The Relationship between Ferritin Levels and Uterine Inertia in Labor Women

Astri Ayu Agus,[1,2] Andi Mardiah Tahir,[1,2] Nurbani Bangsawan,[1,2] Maisuri T. Chalid,[1,2] Efendi Lukas,[1,2] Lenny M. Lisal[1,2]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[2]Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia

Corresponding: Andi Mardiah Tahir, E-mail: mardiahtahir@yahoo.com

Abstract

Objective: To determine the relationship between ferritin levels and the incidence of uterine inertia in pregnant women.

Method: This study uses a prospective cohort design. The study was conducted on all pregnant women aged 20-40 years who had antenatal care and be in labor at the Teaching Hospital in the Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University. Data were analyzed with the chi-square test and the Mann-Whitney test.

Results: Obtained 76 pregnant women where 44.7% of them had uterine inertia. The average ferritin level in the uterine inertia group was significantly lower (3.80±2.84 ng/mL) than without the uterine inertia group (12.99±1.40 ng/mL) with a value p<0.001. The average ferritin level in the mild anemia group was significantly higher (9.83±10.35 ng/mL) than in the moderate anemia group (3.82±2.51 ng/mL) with a p-value<0.05. Pregnant women with moderate anemia were found to be 4.68 *more susceptible* uterine inertia than pregnant women with mild anemia.

Conclusion: There was a relationship between ferritin levels in pregnant women and the incidence of uterine inertia where low ferritin levels was risk factor of uterine inertia.

Key words: Ferritin, Maternal, Uterine Inertia

Hubungan Kadar Feritin dengan Kejadian Inersia Uteri pada Ibu Bersalin

Abstrak

Tujuan: Untuk mengetahui hubungan antara kadar feritin dan kejadian inersia uteri pada ibu bersalin.

Metode: Penelitian ini menggunakan rancangan kohort prospektif. Penelitian dilakukan pada semua wanita hamil usia 20-40 tahun yang melakukan *antebatal care* dan persalinan di Rumah Sakit Pendidikan di bagian Obstetri dan Ginekologi Fakultas Kedokteran Universitas Hasanuddin. Data dianalsiis dengan uji chi square dan uji Mann Whitney.

Hasil: Diperoleh 76 ibu hamil, sebanyak 44,7% di antaranya mengalami inersia uteri. Rata-rata kadar feritin pada kelompok inersia uteri secara signifikan lebih rendah (3,80±2,84 ng/mL) dibandingkan rata-rata kadar feritin pada kelompok tidak inersia uteri (12,99±11,40 ng/mL) dengan nilai p<0,001. Rata-rata kadar feritin pada kelompok anemia ringan secara signifikan lebih tinggi (9,83±10,35 ng/mL) dibandingkan rata-rata kadar feritin pada kelompok anemia moderat (3,82±2,51 ng/mL) dengan nilai p<0,05. Ibu hamil dengan anemia moderat mempunyai risiko mengalami inersia uteri sebanyak 4,68 kali lebih besar dibandingkan ibu hamil dengan anemia ringan.

Kesimpulan: Ada hubungan antara kadar feritin ibu hamil dan kejadian inersia uteri. Rendahnya kadar feritin menjadi salah satu penyebab kejadian inersia uteri.

Kata kunci: Feritin, Ibu Bersalin, Inersia Uteri

Introduction

Maternal mortality is a global health problem. Globally in 2019, the maternal mortality rate is 211 deaths per 100,000 live births.[1] In Indonesia, the maternal mortality rate in 2020 is 305 per 100,000 live births, more than the global maternal mortality rate.[2] One of the 5 main causes of maternal death is postpartum hemorrhage.[3] Approximately 75%–90% of postpartum hemorrhage is caused by uterine atony including uterine inertia.[4]

Uterine inertia is a condition where there are no uterine contractions or initially, there are uterine contractions, then stop due to muscle fatigue, causing prolonged labor.[5] Several studies have reported a link between anemia and uterine inertia. Anemia in pregnancy can interfere with the transport of oxygen to the uterus it can cause uterine inertia.[6] In iron deficiency anemia, low body iron stores (serum ferritin <100 g/L) cause low uterine muscle strength resulting in inefficient uterine contractions.[7]

The etiology of uterine inertia is a result of myometrial muscle fiber dysfunction so the uterus is unable to contract as a result of inflammation. Localized accumulation of uterine exudate is associated with an inflammatory response in the interstitial spaces, progressing to stromal edema and impaired uterine contractile function.8 Meanwhile, inflammatory conditions affect changes in iron homeostasis. Normal iron homeostasis in reticuloendothelial macrophages is associated with the rapid release of iron to circulating transferrin or, if excess, stored in ferritin.[9]

Serum ferritin levels were found to be significantly related to uterine contractions.[10] Meanwhile, ferritin levels correlate with an inflammatory activity where ferritin mediates inflammatory conditions and triggers the production of cytokines that trigger contractions.[11] Uterine inertia is stated as a result of myometrial muscle fiber dysfunction so that the uterus is unable to contract.[8]

The existence of a link between ferritin and uterine contractions due to the inflammatory response made researchers interested in studying the relationship between ferritin levels and the incidence of uterine inertia. Research on the relationship between ferritin levels and the incidence of uterine inertia in women giving birth has never been done before. Uterine inertia is one of the main causes of cesarean delivery. Complications of cesarean delivery for mothers and children can cause serious problems and increase fetal and maternal mortality and morbidity. It is important to identify and diagnose normal delivery and the risk of uterine inertia. This study aimed to determined the relationship between ferritin levels and the incidence of uterine inertia in pregnant women.

Method

This was a prospective cohort study with pregnant women who had antenatal care and childbirth at the Teaching Hospital in the Department of Obstetrics and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar. Sampling technique with consecutive sampling. The inclusion criteria were pregnant women 20–40 years old with haemoglobin laboratory results <11 gr/dl; third trimester of pregnancy from last menstrual period; no history of dysfunctional uterine bleeding before pregnancy; and no history of blood disorders (hemochromatosis, polycythemia vera), epilepsy, bronchial asthma, willing to be involved in research and willing to give birth at the research site. The exclusion criteria were pregnant women with history of preeclampsia/severe preeclampsia, pregnant women having a history of infectious diseases such as HIV and confirmed COVID-19, and receiving tocolytic drugs or muscle relaxants. The study was conducted with Etichal Clearance approval from the Biomedical Research Ethics Commission

at the Faculty of Medicine, University of Hasanuddin Makassar with ethical approval recommendation 41/UN4.6.4.5.31/ PP36/2022. Examination of the duration of labor contractions using a partograph. Serum ferritin levels were analyzed using an ELISA kit. Data were analyzed by the Chi-square test and Mann-Whitney test.

Result

A total of 76 pregnant women with anemia who gave birth were examined for uterine inertia using the WHO Partograph, and the results of uterine inertia were 34 people (44.7%). Comparison of subject characteristics based on the incidence of uterine inertia showed that there was no significant difference between the uterine inertia and non-uterine inertia groups based on age (p=0.234), parity (p=0.066), and BMI (p=0.096) (Table 1).

Ferritin levels in the blood of pregnant women who are undergoing labor were measured with the result that the average ferritin level in the uterine inertia group was 3.80±2.84 ng/mL which was significantly lower than the average ferritin level in the non-inertia uterine group of 12.99±11.40 ng/ mL (p=0.000) (Table 2).

The results of this study showed that the average ferritin level in the mild anemia group was 9.83±10.35 ng/mL which was significantly higher than the average ferritin level in the moderate anemia group of 3.82±2.51 ng/mL. mL (p=0.040) (Table 3).

Table 1 Characteristics of Research Subjects

Characteristics	Uterine Inertia (n= 34)		Non Uterine Inertia (n= 42)		Total		p-value
	N	%	n	%	n	%	
Age (years)							
< 20	3	8.8	3	7.1	6	7.9	
20-35	30	88.2	33	78.6	63	82.9	0.234
>35	1	3.0	6	14.3	7	9.2	
Parity							
Nulipara	16	47.1	11	26.2	27	35.5	
Primipara	12	35.2	15	35.7	27	35.5	0.066
Multipara	4	11.8	15	35.7	19	25.0	
Grand multipara	2	5.9	1	2.4	3	3.9	
BMI							
Underweight	0	0.0	1	2.4	1	1.3	
Normal	18	52.9	14	33.3	32	42.1	0.096
Overweight	14	41.2	17	40.5	31	40.8	
Obesity	2	5.9	10	23.8	12	15.8	

Table 2 Relationship between Ferritin Levels and Uterine Inertia

Uterine Inertia	n	Min (ng/ mL)	Max (ng/mL)	Mean ± SD (ng/mL)	P-value
Yes	34	0.61	16.31	3.80 ± 2.84	0.000**
No	42	0.81	42.63	12.99 ± 11.40	

**Significant with p-value < 0.001.

Table 3 The Relationship between the Anemia Level and Ferritin Levels

Anemia	N	Min (ng/mL)	Max (ng/mL)	Mean ± SD (ng/mL)	P-value
Mild	64	0.61	42.63	9.83 ± 10.35	0.040*
Moderate	12	0.81	9.32	3.82 ± 2.51	

*Significant with p-value < 0.05; Mild: 9-10.9 gr/dl; Moderate: 7-8.9 gr/dl.

Table 4 The relationship between the Anemia Level and the Incidence of Uterine Inertia

Anemia level	Uterine Inertia (n= 34)		Non Uterine Inertia (n= 42)		p-value	OR (Cl95%)
	n	%	n	%		
Moderate	9	75.0	3	25.0	0.022*	4.68
Mild	25	39.1	39	60.9		(1.15-18.97)

* Significant with p-value < 0.05.

A total of 9 pregnant women (75.0%) who were moderately anemic had uterine inertia. There is a significant relationship between the anemia level and the incidence of uterine inertia with a value of p=0.022; OR 4.68; 95% CI 1.15-18.97. Pregnant women with moderate anemia have a 4.68 times greater risk of uterine inertia than pregnant women with mild anemia (Table 4).

Discussion

The results of this study showed that the prevalence of uterine inertia was 44.7%. This result is higher than the prevalence of uterine inertia in Cameroon in 2019 which was only 5.5%.[12] The average ferritin level in the uterine inertia group was significantly lower than the average ferritin level in the group without uterine inertia. This study measured ferritin levels in the third trimester of pregnancy where the lower the ferritin level, the more severe of anemia. Anemia, especially due to iron deficiency, increases Nitric oxide (NO) production; furthermore, in the presence of tissue hypoxia and low oxygen tension (induced by the anemia itself), NO may signal relaxation or failure of smooth muscle to relax and cause uterine inertia.[13] This means that mothers with low ferritin levels during the third trimester of pregnancy may develop uterine inertia when laboring.

When uterine inertia occurs, ferritin levels increase which indicates an inflammatory process that occurs. Ferritin is the main intracellular storage protein that retains iron in an insoluble and non-toxic state, which is reported to increase in some acute phase reactions such as inflammation.[14] Subclinical infections in pregnant women can increase ferritin levels as an acute phase reactant and cause spontaneous rupture of the membranes.[15]

Uterine inertia occurs due to the inability of the uterus to contract due to myometrial fiber dysfunction, an effect of the inflammatory response. Localized accumulation of uterine exudate associated with an inflammatory response in the interstitial space progresses to stromal edema and impaired uterine contractile function.[8]

Ferritin is an acute-phase protein that can also increase during infection.[11] Inflammation or infection causes drastic changes in serum ferritin levels. Serum ferritin can be used as a marker for total body iron stores in healthy individuals, but in diseased conditions, serum ferritin is more likely to indicate an underlying pathophysiology such as organ

damage or infection.[15]

The role of ferritin in inflammation can be explained in the three main regulatory pathways for ferritin expression, namely iron response proteins (IRP)/iron-responsive element (IRE), transcriptional regulation via NF-B, and transcriptional regulation via hypoxia-inducible factor 1 alpha (HIF-1) that bind to the downstream HIF responsive element (HRE) of the IRE system. The IRP/IRE system functions by binding IRP to IRE in the 5' untranslated region (UTR) of ferritin mRNA under low iron conditions, inhibiting its translation. However, under high iron conditions, the binding of IRP to IRE decreases, leading to increased expression of ferritin. Similarly, ferritin gene transcription is upregulated in inflammatory conditions in which inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-2 (IL-2) signal to increase binding of NF-B to the transcription enhancer FER2 downstream of the IRE and the coding region.[15]

The Nuclear factor kappa Beta (NF-β) pathway is highly responsive to inflammation.[16] Evidence for this pathway comes from the activation of the TLR2 receptor in macrophages resulting in an IRP-independent upregulation of H-ferritin, as well as direct pharmacological activation of the NF-β pathway. H-ferritin expression is also responsive to tumor necrosis factor alpha (TNF-α), interleukin-2 (IL-2), and IL-10.[15] Consequently, elevated serum ferritin is a marker of acute-phase inflammation, because elevated serum ferritin levels have been correlated with increased levels of pro-inflammatory cytokines.[9]chronic heart failure (CHF Potential sources of serum ferritin during inflammation include secretion by macrophages and/or release from cells due to tissue damage, either indicator of inflammation or infection.[15]

Thus, ferritin indirectly plays a role in predicting uterine inertia and is directly involved in the mechanism of uterine inertia. However, in this study, ferritin levels were not measured when uterine inertia occurred. Ferritin examination was only carried out during the third trimester of pregnancy so this study emphasized the role of ferritin as a biomarker for predicting uterine inertia.

The results showed that moderate anemia had an average ferritin level that was significantly lower than pregnant women with mild anemia. In addition, it was also reported that pregnant women with moderate anemia had a 4.68 times greater risk of uterine inertia than pregnant women with mild anemia. Uterine inertia occurs in 75.0% of women who have moderate anemia. This result is in line with the research of Premalahta and Krishnegowda who explained that uterine inertia is related to uterine contractions.[17] Factors that interfere with uterine contractions are anemia. Frass reported that severe uterine inertia occurred in 39.6% of women with severe anemia (Hb 6-7 g/dl).[18]

The severity of anemia occurs due to various causes, the diagnosis cannot only be based on the Hb value, but also the red blood count and serum ferritin level. The most reliable parameters for demonstrating iron deficiency are serum ferritin levels, and screening serum ferritin concentrations early in pregnancy. If the serum ferritin level is < 30 g/l, there is a high probability that iron stores are depleted, even in the absence of anemia. A serum ferritin value of <30 g/l is associated with a Hb concentration of <11 g/dl during the third trimester which is diagnostic of iron deficiency anemia in pregnant women. Although anemia is associated with low iron stores, it has been reported that in the presence of an inflammatory process or disease Chronically, ferritin levels may be normal or elevated, despite anemia. This is because ferritin reacts as an acute-phase protein. Evaluation of C-reactive protein (CRP) levels can assist in arriving at the correct diagnosis, excluding infection or inflammation.[19]

The relationship between the anemia level and uterine events can be explained by the fact that in more severe anemia, a deficiency in hemoglobin levels in the blood can result in reduced oxygen being carried and sent to the body's cells as well as the brain and uterine cells. The lack of oxygen in the blood results in the inability of the uterine muscles to contract adequately.[20]as a case group, maternal postpartum hemorrhage with uterine atony and control group, maternal postpartum hemorrhage without uterine atony. The sample size for each selected group 69 (the number of cases during the period from 2015 to 2017 It was also explained that anemia, through its effect on nitric oxide synthesis, plays a role in the occurrence of uterine inertia.[21]

During pregnancy, Nitric Oxide (NO) produced by the trophoblast and placenta can play an important role in maintaining uterine contractility with paracrine effects due to the marginal activity of NO synthase (NOS) in the myometrium. Nitric Oxide (NO) plays a role in the response to acute hypoxia by inducing HIF but contributes to the negative feedback process in chronic hypoxia.[21] NO biosynthesis and cGMP increase during pregnancy and decrease during delivery. Formation of NO by placental NOS, released in the intervillous space, can prevent platelet adhesion and aggregation, and importantly contributes to villous smooth muscle dilatation. Production of NO by the placenta is an important factor that acts paracrine on the uterine myometrium. Placental and fetal NOS are very important in maintaining myometrial contractility in human pregnancy.[22]

In more severe anemia, especially due to iron deficiency, it further increases NO production; furthermore, in the presence of tissue hypoxia and low oxygen tension (induced by anemia itself), NO can signal smooth muscle relaxation and cause uterine inertia. When NO is formed in the vascular endothelium, it penetrates smooth muscle cells, first the vessels, then into other organs, where it activates guanylyl cyclase. This enzyme dephosphorylates guanosine triphosphate into cyclic guanosine monophosphate, which causes uterine inertia by mediating smooth muscle relaxation.[13]

Anemia characterized by low ferritin can increase if there is inflammation at uterine inertia so ferritin levels can increase when uterine inertia occurs even in pregnant women who had history of more severe anemia. The study had limitations in that it did not compare samples of anemic pregnant women and non-anemic pregnant women. In addition, samples taken were limited to mild and moderate anemia samples, not taking samples of severe anemia. This study also only measured ferritin levels during the third trimester of pregnancy and did not measure ferritin levels during the delivery process. This study emphasizes the role of ferritin as a biomarker for the prediction of uterine inertia.

Conclusion

Low ferritin levels are associated with an increased incidence of uterine inertia. Pregnant women with moderate anemia had uterine inertia more than pregnant women with mild anemia. Pregnant women with moderate anemia have a risk of experiencing uterine inertia as much as 4.68 times greater than pregnant women with mild anemia. Giving therapy in the form of iron tablets after detecting iron deficiency anemia can be recommended as a prevention of uterine inertia during labor. In addition, it is necessary to screen for ferritin levels during pregnancy to prevent uterine inertia during labor. Measurement of ferritin levels during parturition is needed in further research to determine the role of ferritin in the etiology of uterine inertia.

Reference

1. World Health Organization. UNICEF. United Nations Population Fund and The World Bank. Trends in Maternal Mortality: 2000 to 2017 WHO. Geneva; 2019.
2. Pritasari K. Arah kebijakan dan rencana aksi program kesehatan masyarakat tahun 2020 - 2024. Rapat Kerja Nas Kementeri Kesehat RI. 2020;1–31.
3. Gill P, Patel A, Hoo J. Uterine Atony. US StatPearls Publ LLC [Internet]. 2020; Tersedia pada: //www.ncbi.nlm.nih.gov/books/NBK493238/
4. Liu G. Prevention effect of hemabate on postpartum hemorrhage caused by uterine inertia. J Hainan Med Univ. 2016;22(6):6–9.
5. Chutia T, Talukdar D, Konwar B, Ahmed F, Lalrintluanga K, Das D. Management of Incomplete Uterine Inertia in a Labrador Bitch - A Case Report. Int J Livest Res. 2016;6(9).
6. Adam I, Kheiri S, Sharif ME, Ahmed ABA, Rayis DA. Anaemia is associated with an increased risk for caesarean delivery. Int J Gynecol Obstet. 2019;147(2):202–5.
7. Kavle JA, Stoltzfus RJ, Witter F, Tielsch JM, Khalfan SS, Caulfield LE. Association between anaemia during pregnancy and blood loss at and after delivery among women with vaginal births in Pemba Island, Zanzibar, Tanzania. J Heal Popul Nutr. 2008;26(2):232–40.
8. Escobar MF, Hincapie MA, Barona JS. Immunological Role of the Maternal Uterine Microbiota in Postpartum Hemorrhage. Front Immunol. 2020;11(March):1–5.
9. Dignass A, Farrag K, Stein J. Limitations of Serum Ferritin in Diagnosing Iron Deficiency in Inflammatory Conditions. Int J Chronic Dis. 2018;2018(Table 1):1–11.
10. Goodarzi M, Bashardoost N. The study of the relationship of serrum ferritin and uterine contractions in pregnant women refer to medical centers of Isfahan. IJNMR. 2009;14(4):12–8.
11. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017;29(9):401–9.
12. Nkwabong E, Mouafo CK, Njamen TN. Risk factors for uterine atony in two semi-urban hospitals. Int J Pregnancy Child Birth. 2020;6(2):45–9.
13. Soltan MH, Ibrahim EM, Tawfek M, Hassan H, Farag F. Raised nitric oxide levels may cause atonic postpartum hemorrhage in women with anemia during pregnancy. Int J Gynecol Obstet [Internet]. 2012;116(2):143–7. Tersedia pada: http://dx.doi.org/10.1016/j.ijgo.2011.09.017
14. Jahedbozorgan T, Yaghmaei M, Naserieh M. Comparison of serum ferritin levels in pregnant women with preterm and term deliveries. Immunopathol Persa. 2020;6(2).
15. Chiou B, Connor JR. Emerging and Dynamic Biomedical Uses of Ferritin. 2018;
16. Hoesel B, Schmid JA. The complexity of NF-_B signaling in inflammation and cancer. Mol Cancer. 2013;12(86).
17. Premalahta H., Krishnegowda R. Prospective study of association of uterine atonicity and serum calcium levels. Int J Reprod Contraception, Obstet Gynecol. 2016;5(7):2221–3.
18. Frass KA. Postpartum hemorrhage is related to the hemoglobin levels at labor: Observational study. Alexandria J Med [Internet]. 2015;51(4):333–7. Tersedia pada: http://dx.doi.org/10.1016/j.ajme.2014.12.002
19. Garzon S, Cacciato PM, Certelli C, Salvaggio C, Magliarditi M, Rizzo G. Iron deficiency anemia in pregnancy: Novel approaches for an old problem.

Oman Med J. 2020;35(5):1–9.
20. Julizar M, Effendi JS, Sukandar H. Analisis Faktor Risiko Atonia Uteri. Care J Ilm Ilmu Kesehat. 2019;7(3):108.
21. Omotayo MO, Abioye AI, Kuyebi M, Eke AC. Prenatal anemia and postpartum hemorrhage risk: A systematic review and meta-analysis. J Obstet Gynaecol Res. 2021;47(8):2565–76.
22. Al-Hijji J, Andolf E, Laurini R, Batra S. Nitric oxide synthase activity in human trophoblast, term placenta and pregnant myometrium. Reprod Biol Endocrinol. 2003;1(July).