**How to Cite**:
Yanti, E. S., & Damayani, A. D. (2022). Iron deficiency increases the risk of postpartum depression. *International Journal of Health Sciences*, *6*(S8), 5833–5839. https://doi.org/10.53730/ijhs.v6nS8.13603

# Iron deficiency increases the risk of postpartum depression

**Eka Safitri Yanti**
Pusat Unggulan IPTEK, Poltekkes Kemenkes Pangkalpinang, Indonesia
Email: esya89virgo@gmail.com

**Ayi Diah Damayani**
Pusat Unggulan IPTEK, Poltekkes Kemenkes Pangkalpinang, Indonesia
Corresponding author email: damayani.ayidiah@gmail.com

***Abstract*---**Background and Objective: Maternal iron deficiency anemia is thought to be related to postpartum depressive in biology pathway. Ferritin is the first test to become abnormal as iron stores decrease and it is not affected by recent iron ingestion. Furthermore, iron deficiency anemia also can decrease Brain Derived Neurotrophic Factor (BDNF) which play role in sinaps plasticity in neuron. The purpose of this study is to determinate difference of maternal BDNF and total score Edinburgh Postnatal Depression Scale (EPDS) between low and normal ferritin among pregnant women. Methods and Study Design: This was an observational study with a cross-sectional design at Health Center Care Lubuk Buaya Padang and Biomedical Laboratory Faculty of Medicine Andalas University in Indonesia in November 2016 to June 2017. Samples in this study are 72 pregnant women in 37 until 42 weeks pregnancy were divided to 2 groups which are low (< 12 ng/mL) and normal ferritin (≥ 12 ng/mL). Ferritin and BDNF measured with ELISA after examination and EPDS were assessed at 2 weeks after delivery. Data analysed using independent t test. Result: The average serum BDNF in low ferritin pregnant women was 3.32 ± 3.95 ng/mL and normal ferritin was 3.71 ± 4.87 ng/mL (p = 0,299). The average total score EPDS in low ferritin was 11,31 ± 2,175 and normal ferritin was 6,69 ± 3,104 (p = 0,000). Conclusion: There was significant difference in total score EPDS but not serum BDNF between low and normal ferritin among pregnant women.

***Keywords*---**ferritin, brain derived neurotrophic factor, Edinburgh postnatal depression scale, anemia, iron deficiency anemia.

## Introduction

The most common cause of anemia is iron deficiency. Approximately 370 million women in the world suffer from anemia due to iron deficiency and 58% of it is contributed by a combination of South Asia and Southeast Asia. Its prevalence is higher in pregnant women (51%) than not (49%).[1] Iron deficiency anemia contribute about 20% of maternal deaths because of its ability to increase the risk of bleeding in delivery.[1] Furthermore, anemia can also cause psychological disturbance of the mother especially during the postpartum period where during the risk for psychiatric disorders increases up to 18-fold.[2] The risk for depressive disorder is increased in women with iron deficiency anemia in the postpartum period.[3] There have been several studies that found an association between maternal iron status with decreased BDNF and incidence of depression, although the results are still controversial. [4,5,6,7,8]

Iron deficiency anemia can lead to postpartum depression because it causes the loss of one of the brain transmitters that is Brain Derived Neurotrophic Factor (BDNF).[9] BDNF is one of four neurotrophin families found in mammals. BDNF is important in the process of neural cell growth (neurogenesis), survival and synapse plasticity. During embryology, BDNF plays a role in the survival of neurons during development. BDNF in the adult brain plays a role in the integration of neurons. Because of its important function, the decrease in BDNF hormones can lead to disruption of synaptic function in the brain. There has been evidence that BDNF deficiency plays an important role in the pathophysiology of depression.[10]

There are many ways to detect early postpartum depression, but the Edinburgh Postnatal Depression Scale (EPDS) is the most widely used and has high validity and reliability. EPDS contains 10 questions with a maximum value of 30 points. Values greater than 10 indicated that the mother had postpartum depression.[11] Patients with iron deficiency show signs and symptoms similar to those of depression. Many of these signs and symptoms occur in the early stages of iron deficiency characterized by decreased serum ferritin before anemia occured.[12] Ferritin is a stable glycoprotein that reflects iron stores in the absence of infection or inflammation. Ferritin is the first test to become abnormal as iron stores decrease and it is not affected by recent iron ingestion.[7] The study showed that postpartum mothers with iron deficiency anemia have a significant relationship between the number of EPDS scores with maternal iron status.[4]

## Materials and Methods

This was an observational study with a cross-sectional design. It was conducted from November 2016 to June 2017 and approved by the Medical Research Ethics Committee of the Andalas University (Project Number 070/KEP/FK/2017). The respondents were all mothers with aterm pregnancy (37-42 weeks of gestation) who came to Lubuk Buaya Health Center Care at the time of the study, aged 20-35 years, without mental disorders history, have given birth to minimal one viable infant, have a high social status, legally married status and supported by the husband or family. Patients who give birth to a disabled child or die will be excluded because it is expected to be a cause of increasing the risk of depression.

In addition, patients suspected of having an infection or inflammation which was observed from the rupture of membrane and leukosit >13.000 $mm^3$ also excluded because it is expected to affect the levels of ferritin assessed.

Those who met the criterias and agreed to participate in the study gave written informed consent and had their blood drawn to obtain their serum. It would be sent to the Biomedical Laboratory of Andalas University to assess ferritin and BDNF level by using ELISA method. All participant were followed for an assessment of depression status using an EPDS questionnaire 2 weeks after delivery. Independent sample t-tests were used to assess significant difference using SPSS program (17.0 version).

**Results**

A total of 72 pregnant women participated, 36 with low feritin (<12 ng/mL) and 36 subjects with normal feritin (≥ 12 ng/mL). Initial samples obtained by the researchers in this study were 116 respondents, 11 people refused to be respondents, 17 people excluded in the middle of the research process caused leukocyte levels >13,000 $mm^3$ or infants born disabled or died, and 16 people can not be assessed their EPDS scoring due to the fact that the researchers unable achieved direct contact with the subject either because the phone was not connected, the address was not found, or because the subject did not show up in the appointment date.

Samples characteristic are shown in Table 1. There were no differences in age, parity, gestational age, leukocyte, erythrocyte, platelets, MCV, MCH, MCHC or BDNF between normal and low ferritin groups ($p > 0.05$). However, there was a significant difference in hemoglobin, hematocrit and EPDS score between the two groups ($p < 0.05$).

**Discussion**

Iron is one of the constituents of hemoglobin. When iron enters the small intestine, it was sent by transferrin to the bone marrow to join the protophorphyrin to form heme. Then, heme will combine with the globin chain to form hemoglobin and will be released into circulation in mature erythrocytes to transport oxygen. Hemoglobin will not form if one of the constituent components above is not available, one of which is iron. This is the cause of the decline in hemoglobin in iron deficiency.[13,14]

Low hemoglobin accompanied by decreased of ferritin is characteristic of anemia due to iron deficiency. Low Ferritin (<12 ng /mL) represents the depletion of iron supply in the bone marrow. Ferritin is the first parameter to show an abnormality when iron deficiency occurs whereas anemia is the final stage where marked by decrease of hemoglobin to <10 g/dl. [13,15]

Our study proof that there was a significant difference in hemoglobin between low ferritin and normal feritin among pregnant women. Low ferritin group had lower hemoglobin compared to normal feritin group. This indicates that the respondents in this study suffered from anemia caused by iron deficiency as evidenced by

decreased of ferritin. In addition to hemoglobin, the parameters that are affected by low ferritin are hematocrit. Hematocrit and hemoglobin are found to be decreased in laboratory tests in the late stages of iron deficiency anemia.[16,17] Decreased of ferritin will influence the amount of hemoglobin formed. Hemoglobin is one of the important components in the formation of erythrocytes. Low hemoglobin affects the production of erythrocytes in the spinal cord. A less than normal amount of erythrocytes is indicated by a decrease in hematocrit.[15,18]

In the case of iron-deficiency anemia, where ferritin <12 ng/mL, expression BDNF decrease.[8,19] BDNF is one type of neurotrophin hormone that is important in neurogenesis, differentiation, repair and survival of neuron.[20] BDNF and its receptor TrKB are seen in the small brain of adult mammals, also found in the cortex, hippocampus and hypothalamus, midbrain, bone marrow and a number of areas that hold vital functions in neurons as well as glial cells. BDNF expression can be detected in blood serum although the levels are lower than in brain tissue.[21] Nevertheless, it has previously been found that serum BDNF reflect changes in BDNF in the brain, therefore measurements of serum BDNF can be used to monitor changes BDNF in brain.[22,23]

As shown in table 1 there is no significant difference in maternal BDNF between ferritin in two groups (p = 0.299) although mean BDNF lower in low ferritin group. Blegen, et al (2013) found similar results, where the mean BDNF were lower in the iron deficiency anemia group compared with the adequate iron group.[9] Besides iron deficiency anemia, there are also several other factors that affect BDNF levels such as age, sex, and depression.[10] BDNF may decrease because of the effects of decreased sex hormones estrogen and progesterone in the postpartum period. Estrogen is involved in increased BDNF transcription, which in some studies proves that the activation of estrogen receptors can restore dead neurons and memory impairment by increasing neurotrophin signals.[24] When estrogen is fall, BDNF transcription will decrease that leads to low BDNF.

As shown in table 1, total score of EPDS in low ferritin pregnant women higher than normal ferritin group and independent t test showed that there was a significant difference in the amount of EPDS score between two groups (p = 0.000). Maternal iron deficiency anemia is one of the causes of postpartum depression that can be detected using EPDS in postpartum.[25] Women who did not take supplements regularly had high EPDS scores.[6]

In previous result, it has been shown that there is no difference between ferritin and BDNF although ferritin is shown to cause depression as indicated by increasing EPDS score. This suggests that low ferritin causes depression not by affecting respondent's BDNF level but through another pathways. In addition to causing a decrease in BDNF, low ferritin can also cause decreased monoamine neurotransmitters and changes in glutamate and GABA signals that will eventually cause neuron atrophy. Other than that, neuron atrophy may also occur due to excessive glucorticoid production caused by severe stress that disrupts the hypothalamic-pituitary-adrenal axis. [26] Although the researchers has done the equivalence of the sample by filtering the risk factors of depression, did not rule out there are other factors that contribute to the high level of maternal stress such as the individual's own ability in the coping mechanism of stress.

This causes glucorticoid remain high in some respondents although all respondents have the same risk of depression.

## Conclusion

There is a difference total score EPDS between normal and low ferritin among pregnant women but not with BDNF. This suggests that there is a higher possibility of a higher risk of postpartum depression in women with low ferritin in pregnancy although this does not precipitate in their BDNF. The use of the CRP examination method is recommended for subsequent studies to replace the leukocyte examination and the need for evaluation of Fe supplement consumption when the time lag between blood taking and EPDS is assessed.

## Acknowledgements

We thank staff at Lubuk Buaya Health Center Care, and biomedical laboratory of Andalas University who facilitated data collection and samples analysis.

## Conflict of interest and funding disclosure

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

## References

Albacar G, Sans T, Martín-Santos R, García-Esteve L, Guillamat R, Sanjuan J, et al. An association between plasma ferritin concentrations measured 48 h after delivery and postpartum depression. Journal of Affective Disorders. 2011; 131: p. 136–142. doi: 10.1016/j.jad.2010.11.006.

Alharbi AA, Abdulghani HM. Risk Factors Associated with Postpartum Depression in the Saudi Population. 2014;: p. 311-316. doi: 10.2147/NDT.S57556.

Armony-Sivan R, Shao J, Li M, Zhao G, Zhao Z, Xu G, et al. No Relationship betweenMaternal Iron Status and Postpartum Depression in Two Samples in China. Journal of Pregnancy. 2012. doi:10.1155/2012/521431.

Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, et al. Maternal Iron Deficiency Anemia Affects Postpartum Emotions and Cognition. The Journal of Nutrition. 2005. PMID: 15671224.

Blegen MB, Kennedy BC, Thibert KA, Gewirtz JC, Tran PV, Georgieff MK. Multigenerational Effects of Fetal-Neonatal Iron Deficiency on Hippocampal BDNF Signaling. Physiological Reports. 2013. doi: 10.1002/phy2.96.

Cox J, Holden J, Henshaw C. Perinatal Mental Health: The Edinburgh Postanatal Depression Scale (EPDS) Manual 2nd Edition London: Royal College of Pschiatrics; 2014.

Cox J, Holden J, Henshaw C. Perinatal Mental Health: The Edinburgh Postanatal Depression Scale (EPDS) Manual 2nd Edition London: Royal College of Pschiatrics; 2014.

Franchini M, Salvagno GL, Montagnana M, Lippi G. Serum ferritin levels correlate with haemoglobin concentration: a report on 589 outpatients from a single centre. Blood Transfus. 2007;: p. 244-245. doi: 10.2450/2007.0021-07.

Fung J, Gelaye B, Zhong QY, Rondon MB, Sanchez SE, Barrios YV, et al. Association of decreased serum brain-derived neurotrophic factor (BDNF) concentrations in early pregnancy with antepartum depression. BMC Psychiatry. 2015. doi:10.1186/s12888-015-0428-7.

Gibney MJ, Margetts BM, Kearney JM, Arab L. Gizi Kesehatan Masyarakat Jakarta: EGC; 2009.

Goshtasebi A, Alizadeh M, Gandevani SB. Association between Maternal Anaemia and Postpartum Depression in an Urban Sample of Pregnant Women in Iran. J Health Population Nutrition. 2013. doi: 10.3329/jhpn.v31i3.16832.

Greer J, Arber D, Glader B, List A, Means R, Paraskevas F, et al. Wintrobe Clinical Hematology Volume One 13th Edition. USA: Lippincott Williams & Wilkins a Wolters Kluwer; 2014.

Hauser S. Harrison's Neurology in Clinical Medicine USA: McGraw Hill Education; 2013.

Hoffbrand A, Moss P. Hoffbrand's Essential Haematology USA: Wiley Blackwell; 2016.

Hoffman R, Benz E, Silberstein L, Heslop H, Weitz J, Anastasi J. Hematology: Basic Priciples and Practice 6th Edition New York: Elsevier; 2013.

Lanni C, Govoni S, Lucchelli A, Boselli C. Depression and Antidepressants: Molecular and Cellular Aspects. Cellular and Molecular Science. 2009; 66: p. 2985-3008. doi: 10.1007/s00018-009-0055-x.

Longo D. Harrison's Hematology and Oncology 2nd Edition USA: McGraw-Hill Education; 2013.

Lopez-Munoz F, Alamo C. Neurobiology of Depression New York: CRC Press; 2012.

Ninan I. Synaptic Regulation of Affective Behaviors; Role of BDNF. Neuropharmacology. 2014; 76.

Ortíz BM, Emiliano JR, Ramos-Rodríguez E, Martínez-Garza S, Macías-Cervantes H, Solorio-Meza S, et al. Brain-derived neurotrophic factor plasma levels and premature cognitive impairment/dementia in type 2 diabetes. World Journal of Diabetes. 2016;: p. 615-620. doi: 10.4239/wjd.v7.i20.615.

Pairman S. Midwifery: Preparation for Practice 3rd Edition Australia: Elsevier; 2015.

Preedy VR, Watson RR, Martin CR. Handbook of Behavior, Food and Nutrition New York: Springer; 2011.

Puri B, Laking P, H. Treasaden I. Buku Ajar Psikiatri Edisi 2 Jakarta: EGC; 2011.

Sartorius A, Hellweg R, Vogt JL, Dormann C, Vollmayr B, Danker-Hopfe H, et al. Correlations and Discrepancies between Serum and Brain Tissue Levels of Neurotrophins after Electroconvulsive Treatment in Rats. Pharmacopsychiatry. 2009;: p. 270-276. doi: 10.1055/s-0029-1224162.

Shariatpanaahi M. The Relationship between Depression and Serum Ferritin Level. Europen Journal of Clinical Nutrition. 2007; 61: p. 532-535. doi:10.1038/sj.ejcn.1602542.

Tran PV, Carlson ES, Fretham SJ, Georgieff MK. Early-Life Iron Deficiency Anemia Alters Neurotrophic Factor Expression and Hippocampal Neuron Differentiation in Male Rats. Ingestive Behavior and Neurosciences. 2008;: p. 2495-2501. doi: 10.3945/jn.108.091553.

Vanarsa K, Ye Y, Han J, Xie C, Mohan C, Wu T. Inflammation associated anemia and ferritin as disease markers in SLE. Arthritis Research & Therapy. 2012. doi: 10.1186/ar4012.

Table 1. Characteristics of Research Subjects between Low and Normal Ferritin Among Pregnant Women

| Respondent Characteristic | Group | | 95% CI | *p* value* |
|---|---|---|---|---|
| | Low Ferritin (<12 ng/ml) n=36 Mean ± SD | Normal Ferritin (≥12 ng/ml) n=36 Mean ± SD | | |
| Age (years) | 29.89 ± 4.28 | 30.36 ± 3.90 | -2.39-1.45 | 0.601 |
| Parity | 2.53 ± 0.91 | 2.75 ± 1.08 | -0.69-0.25 | 0.658 |
| Gestational age (weeks) | 38.83 ± 0.85 | 39.14 ± 1.15 | -0.78-0.17 | 0.212 |
| Hemoglobin (g/dl) | 10.51 ± 0.94 | 11.22 ± 0.69 | -1.09- (-0.33) | 0.000* |
| Leukocyte ($10^3$/µL) | 9.97 ± 1.93 | 10.24 ± 1.78 | -1.14- 0.6 | 0.537 |
| Erythrocyte ($10^6$/µL) | 3.86 ± 0.37 | 3.96 ± 0.41 | -0,28-0.83 | 0.279 |
| Platelets ($10^3$/µL) | 292.77 ± 62.85 | 296.17 ± 56.12 | -31.39-24.62 | 0.810 |
| Hematocrit (%,) | 31.93 ± 2.52 | 33.74 ± 2.09 | -2.89 – (-0.72) | 0.001* |
| MCV (fl) | 82.89 ± 7.33 | 85.00 ± 6.33 | -5.33-1.10 | 0.195 |
| MCH (pg) | 27.59 ± 2.73 | 28.54 ± 2.31 | -2.14-0.23 | 0.113 |
| MCHC (g/dl) | 32.87 ± 0.70 | 32.98 ± 1.46 | -0.66-0.42 | 0.659 |
| Ferritin (ng/ml) | 5.19 ± 3.08 | 51.38 ± 54.45 | -64.32-(-28.06) | 0.000* |
| BDNF (ng/ml) | 3.32 ± 3.95 | 3.71 ± 4.87 | -2.47-1.69 | 0.299 |
| EPDS Score | 11.31 ± 2.175 | 6.69 ± 3.104 | 3.64 - 5.59 | 0.000 |

SD: standard deviation

*p values are obtained by independent t-test.