

## Original Article

# Differences in brain-derived neurotrophic factor between neonates born to mothers with normal and low ferritin

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**Background and Objectives:** Maternal iron deficiency in late pregnancy, labor, and the postpartum period has an indirect impact to decrease neurotrophin concentration in the fetal hippocampus, namely brain-derived neurotrophic factor (BDNF). It plays an important role in the development of learning, memory, and behavior. The aim of this study was to determine the differences in BDNF between neonates born to mothers with normal and low ferritin. **Methods and Study Design:** This was an observational study with a cross-sectional design involving 20 term pregnant women with normal ferritin ( $\geq 12$  ng/mL) and 20 term pregnant women with low ferritin ( $< 12$  ng/mL). Samples were taken from Yarsi hospital, BMC hospital, and Hardi clinic located in Padang, from August 2015 to February 2016. Umbilical cord plasma was examined directly after delivery using an enzyme-linked immunosorbent assay (ELISA) employed at the Biomedical Laboratory of Andalas University. Mean differences were statistically assessed by independent samples *t*-test. **Results:** Plasma BDNF concentrations in neonates born to mothers with normal and low ferritin were  $3.81 \pm 1.37$  ng/mL and  $2.78 \pm 1.19$  ng/mL, respectively ( $p=0.015$ ). **Conclusions:** Plasma BDNF was lower in neonates born to mothers with low serum ferritin.

**Key Words:** brain-derived neurotrophic factor, ferritin, maternal, neonates, iron deficiency anemia

## INTRODUCTION

Nutrition plays a role in the intellectual development of a child during intrauterine life. The most common nutritional deficiency found in pregnant women is iron deficiency.<sup>1,2</sup> Pregnancy is a condition that increases the iron requirement to meet fetal and placental needs. Insufficient iron stores before pregnancy and inadequate iron intake during pregnancy can lead to iron deficiency anemia.<sup>3</sup> The iron deficiency can be examined by assessing the serum ferritin that directly correlates with the total amount of iron stored in the body. Iron deficiency anemia is usually found when the serum ferritin is less than 12  $\mu\text{g/dL}$ .<sup>4,5</sup>

A study by Milman et al (1991) suggested that neonates born to mothers receiving iron supplementation during pregnancy had higher serum ferritin than neonates born to mothers receiving placebo.<sup>6</sup> Consistent with the previous study, Gaspar et al (1993) and Perez et al (2005) reported that neonates born to mothers with low serum ferritin tend to have low serum ferritin as well.<sup>7,8</sup> Shao et al (2012) also found that there was a positive correlation between maternal serum ferritin and iron reserve in term neonates.<sup>9</sup>

Iron deficiency is associated with decreased intellectual or cognitive function. The brain region that serves as a

center of memory, learning, and behavior is the hippocampus. Iron is essential for the hippocampus to undertake dendritogenesis, synaptogenesis, neurogenesis, and synthesis of neurotrophic factors that facilitate brain growth and development commencing in intrauterine life. The main neurotrophic factor in the hippocampus for learning, memory, and behavior is brain-derived neurotrophic factor (BDNF). BDNF is a family of neurotrophins that plays an important role in neuronal cell plasticity, oligodendrocyte growth modulation, myelin formation, dendritogenesis, augmentation of glutamatergic synapse transmission, and mitigation of the gamma-aminobutyric acid (GABA) inhibitory signal.<sup>10,11</sup>

Animal studies have found that iron deficiency in early life leads to epigenetic changes which alter the structure

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of chromatin and gene expression of BDNF, thus causing a decrease in neuronal differentiation in the hippocampus. This is also associated with abnormalities of behavior and cognitive function.<sup>12</sup> Acute iron deficiency that occurs in late pregnancy, delivery, and postpartum periods may result in reduction of BDNF and mitochondrial dysfunction. This can lead to impairment of neuron structure, neuron electrophysiology, and behavioral development. If the iron deficiency still persists into adulthood, it may also contribute to learning and memory problems.<sup>5,13</sup>

The susceptibility of pregnant women to iron deficiency anemia, the positive correlation between maternal and neonatal ferritin, and the negative effect of iron deficiency on brain function have encouraged us to study the differences in BDNF among term newborns from mothers with normal and low ferritin.

## METHODS

This was an observational study with a cross-sectional design. It was conducted from August 2015 to February 2016 and approved by the Medical Research Ethics Committee of the Dr. M. Djamil Hospital (Project Number PE.07.2016). Term pregnant patients with normal leukocyte counts and willing to participate were included. The exclusion criteria were any evidence of infectious disease, vascular disease, kidney disease, diabetes mellitus, or vaginal bleeding. Eligible patients were identified through the cooperation of three participating medical institutions located in Padang, West Sumatra, Indonesia, namely, Yarsi hospital, BMC hospital, and Hardi clinic. Those who agreed to participate in the study gave written informed consent and had their blood checked for serum

ferritin. A total of 40 pregnant women participated, 20 with normal serum ferritin ( $>12$  ng/mL) and 20 with low serum ferritin ( $<12$  ng/mL).

All participants were followed until delivery and the cord-blood of their newborns was examined immediately after birth for BDNF using an enzyme-linked immunosorbent assay (ELISA) method available in the Biomedical Laboratory of the Medical faculty of Andalas University. Independent sample t-tests were used to assess significant difference (SPSS program (22.0 version)).

## RESULTS

Maternal characteristics are shown in Table 1. There were no differences in age, parity, Body Mass Index (BMI) or leukocyte counts between normal and low ferritin groups ( $p>0.05$ ). However, there was a significant difference in hemoglobin between the two groups ( $p<0.05$ ).

Neonatal characteristics are shown in Table 2. The differences in birth weight, body length, and head circumference among newborns from mothers with normal and low ferritin were not statistically significant ( $p>0.05$ ). There was a significant difference in neonatal BDNF between the normal and low maternal ferritin groups ( $p<0.05$ ) (Figure 1).

## DISCUSSION

As shown in Table 1, we found that those with low ferritin had a lower hemoglobin than those with normal ferritin ( $p<0.05$ ). This is consistent with a study by Milman et al (1991) which was a placebo controlled study of 207 healthy Danish women after 16 week gestation. They reported that the placebo-treated group had a lower he-

**Table 1.** The maternal characteristics by maternal ferritin

Characteristics	Normal ferritin ( $\geq 12$ ng/mL) N=20	Low ferritin ( $<12$ ng/mL) N=20	<i>p</i> value*
Age (years) <sup>†</sup>	31.1 $\pm$ 5.42	29.9 $\pm$ 5.29	0.268
Parity <sup>‡</sup>			
Primipara	10 (50%)	13 (65%)	0.344
Multipara	10 (50%)	7 (35%)	
BMI (kg/m <sup>2</sup> ) <sup>†</sup>	23.0 $\pm$ 2.13	23.1 $\pm$ 4.34	0.355
Hb (gr/L) <sup>†</sup>	109 $\pm$ 6.9	101 $\pm$ 12.3	0.025
Leukocytes (10 <sup>9</sup> /L) <sup>†</sup>	9.7 $\pm$ 1.7	10.3 $\pm$ 2.0	0.319

BMI: body mass index; Hb: haemoglobin.

<sup>†</sup>Data are reported as mean $\pm$ SD.

<sup>‡</sup>Data are reported as percentage.

\**p* values are obtained by independent t-test.

**Table 2.** The neonatal characteristics by maternal ferritin

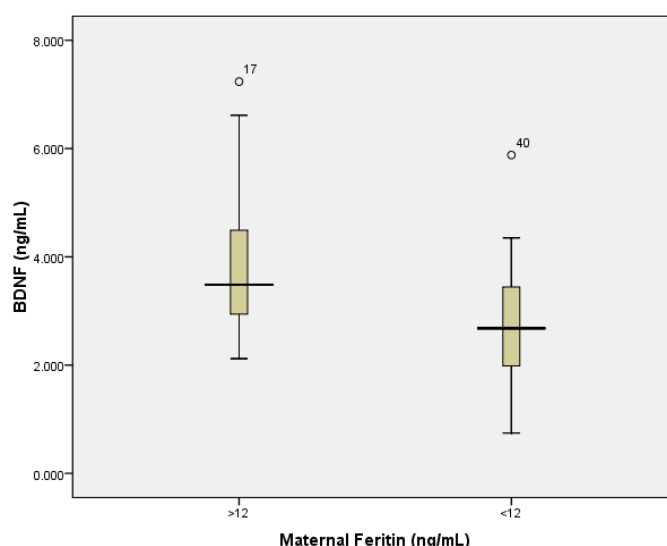
	Normal ferritin ( $\geq 12$ ng/mL) N=20	Low ferritin ( $<12$ ng/mL) N=20	Mean difference (95% CI)	<i>p</i> value*
Sex <sup>†</sup>				
Men	9 (45%)	15 (75%)		
Women	11 (55%)	5 (25%)		
Birth weight (kg) <sup>‡</sup>	3.16 $\pm$ 0.31	3.29 $\pm$ 0.34	124 (87.1-336)	0.241
Body length (cm) <sup>‡</sup>	48.8 $\pm$ 2.09	48.4 $\pm$ 1.73	0.40 (0.33-1.63)	0.319
Head circumference (cm) <sup>‡</sup>	34.4 $\pm$ 0.59	34.3 $\pm$ 0.470	0.1 (0.04-0.44)	0.667
BDNF serum (ng/mL) <sup>‡</sup>	3.81 $\pm$ 1.37	2.78 $\pm$ 1.19	1.03 (0.21-1.86)	0.015

BDNF: brain-derived neurotrophic factor; CI: confidence interval.

<sup>†</sup>Data are reported as percentage.

<sup>‡</sup>Data are reported as mean $\pm$ SD.

\**p* values are obtained by independent t-test.



**Figure 1.** Differences in mean level of Brain Derived Neurotrophic Factor (BDNF) between the newborns babies from mother with normal ferritin levels and low ferritin levels.

moglobin than the iron-treated group ( $p < 0.001$ ). Sao et al (2012) conducted a study in Southeastern China of 3702 pregnant women after 37 week gestation. They found that maternal anemia (Hb  $< 11$  g/dL) was present in 27.5% women and associated with low maternal serum ferritin ( $< 20$  ng/mL) in 86.9% women.<sup>6,9</sup>

Iron plays an important role in the synthesis of neurotransmitters such as serotonin, norepinephrine, and dopamine that are essential for the synthesis of BDNF.<sup>11</sup> Acute iron deficiency that occurs in late pregnancy and postpartum will interfere with neuronal structure and electrophysiology. As indicated above, if the iron deficiency persists into adulthood, learning and memory disorders may supervene.<sup>5,12</sup> The associated decrease in BDNF expression compromises neuron differentiation in several brain areas. This underscores the importance of iron homeostasis from the commencement of central nervous system (CNS) intrauterine development.<sup>12</sup>

The observed association of lower neonatal BDNF with a low maternal ferritin is biologically plausible. Serum ferritin has a direct correlation with the total amount of iron stored in the body. Maternal iron deficiency during pregnancy has a negative effect on fetal iron homeostasis. Iron transfer from mother to fetus is a regulated process involving iron status in the maternal circulation, its transport across the placenta and subsequent transfer into the fetal circulation. The resulting iron deficiency in neonates may decrease the expression and function BDNF in specific areas of the brain and be reflected in a low plasma BDNF. Similar to the present findings, Gaspar found that cord-blood ferritin in neonates born to mothers with low serum ferritin was lower than in those born to mothers with normal serum ferritin.<sup>7</sup> This is also in accordance with studies conducted by Perez in 2005 and Shao in 2012 who found that positive correlations between maternal serum ferritin and the iron reserve of term neonates.<sup>8,9</sup>

Given the role of BDNF in learning and memory, it is imperative that all pregnant women should be given iron replete not only to prevent any iron deficiency-related morbidity, but also to provide the mother the optimal opportunity of having intelligent offspring. The World

Health Organization (WHO) recommends a daily supplement of 30 to 60 mg of elemental iron as part of the antenatal care in settings where anemia in pregnant women is a public health problem. A higher dose may be necessary if the pregnant women is diagnosed with anemia and until her hemoglobin concentration becomes normal.<sup>14</sup>

A limitation of our study is the absence of neonatal ferritin data so that the direct relationship between maternal and neonatal ferritin could not be determined. Whether the decreased neonatal BDNF was attributable to decreased neonatal ferritin could not be determined.

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#### AUTHOR DISCLOSURES

The authors have no financial interest or other potential conflict of interest to disclose.

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