Iron deficiency anaemia in early pregnancy is associated with an increased risk of having a low birth weight baby and preterm birth. In a randomised observational study conducted in Nepal, it was found that the introduction of iron supplements, folic acid, and vitamin A significantly reduced the incidence of low birth weight incidence (19%) when compared with vitamin A supplementation alone [15]. It is known that iron deposits in neonates may be affected by maternal iron status so that infants born to mothers with low ferritin levels will have lower levels of ferritin than babies born to mothers with normal ferritin levels. The significant difference in mean birth weight of the newborns in this study was thought to be indirectly caused by the level of neonatal ferritin which was influenced by maternal ferritin levels.

The head circumference at birth is known to represent brain volume in newborns and had been used in previous studies to measure cognitive function [16]. Veena et al., in 2011 found a positive correlation between birth weight and head circumference with learning ability, long-term memory, and visuospatial ability ( $p < 0.05$ ). There was an association between neonatal neurotrophin and neuronal growth, and the association between cognitive and neonatal head circumference were estimated to influence the findings obtained in this study [16]. Neurotrophin may play an important role in brain development during the antenatal and postnatal periods [13].

Neurotrophin is responsible for modulation of synapse function, neuron cell plasticity, modulation of oligodendrocyte growth, myelin formation, and dendritogenesis how the relationship between the weight and neonatal neurotrophin levels had not been studied previously. Rao et al., a study in 2008 found there was no significant relationship between birth weight and neonatal neurotrophin levels [17]. In this study, however, there was a significant mean

difference between newborns who had low neurotrophin levels and high neurotrophin levels ( $p < 0.005$ ).

In conclusion, maternal iron deficiency correlates with neonate growth, iron deficiency, and neurotrophin expression that affected neonate cognition in the future.

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