Indonesian Journal of Health Science
Volume 5 No.4, 2025

THE IMPACT OF ENDOMETRIOSIS ON THE SEVERITY OF ANEMIA

Salsa Evva Nurjanah[1)], Ira Citra Ningrom[2)], Mustika Ratnaningsih Purbowati[3)], Norina Agatri[4)], Megawati Al'badly Ponco Dewi Poernomo[5)], Dina Marlina[6)], Aditya Utomo[7)], Beni Samsul Amri[8*)]

[1, 2, 3, 4] helpinpublisher@gmail.com, Universitas Muhammadiyah Purwokerto
[5] helpinpublisher@gmail.com, Universitas Jenderal Soedirman
[6,7] helpinpublisher@gmail.com, Universitas Padjadjaran
[8*] spogamrisamsulbenidr@gmail.com, Universitas Hasanuddin

Abstract
The objective of this study was to investigate the relationship between endometriosis and the severity of anemia, as well as other contributing factors. The study was conducted at Margono Hospital, Indonesia, and involved patients diagnosed with endometriosis between 2020 and 2024. Inclusion and exclusion criteria were applied, and statistical analyses, including odds ratios and prevalence ratios, were performed. The analysis revealed that women of reproductive age had a significantly higher likelihood of having endometriosis, with an odds ratio of 3.033 [95% CI: 1.703–5.403, $p < 0.001$]. Increasing age was associated with a 0.9% increase in the likelihood of endometriosis. Parity also showed a significant correlation with endometriosis, with nulliparous women having an odds ratio of 11.883 [95% CI: 2.103–67.163, $p < 0.001$]. However, the association between endometriosis and anemia severity, which was the main focus of this study, was found to be not statistically significant. Further research is warranted to obtain more definitive confirmation.
Keywords: Anemia, Endometriosis, Iron Deficiency

Abstrak
Tujuan dari penelitian ini adalah untuk menyelidiki hubungan antara endometriosis dan tingkat keparahan anemia, serta faktor-faktor lain yang dapat mempengaruhi. Penelitian ini dilakukan di Rumah Sakit Margono, Indonesia, dan melibatkan pasien endometriosis yang terdaftar dari tahun 2020 hingga 2024. Kriteria inklusi dan eksklusi diterapkan, dan analisis statistik, termasuk rasio odds dan rasio prevalensi, dilakukan. Analisis menunjukkan bahwa wanita usia reproduksi memiliki kemungkinan yang signifikan untuk mengidap endometriosis, dengan rasio odds 3,033 [95% CI 1,703-5,403, p<0,001]. Peningkatan usia berkontribusi 0,9% terhadap kemungkinan endometriosis, dan paritas memiliki korelasi yang signifikan dengan endometriosis, dengan wanita nullipara memiliki rasio odds 11,883 [95% CI 2,103-67,163, p<0,001]. Sedangkan, asosiasi antara endometriosis dengan tingkat keparahan anemia pada studi ini ditemukan tidak terdapat korelasi signifikan. Meskipun endometriosis tidak memiliki dampak signifikan terhadap tingkat keparahan anemia dalam penelitian ini, penelitian lebih lanjut diperlukan untuk mengkonfirmasi lebih lanjut.
Kata Kunci: Anemia, Endometriosis, Kekurangan Zat Besi.

INTRODUCTION

Endometriosis is a chronic condition where endometrial tissue grows outside the uterus, causing pain and infertility (Saunders & Horne, 2021). It can affect the peritoneum, ovaries, fallopian tubes, and distant organs. In 2017, the Global Burden of Disease Study (GBD) showed yearly decreases, respectively, by 0.21%, 0.29%, and 0.28% endometriosis age-standardized incidence, prevalence and life with disability (Zhang, S., et al 2021). Endometriosis affects about 10% (190 million) of reproductive-age women worldwide in 2023. Asian women, representing 30% of the global population, have a 1.63 times higher risk (Christopher & Donovan, 2023).

In 2019, an estimation of age-standardized endometriosis incidence rate in Southeast Asia countries reached 43.04 per 100.000 [95% CI 30.74 - 60.21] (Feng et al., 2022). Endometriosis is a leading cause of gynecologic hospitalization and is linked to infertility, psychosocial issues, cardiovascular disease, ovarian cancer, and iron deficiency from heavy bleeding or chronic inflammation (Dereje et al., 2024; James et al., 2023) .

Iron deficiency, alongside endometriosis, is a major global issue affecting reproductive-age women and children <5, significantly contributing to maternal and child morbidity. In 2019, anemia affected roughly 30% of reproductive age women globally, and 50% of reported cases were caused by iron deficiency with the African and South-East Asia regions being most affected (Dereje et al., 2024; World Health Organization, 2024). Heavy menstrual bleeding and chronic inflammation may contribute to iron deficiency in endometriosis. However, the mechanisms of iron metabolism and erythropoiesis in affected women remain poorly understood (Atkins et al., 2018). Some studies suggest that endometriosis lesions respond to hormones like healthy endometrium, undergoing hormone-driven proliferation that promotes adhesion formation. Additionally, an abnormal peritoneal response to retrograde menstruation may cause repeated erythrocyte buildup, leading to excess iron in endometriotic tissue due to ongoing red blood cell degradation (James et al., 2023). There is a lack of research investigating the relationship between endometriosis and the severity of anemia. This study aims to assess the association between endometriosis and anemia severity through a population-based case-control design involving women aged 15–65 years. It is hypothesized that endometriosis is significantly associated with increased anemia severity.

METHODS

Approved by the Ethics Committee of the General Hospital, Prof. Dr. dr. Margono Soekarjo, Purwokerto. In this cohort retrospective study, we compare between endometriosis and non-endometriosis groups. The case group is those who were confirmed as endometriosis and the control group is those confirmed as non-endometriosis cases. Then, we're looking for the occurrence of anemia between both groups at the Fertility Endocrinology Reproduction Polyclinic between 2020 and 2024. The study investigated the women who had anemia at any stage within a history of endometriosis. We compared two populations and sought to find the difference using chi-square statistical analysis. The association was calculated using the odds ratio (OR).

Anemia severity was defined as haemoglobin lower than 12g/dL for adults aging 15-65 years old and classified based on the severity into 1) no anemia (≥12 g/dL), 2) mild anemia (11-11,9 g/dL), 3) moderate anemia (8-10.9 g/dL), and 4) severe anemia (< 8 g/dL). Endometriosis was defined as cases confirmed histopathologically and classified into 1) Endometriosis, and 2) Non-endometriosis. Age was defined as women aged 15-65 years old and classified into 1) reproductive age (15-49 years old) and 2) non-reproductive age (>49 years old). Body mass index was classified into 4 categories: 1) Underweight (<18 kg/m2), 2) Normal weight (18-24.9 kg/m2), 3) Overweight (25-29.9 kg/m2), and 4) Obese (≥ 30 kg/m2). Menstrual cycle duration was classified into 1) short (<4 days), 2) normal (4-8 days), 3) Prolonged (>8 days).

For all patients, the severity of anemia following endometriosis diagnosis in women aged 15-65 years. The case group consisted of women of reproductive age who had endometriosis after histopathological confirmation and were diagnosed with other diseases. The control group consisted of women of reproductive age without endometriosis after histopathological confirmation. The inclusion criteria are all women aged 15-65 years who had been diagnosed with endometriosis at their first coming to the hospital and underwent histopathological confirmation. The exclusion criteria are adolescence and women aged >65 years old, pregnant women, history of chronic diseases that cause anemia (including chronic hypertension and complications related to blood diseases), history of chronic infection, and other gynecological diseases especially related to anemia.

This study used total sampling methods. After data collection, 243 patients were included: 112 in the case group and 131 in the control group. Following exclusion criteria, 234 patients remained with 109 cases and 125 controls for analysis. With Ethics Committee

approval, eligible case and control patients were selected from the Fertility Endocrinology Reproduction Polyclinic database. Pregnancies not meeting the inclusion criteria were excluded, with 109 patients with endometriosis forming the case group and 125 patients without endometriosis forming the control group. The severity of anemia between the case and control groups was compared using Chi-square tests ($p < 0.05$). Crude odds ratios (OR) with 95% confidence intervals (CI) assessed the association, using IBM SPSS Statistics version 29.0.1.0.

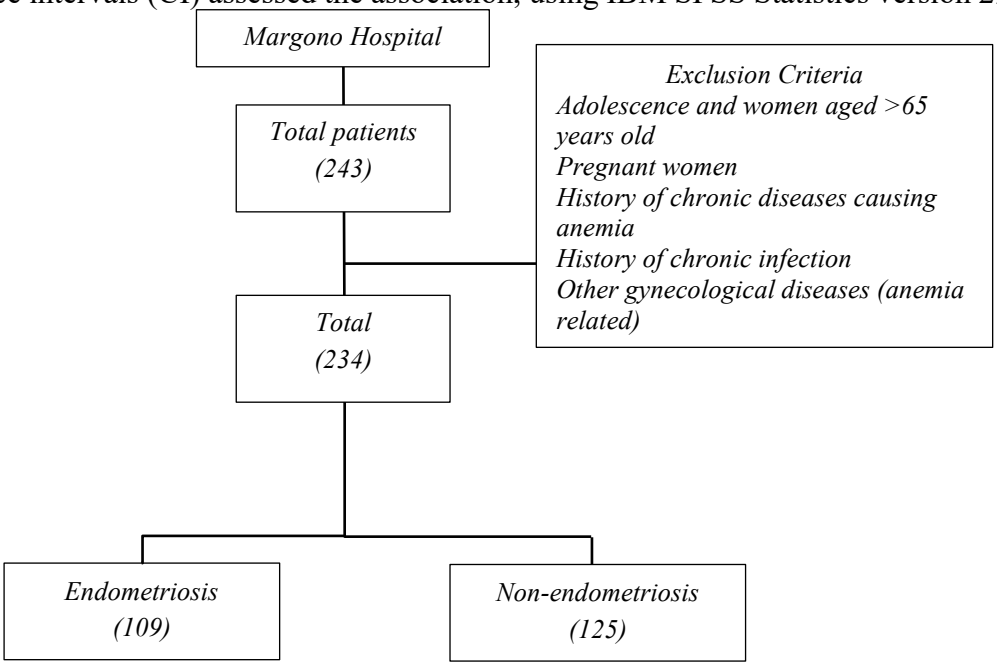

Figure 1. Sampling method

RESULT AND DISCUSSION

Results

Table 1. Characteristics of Cases

Parameters	Endometriosis (%)	Non-Endometriosis (%)	p-value (sig. 2-sided)
N	109 (46.6)	125 (53.4)	
Age			< 0.001*
Reproductive (15-49 y.o)	85 (36.3)	68 (29.1)	
Non-reproductive (>49 y.o)	24 (10.3)	57 (24.4)	
Educational Background			0.051
Graduate	2 (0.9))	1 (0.4)	
Diploma	6 (2.6)	3 (1.3)	
Undergraduate	8 (3.4)	6 (2.6)	
Senior High School	34 (14.5)	27 (11.5)	
Junior High School	22 (9.4)	18 (7.7)	
Elementary School	23 (9.8)	45 (19.2)	
None	14 (6)	25 (10.7)	
Parity			< 0.001*
Nulliparous	10 (4.3)	2 (0.9)	
Primiparous	40 (17.1)	26 (11.1)	
Multiparous	51 (21.8)	77 (32.9)	
Grand Multiparous	8 (3.4)	20 (8.5)	

Body Mass Index			0.074
Underweight (<18.5kg/m2)	12 (5.1)	6 (2.6)	
Normoweight (18.5-24.9 kg/m2)	44 (18.8)	55 (23.5)	
Overweight (25-29.9 kg/m2)	28 (12)	46 (19.2)	
Obese (≥30 kg/m2)	25 (10.7)	19 (8.1)	
Anemia severity			0.613
Non-Anemic	27 (11.5)	26 (11.1)	
Mild anemia (Hb <11-11.9 g/dL)	22 (9.4)	26 (11.1)	
Moderate anemia (Hb < 8-10.9 g/dL)	58 (24.8)	67 (28.6)	
Severe anemia (Hb < 8 g/dL)	2 (0.9)	6 (2.6)	

Table 1 showed the basic characteristics this research is looking for. The characteristics are age, body mass index, education background, and parity. Seen from the age, the reproductive group (15-49 years) is higher in both endometriosis (36.3%) and non endometriosis (29.1%) cases. Seen from the educational background, although there is no difference and significance between levels and cases (p-value 0.051), most of the patients are senior high school graduates. Seen from the parity status, both endometriosis and non-endometriosis cases are dominated with multiparity (21.8% v 32.9%) and hold significant value (p value <0.001). Seen from the BMI, both endometriosis (18.8%) and non endometriosis (23.5%) are considered normal weight groups. Both endometriosis and non-endometriosis cases are dominated with moderate anemia (24.8% v 28.6%), however there is no difference and significance between level and cases (p-value 0.613).

Table 2 Crude OR from Univariate analysis, p value and confidence interval of Endometriosis and Anemia severity

Parameters	**Anemia Severity**						
	Non-anemic	Mild Anemia (Hb 11-11.9 g/dL)	OR (CI95%)	Moderate Anemia (Hb 8-10.9 g/dL)	OR (CI95%)	Severe Anemia (Hb < 8 g/dL)	OR (CI95%)
Endometriosis	27 (11.5)	22 (9.4)	0.680 (0.442-1.047)	58 (24.8)	0.744 (0.520-1.063)	2 (0.9)	0.730 (0.255-2.094)
Non-endometriosis	26 (11.1)	26 (11.1)		67 (28.6)		6 (2.6)	

Table 2 explains the association between the severity of anemia and endometriosis. This study found no significant relationship between endometriosis and the occurrence of anemia, at any level.

Table 3 Crude OR from Univariate analysis, p value and confidence interval of Age and parity towards Endometriosis

Parameters	**Endometriosis**	**Non-endometriosis**	**OR**	**CI 95%**
Age				
Reproductive age	85 (36.3)	68 (29.1)	3.033	1.703 - 5.403
nAge x endometriosis			0.945	0.913 - 0.977
Parity				

Nulliparous	10 (4.3)	2 (0.9)	11.883	2.103-67.163
Primiparous	40 (17.1)	26 (11.1)	3.775	1.447-9.850
Multiparous	51 (21.8)	77 (32.9)	1.610	0.656-3.950
Grand Multiparous	8 (3.4)	20 (8.5)	~	~

Table 3 There is a relationship between the patient's age and parity with the occurrence of endometriosis. For age, reproductive-age patients are 3.033 times more likely to have an association with endometriosis [95% CI = 1.703-5.403] and every increase of age contributes 0.9% towards endometriosis risk of occurrence. Meanwhile, for parity, an odds ratio (OR) of 11.883 [95% CI = 2.103-67.163] was found, indicating that nulliparity is more likely to increase the risk of developing endometriosis. Although this was not the main focus or objective of the study, it serves as a trigger for further research on the relationship between patients' basic characteristics and the occurrence of endometriosis.

Discussion

Regarding the severity of anemia in endometriosis, the result of this study showed that the prevalence of moderate anemia was higher than other grades of anemia. However, no significant associations were found between the two variables. Considering a previous study by Cho et al., stated the negative correlation between endometriosis and red blood cell indices due to dysregulated iron metabolism [OR = 2.331; 95% CI = 1.211-4.484]. Normally, the human body contains 45 mg Fe/Kg body weight of iron which typically has higher values in men than in women. Most of this iron is contained in circulating RBCs which will bind to the oxygen transport protein. In endometriosis cases, increased concentrations of erythrocytes have been reported in the peritoneal cavity and iron overload may originate from the lysis of pelvic erythrocytes. This can affect numerous mechanisms involved in the development of endometriosis (Cho et al., 2024). Additionally, some studies have shown an increased level of hemoglobin in the peritoneal fluid of women with endometriosis than those of normal women. Excessive RBC degradation from menstrual reflux and lesion bleeding releases heme, generating active iron and iron-ferritin deposits that disrupt iron homeostasis. This iron overload promotes ROS production and NF-κB activation, increasing MMP expression, inflammation, angiogenesis, and cell adhesion driving endometriosis progression (Li et al., 2023).

In this study, even though the majority of patients are included in multiparous for both endometriosis and non-endometriosis cases (21.8% v 32.9%), patients with nulliparity has 11.883 times higher odds of endometriosis [95% CI = 2.103-67.163]. From the result, we could see the decrease of chances in endometriosis occurrence align with the increase of parity. This is in line with a study by Ranjan et al stating that the risk of endometriosis is declining with an increase of parity. Traditionally, pregnancy was believed to have a beneficial effect on endometriosis and symptoms. Pregnancy could cause increased apoptosis and decreased cell proliferation of endometriosis lesions. An experimental study done by Bilotas et al. evaluating the interplay between pregnancy and endometriosis shows that although endometriosis lesions sizes were increased in pregnant mice, however, apoptosis in the stroma and cell proliferation decreased in the epithelium of these lesions. Thus, resulting in a beneficial effect of pregnancy (Bilotas, M. A., Olivares, C. N., Ricci, A. G., Baston, J. I., Bengochea, T. S., Meresman, 2015)). Additionally, anovulation and amenorrhea help reduce anatomical distortions from bleeding endometriotic lesions and counter the disease's hormonal, inflammatory, and angiogenic effects. This suggests pregnancy may induce molecular and cellular changes that offer long-term benefits for endometriosis (Ranjan et al., 2023).

Endometriosis is a chronic condition that primarily affects women aged 25–35 but can also occur in adolescents and older women. However, diagnosis is often delayed due to non-specific symptoms or frequent misdiagnosis (Kvaskoff et al., 2015; Vercellini et al., 2014).

Aligned with that, in this study, we found significance of reproductive age (p-value <0.001; OR 3.033; CI 95%; 1.703 - 5.403) with a higher rate in endometriosis cases (36.3%) rather than non-endometriosis (29.1%). Women in their reproductive age have chances with 3.033 times higher odds of endometriosis and an increased probability of 0.9% with each increased age. In younger women and adolescents, endometriosis diagnosis is often delayed by an average of 7–12 years. While less commonly diagnosed in postmenopausal women, the condition may persist or become symptomatic in some cases (Zondervan et al., 2020).

CONCLUSION

Several studies have shown the impact of endometriosis on iron deficiency and the risk of anemia. However, in our study, there was no significant association between the two variables, meaning endometriosis doesn't hold any significance towards the severity of anemia. This could be affected by our limited data due to the unexamined serum iron and other prior history of received therapy before admission. Although there are still some possibilities of endometriosis can impact to increased severity of anemia. Thus, we recommend future research observing types of endometriosis and its impact on molecular stage erythropoiesis.

REFERENCES

Atkins, H. M., Susan, E. A., Taylor, R. N., Mendoza, Y. T., Lenk, E., & Rosenthal, N. S. (2018). Systemic Iron Deficiency in a Nonhuman Primate Model of Endometriosis. Journal of Comparative Medicine, 64(4), 298–307.

Bilotas, M. A., Olivares, C. N., Ricci, A. G., Baston, J. I., Bengochea, T. S., Meresman, G. F. (2015). Interplay between Endometriosis and Pregnancy in a Mouse Model. PLOS ONE.

Cho, H. Y., Park, S. T., & Park, S. H. (2024). Red blood cell indices as an effective marker for the existence and severity of endometriosis (STROBE). Medicine Open Access Journal, 101(42).

Christopher, S., & Donovan, C. (2023). Improving the diagnosis of endometriosis in Asia-Pacific: Consensus from the Asia-Pacific Endometriosis Expert Panel for Endometriosis. Wiley Bayer.

Dereje, G. G., Jenny, D., Sally, M., Grant, M., & Gita, D. (2024). Risk of Iron Deficiency in Women With Endometriosis: A Population-Based Prospective Cohort Study. Women's Health Issues, 34(3).

Feng, J., Zhang, S., Chen, J., Zhu, J., & Yang, J. (2022). Global Burden of Endometriosis in 204 Countries and Territories from 1990 to 2019. Clinical and Experimental Obstetric & Gynecology, 49(10).

James, W., Fernando, S. M., Powell, S. G., Hill, C. J., Arshad, I., & Probert, C. (2023). The role of iron in the pathogenesis of endometriosis: a systematic review. Human Reproductive Open Journal, 3.

Kvaskoff, M., Mu, F., Terry, K. L., & Harris, H. R. (2015). Endometriosis: A High-Risk Population for Major Chronic Disease? Human Reproduction Update, 21(4), 1–17.

Li, Y., He, Y., Cheng, W., Zhou, Z., Ni, Z., & Yu, C. (2023). Double-edged roles of ferroptosis in endometriosis and endometriosis-related infertility. Cell Death Discovery Journal, 22(9).

Ranjan, Y. S., Ziauddeen, N., Stuart, B., & Alwan, N. (2023). The role of parity in the relationship between endometriosis and pregnancy outcomes. Reproduction and Fertility Open Access Journal, 4(1).

Saunders, P. T. K., & Horne, A. W. (2021). Endometriosis: Etiology, pathobiology, and therapeutic prospects. Cell, 184(11), 2807–2824. https://doi.org/10.1016/j.cell.2021.04.041

Vercellini, P., Vigano, P., Somigliana, E., & Fedele, L. (2014). Endometriosis : Pathogenesis and Treatment. Nature Reviews Endocrinology, 10, 261–275.

World Health Organization. (2024). Guideline on Haemoglobin Cutoffs to Define Anaemia in Individuals and Populations.

Zhang, S., Gong, T. T., Wang, H. Y., Zhao, Y. H., and Wu, Q. J. (2021). Global, Regional, And National Endometriosis Trends From 1990 to 2017. Annals of the New York Academy of Sciences, 1484(1), 90–101.

Zondervan, K. T., Becker, C. M., & Missmer, S. A. (2020). Endometriosis. The New England Journal of Medicine, 382, 1244–1256.