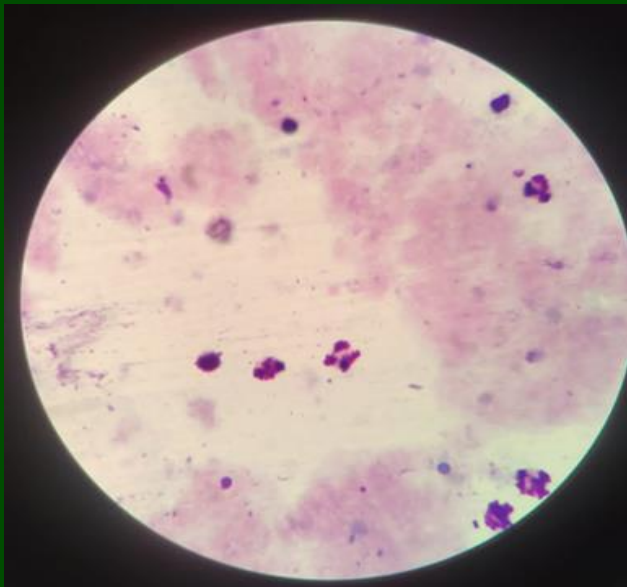


# Majalah Obstetri & Ginekologi



JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

Vol. 31 No. 3 December 2023



Blood smear evaluation after 7 days in pregnant patient with vivax malaria

## Original Research

- Parity and anemia among pregnant women at a public health center in Bojonegoro, Indonesia
- Comparison of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio levels in ovarian cyst among epithelial ovarian cancer patients at RSUP H. Adam Malik Medan, Indonesia
- Incidence of radiation proctitis in cervical cancer receiving radiation therapy at Dr. Kariadi Hospital, Semarang, Indonesia

## Systematic Reviews

- The role of stem cells in obstetrics and gynecology: A systematic review
- The combination of NLR and MEOWS as a potential modality for detecting the severity of preeclampsia: A systematic review
- Stress exposure due to the COVID-19 pandemic on menstrual abnormalities: A systematic review

## Case Reports

- The effectiveness of McDonald Transvaginal Cerclage in preventing preterm labor
- Complicated vivax malaria in pregnancy: A case report in rural area of Indonesia

Published by

Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga  
In Collaboration with Indonesian Society of Obstetrics and Gynecology

Accredited by Ministry of Education, Culture, Research, and Technology, Republic of Indonesia  
No. 105/E/KPT/2022

# *Majalah* *Obstetri & Ginekologi*

**JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE**

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# *Majalah* *Obstetri & Ginekologi*

**JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE**

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## CONTENT

### ORIGINAL RESEARCH :

1. Parity and anemia among pregnant women at a public health center in Bojonegoro, Indonesia  
**Toto Siswantoro, Masfuah Ernawati** ..... 110 – 116
2. Comparison of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio levels in ovarian cyst among epithelial ovarian cancer patients at RSUP H. Adam Malik Medan, Indonesia  
**Mega Sari Dewi, Roy Yustin Simanjuntak, Letta Sari Lintang, Muhammad Fadhy, Deri Edianto, Makmur Sitepu** ..... 117 – 122
3. Incidence of radiation proctitis in cervical cancer receiving radiation therapy at Dr. Kariadi Hospital, Semarang, Indonesia  
**Teuku Mirza Iskandar, Endy Cahyono Kristiawan, Teuku Rendiza Faizal, Ediwiwobo Ambari, Very Great Eka Putra, Lubena Achmad** ..... 123 – 128

### SYSTEMATIC REVIEWS :

4. The role of stem cells in obstetrics and gynecology: A systematic review  
**Putri Mirani, Legiran, Cindy Kesty, Hana Andrina** ..... 129 – 138
5. The combination of NLR and MEOWS as a potential modality for detecting the severity of preeclampsia: A systematic review  
**Rendy Singgih, Meilyana Maria Isabela Kwary, Yosi Tamara** ..... 139 – 149
6. Stress exposure due to the COVID-19 pandemic on menstrual abnormalities: A systematic review  
**Salsabila Bestari Nugroho, Budi Utomo, Endyka Erye Frety, Ashon Sa'adi, Shifa Fauziyah** ..... 150 – 156

### CASE REPORTS :

7. The effectiveness of McDonald Transvaginal Cerclage in preventing preterm labor  
**Adhi Pribadi** ..... 157 – 161
8. Complicated vivax malaria in pregnancy: A case report in rural area of Indonesia  
**Raymond Surya, Edward Sugito Manurung, Yudianto Budi Saroyo** ..... 162 – 166

Cover :

**Blood smear evaluation after 7 days  
in pregnant patient with vivax malaria**

This edition page 164

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Rose ME, Huerbin MB, Melick J, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. *Brain Res.* 2002;935(1-2):40-6.

### 2. Books

Butler SW. *Secrets from the black bag.* London: The Royal College of General Practitioners; 2005.

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*Translated book*

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Muller S, editor. *Proceedings of the 10th international conference on head-driven phrase structure grammar* [Internet]; 2003 Jul 18-20; East Lansing (MI). Stanford (CA): CSLI Publications; 2003 [cited 2017 Nov 16]. Available from: <http://web.stanford.edu/group/cslipublicationsSta/cslipublications/HPSG/2003/toc.shtml>

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The family impact of Attention Deficit Hyperactivity Disorder (ADHD) [Internet]. 2009 Nov 1 [updated 2010 Jan 1; cited 2010 Apr 8]. Available from: <http://www.virtualmedical-centre.com.au/healthandlifestyle.asp?sid=192&title=The-Family-Impact-of-Attention-Deficit-Hyperactivity-Disorder-%28ADHD%29page=2>

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- the citation number can be placed next to the author name where emphasis is placed on the author eg. Smith<sup>2</sup>

- When multiple references are cited at a given place in the text, use a hyphen to join the first and last numbers that are inclusive. Use commas (without spaces) to separate non-inclusive numbers in a multiple citation e.g. (2,3,4,5,7,10) is abbreviated to (2-5,7,10).
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For example:

Moir and Jessel maintain “that the sexes are interchangeable”.<sup>1</sup>  
Numerous studies<sup>20-22</sup> have.....  
Smith's research .....<sup>21</sup>  
Smith and Jones'<sup>22</sup> research .....

Up to 3 authors eg. Smith, Jones and McDonald reported that .....<sup>23</sup>

More than 3 authors eg. Smith et al.<sup>24</sup> reports.






## ORIGINAL RESEARCH

### Parity and anemia among pregnant women at a public health center in Bojonegoro, Indonesia

Toto Siswanto, Masfiah Ernawati \*

Diploma Program of Bojonegoro Midwifery  
Poltekkes Kemenkes Surabaya, Indonesia

Article Info	ABSTRACT
<p>Received Feb 10, 2023 Revised May 5, 2023 Accepted May 19, 2023 Published Dec 1, 2023</p> <p><b>*Corresponding author:</b> Masfiah Ernawati masfiahbjn8990@gmail.com</p> <p><b>Keywords:</b> Anemia Knowledge Parity Attitude Factors of Pregnancy Maternal Health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p><b>Objective:</b> The purpose of this study was to analyze the factors that influenced anemia in pregnant women at the Public Health Center of Kedewan, Bojonegoro, Indonesia.</p> <p><b>Materials and Methods:</b> This was an analytic study using a retrospective approach. The population of this study was all pregnant women in 2018 at Public Health Center in Kedewan, Bojonegoro, Indonesia, involving 173 pregnant women, consisting of 117 anemic pregnant women and 56 non-anemic pregnant women. The sample of this study consisted of 119 pregnant women in 2018 consisting of 80 anemic pregnant women and 39 non-anemic pregnant women, who were selected using proportional stratified random sampling and simple random sampling. Bivariate and multivariate analyses were performed using multiple logistic regression.</p> <p><b>Results:</b> Variables that did not significantly affect anemia in pregnant women were age (<math>p=0.384</math>), education (<math>p=0.460</math>), occupation (<math>p=0.234</math>), income (<math>p=0.482</math>), food abstinence (<math>p=0.465</math>), and ANC examination (<math>p=0.319</math>), while variables that significantly affected anemia in pregnant women were knowledge (<math>p=0.002</math>), parity (<math>p=0.000</math>) and the regularity of consuming blood-booster tablets (<math>p=0.041</math>).</p> <p><b>Conclusion:</b> The most influential variable on anemia in pregnant women was parity.</p>

**How to cite:** Siswanto T, Ernawati M. Parity and anemia among pregnant women at a public health center in Bojonegoro, Indonesia. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology)*. 2023;31(3):110-116. doi: 10.20473/mog.V31I32023.110-116.

#### Highlights:

1. One of the most common maternal health problems is anemia during pregnancy.
2. Factors that lead to anemia incidence were analyzed to be able to provide adequate precautions.
3. It was found that knowledge, parity, and consistency in taking blood supplement tablets during pregnancy are factors that influence the incidence of anemia in pregnant women.

## INTRODUCTION

Anemia is one of the major causes of maternal mortality. Anemia that occurs until the third trimester may affect the condition of the fetus and the continuity of labor.<sup>1</sup> Anemia is a clinical syndrome characterized by the reduction of hematocrit, hemoglobin, and erythrocyte count in the blood.<sup>2</sup> Anemia in pregnancy is the condition of pregnant women with hemoglobin (Hb) levels less than 11 g/dL in the first and third trimester of pregnancy, while in the second trimester, the hemoglobin level is less than 10.5 g/dL.<sup>3</sup>

Based on data from the World Health Organization (WHO), 15-20% of maternal deaths, either directly or indirectly, are caused by anemia. The frequency of anemia in pregnancy in the world ranges from 10% - 20%.<sup>3</sup> According to the 2018 Basic Health Research (Risksda), the prevalence of anemia for pregnant women in Indonesia in 2018 was 48.9%, higher than the prevalence of anemia for pregnant women in 2013, which was 37.1%.<sup>4</sup> The incidence of anemia for pregnant women in Bojonegoro Regency, Indonesia, in 2018 was 8.77% of the pregnant women. Meanwhile, the prevalence of anemia in the working area of the Public Health Center in Kedewan, Bojonegoro, in 2018 was 67.63%. This percentage was the highest compared to all anemia cases in 37 other public health centers in the district of Bojonegoro.<sup>5</sup>

Anemia occurs relatively often in pregnancy because pregnant women need more iron for the process of pregnancy and childbirth. Several factors that may cause anemia in pregnancy include the level of knowledge, socio-economic level, culture, gravidas, age, parity, level of adherence to the consumption of blood-booster tablets, and diet. The effects of anemia in pregnancy can be fatal if it is not immediately treated. Those effects are including miscarriage, preterm labor, uterine inertia, prolonged labor, uterine atony, bleeding, and shock, while the effects of anemia on the outcome of conception include miscarriage, fetal death in the womb, fetal death at birth, high perinatal mortality, prematurity, and congenital defects.<sup>6</sup>

To prevent nutritional anemia in pregnant women, supplementation of blood-booster tablets is carried out with a daily dose of one tablet of 60 mg of elemental iron and 0.4 mg of folic acid in a row for at least 90 days during pregnancy.<sup>7</sup> Prevention of anemia deficiency in pregnant women can be conducted with iron and folic acid supplementation. WHO recommends providing 60 mg of iron for 6 months to meet the physiological needs during pregnancy. However, many literatures recommend 100 mg of iron for 16 weeks or more during pregnancy.<sup>8</sup> The government has been

conducting various ways as efforts to prevent and control efforts of anemia in Indonesia. Various efforts have been conducted in the context of preventing and overcoming anemia. Pregnant women should increase their consumption of Fe tablets, increase their intake of foods containing iron and vitamin C, improve their diet, as well as eradicate worms to avoid iron loss.<sup>9</sup>

The authors were interested in the characteristic factors of pregnant women (knowledge, age, and parity), socio-economic (education, work, and income), food abstinence factor, regularity of ANC visits, consumption of blood-boosting tablets against anemia in pregnant women at the Kedewan Health Center, Bojonegoro.

## MATERIALS AND METHODS

The type of research used was quantitative analytic research with a case-control study design. The population of this study was all pregnant women in 2018 at the Kedewan Health Center, a total of 173 pregnant women consisting of 117 anemic pregnant women and 56 non-anemic pregnant women. The samples in this study were enrolled using proportional stratified random sampling. The sample for this study was a portion of pregnant women in 2018, totaling 119 pregnant women. Using the proportionate formula, there were 80 anemic pregnant women and 39 non-anemic pregnant women.

Data collection from the independent variables was carried out using a closed questionnaire, by inviting respondents to the local village midwife who acted as an enumerator, while data collection from the dependent variable used the mother's cohort register. The collected research data were then edited, entered, and tabulated. The data analysis used in this study was a multiple logistic regression test using SPSS version 16 computer program. Univariate analysis was used to determine the frequency distribution of the variable characteristics of pregnant women (knowledge, age, parity), mother's socio-economic factors (education, occupation, income), food abstinence culture, regular ANC check-ups, and consumption of iron tablets. Bivariate analysis was used to determine the effect between two variables, then multivariate analysis was used to determine the joint effect of several factors of pregnant women on anemia in pregnant women.

## RESULTS AND DISCUSSION

### Effect of each variable on anemia in pregnant women



Bivariate analysis results of the multiple logistic regression test on the maternal factors of anemia in pregnancy that affected the occurrence of anemia in pregnant women can be seen in Table 1.

Table 1 shows that variables that have a significant effect on anemia in pregnant women ( $p < 0.05$ ) are knowledge of pregnant women, maternal parity, and regular consumption of blood-booster tablets. Variables that did not significantly affect anemia in pregnant women ( $p > 0.05$ ) were the pregnant women's age, education, occupation, income, culture of abstinence from food, and ANC regularity.

The results of this study indicated that the knowledge of pregnant women about anemia significantly affected anemia in pregnant women ( $p = 0.000$ ). This was in line with research conducted by Roni et al. (2020)<sup>10</sup> that there was a strong correlation between knowledge and the incidence of anemia ( $p = 0.021$ ;  $r = 0.781$ ). Pregnant women with low knowledge of the importance of iron in pregnancy have problems with their nutritional intake patterns and consumption of iron tablets, so they are at risk for anemia.<sup>11</sup>

The results of this study indicated that the age of pregnant women had no significant effect on anemia in pregnancy. This was not in line with the research conducted by Astriana (2018), who studied the incidence of anemia in pregnant women in terms of their parity and age, and found that maternal age had an effect on the incidence of anemia in pregnant women.<sup>12</sup> It was also not in line with a study by Amallia et al. (2017), who studied the risk factors of anemia in pregnant women, in which there was a relationship between age and parity of pregnant women with the

incidence of anemia in pregnant women and there was no relationship between the level of education and work with the incidence of anemia in pregnant women.<sup>13</sup> In this study, as many as 102 or 85.7% of pregnant women were found not to have the risk of having anemia during pregnancy. This indicated that maternal age did not affect anemia in pregnant women.

The results of this study indicated that maternal parity has a significant effect on anemia in pregnant women. This was also found in a research conducted by Anggraeni (2018) on factors associated with the incidence of anemia in pregnant women. She found that parity affected anemia in pregnant women. It was also revealed in a research conducted by Astriana (2018) studying the incidence of anemia in pregnant women in terms of parity and age. She found that parity affected the incidence of anemia in pregnant women. Likewise, according to Amallia et al. (2017), who studied the risk factors of anemia in pregnant women, there was a relationship between the age and parity with the incidence of anemia in pregnant women and there was no relationship between the level of education and work with the incidence of anemia in pregnant women.

Parity is the number of pregnancies that produce a fetus that can live outside the womb. The number of children born greatly affects the health of the mother and the children themselves. Women who often experience pregnancy and childbirth are increasingly anemic because of a lot of iron loss. This is because during pregnancy a woman uses the iron reserves in her body. The more often a woman gives birth, the greater the risk of blood loss and the impact on decreasing Hb levels. Each time a woman gives birth, the amount of iron lost is estimated at 250 mg.<sup>14</sup>

Table 1. Bivariate analysis results of the effect of maternal factors of anemia in pregnant women

No	Variables	values
1.	Characteristics of the pregnant women	
	a. Knowledge	0.000
	b. Age	0.384
	c. Parity	0.000
2.	Socioeconomic factors of the pregnant women	
	a. Education	0.460
	b. Occupation	0.234
	c. Income	0.482
3.	Culture of abstinence for pregnant women	0.465
4.	ANC regularity	0.319
5.	Blood-booster tablet regularity	0.007

Parity of more than four can increase the frequency of complications in pregnancy and childbirth, such as the increased risk of fetal death in the womb and bleeding before and after childbirth that can be fatal. because women who have often given birth can result in damage to blood vessels and uterine wall vascularization due to past deliveries, resulting in insufficient blood flow to the placenta, which ultimately can reduce its function and affect the circulation of nutrients to the fetus. Having a history of bleeding a lot can cause anemia in subsequent pregnancies.<sup>15</sup> In this case, the government has attempted to reduce high parity by activating the family planning program. Apart from that, to prevent anemia for pregnant women, the government has created a program to provide supplements to pregnant women. The administration of iron tablets or supplementation of blood-boosting tablets is an effort to prevent anemia in pregnant women who are given as many as 90 tablets consumed a day (60 mg elemental iron and 0.25 mg folic acid) consecutively for at least 90 days during pregnancy.<sup>16</sup>

The results of this study indicated that the education of pregnant women had no significant effect on anemia during pregnancy. This was in line with a study by Amallia et al. (2015) on the risk factors for anemia in pregnant women, stating that there was no correlation between education and anemia in pregnant women.<sup>13</sup> In contrast to other studies conducted by Purba et al. (2018) analyzing the risk factors of anemia in pregnant women, a significant relationship was found between education and the incidence of anemia.<sup>17</sup>

Education is the process of changing behavior towards maturity and the perfection of life. The level of education of pregnant women also affects the occurrence of anemia during pregnancy.<sup>11</sup> In this study, it was found that pregnant women with a higher level of education were 31.1%, indicating that education did not affect anemia in pregnant women.

The results of this study indicated that the work of pregnant women has no significant effect on the anemia of pregnant women ( $p=0.234$ ). This was in line with the results of research by Amallia et al. (2017) who studied the risk factors for anemia in pregnant women, where there was a relationship between age and parity of pregnant women and the incidence of anemia in pregnant women and there was no relationship between education and occupational level with the incidence of anemia in pregnant women.<sup>13</sup>

Pregnant women who work have challenges in keeping the health condition of their pregnancy. Moreover, working condition that takes time and energy may have an impact on their physical and mental health. However, pregnant women can still carry out their work activities by maintaining physical condition so they are not tired and able to avoid stress.<sup>11</sup> In this study, it was found that most pregnant women who did not work reached 91.6%, indicating that work did not affect anemia in pregnant women.

The results of this study indicated that the income of pregnant women had no significant effect on anemia in pregnancy ( $p=0.482$ ). However, a study by Purba et al. (2017) found a significant relationship between income and the incidence of anemia. A person's income is a description of the family's economic position in the society. Therefore, everyone who is involved in a certain type of work, including work in the informal sector or trade, may have a chance to increase their income to meet the needs of their family to improve their standard of living.<sup>18</sup>

The results of this study showed that the culture of abstinence from food for pregnant women had no significant effect on anemia in pregnancy, while Sunarti et al. (2019) found that dietary restrictions were associated with the incidence of anemia in pregnant women.<sup>19</sup> Many myths and false beliefs have developed into a culture in the society about maternal intake during pregnancy, such as the prohibition to eat fish during pregnancy. This often causes problems for the health of pregnant women and their fetuses. It also leads to the risk of anemia in pregnant women. In this study, it was found that the majority of pregnant women who did not abstain from food reached 96.6%, which possibly indicated that the culture of abstaining from food did not affect anemia in pregnant women.

This study found that the regularity of ANC visits did not significantly affect anemia in pregnant women. This finding was different from the research conducted by Roni et al. (2020) who found a strong correlation between antenatal care visits and the incidence of anemia in pregnant women.<sup>9</sup> The implementation of ANC activities has an important role in enhancing the health of mothers and children because ANC visits are one of the main sources for mothers to obtain iron tablets and their education about important nutritional needs during pregnancy.<sup>20</sup>

Table 2. Results of multivariate analysis on the effect of maternal factors of anemia on pregnancy

No	Variables	B	Wald	Sig.	OR	CI 95%	
						Lower	Upper
1	Knowledge	1.747	10.075	0.002	5.740	1.951	16.884
2	Parity	3.246	20.822	0.000	25.699	6.373	103.634
3	BBT	1.357	4.158	0.041	3.884	1.054	14.311

In this study, it was found that the majority of pregnant women, reaching 86.6%, implemented regular ANC visits. However, those pregnant women who did not regularly consume blood-booster tablets were about 23.5%. This could be a contributing factor that the regularity of ANC visits did not affect anemia in pregnant women.

The results of this study indicated that the consumption of blood-booster tablets had a significant effect on anemia in pregnant women. A study by Putri Dwi Anggraeni (2018) on the factors associated with the incidence of anemia in pregnant women found that the consumption of Fe tablets affected anemia in pregnancy.<sup>21</sup> Another study conducted by Purba et al. (2017) found that there was a significant relationship between the consumption of Fe tablets and the incidence of anemia in pregnant mothers.<sup>17</sup> Consumption of iron tablets is very important for pregnant women to avoid anemia. Pregnant women should consume at least 90 Fe tablets during pregnancy because food intake is still insufficient to meet their needs.<sup>22</sup>

### The combined effect of maternal factors of anemia on pregnancy

Table 1 shows that variables with  $p < 0.25$  are knowledge, parity, occupation, and regularity of consumption of blood-booster tablets, so these four variables met the requirements for being subjected to multivariate analysis. The results of the multivariate logistic regression analysis on the combined effect of maternal anemia factors on pregnancy are shown in Table 2.

Table 2 shows that the variables of maternal knowledge ( $p=0.002$ ), maternal parity ( $p=0.000$ ), and consumption of blood supplement tablets have a significant effect on anemia in pregnant women. The mother's parity variable was the variable that had the highest influence on anemia in pregnant women with the largest odds ratio of 25.699.

The results of this study indicated that the factors that had a significant combined effect on anemia in pregnant women were knowledge, maternal parity, and the regularity of consuming blood-added tablets. The most influential factor on anemia in pregnant women was

maternal parity (OR=25.699), then the second one was knowledge (OR=5.740) and the last was the regularity of consumption of blood-booster tablets (OR=3.888). Knowledge, maternal parity, and regularity of blood-booster tablet consumption were proved to be the independent variables of anemia in pregnancy, while occupation served as a confounding variable. Rismawati & Rohmatin (2018), however, found that Fe consumption had the highest influence on the incidence of anemia in pregnancy.<sup>22</sup>

Primiparous pregnant women do not have much experience in meeting their nutritional needs during pregnancy, especially if they also have a lack of knowledge about anemia and non-compliance with the consumption of blood-booster tablets. They will tend to suffer from anemia. On the other hand, grand multiparous pregnant women have the risk of suffering from anemia due to frequent births, so they are more often at risk of losing blood. It may also be aggravated by the lack of knowledge about anemia and also non-compliance with consuming blood-booster tablets during pregnancy.

However, this study still had limitations. This was a retrospective study, using secondary data. These secondary data were those kept within the register books where there might be errors in writing the data.

### CONCLUSION

This study had disclosed that socio-economic variables, culture of abstinence, and regular ANC visit did not significantly affect anemia in pregnancy, while maternal parity, knowledge, and regular consumption of blood-booster tablets did significantly affect anemia in pregnancy.

### DISCLOSURES

#### Acknowledgment

Thank you to all parties involved in this research

#### Conflict of interest



All authors have no conflict of interest in funding

## Funding

DIPA Poltekkes Kemenkes Surabaya

## Author contribution

All authors have contributed to all processes in this research, including preparation, data gathering, analysis, drafting, and approval for publication of this manuscript.

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## ORIGINAL RESEARCH

### Comparison of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio levels in ovarian cyst among epithelial ovarian cancer patients at RSUP H. Adam Malik Medan, Indonesia

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Article Info	ABSTRACT
<p>Received Jun 27, 2023 Revised Sep 4, 2023 Accepted Sep 15, 2023 Published Dec 1, 2023</p> <p><b>*Corresponding author:</b> Mega Sari Dewi saridewimega4@gmail.com</p> <p><b>Keywords:</b> Ovarian cyst Ovarian cancer Neutrophil Lymphocyte Ratio Platelet Lymphocyte Ratio Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p><b>Objective:</b> To assess Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) as independent prognostic markers in epithelial ovarian cancer patients at RSUP H. Adam Malik Medan, Indonesia, considering the disease's common occurrence and typically late-stage diagnosis with a poor prognosis due to inflammatory processes implicated in malignancy mechanisms.</p> <p><b>Materials and Methods:</b> A comparative case-control study was conducted at the Department of Obstetrics and Gynecology, RSUP H. Adam Malik Medan, from December 2019 to February 2020. The study included 40 patients each diagnosed with ovarian cysts and epithelial ovarian cancer. Bivariate analysis was conducted using independent T-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. Significance was established at <math>p &lt; 0.05</math>.</p> <p><b>Results:</b> The median NLR in the ovarian cancer group was 2.45 (1.06 to 38.44) and in the ovarian cysts group was 2.34 (1.44 to 3.78). Median PLR levels in ovarian cancer were 12813.94 (3178.08 to 19040.0) and in ovarian cysts were 11138.15 (5026.18 to 22839.51). Statistical analysis revealed no significant difference in NLR and PLR levels between ovarian cancer and ovarian cysts (<math>p &gt; 0.05</math>).</p> <p><b>Conclusion:</b> NLR and PLR levels demonstrated no significant difference between ovarian cancer and ovarian cyst patients at RSUP H. Adam Malik Medan, Indonesia. However, NLR and PLR can still serve as valuable markers for identifying malignant processes in patients suspected of malignancy.</p>

**How to cite:** Dewi MS, Simanjuntak RY, Lintang LS, et al. Comparison of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio levels in ovarian cyst among epithelial ovarian cancer patients at RSUP H. Adam Malik Medan, Indonesia. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science)*. 2023;31(3):117-122. doi: 10.20473/mog.V31I32023.117-122.

#### Highlights:

1. Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) have potential as independent prognostic markers for ovarian cancer.
2. This research was to evaluate NLR and PLR levels in ovarian cysts with epithelial ovarian cancer patients at RSUP H. Adam Malik Medan, Indonesia.



## INTRODUCTION

Ovarian cancer ranks 6<sup>th</sup> and 10<sup>th</sup> among all cancers, constituting the most prevalent malignancy with 13,310 (7.1%) new cases in 2018, as per GLOBOCAN data.<sup>1</sup> The majority of diagnoses occur at advanced stages (stages 3 and 4), yielding a discouraging 5-year survival of 40%. Early detection significantly improves prognosis, raising the 5-year survival rate to approximately 90%.<sup>2,3</sup>

Inflammation and immunology intricately influence cancer development and metastasis. The Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) serve as indicators of systemic and immunological inflammation.<sup>4</sup> These parameters, reflecting the systemic inflammatory response, emerge as independent prognostic markers for adverse clinical outcomes in ovarian cancer.<sup>5,6</sup>

Williams et al. (2014) demonstrated that elevated NLR levels correlate with advanced disease stages, moderate to poor histological and pathological differentiation, and an unfavorable prognosis.<sup>7</sup> Previous studies underscore the diagnostic utility of NLR (2.25) and PLR (128.08) in benign ovarian cysts, contrasting with NLR (3.54) and PLR (198.87) values for ovarian cancer.<sup>8</sup> Additionally, Miao et al. emphasized the association between elevated NLR levels and more severe progression-free survival (PFS).<sup>9</sup> In a study by Chen et al., the ovarian cancer group exhibited significantly higher platelet counts and PLR compared to the endometriosis group. Platelet count and PLR emerge as valuable parameters for detecting ovarian cancer. These findings collectively underscore the important role of NLR and PLR in assessing ovarian cancer prognosis and potential diagnostic applications.<sup>10,11</sup>

In view of conflicting findings from various studies regarding the Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) in individuals with ovarian cancer and ovarian cysts, correlations with prognosis and disease trajectory have been subjects of debate. Therefore, we attempted to investigate the NLR and PLR cut-off values in ovarian cancer and ovarian cyst patients. This study aimed to ascertain the potential utility of these parameters as independent predictive diagnostics for malignancies.

## MATERIALS AND METHODS

This comparative case-control study, undertaken at the Department of Obstetrics and Gynecology, RSUP H. Adam Malik Medan, from December 2019 to February 2020, involved 40 patients diagnosed with ovarian cysts

and epithelial ovarian cancer at the Department of Gynecology-Oncology, RSUP H. Adam Malik Medan.

Inclusion criteria comprised histopathologically confirmed ovarian cyst patients with pertinent medical records at RSUP H. Adam Malik Medan and histopathologically confirmed epithelial ovarian cancer patients with corresponding medical records at the same institution. Exclusion criteria encompassed patients with concurrent oncological diseases, those with coexisting conditions such as heart valve disorders, viral infections, autoimmune disorders, and blood disorders potentially affecting neutrophil, lymphocyte, and platelet values. Additionally, patients lacking routine preoperative blood laboratory data and complete operating reports, as well as those with concurrent gynecological diseases, were excluded.

Histopathological data from ovarian cysts and epithelial ovarian cancer patients were retrieved from anatomic pathology records. Anthropometric details, including height and weight, were extracted from medical records. Complete blood count, patient age, parity history, Neutrophil Lymphocyte Ratio (NLR), and Platelet Lymphocyte Ratio (PLR) data were collected from the medical records. Ethical approval for this study was obtained from the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, Indonesia.

## Statistical analysis

Univariate and multivariate statistical analyses were conducted to evaluate the frequency distribution of study sample characteristics, including age, parity, neutrophils, platelets, and lymphocytes. The Kolmogorov-Smirnov normality test was employed to assess the normality of data distribution. Bivariate analysis utilized the independent T-test for normally distributed data and the Mann-Whitney test for non-normally distributed data. A significance level of <0.05 was applied to all results, which were presented in tabulated format.

## RESULTS AND DISCUSSION

Among patients with ovarian cancer, 31 patients (77.5%) aged 18-49 years, and 9 patients (22.5%) were 50 years old. Regarding patients with ovarian cysts, 29 patients (72.5%) aged 18-49 years, 10 patients (25.0%) were 50 years old, and 1 individual (2.5%) aged <18 years. In terms of menopausal status, the majority of the patients not in menopause experienced ovarian cancer, with 33 patients (82.5%) and 34 patients (84.6%) in each respective group.

Table 1. Research patient characteristics

Characteristics	Ovarian cancer	Ovarian cyst	p value
Age (years old)	<18	0 0.0%	1 2.5%
	18-49	31 77.5%	29 72.5%
	≥50	9 22.5%	10 25.0%
Menopause Status	Yes	7 17.5%	6 15.4%
	No	33 82.5%	34 84.6%
Parity	Primiparous	5 12.5%	8 20.5%
	Secundi-Multiparous	14 35.0%	8 20.5%
	Grand multiparous	21 52.5%	24 59.0%

Table 2. Differences in mean levels of NLR and PLR in ovarian cancer and ovarian cysts patients

	Mean	SD	Median	Min	Max	P value*
NLR	Ovarian Cancer	5.27	8.39	2.45	1.06	38.44
	Ovarian Cyst	2.38	0.48	2.34	1.44	3.78
PLR	Ovarian Cancer	20881.74	31973.82	12813.94	3178.08	190400.0
	Ovarian Cyst	11894.29	4814.34	11138.15	5026.18	22839.51

\* Mann Whitney Test

In terms of parity, 21 patients (52.5%) with ovarian cancer were grand multiparous, while in the ovarian cysts group, 24 patients (59.0%) had a history of grand multiparity. No significant differences were observed in age, menopausal status, or parity between patients with ovarian cancer and those with ovarian cysts ( $p > 0.05$ ).

The median NLR in the ovarian cancer group was 2.45 (1.06 – 38.44), and in the ovarian cysts group, it was 2.34 (1.44 – 3.78). The median PLR in the ovarian cancer group was 12813.94 (3178.08 – 19040.0), and in the ovarian cysts group, it was 11138.15 (5026.18 – 22839.51). Statistical analysis revealed no significant differences in NLR and PLR levels between patients with ovarian cancer and those with ovarian cysts ( $p > 0.05$ ).

Regarding age distribution, patients with ovarian cancer were predominantly aged 18-49 years (77.5%), followed by those aged 50 years (22.5%). Similarly, the ovarian cysts group was dominated by patients aged 18-49 years (72.5%), with 2.5% aged <18 years and 25.0% aged 50 years. The analysis indicated no significant differences in age distribution between the ovarian cancer and ovarian cysts groups, different from the results of previous studies. For example, Nurlailiyani's research reported that from 82 ovarian cancer patients, only 1.2% of the patients aged <20 years, followed by 12.2% aged 20-34 years, 37.8% aged 35-50 years, and the largest age group (48.8%) comprised individuals over 50 years. The mean age at diagnosis for women with ovarian cancer was 63 years, highlighting age as a major risk

and prognosis factor, with worse outcomes in elderly patients.<sup>12</sup>

In this research, it was also found that 33 (82.5%) patients with ovarian cancer had not experienced menopause, and ovarian cyst patients who have not experienced menopause were as many as 34 people (84.6%). Each year, over 23,000 cases of epithelial ovarian cancer are reported in the United States, with a median age at diagnosis being 63 years old.<sup>13</sup> Although post-menopausal women account for more than two-thirds of ovarian cancer incidences, the majority of established risk factors arise predominantly when women are in their twenties or thirties. According to one study, menopausal age is negatively connected to the development of ovarian cancer. These studies suggest that menopause at a later age is associated with an increased risk of ovarian cancer.<sup>14</sup>

The majority of postmenopausal ovarian cancer patients are between the ages of 60 and 64 worldwide; with the median age upon diagnosis in developed countries is 63 years old. According to the research by Shen et al, 38% of women diagnosed with epithelial ovarian cancer and 76% of women diagnosed with borderline epithelial ovarian cancer were diagnosed before menopause, implying that the age at diagnosis of ovarian cancer in Chinese (Asian) women is younger than in Caucasians. Therefore, it is crucial to study if Asian women's younger age at diagnosis could explain their poor clinical prognosis.<sup>15-17</sup>



Tumor-associated inflammation is thought to have a key role in carcinogenesis and tumor progression. In clinical practice, assessing tumor inflammatory response is simpler and less expensive. The immune system's function in disease remission or progression has been studied, and hematological markers such as leukocytes have been postulated as diagnostic and prognostic criteria in a variety of malignancies. The NLR has been suggested as simple index of systemic inflammatory response in patients with cancer. NLR and PLR are considered as predictive factors in survival of ovarian cancer patients. In addition, preoperative NLR and PLR can help differentiate malignant ovarian masses from benign ovarian masses.<sup>18</sup>

In this research, mean NLR value for ovarian cancer group was 5.27, the median was 2.45 and SD was 8.39 and mean NLR value for ovarian cysts group was 2.38, median was 2.34 and SD was 0.48. The statistical test result showed the p value of this comparison was 0.351. Based on this result, NLR levels did not differ statistically between ovarian cancer and ovarian cyst patients ( $p > 0.05$ ).

In this research, mean PLR value for ovarian cancer group was 20881.74, the median was 12813.94 and SD was 31973.82 compared to Mean PLR value for ovarian cysts group was 11894.29, median was 11138.15 and SD was 4814.34. The statistical test results result showed the p value of this comparison was 0.285. Based on this result, there was no statistically significant difference in PLR levels between ovarian cancer patients and ovarian cysts patients ( $p > 0.05$ ).

In this study, we analyzed the calculation of NLR and PLR as markers of inflammation in epithelial ovarian cancer and ovarian cysts patients. Statistical studies on each level of NLR and PLR revealed no statistically significant correlation between NLR and PLR levels and the prevalence of epithelial ovarian cancer and ovarian cysts ( $p > 0.05$ ). However, mean and median NLR values of subjects with ovarian cancer had higher values (5.27 and 2.45) than subjects with ovarian cysts which could have clinical significance (2.38 and 2.34).

However, this was not in accordance with the study conducted by Yildirim (2015).<sup>8</sup> It was found that individuals with ovarian cancer had significantly elevated NLR and PLR levels ( $p < 0.05$  and  $p < 0.001$ ). According to a multivariate analysis, greater NLR and PLR levels predicted ovarian cancer at a cut-off value of 3.35, with 55% sensitivity and 81% specificity for NLR (95% CI: 0.544-0.752,  $p < 0.05$ ) and cut-off value of 572.9, with 100% sensitivity and 0.38% specificity for PLR (95% CI: 0.192-0.381,  $p = 0.001$ ). According to the findings of the study, preoperative NLR and PLR

readings could detect ovarian cancer in patients with adnexal masses.<sup>19</sup>

In another study, 316 patients with benign adnexal masses and 253 patients with malignant adnexal masses underwent surgical treatment. Contrary to our findings, this study revealed higher values of NLR, PLR, neutrophil count, CA-125, and platelets in malignant cases compared to benign cases ( $p < 0.01$ ). These elevated biomarker values suggest potential use in early-stage detection of ovarian malignancy, thereby enhancing treatment options and improving survival rates.<sup>20</sup> While our study did not observe a significant difference in PLR values between ovarian cancer and ovarian cyst patients, the overall PLR values for ovarian cancer were higher than those for ovarian cysts patients.

Nevertheless, this study was not without limitations. The case-control design within a retrospective framework posed challenges in determining external variables due to technical constraints and insufficient information on numerous risk factors. Additionally, the single-center nature of this study, conducted at RSUP H. Adam Malik Medan, a national referral hospital, introduced variations in patient characteristics, including undetected comorbidities upon admission. Statistical associations between mean NLR and PLR levels in ovarian cancer and ovarian cyst patients could not be conclusively established due to limited sample size, research factors, and the relatively short study duration.<sup>20</sup> Despite these limitations, the significance of this study lies in being the first to explore differences in mean NLR and PLR levels between patients with epithelial ovarian cancer and ovarian cysts, providing a foundational basis for future investigations.

## CONCLUSION

While no statistical difference was found in Neutrophil Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) levels between ovarian cancer and ovarian cyst patients at RSUP H. Adam Malik Medan, Indonesia, the persistent correlation of NLR and PLR with inflammatory process in malignancy mechanisms highlights their clinical relevance. The absence of statistical difference does not deny the benefit of NLR and PLR levels in suspected malignancy cases. Future studies should prioritize larger, more homogenous samples for enhanced outcomes and deeper insights into the clinical implications of NLR and PLR in ovarian pathologies.

## DISCLOSURES

### Acknowledgment

The authors would like to express gratitude for supervisors of the Department of Obstetrics and Gynecology RSUP H. Adam Malik Medan and all parties involved in completion of this research.

### Conflict of interest

There are no conflicts of interest among the authors.

### Funding

There was no external funding for this study.

### Author Contribution

All authors participated to all aspects of this study, including preparation, data collection and analysis, drafting, and approval for publishing.

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## ORIGINAL RESEARCH

### Incidence of radiation proctitis in cervical cancer receiving radiation therapy at Dr. Kariadi Hospital, Semarang, Indonesia

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#### Article Info

Received Jul 2, 2023  
Revised Oct 5, 2023  
Accepted Oct 13, 2023  
Published Dec 1, 2023

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#### Keywords:

Cervical cancer  
Radiation therapy  
Radiation proctitis  
Maternal health

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#### ABSTRACT

**Objective:** To determine the incidence of radiation proctitis in cervical cancer patients after radiation at Dr. Kariadi Hospital, Semarang, Indonesia.

**Materials and Methods:** A descriptive analytic study on 356 cervical cancer patients who received radiation therapy at Dr. Kariadi Hospital Semarang from January 2017 to December 2018 who met the inclusion criteria. Factors assessed included age, BMI, hematologic, stage, histopathology, history of radical hysterectomy surgery and duration of radiation. Cervical cancer staging was assessed using FIGO 2018. Statistical analysis was performed using Mann Whitney with a significant value of  $p < 0.05$ .

**Results:** From the Chi-square analysis, the relationship between radiation period (less than 56 days and more than 56 days) ( $p=0.164$ ), the relationship between age  $\geq 45$  and the incidence of proctitis ( $p=0.208$ ), BMI  $\geq 25$  and the incidence of proctitis ( $p=0.838$ ), Hb  $< 10$  with the incidence of proctitis ( $p=0.492$ ), parity  $\leq 1$  with the incidence of proctitis ( $p=0.137$ ), the relationship between the histopathological examination results with the incidence of proctitis ( $p=0.253$ ), and stage level with the incidence of proctitis ( $p=0.226$ ) were not significant. The highest incidence of proctitis occurred in stage 3B of the cervical cancer patients (14.5%).

**Conclusion:** The prevalence of proctitis in cervical cancer patients for the period 2017-2018 was 15.4%. Age, histopathological appearance, stage, history of anemia, history of radical surgery and appearance of symptoms after surgery with symptoms of proctitis did not show a significant relationship.

**How to cite:** Iskandar M, Cahyono K, Faizal TR, et al. Incidence of radiation proctitis in cervical cancer receiving radiation therapy at Dr. Kariadi Hospital, Semarang, Indonesia. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science)*. 2023;31(3):123-128. doi: 10.20473/mog.V31I32023.123-128.

#### Highlights:

1. Radiation proctitis is a post-radiotherapy concern, urging research to reduce its occurrence and improve the well-being of patients.
2. Radiotherapy is the primary treatment for advanced cervical cancer, offering hope and preserving quality of life for patients.

#### INTRODUCTION

Cervical cancer is an important problem for women, especially in developing countries. Cervical cancer is known as the number one killer disease for women in

Indonesia. In Indonesia, in 2020, there were 213,546 new cancer cases out of 135 million women. Data from Globocan 2020 explains that the mortality rate for cervical cancer in Indonesia reaches 21,003 (9%) of the entire population.<sup>1</sup>



The etiology of cervical cancer is infection with oncogenic HPV subtypes (subtypes 16 and 18). Several factors that can increase the risk of cervical cancer include sexual activity at a young age, sexual activity with multiple partners, smoking, multiparity, sexually transmitted diseases, and immunosuppressant states.<sup>2</sup>

Cervical cancer treatment involves surgery (e.g., cervical conization or radical hysterectomy) and non-operative approaches like chemotherapy and radiation. Selection of treatment depends on the International Federation of Gynecology and Obstetrics (FIGO) stage. Patients in stage IA1 typically undergoes cervical conization, while those in IB1, IB2, IIA1, and IIA2 receive radical hysterectomy with pelvic lymphadenectomy, occasionally followed by postoperative radiation or chemoradiation. Patients in stages IIB-III B generally undergo chemoradiation or radiation, while those in stages IVA-IVB may receive palliative chemoradiation or palliative radiation based on individual circumstances.<sup>3-6</sup>

However, radiation therapy can cause several complications, including radiation proctitis. Radiation with a dose of more than 20 Gy can cause a decrease in ovarian follicular volume and activity so that it can lead to permanent infertility and ovarian dysfunction, ovarian stenosis, and cystitis. Previous studies have shown that the most common complications of radiotherapy for cervical cancer are rectal complications. This was possible because almost all patients were treated with Cobalt-60, with opposing AP/PA planes and subsequent low-dose brachytherapy involving the risk of underpacking (especially the posterior vagina) and displacement of the applicator due to the long treatment time.<sup>7-9</sup> There are several factors that influence the occurrence of radiation proctitis after radiotherapy in cervical cancer, including high doses radiation that can cause damage to cancer cells and one of the most commonly affected is the rectum and the most common is radiation proctitis.<sup>8,10</sup> The objective of this study was to determine the incidence of radiation proctitis in cervical cancer patients after radiation at Dr. Kariadi Hospital, Semarang, Indonesia.

## MATERIALS AND METHODS

This was a descriptive analytic study with analytical work on 356 cervical cancer patients who received radiation therapy at Dr. Kariadi Hospital Semarang from January 2017 - December 2018 who met the inclusion criteria. The inclusion criteria included being diagnosed with cervical cancer based on histopathological examination and internal examination, having been diagnosed as a patient with cervical cancer based on

vaginal touch examination, having completed 25 times external rays and three times inner rays or according to the full radiation dose (after complete radiation) and there were no complaints of blood stools (haematochezia) after complete radiation which had been confirmed by colonoscopy examination. The exclusion criteria were cervical cancer patients who did not receive radiation therapy, cervical cancer patients who received radiation therapy but not complete, patients who were not examined at the time of definitive therapy, patients who died, and patients with incomplete data.

Factors assessed included age, BMI, hematologic, stage, histopathology, history of radical hysterectomy surgery and duration of radiation. Cervical cancer staging was assessed using FIGO 2018.

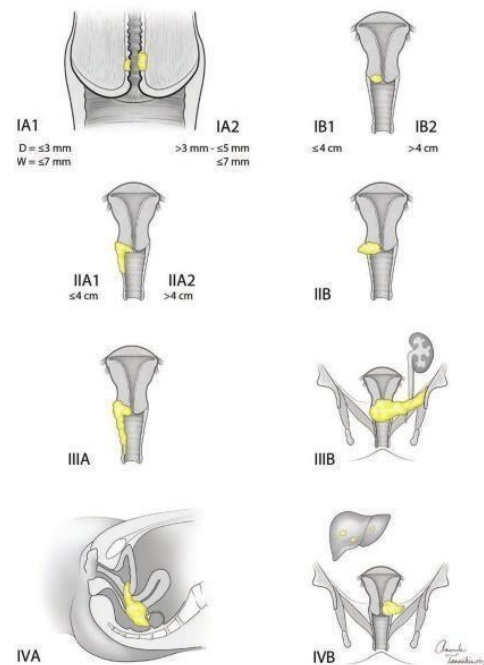


Figure 1. Cervical cancer staging based on FIGO 2018.<sup>5</sup>

Univariate analysis was carried out to see the characteristics. Bivariate analysis was performed to see the relationship between characteristic factors and the incidence of radiation proctitis. Data processing and analysis used SPSS program for computer. The value was considered significant if  $p < 0.05$ .

## RESULTS AND DISCUSSION

From the data collection of cervical cancer patients who searched for treatment at Dr. Kariadi Hospital Semarang

in 2017 and 2018, there were a total of 1274 patients. From these 1274 patients, only 356 patients met the inclusion and exclusion criteria in this study. The characteristics and results of the research data analysis are shown in Table 1.

Bivariate test between mean age, histopathological appearance, stage, history of anemia, history of radical surgery and appearance of symptoms after surgery with symptoms of proctitis did not show a significant relationship ( $p > 0.05$ ).

From the Chi-square analysis, the relationship between radiation period of less than 56 days and more than 56 days showed  $p=0.164$ , the relationship between age 45 and the incidence of proctitis ( $p=0.208$ ), BMI  $\geq 25$  and the incidence of proctitis ( $p=0.838$ ), Hb  $< 10$  with the incidence of proctitis ( $p=0.492$ ), parity  $\leq 1$  with the incidence of proctitis ( $p=0.137$ ) and the relationship between the results of histopathological examination and proctitis incidence ( $p=0.253$ ) all were not significant.

From these results, none of the 7 patients in the small cell and clear cell groups had proctitis. Results of Chi-square test of operated cervical cancer patients revealed  $p=0.799$ , while stage level with incidence of proctitis had  $p=0.226$ . Of the 356 patients included in this study, the highest incidence of proctitis occurred in stage 3B cervical cancer patients, comprising 39 patients (14.5%).

Table 1. Characteristics and results of research data analysis

No	Variables	n (%)	Mean $\pm$ SD	p
1	Patients' age	356 (100%)	53.73 $\pm$ 0.5	
2	Histopathological type			0.827
	Epidermoid Ca	166 (46.6%)		
	Cervical Adeno Ca	44 (12.4%)		
	Cervical Adeno Squamous Cell Ca	139 (39%)		
	Small Cell Cervical Ca	3 (0.8%)		
	Clear Cell Cervical Ca	4 (1.1%)		
3	Stages			0.356
	Stage 1 B	7 (2%)		
	Stage 2 A	4 (1.1%)		
	Stage 2 B	63 (17.7%)		
	Stage 3 A	2 (6%)		
	Stage 3 B	269 (75.6%)		
	Stage 4 A	3 (0.8%)		
	Stage 4 B	8 (2.2%)		
4	History of Anemia			0.632
	Anemia	55 (15.44%)		
	No Anemia	301 (84.55%)		
5	Average parity			0.682
	0	10 (2.8%)		
	1	28 (7.9%)		
	2	115 (32.3%)		
	3	102 (28.7%)		
	4	56 (15.7%)		
	5	26 (7.3%)		
	6	10 (2.8%)		
	7	4 (1.1%)		
	8	5 (1.4%)		
6	Previous radical operation			0.226
	Yes	11 (15.4%)		
	No	345 (84.6%)		
7	Proctitis			
	Yes	55 (15.4%)		
	No	301 (84.6%)		
8	Duration of radiation			0.699
	$\leq 56$ days	61 (17.13%)		
	$> 56$ days	295 (82.8%)		
9	Body mass index	356 (100%)	22.29 $\pm$ (4.53)	0.24

Table 2. The relationship of independent variables with the incidence of proctitis

Independent variables	Dependent variables (Proctitis)		Significance (X <sup>2</sup> )	
	Yes	No		
Duration of Therapy (days)	$< 56$	8	53	0.164
	$> 56$	47	248	
Age	$\geq 45$	50	254	0.208
	$< 45$	5	47	
BMI	$\geq 25$	12	62	0.838
	$< 25$	43	239	
Hb	$< 10$	25	152	0.492
	$\geq 10$	30	149	
Parity	$\leq 1$	9	29	0.137
	$> 1$	46	272	
Histopathology	Epidermoids and cervical adeno ca	47	294	0.253
	Small cell and clear cell	0	7	
Operation	Yes	2	9	0.799
	No	53	292	
Stages	Stage 1B	0	7	0.226
	Stage 2A	2	2	
	Stage 2B	12	51	
	Stage 3A	1	1	
	Stage 3B	39	230	
	Stage 4A	0	3	
	Stage 4B	1	7	



In this study, 918 (72%) data could not be included in the study because the data were incomplete. The analysis was made only to 28% of all existing patients. Besides, in daily life not all patients who came with complaints of haematochezia and melena underwent colonoscopy.

In patients with early-stage cervical cancer, surgery is performed and then the radicality of the operation and the results of anatomic pathology are assessed or adjuvant therapy is given in the form of radiation or a combination of chemoradiation if necessary. Meanwhile, for advanced cervical cancer, chemo-radiation is performed, the external radiation and intracavitary radiation/brachytherapy. The dose of external radiation or External Beam Radiotherapy (EBRT) is given in the range of 40-60 Gy, with fractional administration at a dose of 1.8 – 2 Gy per day. For the administration of brachytherapy, 7 Gy per administration was used.<sup>11,12</sup>

At Dr. Kariadi Hospital, Semarang, Indonesia, brachytherapy is given 3 times with a dose of 7 Gy each with an interval of 1 week. While external radiation was given 2 Gy every day for 5 times every week. Several devices are used for radiation therapy. The advantages of 3D and IMRT are that targets and organs at risk can be determined more precisely, because radiation planning is done with a CT simulator. Whereas, if we use 2D tool, the simulator uses bone landmarks, so that targets and risk organs are determined from existing imaging results or determined from general anatomical locations.

From the results of this study, the minimum age was 30 years, and the highest age was 98 years. In a study by Soebagyo (1992), it was found that the 41-45 year-age group mostly underwent radiation therapy, where 32.1% received external radiation and 23.2% received radium. In a study by Widaya and Mirza (2012), the average age of patients with stage IIB - IIIB was 48 years, while the average age of cervical cancer patients who experienced recurrence was 51.49.<sup>10</sup> From this study, it can be seen that there was a shift in the average age, where in 1992 the average age of cervical cancer was 40.5 and the average age in 2021 was found to increase to 48 years and in this study it was 53 years. This can be used as an evaluation that the age shift is increasing, and it is assumed that there is an increase in life expectancy and problems with early detection.

According to Juergen et al. (2003), Hb level during radiotherapy is the strongest prognostic factor to describe local control and life expectancy.<sup>13,14</sup> Meanwhile, according to Pablo et al. (2016), anemia and examination of IHC, Growth-1 and HK-II will

describe the response to therapy and are associated with low life expectancy.<sup>15</sup>

In this study, the mean Hb level was 10.13 (SD 4.20). At Dr. Kariadi Hospital, the Hb standard used was 10. This study only observed the effect of radiation on the incidence of anaemia, instead of the success of therapy and the survival of the cervical cancer patients. In previous research in 1992, most clinical stages were in stage IIB, where the external radiation group was 55.4% and the radium group was 44.8%, while those in stage IB was quite a lot, as much as 16.1% and 25.6%. Those in stage IIA were as much as 5.35% and 12.8%. For stage III the percentages were 17.9% and 16.8%. For stage IV, it was 5.35% and 0% (p <0.01).<sup>15</sup>

Meanwhile, in a study at Dr. Kariadi Hospital (2012), there was a shift in the number of cervical cancer patients where most of the patients (76.2%) was in stage IIIB. In this study, the most stages were in stage IIIB, as many as 269 patients (75.6%). Interestingly, the study in 1992 found many patients in stage IB (16.1%), while this study obtained those in stage IB as much as 2% (7 cases).<sup>15</sup>

In this study, the most common histopathological type was squamous type, which was found in 166 cases (46.6%), not much different from adenosquamous type of 139 cases (39%). There was no significant relationship between the type of histopathology with the incidence of radiation proctitis.

In general, this type of histopathology is associated with the success rate of therapy. At Dr. Kariadi Hospital in 2012 there were 61.4% of resident cases with normal BMI status.<sup>13</sup> In this study, the mean BMI of 22.29 was still classified as normal. If we observed the body mass index only, there would be no shift for 3 decades in cervical cancer patients managed at Dr. Kariadi Hospital. In a study at the hospital in 2012 it was found that there was a significant relationship between radiation duration and anemia, where anemia increased the incidence of recurrent uterine cervical cancer. From this study, there was no significant relationship between the incidence of proctitis and BMI.<sup>13</sup>

A study showed that the recommended duration of radiotherapy is in a maximum of 55 days,<sup>15</sup> while other studies found no significant difference in life expectancy for total radiation less than 8 weeks and more than 8 weeks, and the lengthening of the total duration of radiation is a prognostic factor for poor outcomes in cervical cancer patients, where the ideal duration limit is less than 56 days.<sup>16,17</sup>

In this research, only 17.13% (61 patients) received radiotherapy for less than 56 days. When examining the association, the duration of radiation showed a statistically non-significant correlation with the occurrence of radiation proctitis. Further investigation is needed to explore the relationship between radiation duration and proctitis incidence in this study, while the proctitis rate was 15.4% when the radiation period exceeded 56 days.

Radiation proctitis is a condition in the gastrointestinal tract caused by the radiation process in the management of cervical cancer, characterized by the presence of haematochezia and or melena. Colonoscopy examination is required to determine the presence of proctitis, indicated by hyperaemic and telangiectatic surfaces of the digestive tract found.<sup>18,19</sup>

The radiation tolerance dose from the gastrointestinal tract, large intestine and rectum is 60-80 Gy. The pathogenesis of radiation proctitis is not known with certainty. Initially there will be mucosal injury accompanied by slow growth and tissue remodelling and then ischemia occurs. Intestinal crypt damage cannot be replaced by surface epithelial cells which are expected to produce involution crypts, resulting in mucosal injury and in the lamina propria of the intestine, an inflammatory reaction occurs which will involve T lymphocytes, macrophages, and neutrophils. Furthermore, there will be degradation of the sub-mucosa, so that there will be interference with the formation of enzymes and reactive oxygen metabolites. After the radiation is complete, regeneration will occur so that the mucosa is filled again.<sup>20,21</sup>

This study had several limitations, where the data collection system was obtained from incomplete and inconsistent medical records. In addition, there were patients whose management of radiation proctitis due to cervical cancer was not one-way. Data on the type of equipment used for radiation was not included, so that this study only observed the prevalence. Finally, there was no standard management of radiation proctitis cases, with the result that not all patients with complaints of melena or hematoschizia were confirmed with colonoscopy or endoscopy.

## CONCLUSION

The prevalence of proctitis in cervical cancer patients for the period 2017-2018 was 15.4%. Patients' age, histopathological appearance, stage, history of anemia, history of radical surgery and symptoms of proctitis did not show a significant relationship. The continuation of this research would improve cervical cancer manage-

ment services and can better understand the effects of radiation on healthy organs, especially the gastrointestinal tract. Many cases of radiation proctitis cases marked by the presence of hematoschizia by colonoscopy examination will become a problem in the management of post-radiation cervical cancer. The onset of hematoschizia is only the beginning of the occurrence of radiation proctitis which will subsequently become more severe to illeus and even rectovaginal fistula. The clinical occurrence of this radiation proctitis must be able to be diagnosed in the early stages and the causative factors should have been recognized inherent from the source of the output of radiotherapy devices. The presence of complaints of abdominal pain, diarrhea, haematochezia, and melena should be followed up with a colonoscopy or endoscopy, so that the side effects of radiation, the radiation proctitis, can be identified.

## DISCLOSURES

### Acknowledgment

We are grateful to all patients who came from Dr. Kariadi General Hospital Medical Center Semarang and Satellite Hospital in Central Java, Indonesia.

### Conflict of interest

The authors declare that they have no competing interests. that may be perceived as inappropriately influencing the representation or interpretation of reported research results.

### Funding

This study was funded by private funding

### Author contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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## SYSTEMATIC REVIEW

### The role of stem cells in obstetrics and gynecology: A systematic review

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Article Info	ABSTRACT
<p>Received May 2, 2023 Revised Jun 8, 2023 Accepted Jun 16, 2023 Published Dec 1, 2023</p> <p><b>*Corresponding author:</b> Legiran dr.legiran@fk.unsri.ac.id</p> <p><b>Keywords:</b> Amniotic fluid stem cells Gynecology Bone marrow stem cells Mesenchymal stem cells Obstetrics Stem cells Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p><b>Objective:</b> This study aimed to review the role of stem cells in obstetrics and gynecology.</p> <p><b>Materials and Methods:</b> This review used several databases, the PubMed, Wiley Online Library, and ScienceDirect to search open access original and review articles in English related to stem cells, obstetrics, and gynecology in the last 10 years. The results were analyzed qualitatively.</p> <p><b>Results:</b> Out of 1,016 records identified through database searching, fifteen articles were eligible for review. Several articles reported the role of stem cells in endometrium repair. Stem cell can also increase endometrial thickness and increase the likelihood of pregnancy. In the field of gynecology, stem cells can be used as potential treatment for stress urinary incontinence and anal incontinence. Despite of all those abilities, stem cells might have errors, such as chromosomal abnormalities, epigenetic and genetic defect, which could potentially turn the stem cells into tumor initiating cells (TICs), thus can contribute to ectopic growth of endometrium (endometriosis), leiomyoma, leiomyosarcomas, and adenomyosis.</p> <p><b>Conclusion:</b> Stem cell technology has various roles in the field of obstetrics and gynecology, including fertility study as well as tissue damage repair. However, in-depth research to ensure the safety profile of stem cells technology use in human is necessary.</p>

**How to cite:** Mirani P, Legiran, Kesty C, et al. The role of stem cells in obstetrics and gynecology: A systematic review. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science)*. 2023;31(3):129-138. doi: 10.20473/mog.V31I32023.129-138.

#### Highlights:

1. Stem cell technology has various roles in the field of obstetrics and gynecology, including fertility study as well as tissue damage repair.
2. Safety profile of stem cells technology use in human still need to be assessed.

## INTRODUCTION

Stem cells are a type of undifferentiated cell that can multiply indefinitely (self-renewal), starting from a single cell (clonal), and differentiate into a variety of cells and organs (potent).<sup>1,2</sup> Stem cells are unique to a particular variety of cell or tissue because they have not yet formed specific structures or proteins.<sup>3</sup> Stem cells have the capacity to differentiate while still having the capacity for self-replication and keeping the properties of progenitor cells. A cell is referred to as totipotent if it has the ability to split and develop into any embryonic cell as well as any extraembryonic cell, according to the spectrum of cell potential. For instance, a totipotent cell in human growth develops from an embryo, which is also a totipotent cell. With fertilization, the zygote splits, and the identical daughter cells maintain their totipotency up until the blastocyst is created. The bulk of the cell starts to divide at this point, and the cells that follow are categorized as pluripotent cells.<sup>4</sup>

Stem cells derived from the ever-increasing requirement to replace or regenerate damaged tissue caused by age-associated or degenerative conditions, trauma, tumors, and birth defects. Reconstructing damaged tissues with differentiated cells collected from biopsy, expanded in vitro, and implanted on artificial and/or natural scaffolds is the primary choice in regenerative therapy. The differentiated cells have the appropriate phenotype to carry out the desired biological functions. In spite of that, its use for tissue engineering is frequently constrained by the small number of harvested cells as well as their low proliferative capacity in vitro. Following this, advanced regenerative therapies concentrate on stem cells can be used for direct application to injured sites for tissue engineering, using appropriate scaffolds to transport these cells.<sup>5</sup>

Embryonic stem cells (ESCs) as well as tissue-derived (somatic) stem cells are the two principal cell types based on origin. Further classifications of tissue-derived stem cells include fetal stem cells, adult stem cells, as well as induced pluripotent stem cells.<sup>4,6,7</sup>

In obstetrics and gynecology, stem cell research has been conducted under various conditions. The treatment of pelvic floor prolapse, stress urinary incontinence, as well as vaginal and uterine reconstruction are these conditions. Other research has examined stem cell therapy for primary ovarian insufficiency.<sup>8,9</sup> In addition, there are studies utilizing stem cell therapy to treat endometrial disorders such as endometrial atrophy and Asherman's syndrome.<sup>10,11</sup> The outcomes of these diverse studies vary; some are fruitful and promising, while others are inconclusive.<sup>12</sup> Therefore, this review

aimed to find evidence regarding the role of stem cells in obstetrics and gynecology.

## MATERIALS AND METHODS

This review used the help of several databases, the PubMed, Wiley Online Library, and ScienceDirect (Table 1). Articles search were carried out in the mid-March to early April 2023. Inclusion criteria consisted of all articles in English, both research and review, related to the topic of the review (stem cell and obstetrics and gynecology), and open access. The exclusion criteria were unrelated research and results, incomplete data, and articles in languages other than English. The articles included in this research were those from the last 10 years.

The basic characteristics of the research are displayed in a tabular form (Table 2). Review and extraction of the contents of the article are presented in the form of a narrative and presented in the discussion section.

The articles included in this review had been guaranteed for quality. Each article had been confirmed and reviewed in the journal with the help of Scimago Journal Rankings. Each article was then assessed for validity with the help of the NIH Quality Assessment Tool. In searching for articles and assessing them, the authors avoided bias that could be caused by authors, affiliations, sponsors, regions, and journals, thus the focus was on the articles' quality.

## RESULTS AND DISCUSSION

From the search conducted, a total of 1,016 articles were included in this review. After that, deduplication was carried out, and 64 duplicate articles were obtained. After further screening, 21 articles were found that matched the research inclusion criteria. After reading the full text to see if the contents of the articles obtained were appropriate and included in the review, there were 15 articles that matched the topic of the review, so 6 articles were excluded.

The reasons for article exclusion were: it was not in accordance with the purpose of this review (n=5), and one was an editorial article. The article search flowchart for this review is shown in Figure 1. Of the 15 studies obtained, there were eleven review articles, two research articles, one prospective article study, and one experimental article.

Table 1. Search queries of this literature review

Databases	Search queries	Hits
PubMed	("Stem Cell") AND ("Obstetric") and ("Stem Cell") AND ("Gynecology")	154
Wiley Online Library	(Stem cell AND Obstetrics) and (Stem cell AND Gynecology)	852
ScienceDirect	Stem cell, Obstetrics, Gynecology	10

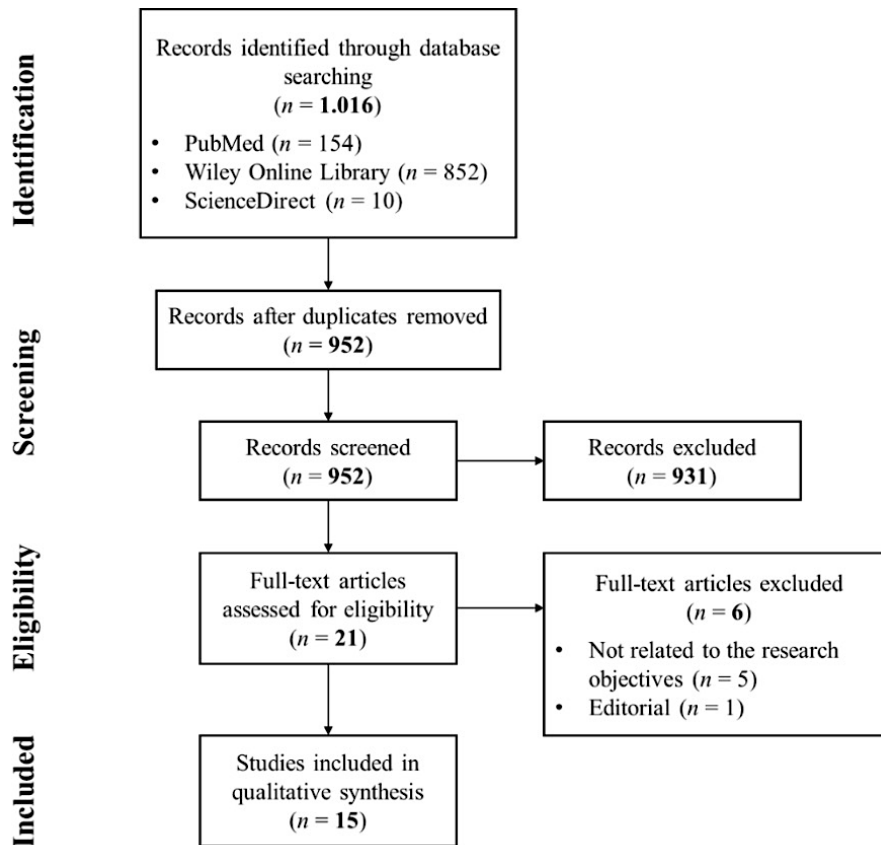


Figure 1. Flow diagram of article selection

Table 2. Study characteristics and findings

First Author (Years)	Titles	Types	Findings
Lane FL (2012) <sup>13</sup>	"Stem cells in gynecology"	Review article	<ul style="list-style-type: none"> <li>Mesenchymal and muscle-derived stem cells used in urinary and anal incontinence treatment to engraft after transplantation. It also has bulking effect, elicit trophic effect on the host, and can modulate inflammation, which improve histological, functional, and clinical outcomes.</li> <li>Existing data support the potency of stem cell transplantation for pelvic floor disorder treatment, fistula repair, graft material improvement, as well as vaginal tissue engineering.</li> </ul>
Hanna CB (2014) <sup>14</sup>	"Ovarian germline stem cells: An unlimited source of oocytes?"	Review article	<ul style="list-style-type: none"> <li>There is evidence that germline stem cells (GSCs) can self-renew and survive in oocyte development.</li> </ul>



Mutlu L (2015) <sup>15</sup>	“The Endometrium as a Source of Mesenchymal Stem Cells for Regenerative Medicine”	Review article	<ul style="list-style-type: none"> <li>The endometrium can be a source of non-embryonic stem cells with remarkable differentiation capacity.</li> <li>Endometrium-derived stem cells are capable of differentiating into neuronal phenotypes (dopamine producing cells, oligodendrocyte-like cells, cholinergic neuron-like cells), megakaryocyte-like cells, cardiomyocyte-like cells, urothelial cells, insulin producing cells, and other mesenchymal cell types.</li> </ul>
Dziadosz M (2016) <sup>16</sup>	“Human amniotic fluid: A source of stem cells for possible therapeutic use”	Review article	<ul style="list-style-type: none"> <li>Amniotic fluid stem cells easy retrieval, high proliferation rate, differentiation potential into all embryonic germ cell layers and stability of both genetics and phenotype.</li> </ul>
Edessy M (2016) <sup>8</sup>	“Autologous Stem Cells Therapy, The First Baby of Idiopathic Premature Ovarian Failure”	Prospective study	<ul style="list-style-type: none"> <li>Stem cell therapy and transplantation in premature ovarian failure (POF) is a good procedure in hope of a healthy pregnancy and baby, and showed good clinical, histopathology, and immunohistochemical outcome.</li> </ul>
James JL (2016) <sup>17</sup>	“Stem Cells and Pregnancy Disorders: From Pathological Mechanism to Therapeutic Horizons”	Review article	<ul style="list-style-type: none"> <li>Stem cells are being used for early pregnancy disorder (infertility problem, Asherman’s syndrome).</li> <li>Stem cell treatment appears most promising in placental pathologies such as placental infarction, chronic villitis, and FGR.</li> </ul>
Hamid AA (2017) <sup>18</sup>	“Highly potent stem cells from full-term amniotic fluid: A realistic perspective”	Review article	<ul style="list-style-type: none"> <li>Amniotic fluid derived stem cells have high differentiation potential, rapid expansion, and low immunogenic properties, and have multiple possible application including neural, cardiac, lung epithelial, kidney, bone, and cartilage regeneration.</li> </ul>
Mohamed SA (2017) <sup>19</sup>	“Human Mesenchymal Stem Cells Partially Reverse Infertility in Chemotherapy-Induced Ovarian Failure”	Research article	<ul style="list-style-type: none"> <li>Intraovarian administered bone marrow mesenchymal stem cells (BMSCs) are able to restore ovarian hormone production and reactivate folliculogenesis in chemotherapy-induced ovarian failure mouse model.</li> </ul>
Azizi R (2018) <sup>10</sup>	“Stem cell therapy in Asherman’s syndrome and thin endometrium: Stem cell-based therapy”	Review article	<ul style="list-style-type: none"> <li>Transplantation of different stem cells with a diverse source in the endometrial zone can reduce fibrotic area. It also resulted in increased number of glands, angiogenesis stimulation, endometrium thickness enhancement, better formed tissue construction, as well as increased pregnancy rate.</li> </ul>
He Y (2018) <sup>9</sup>	“The therapeutic potential of bone marrow mesenchymal stem cells in premature ovarian failure”	Review article	<ul style="list-style-type: none"> <li>Bone marrow stem cells are a good candidate for transplantation in premature ovarian failure (POF) because bone marrow stem cells can migrate to the injured ovary and secrete crucial cytokines that function as anti-inflammation, antifibrosis, antiapoptotic, and immunoregulation, which improves ovarian function.</li> <li>However, current therapeutic ratio in clinical trials can ensure ovarian reserve recovery in patients with POF.</li> </ul>
Santamaria XM (2018) <sup>20</sup>	“Uterine stem cells: from basic research to advanced cell therapies”	Review article	<ul style="list-style-type: none"> <li>Endometrial stem cells used in therapy of Asherman’s syndrome as well as endometrial atrophy.</li> <li>There is potential use of myometrium stem cells, but it has drawback, such as developmental errors such as chromosomal abnormalities and genetic and epigenetic defect, could promote the developmental of tumor initiating cells (TICs) and thus contribute to myometrial tumors such as leiomyoma, leiomyosarcoma.</li> </ul>
Hu J (2019) <sup>11</sup>	“Effects of menstrual blood-derived stem cells on endometrial injury repair”	Experimental (in vitro)	<ul style="list-style-type: none"> <li>Model mice treated with menstrual blood stem cells exhibited increased endometrial thickness and increased the pregnancy rates.</li> <li>By stimulating the expression of vimentin, VEGF, and keratin, stem cells derived from menstrual blood may facilitate the repair of endometrial lesions in rodents.</li> </ul>
Sarma UC (2019) <sup>21</sup>	“Oocyte from stem cells”	Review Article	<ul style="list-style-type: none"> <li>The use of oogonial stem cells (OSCs) and embryonic stem cells (ESCs) for the production of new oocytes to repopulate follicle-depleted ovaries is a prospective of stem cells application for fertility preservation.</li> </ul>
El Sabeh M (2020) <sup>22</sup>	“Uterine stem cells and benign gynecological disorders: Role in pathobiology and therapeutic implications”	Review article	<ul style="list-style-type: none"> <li>Stem cells enhanced the proliferation and renewal of normal or injured endometrium, but they also have the ability to cause ectopic endometrial growth (endometriosis), uterine leiomyoma, and adenomyosis.</li> </ul>
Zhang Y (2021) <sup>23</sup>	“Mesenchymal stem cell transplantation for vaginal repair in an ovariectomized rhesus macaque model”	Research article	<ul style="list-style-type: none"> <li>The content of collagen I, elastin, and microvascular density in the lamina propria of the vagina increased significantly in the MSC group compared with the saline group. And the fraction of smooth muscle in the muscularis of vagina increased significantly in the MSC group.</li> <li>In addition, MSC transplantation improved the biomechanical properties of the vagina by enhancing the elastic modulus.</li> </ul>

Reproductive tissues are currently acknowledged as source of progenitor cell or SCs. Stem cells originated from reproductive tissues have been widely studied for their possible use in other areas, for example, hematological disease treatment as well as bone tissue engineering.<sup>24</sup> In short, stem cells possess the capacity to undergo self-renewal or multiple cell divisions but still remains undifferentiated. Multipotency is defines as the ability to differentiate into any types of mature cell. Morula-derived totipotent SCs are able to differentiate into both embryonic and also extraembryonic cell types. It can also generate a viable and complete organism. Pluripotent SCs are derived from totipotent cells. Pluripotent SCs can differentiate into any type of germ layers' tissues, including embryonic tissues, i.e. umbilical cord, amniotic fluid cells, amnion, and placenta). Being derived from the interior cell mass of a blastocyst, embryonic stem cells are pluripotent. Multipotent SCs, e.g. mesenchymal and hematopoietic SCs, differentiate into multiple tissues originating from a single embryonic layer. Unipotent cells, such as muscle satellite cells, produce only their own cell type but have a greater capacity for self-renewal compared to fully mature cells. Theoretically, the more rudimentary or "potent" the SC, the greater its propensity for unrestrained cell division and oncogenic potential. However, there are some issues about the oncogenic potential of pluripotent SCs like embryonic and induced pluripotent SCs, that is the non-pluripotent cell sources are not inherently oncogenic.<sup>24</sup>

Embryonic SCs offer a potential treatments for regenerative diseases, despite the controversy surrounding their sources, which has slowed progress in this area. Nonetheless, multipotent SCs are currently being isolated from a variety of fetal tissues, which currently are easily obtained from the specimens of diagnostic tests during pregnancy termination and delivery. In the field of regenerative medicine, in order to heal or restore damaged or diseased urogenital tract organs (i.e. urinary sphincter, pelvic floor, vagina, uterus, and ovary), SCs are present in both the preclinical as well as clinical phases of research. In obstetrics researches, SC transplantation has been concentrated primarily on fetal therapy.<sup>24</sup>

Over the past decade, embryonic, fetal, and extrafetal tissues, as well as adult gonads, have been used to isolate stem cells. The inner cell mass of the blastocyst is the origin of extra-fetal tissues such as placenta and amniotic membranes. They contain a heterogeneous population of progenitor cells, presumably due to their shared origin. This consists of hematopoietic, trophoblastic, mesenchymal, and possibly even more primitive SCs. Despite the fact that the composition of amniotic fluid varies with embryonic health and

gestational age, mesenchymal SC can be consistently isolated at any gestational age. Amniotic fluid and placental mesenchymal SC have been demonstrated to differentiate into the majority of mesodermal cell types, but also can differentiate into ectodermal and endodermal cell types.<sup>25</sup> Other cell types, such as a population of CD-117 positive cells, have been isolated from amniotic fluid. They express pluripotential markers and perform self-renewal up to more than 50 population doublings, with the same telomere length. Their use as allogeneic and autologous cell sources is currently being studied in the field of regenerative medicine. To do so, supportive facility dedicated to their characterization, immunogenicity, as well as storage, is necessary.<sup>26</sup>

From numerous fetal tissues, embryonic SCs have been isolated. Early gestational HSC from liver and bone marrow are well-characterized,<sup>27</sup> whereas placental HSC have only been studied relatively recently.<sup>28</sup> Primitive human fetal mesenchymal SC (hfMSC) collected from all parts of the developing fetus with higher proliferative ability express more telomerase with longer telomeres than their adult counterparts.<sup>29-31</sup> In addition, hfMSC can differentiate rapidly into muscle and neuronal lineages. Moreover, compared to later perinatal and adult sources of MSC, they have also been demonstrated to have more robust differentiation down the osteogenic lineage, and thus indicating their potential for bone tissue engineering in postnatal applications.<sup>32</sup> Primitive hfMSCs are rapidly transduced through the integration of vectors. They do not express HLA-II nor CD80 and CD86 costimulatory molecules, suggesting their applicability for gene therapy as well as their allogeneic use ex vivo.<sup>33,34</sup>

Blood remaining within the umbilical cord as well as placenta following delivery was routinely disposed until recently. Now that it is known that this blood contains both hematopoietic stem cells and pluripotent mesenchymal cells, clinical application as well as the investigation of umbilical cord blood in hematopoietic transplantation as well as regenerative medicine have significantly increased.<sup>35</sup>

Historically, it has been recognized that umbilical cord blood contains hematopoietic SCs with the capacity to produce clonogenic progeny. Knudtzon first confirmed the presence of hematopoietic clonogenic cells in in vitro cord blood in 1974.<sup>36</sup> Broxmeyer and associates confirmed the presence of hematopoietic stem cells in cord blood in a report published in 1989.<sup>37</sup> Additional research confirmed their clonogenic potential, capacity for self-renewal, and expansion in vitro.<sup>38,39</sup> The umbilical cord remains was deemed to have no scientific value. In 2004, it was determined that these



cells were MSCs as they expressed CD105, CD73, CD51, CD44, and CD29, lacked CD45 and CD34 expression. Other than that, they are also able to transform into adipogenic and osteogenic cells. As for now, umbilical cord MSCs can be originated from the entire or parts of umbilical cord, including perivascular, intervacular, and subamniotic zones of subendothelial layer, as well as Wharton's jelly.<sup>40</sup>

Human embryo becomes affixed to the developing placenta via a stalk in the third week of gestation. During 5th week, primitive umbilical cord takes the form of an umbilical ring. At 10th week, after gastrointestinal maturation in the neonate, the umbilicus appears as a fistula connecting to the umbilical cord.<sup>41</sup>

Wharton's jelly is an elastic and gelatinous matrix composed of mucopolysaccharides, primarily chondroitin sulphate and hyaluronic acid that protects the umbilical cord epithelium. Wharton's fluid, along with amnion, shield three blood vessels that are important for fetal and embryonic development. A single large umbilical vessel provides placental blood, which is abundant in nutrients and oxygen, to develop fetus. In the final trimester, it also provides the mother's vital antibodies. A pair smaller umbilical vessel return blood containing carbon dioxide, pollutants, and other contaminants from the fetus.<sup>41</sup>

Blood in the umbilical vessels, vessel walls, and Wharton's fluid can provide stem cells from the umbilical cord. Cord blood is usually collected at delivery using a sterile collection container containing an anticoagulant (typically citrate or heparin) and one or more collecting needles. It can be collected intrauterine or extrauterine, in both spontaneous deliveries and caesarean sections, without causing suffering to the mother or child.<sup>41</sup> Typically, the units are transported to a laboratory for cell separation in order to isolate the buffy coat and/or stem cell-rich cell preparations. There are numerous ways to extract cells from cord blood, including centrifugal elutriation, starch-based methods, rouleaux formation, as well as density-gradient methods.<sup>42-44</sup>

The HSC population within UCB has a greater capacity to proliferate and differentiate than HSC obtained from bone marrow as well as peripheral blood. Moreover, it is simpler to collect UCB because it poses fewer risks to the maternal donor, has a lower risk of infection, is readily available, and the Human Leukocyte Antigen (HLA) typing criteria are less stringent, resulting in less graft-versus-host disease.<sup>45-47</sup>

Mesenchymal stem cells (MSCs) are in fact multipotent adult stromal cells with the capacity to differentiate into

various cell lineages. The Umbilical Cord MSCs (UCMSCs) are one of the most desirable sources of MSCs for clinical applications. UCMSCs have a superior capacity for differentiation, migration, and self-renewal compared to other types of MSCs and can be collected invasively. There is mounting evidence that UCMSCs aid in the restoration of damaged endometrium. In a rodent model, for instance, UCMSC transplantation recovers endometrial thickness and reduces excessive fibrosis. These UCMSCs strengthen the endometrial response towards hormones as well as endometrial proliferation and angiogenesis. Moreover, endometrial stromal cells (ESCs) serve as an important cellular component within the endometrium essential for the endometrium's normal physiological functions. These ESCs are involved in implantation as well as the maintenance of pregnancy.<sup>48</sup>

From several journals obtained through database searches, we obtained several findings related to stem cells in the field of obstetrics and gynecology. The first was the potential for direct use of stem cells in obstetric and gynecological diseases. The second was the use of stem cells sourced from the fields of obstetrics and gynecology.

Several articles showed the benefit of stem cells to repair the endometrium. Gargett's article discussed adult stem cells and bone marrow-derived stem cells in human endometrium. The adult stem cells are clonogenic cells, tissue-reconstructing cells, side population cells, and menstrual blood stem or progenitor cells. Bone marrow-derived SCs include hemopoietic, mesenchymal, and endothelial progenitor cells that circulate in small numbers in injured tissues. These evidences suggest the presence of human endometrial stem cells that can be activated for cases of dysfunctional thin endometrium or atrophic endometrium. In addition, stem cells can be transplanted to treat Asherman's syndrome.<sup>13,19</sup> The same finding was found in the article by Azizi, which stated that several studies were performed for the regeneration of human endometrium, and it was found that stem cells (from various sources, adult stem cells, such as menstrual blood stem cells and bone marrow) can increase the number of menstrual volume and endometrial thickness in Asherman's syndrome.<sup>10</sup> Research by Hu (2019) showed that SCs can increase endometrial thickness and increase the likelihood of pregnancy, using menstrual blood-derived SCs under in vitro conditions.<sup>11</sup> A study by Santamaria also stated the same, that endometrial SCs can be used in Asherman's syndrome and endometrial atrophy.<sup>20</sup> Another article was written by Zhang et al. that evaluated how mesenchymal stem cell (MSC) therapy can repair weak vaginal tissue in an ovariectomized rhesus macaque

model. This study found that vaginal MSC transplantation could repair the weak vaginal tissue by promoting extracellular matrix ingrowth, neovascularization, and smooth muscle formation and improve the biomechanical properties of the vagina, providing a new prospective treatment for POP.<sup>23</sup>

Although the rigorous mechanism is not entirely understood; mesenchymal stem cells (MSCs) can be used in allogeneic transplantations without immunosuppressive therapy. MSCs secrete a plethora of immune-modulating cytokines, such as Interleukin-10 and Transforming Growth Factor  $\beta$  (TGF- $\beta$ ), that create an immune-suppressed zone around the area of MSCs implantation. Whereas, the administration of MSCs has been shown to improve the clinical symptoms of graft-versus-host disease in clinical trials. It has demonstrated that spectrum of reproductive dysfunction can be treated by allogeneic BMSCs.<sup>19</sup> Apart from endometrium and thickening repairing, stem cells have also been tried to treat Premature Ovarian Failure (POF). Edessy et al. (2016) conducted a trial with patients suffering from premature ovarian failure. Bone marrow stem cells were injected into the ovaries via laparoscopy, then the patients were followed up every month for hormonal, clinical, and pregnancy checks. It was found that stem cell transplantation can improve the hormone profile of patients with premature ovarian failure, and restore menstruation and even patients can get pregnant and give birth at term. Histopathological and immunohistochemical examinations can also show an increase in the results, from atrophic endometrium to secretory endometrium and good glandular function.<sup>8</sup>

An article by He (2018) also discusses a similar issue on the bone marrow stem cells (BMSCs) transplant for the treatment of POF. These BMSCs are adult SC with low immunogenicity, mostly located in the bone marrow. The advantages of BMSCs are that they are easy to isolate and propagate in vitro. These cells can also migrate to the site of tissue injury, due to their paracrine and immunomodulating properties, and differentiate into specific cell types by induction of various factors that mimic the environment surrounding the damaged tissue. In addition, BMSCs have antiapoptotic, antifibrotic effects, angiogenesis, anti-inflammatory, and immunoregulation. Thus, these BMSCs have become good candidates for transplantation into POF patients, despite their current drawbacks.<sup>9</sup> The same results are found in Mohamed's article that intraovarian-administered BMSCs are able to restore ovarian hormone production and reactivate folliculogenesis in chemotherapy-induced ovarian failure mouse model.<sup>19</sup> Human BMSCs could work as a potential treatment modality that either rescues follicles undergoing early atresia or quiescent primordial follicles from the adverse

effects of CTX in the ovarian microenvironment. Millions of women take fertility treatments each year due to age-related or non-age-related loss of oocytes. In young women who are sterile especially by CTX, those treatments offer only uncertain improvements in their fertility. If oocytes remain viable, it is potential to reestablish fertility using a stem cell administration for the revival of folliculogenesis. This evaluation of the regenerative use of BMSCs gives a chance to women affected by POF and direct us to enquire if fertility restoration using BMSCs is a viable therapeutic option.<sup>19</sup>

In addition, there are articles that show the possibility of restoring one's fertility by using stem cells. A study by Hanna et al. (2014) explained that the potential of germline stem cells in the process of oocyte development may be able to open this up.<sup>14</sup> The article by Sarma (2019) shows the potential of stem cells to preserve fertility by using oogonial stem cells, embryonic stem cells, and induced pluripotent stem cells.<sup>21</sup> There are also potential use of stem cells to treat placental pregnancy disorders such as placental infarction, chronic villitis, and FGR.<sup>19</sup>

In the field of gynecology, there are several potential benefits from the use of stem cells, such as in cases of stress urinary incontinence and anal incontinence. So far, the choice of therapy for both cases are still limited, such as through surgery. Both of these are caused by the same basic pathogenesis, the loss of muscle integrity and function, so that building muscle from a cellular level is an ideal management concept. In addition, the application of stem cells in the field of gynecology is not limited to this, such as in repairing vaginal tissue, repairing fistulas, and increasing grafting materials.<sup>14</sup>

Other studies stated that stem cells from obstetrics and gynecology field, such as endometrial stem cells, myometrial stem cells, and amniotic stem cells could be used as therapy modality. The advantages of endometrium stem cells are that they have remarkable differentiation ability, i.e. neuronal (dopamine producing cells, cholinergic neuron-like cells, oligodendrocyte-like cells), insulin producing cells, cardiomyocyte-like cells, megakaryocyte-like, urothelial cells, and other mesenchymal cell types.<sup>17</sup> Amniotic fluid stem cells also have special consideration because it is easy to retrieve, having high proliferation rate, ability to differentiate into many type of cells, stability in both phenotype and genotype, and low immunogenic profile.<sup>18,20</sup>

Despite of all those abilities, there are some drawbacks, especially with uterine source of stem cells. When in developmental process, and the stem cells have errors,

such as chromosomal abnormalities, epigenetic and genetic defect, which could potentially turn the stem cells into Tumor Initiating Cells (TICs), thus can contribute to ectopic growth of endometrium (endometriosis), leiomyoma, leiomyosarcomas, and adenomyosis.<sup>21,23</sup>

## CONCLUSION

This review showed that there are many advantages of stem cells in obstetrics and gynecology, both in infertility and in repairing tissue damage. However, it is necessary to conduct further and in-depth research to ensure the safety profile of stem cells in human in the field of obstetrics and gynecology.

## DISCLOSURES

### Acknowledgment

We thank for all lecturers, colleagues, and Doctoral Programme Faculty of Medicine Universitas Sriwijaya, Palembang, South Sumatera, Indonesia for the contributions and suggestions in this literature review.

### Conflict of interest

All authors declare no conflict of interest.

### Funding

This study did not receive any specific grants from public, commercial, or non-profit funding agencies.

### Author contribution

Each of the authors made contributions to all processes in this research, including preparation, data collection and analysis, drafting, as well as approval for publication of this manuscript.

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## SYSTEMATIC REVIEW

### The combination of NLR and MEOWS as a potential modality for detecting the severity of preeclampsia: A systematic review

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Article Info	ABSTRACT
<p>Received Apr 20, 2023 Revised Jul 5, 2023 Accepted Jul 14, 2023 Published Dec 1, 2023</p> <p><b>*Corresponding author:</b> Rendy Singgih rendyssinggih@gmail.com</p> <p><b>Keywords:</b> Preeclampsia Neutrophil-to-lymphocyte ratio (NLR) Modified Obstetric Early Warning Systems (MEOWS) Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p><b>Objective:</b> To describe modalities of detecting the severity of preeclampsia (PE) between neutrophil-to-lymphocyte ratio (NLR) levels and Modified Obstetric Early Warning Systems (MEOWS).</p> <p><b>Materials and Methods:</b> We used a systematic search in PubMed, ScienceDirect, and Google Scholar for fully-accessed English articles, published between 2015 – 2023 that evaluated modalities between NLR levels and MEOWS for detecting the severity of preeclampsia, which resulted in 208 works of literature. Among the studies, we found 14 literature that met the PICO inclusion criteria and included in this study.</p> <p><b>Results:</b> PE is still one of the high causes of morbidities and mortality in maternal patients. It is important to predict the possible risk of PE events. NLR is one of the markers that become a prognostic modality to determine the severity of PE. MEOWS is one of the tools to assess the level of care of patients who carry out the treatment. NLR and MEOWS can be modalities for predicting PE severity.</p> <p><b>Conclusion:</b> NLR and MEOWS can be used even with limited resources. The combined use of NLR and MEOWS can be an alternative and potential modality in detecting PE severity.</p>

**How to cite:** Singgih R, Kwary MMI, Tamara Y. The combination of NLR and MEOWS as a potential modality for detecting the severity of preeclampsia: A systematic review. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science)*. 2023;31(3):139-149. doi: 10.20473/mog.V31I32023.139-149.

#### Highlights:

1. Preeclampsia is still one of the contributors to morbidity and mortality which is quite high for pregnant women in Indonesia.
2. The use of NLR and MEOWS modalities as predictors of preeclampsia incidence shows significant potential and can be applied especially in facilities with limited resources.

## INTRODUCTION

Maternal mortality rate (MMR) indicates a country's public health degree. Information regarding the level of MMR helps develop sustainable health improvement programs. Data from the World Health Organization states that every day in 2017, an estimated 810 women died due to the conditions of their pregnancy and childbirth. The most significant contributor to all maternal deaths of 94% occurs in developing countries, especially countries with low and middle incomes.<sup>1</sup> Based on 2017 World Bank data, the MMR in the world was 222.<sup>2</sup> In Indonesia, MMR ranges from 305 per 100,000 according to the 2015 *Survei Penduduk Antar Sensus* (Supas).<sup>3</sup> The report describes that most maternal deaths occur mainly in hospitals.<sup>4</sup> Several factors lead to poor pregnancy outcomes, such as socio-economic conditions and health conditions like antepartum and intrapartum events during pregnancy.<sup>5</sup> The government is trying to reduce the still high MMR by targeting the number of MMR in 2024 to be 232 and targeting the Sustainable Development Goals (SDGs) in 2030 for MMR to be less than 70 per 100,000 live births.<sup>4,6</sup>

The most considerable maternal morbidity and mortality to date include thrombosis, bleeding, sepsis, and hypertension.<sup>7</sup> Hypertension in pregnancy affects 10% of all pregnancies and is currently defined as a new onset of hypertension ( $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic) after 20 weeks gestation. This term includes chronic hypertension, gestational hypertension, and preeclampsia (de novo or superimposed).<sup>8</sup> Preeclampsia (PE) is hypertension in pregnancy that often occurs for more than 20 weeks of gestation or close to the age of term.<sup>9</sup> PE is a multisystem idiopathic disorder with no known exact cause and regarding 2-8% of all pregnancies.<sup>10</sup> PE in pregnancy is divided into two categories, mild PE and severe PE, characterized by proteinuria and new onset of thrombocytopenia, renal insufficiency, renal function disorders, visual, brain, and pulmonary edema.<sup>11</sup> PE is the leading cause of fetomaternal morbidity and mortality.<sup>12</sup> Neonatal risks include intra-uterine growth restriction and low birth weight, perinatal death, and premature iatrogenic due to placental dysfunction and hypoxia.<sup>13</sup> Normal pregnancy occurs because there is a semi-allograph reaction. Conditions of the balance of inflammatory response and systemic immune system are needed such as blastocyst implantation, trophoblast cell proliferation, differentiation, inflation, and placental growth and development so that pregnancy goes well.<sup>10</sup>

In PE, the excess inflammatory response is activated due to abnormal maternal immune tolerance. Changes occur in inflammatory cells in the blood, subsets of T

lymphocytes, acute protein reactive, plasma inflammatory cytokine factors, complement activity, and coagulation systems that can later cause PE.<sup>10,12</sup> Neutrophil/Lymphocyte ratio (NLR) is one of the inflammatory markers and is being widely studied today. The combination of two essential mechanisms in PE pathogenesis, the abnormal immune and inflammatory responses is the basis for evaluating the value of NLR as a prognostic modality to determine the severity of PE.<sup>14</sup> Good confectionery management including the duration of identification time can prevent the severity of obstetric complications so that the burden of maternal death and long-term complications can be prevented.

Early warning systems (EWS) is one assessment for detecting high-risk conditions. EWS consists of a combination of clinical observations such as vital signs, physical examinations, and laboratory tests and has been used since 1997.<sup>15</sup> At that time, EWS was designed for general population and was challenging to apply to obstetric patients, due to the physiological changes that occur during the gestation and puerperal phases.<sup>16</sup> Based on the same principle as EWS, a modified prognostic modality has been developed to be applied to obstetric patients, i.e. modified obstetric early warning systems (MEOWS). Adaptation of MEOWS was recommended in 2007 from Confidential Enquiries into Maternal and Child Health (CEMACH) in the UK.<sup>17</sup> MEOWS itself has been widely used in the UK and evaluated its use in the United States because it shows a reduction in maternal morbidity rates. However, this modality has not been widely used primarily in areas with less resources.<sup>18</sup> Assessment and early detection is required for PE management. One of the predictors of PE is the value of NLR and the assessment of the level of care of PE patients with the modality of MEOWS although the research on these modalities is still limited. Therefore, in this systematic review, the authors described the combination of NLR values with MEOWS values as a predictor for detecting PE severity.

## MATERIALS AND METHODS

### Search strategy

We conducted a systematic literature review search on several databases such as ScienceDirect, PubMed, and Google Scholar for articles published from 2015 to June 2023 to evaluate the combination of the use of NLR and MEOWS modalities as predictors of preeclampsia severity. We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist rules and flow diagrams for searching, and selecting literature found to be in accordance with

PICO, inclusion, and exclusion criteria. Search terms were created using the term Medical Subject Headings (Mesh) with searches using the Boolean operator method: ("maternal early obstetric warning system" OR "modified early obstetric warning system") OR "neutrophil-to-lymphocyte ratio") AND preeclampsia. The article selection process was carried out by two reviewers (RS and MM). Details of literature search, screening, and selection can be found in Figure 1.

### Eligibility criteria and quality assessment

Eligibility criteria were formulated using the Population, Intervention, Comparison, and Outcomes (PICO) framework as shown in Table 1. We included studies: (1) Investigation of the relationship between MEOVS scores and NLR scores as predictors of the incidence or severity of preeclampsia; (2) The subject of pregnant women undergoing treatment; and (3) The language used is English. The exclusion criteria included: (1) Articles in the form of abstracts, reviews, case reports, and case series; (2) Inaccessible articles; and (3) Articles not in accordance with the research topic. Then, we assessed the quality of the methodology using the Joanna Briggs Institute (JBI) critical appraisal checklist. Critical appraisal was performed by two reviewers (RS and MM), and only studies with a score of  $\geq 50\%$  were included further. If there was a disagreement on the points in the critical appraisal, it was resolved through discussion by inviting a third reviewer (YT) to determine a solution.

### Data extraction

Data extraction was carried out by two reviewers (RS and MM) with components including: (1) year of publication; (2) study design; (3) sample size; (4) NLR rate; (5) MEOVS score; and (6) study outcomes and results.

## RESULT AND DISCUSSION

From literature searching, we obtained as many as 208 studies. Then, after passing through several selection processes, 14 studies were obtained that were in accordance with PICO and inclusion criteria. Of the fourteen studies, two were cross-sectional studies, five were cohort studies, and seven were case-control

studies.<sup>13,14,19-30</sup> The studies included samples of women with median age of 17.4 to 35.5 years and a range of 101 to 1481. This systematic review revealed that NLR and MEOVS had the ability to detect the incidence and severity of preeclampsia. Some studies were described in the form of tables related to the level of meaning and its ability to detect preeclampsia. We present the data extraction and methodological assessment scores in Table 2.

The study of Sitotaw et al. (2018) showed that NLR values significantly increased in women with PE compared to healthy women. NLR is shown to increase significantly along with the severity of PE with  $p < 0.05$ .<sup>19</sup> Gogoi et al. (2018) in their study found similar results that the average NLR value was higher in women with PE ( $6.8 \pm 7.6$ ) compared to the control group ( $3.0 \pm 0.98$ ) with a value ( $p=0.001$ ). This suggests that inflammatory markers such as NLR are higher in women with PE.<sup>20</sup> Mannaerts et al. (2017) divided the NLR value between gestational age before 20 weeks and shortly before delivery. However, significant results were found at the end of pregnancy ( $p < 0.00$ ) just before delivery, NLR values tended to be higher ( $6.79 \pm 2.84$ ) than the control group ( $3.60 \pm 1.17$ ).<sup>13</sup>

In a study by Sachan et al. (2017), where the group was divided between severe PE, mild PE, and control or healthy groups, the mean values of each group in the healthy mild, and severe PE groups were respectively as follows  $3.14 \pm 0.16$ ,  $3.38 \pm 0.16$ , and  $4.26 \pm 0.31$ .<sup>23</sup> Faraji et al. (2022) stated that NLR was higher in the mild and severe PE groups than in the gestational hypertension group in the first and early third trimesters ( $p < 0.05$ ).<sup>24</sup> A case-control study conducted by Cakmak et al. (2017) found that NLR increased significantly in PE group compared to control group and in comparison between mild and severe PE groups, NLR values were also higher in severe PE group ( $p=0.001$ ).<sup>25</sup> Oglak et al. (2021) divided three groups into control groups, mild PE, and severe PE. Significant results were obtained in the comparison between the control group with mild PE and the control group with severe PE ( $p < 0.001$ ), while the comparison between the mild and severe PE groups was less ( $p=0.441$ ).<sup>26</sup> Gezer et al. (2016) performed a complete blood count in the early trimester to predict the incidence of PE. From the study, NLR was found to be a predictor of PE in their analysis ( $p=0.005$ ).<sup>27</sup>



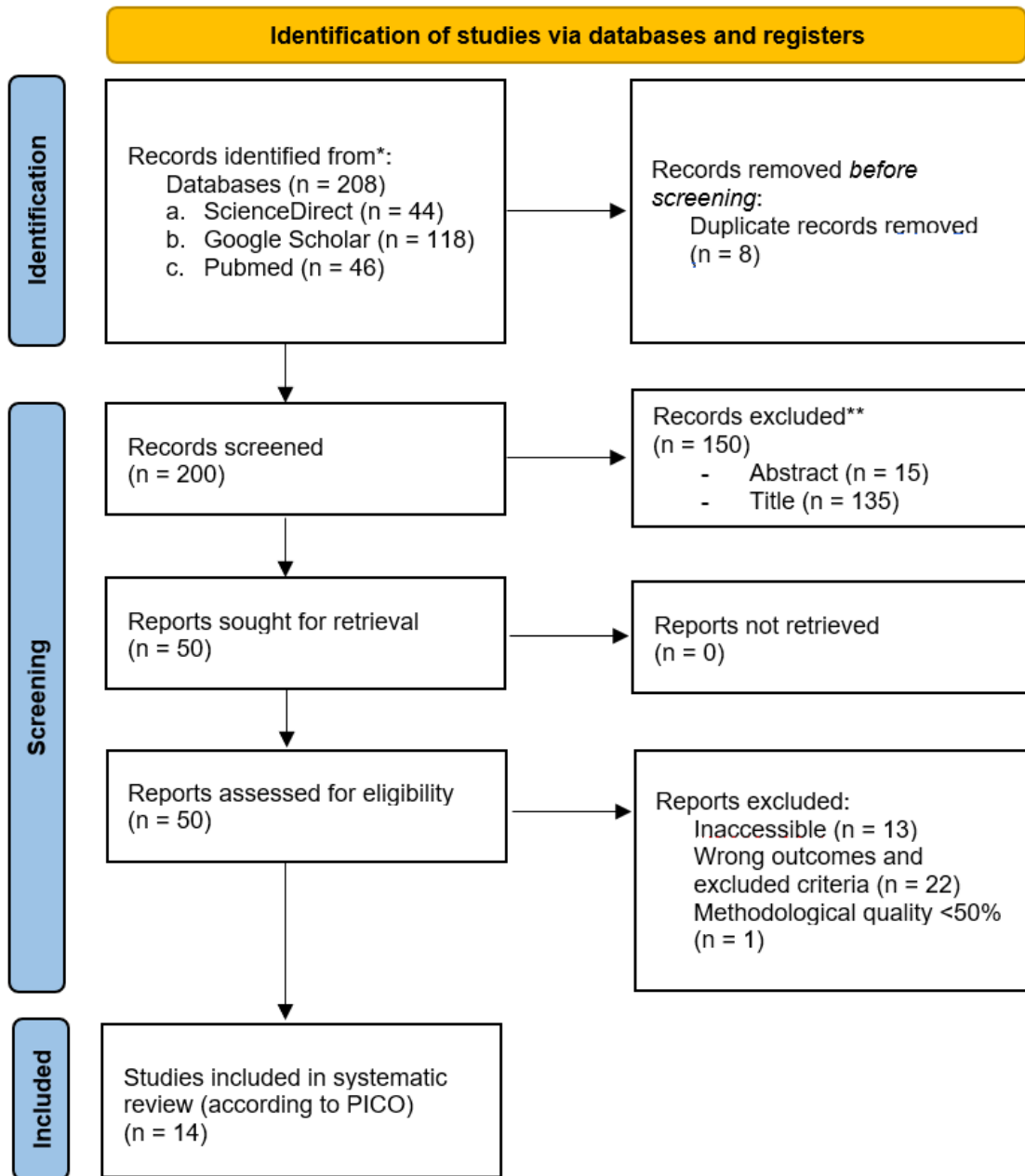


Figure 1. PRISMA flowchart diagram of the screening process and the included final articles

Table 1. PICO Table

Population (P)	Pregnant women
Intervention (I)	NLR (neutrophil-lymphocyte ratio) rate and MEOWS (modified early obstetric warning system) score
Comparison (C)	No intervention
Outcome (O)	Determine the severity of preeclampsia

Table 2. Summary of included studies showing the combination of NLR and MEOWS in a review

First Author (Year)	Study design	Age (median in years)	Sample size	Outcomes	NLR/MEOWS Parameter	Results	JB1 score
Sitotaw et al., (2018) <sup>19</sup>	Cross-sectional study	25 - 26	126	NLR parameter and preeclampsia women	NLR (control $2.92 \pm 0.50$ , PE $4.67 \pm 1.50$ )	<ul style="list-style-type: none"> <li>NLR showed significant elevation in women with PE.</li> <li>NLR significantly increased with the severity of PE (<math>p &lt; 0.05</math>).</li> <li>NLR correlation analysis (<math>\rho = 0.31</math>) in PE group.</li> </ul>	100%
Gogoi et al., (2018) <sup>20</sup>	Cross-sectional study	27 - 28	134	NLR between women with pre-eclampsia and normotensive	NLR (control $6.8 \pm 7.6$ , PE $3.0 \pm 0.98$ )	<ul style="list-style-type: none"> <li>NLR was higher in women with pre-eclampsia.</li> <li>Mean NLR was higher in women with preeclampsia (<math>p=0.001</math>).</li> </ul>	100%
Singh et al., (2016) <sup>21</sup>	Cohort study	-	1065	MEOWS chart evaluation: <ul style="list-style-type: none"> <li>Single markedly abnormal observation (red trigger)</li> <li>Combination of two simultaneously mildly abnormal observations (two yellow triggers)</li> </ul>	Trigger (284) 26.6% vs Non-Trigger (781) 73.4%	<ul style="list-style-type: none"> <li>Two hundred and eighty-four (26.60%) women were triggered to abnormal zones after admission.</li> <li>One hundred and seventy-seven (16.61%) fitted our criteria for morbidity.</li> <li>Most common morbidity was hypertensive disorders (69.4%)</li> </ul>	63%
Kaur et al., (2023) <sup>22</sup>	Cohort study	33.4	267	Trigger definition: <ul style="list-style-type: none"> <li>Single severely abnormal parameter (red zone)</li> <li>Two mildly abnormal parameters (yellow zone)</li> </ul>	Criteria for a trigger: <ul style="list-style-type: none"> <li>88 patients (33.0%) during triage</li> <li>44 patients (17.6%) during the first treating nurse assessment</li> </ul>	<ul style="list-style-type: none"> <li>Twenty-one (7.9%) patients met the criteria for severe maternal morbidity.</li> <li>There were no maternal deaths.</li> <li>Sensitivity of MEOWS tools 85.7% (95% CI 63.7-97%)</li> <li>Specificity 67.9% (95% CI 61.7-73.7%)</li> <li>PPV 18.6% (95% CI 15.1-22.7%)</li> <li>NPV 98.2% (95% CI 95.1-99.4%)</li> <li>Severe preeclampsia and eclampsia were the most common outcome category of severe maternal morbidity in 16 (76.2%) cases.</li> </ul>	100%
Mannaerts et al., (2017) <sup>13</sup>	Cohort study	28.9 – 30.2	1613	Usability of NLR between women who develop PE and those that will not	NLR (preeclampsia group $2.81 \pm 0.95$ , control group $3.08 \pm 1.07$ )	<ul style="list-style-type: none"> <li>NLR before 20th pregnancy week (<math>p = 0.173</math>)</li> <li>NLR before primary cesarean section (<math>p &lt; 0.00</math>)</li> <li>NLR (AUC 0.863), (95% CI 0.783 – 0.944), (Optimal cut-off point 3.92), (Sensitivity 84.4%), (Specificity 69.4%)</li> </ul>	100%



Sachan et al., (2017) <sup>23</sup>	Cohort study	25.1 – 25.9	101	Accuracy of NLR in the prediction of nonsevere PE and severe PE	NLR (mean±standard error) of three groups (13-20 weeks of gestation). Mild PE (Group 1), severe PE (Group 2), normotensive (Group 3) : <ul style="list-style-type: none"> <li>• Group 1 NSPE (n=34) (3.38±0.16)</li> <li>• Group 2 SPE (n=16) (4.26±0.31)</li> <li>• Group 3 Controls (n=51) (3.14±0.16)</li> </ul>	Comparison of mean NLR between groups at 13-20 weeks : <ul style="list-style-type: none"> <li>• Group 3 vs Group 1 (p &lt; 0.006)</li> <li>• Group 3 vs Group 2 (p &lt; 0.001)</li> <li>• Group 1 vs Group 2 (p &lt; 0.001)</li> </ul> NLR comparison before and after the development of preeclampsia: <ul style="list-style-type: none"> <li>• Before (13-20 weeks)                             <ul style="list-style-type: none"> <li>- Group 1 (NSPE) 3.38±0.16</li> <li>- Group 2 (SPE) 4.26±0.31</li> </ul> </li> <li>• After (development of hypertensive disorders)                             <ul style="list-style-type: none"> <li>- Group 1 (NSPE) 4.26±0.31</li> <li>- Group 2 (SPE) 4.79±0.53</li> </ul> </li> </ul>	100%
Faraji et al., (2022) <sup>24</sup>	Cohort study	17.4 – 22.7	449	Accuracy of NLR for predicting PE in the first and early-third trimester of pregnancy in a normal population	NLR First trimester: <ul style="list-style-type: none"> <li>• Normotensive (2.21±0.62)</li> <li>• Gestational HTN (2.3±0.91)</li> <li>• Mild PE (2.96±0.4)</li> <li>• Severe PE (3.13±0.25)</li> </ul> NLR Early-third trimester: <ul style="list-style-type: none"> <li>• Normotensive (2.77±0.69)</li> <li>• Gestational HTN (70±0.4)</li> <li>• Mild PE (3.8±1.14)</li> <li>• Severe PE (4.1±1)</li> </ul>	NLR comparison between first trimester and early-third trimester : <ul style="list-style-type: none"> <li>• First trimester                             <ul style="list-style-type: none"> <li>- Mild PE (AUR 0.92), (Sensitivity 85%), (Specificity 90.9%), (PPV 96.5%), (NPV 38.8%).</li> <li>- Severe PE (AUR 0.95), (Sensitivity 85.7%), (Specificity 90.0%), (PPV 96.5%), (NPV 67.9%).</li> </ul> </li> <li>• Early-third trimester                             <ul style="list-style-type: none"> <li>- Mild PE (AUR 0.92), (Sensitivity 90.51%), (Specificity 79.4%), (PPV 92.9%), (NPV 38.1%).</li> <li>- Severe PE (AUR 0.91), (Sensitivity 90.5%), (Specificity 79.4%), (PPV 92.9%), (NPV 73.5%).</li> </ul> </li> </ul>	73%
Cakmak et al., (2017) <sup>25</sup>	Case-control study	27.5 – 28.5	140	Evaluation of the relations between NLR with the presence and severity of preeclampsia	NLR baseline between PE and control : <ul style="list-style-type: none"> <li>• Preeclampsia (5.3±1.4)</li> <li>• Control (3±0.8)</li> <li>• p=0.001</li> </ul> NLR baseline between Mild PE and Severe PE: <ul style="list-style-type: none"> <li>• Mild PE (4.5±1)</li> <li>• Severe PE (6.3±1.1)</li> <li>• p=0.001</li> </ul>	Result of univariate and multivariate regression NLR analysis : <ul style="list-style-type: none"> <li>• Univariate                             <ul style="list-style-type: none"> <li>- (p=0.001), (OR 9.154), (95% CI) 4.139 - 20.247</li> </ul> </li> <li>• Multivariate                             <ul style="list-style-type: none"> <li>- (p=0.001), (OR 8.161), (95% CI) 3.091 – 21.548</li> </ul> </li> </ul>	70%

Oglak et al., (2021) <sup>26</sup>	Case-control study	27.4 – 28.7	301	Examination of the diagnostic value of the SIR marker (NLR) during the first trimester of pregnancy to predict PE development.	First trimester NLR marker (mean±SD): <ul style="list-style-type: none"> <li>• Control Group (3.1±1.1)</li> <li>• Mild PE Group (4.3±1.4)</li> <li>• Severe PE Group (4.6±1.8)</li> </ul>	Area Under the Receiver Operating Characteristic (ROC) of NLR : <ul style="list-style-type: none"> <li>• ROC (0.767), Standard Error (0.030), (95% CI) 0.709 – 0.826, (<i>p-value</i> &lt;0.001)</li> </ul>	90%
Gezer et al., (2016) <sup>27</sup>	Case-control study	25.8 – 26.6	430	Determine whether first-trimester NLR would be useful as new predictors of subsequent preeclampsia.	Clinical characteristic of the study group (mean±SD) : <ul style="list-style-type: none"> <li>• PE group (3.8±1.5)</li> <li>• Normotensive group (3.1±1.3)</li> <li>• <i>P-value</i> &lt;0.001</li> </ul>	Prognostic value of optimum cut-off for first trimester NLR in predicting preeclampsia: <ul style="list-style-type: none"> <li>• (AUC 0.716), (Sensitivity 74.6), (Specificity 70.1), (PPV 70.3%), (NPV 74.5%), (LR<sup>+</sup> 2.5), (LR<sup>-</sup> 0.4), (cut-off value 3.08)</li> </ul>	70%
Panwar et al., (2019) <sup>28</sup>	Case-control study	-	440	Conducted to evaluate the role of NLR in predicting the development and severity of PE.	Distribution of the mean value of NLR between 16-18 weeks in normal women and who developed PE: <ul style="list-style-type: none"> <li>• Normal women (4.55±0.66)</li> <li>• PE (5.55±0.81)</li> <li>• <i>p</i> &lt;0.001</li> </ul> Distribution of the mean value of NLR between 16-18 weeks in who developed mild PE and severe PE: <ul style="list-style-type: none"> <li>• Mild PE (5.39±0.84)</li> <li>• Severe PE (6.08±0.43)</li> <li>• <i>p</i>=0.001</li> </ul>	Distribution of the sensitivity (SN) and specificity (SF) of NLR between 16-18 weeks in predicting the development of PE: <ul style="list-style-type: none"> <li>• (AUC 0.84), (95% CI) 0.77 – 0.90, (cut off ≥ 5.6), (SN 73.4%), (SF 88.6%)</li> </ul> Distribution of the sensitivity (SN) and specificity (SF) of NLR between 16-18 weeks in predicting the development of severe PE: <ul style="list-style-type: none"> <li>• (AUC 0.95), (95% CI) 0.90 – 1.00, (cut off ≥ 5.61), (SN 93.3%), (SF 86.6%)</li> </ul>	70%
Kirbas et al., (2015) <sup>29</sup>	Case-control study	27 – 29.3	934	To investigate hematological changes in early pregnancy using simple complete blood count such as NLR.	Comparison NLR results of severe PE (group 1), mild PE (group 2), and the control group (Group 3): <ul style="list-style-type: none"> <li>• Group 1 (4.54±2.98)</li> <li>• Group 2 (3.97±1.34)</li> <li>• Group 3 (3.23±1.33)</li> </ul> <i>P-values</i> : <ul style="list-style-type: none"> <li>• <i>P</i><sup>1vs2</sup> 0.86</li> <li>• <i>P</i><sup>1vs3</sup> &lt;0.001</li> <li>• <i>P</i><sup>2vs3</sup> 0.005</li> </ul>	NLR accurately predicted PE: <ul style="list-style-type: none"> <li>• {AUC=0.568 (95% CI 0.524-0.612), <i>p</i>=0.002}, (Sensitivity 79.1%), (Specificity 38.7%), (PPV 73.6%), (NPV 72.3%)</li> </ul>	80%



Ali et al., (2021) <sup>14</sup>	Case-control study	26.6 – 28.5	132	To evaluate NLR in the diagnosis of preeclampsia and its severity and to determine the correlation between them.	Comparison of NLR among the study groups: <ul style="list-style-type: none"> <li>• Controls (3.90±1.8)</li> <li>• Non-severe PE (4.10±3.41)</li> <li>• Severe PE (5.81±5.25)</li> <li>• p= 0.025</li> </ul>	ROC curve showed non-significant criterion for severe and non-severe cases: <ul style="list-style-type: none"> <li>• p &gt;0.05, (AUC 0.56), (95% CI) 0.4-0.7, (p=0.46)</li> <li>• Spearman’s correlation coefficient of 0.107 and p=0.39</li> </ul>	50%
Ryan et al., (2017) <sup>30</sup>	Case-control study	34 – 35.5	1841	To evaluate the performance of the Modified Early Obstetric Warning System (MEOWS) to predict maternal ICU admission in an obstetric population.	Comparison of demographic variables, patient characteristics and MEOWS variables: <ul style="list-style-type: none"> <li>• ICU admitted women (n=46)</li> <li>• Non-ICU admitted women (n=138)</li> </ul> MEOWS activation was defined as the occurrence ≥ 1 “red” or ≥ 2 “yellow” MEOWS triggers.	MEOWS chart triggers: <ul style="list-style-type: none"> <li>• ≥ 1 red or ≥ 2 amber                     <ul style="list-style-type: none"> <li>- (p &lt;0.0001), RR (95% CI) 15.83 (3.96-63.36), (Sensitivity 0.96%), (Specificity 0.54%), (PPV 41%), (NPV 97%), (LR<sup>+</sup> 2.10), (LR<sup>-</sup> 0.08)</li> </ul> </li> <li>• ≥ 1 red                     <ul style="list-style-type: none"> <li>- (p &lt;0.0001), RR (95% CI) 13.35 (4.99-35.71), (Sensitivity 0.91%), (Specificity 0.72%), (PPV 52%), (NPV 96%), (LR<sup>+</sup> 3.23), (LR<sup>-</sup> 0.12)</li> </ul> </li> <li>• ≥ 2 red                     <ul style="list-style-type: none"> <li>- (p &lt;0.0001), RR (95% CI) 5.79 (3.49-9.60), (Sensitivity 0.65%), (Specificity 0.89%), (PPV 67%), (NPV 89%), (LR<sup>+</sup> 6.00), (LR<sup>-</sup> 0.39)</li> </ul> </li> </ul>	70%

Panwar et al. (2019) conducted blood sampling at the beginning of the second trimester to compare groups of healthy women with PE and the between mild and severe PE. Both comparisons obtained significant results ( $p < 0.001$ ).<sup>28</sup> Kirbas et al. (2015) divided three groups between the control, mild, and severe PE group. However, the results were found only between the comparison of the control group with severe PE ( $p < 0.001$ ) and the control with mild PE ( $p = 0.005$ ).<sup>29</sup> Ali et al. (2021) compared the three groups directly, the control group, mild, and severe PE. From these three comparisons, significant differences in NLR between the groups studied were obtained ( $p = 0.027$ ).<sup>14</sup>

Furthermore, starting with a discussion of MEOWS parameters a study conducted by Singh et al. (2016) found that as many as two eighty-four patients (26.60%) met the abnormal criteria after admission and the greatest morbidity due to hypertension (69.4%).<sup>21</sup> Kaur et al. (2023) conducted a similar study on MEOWS parameters. Of 267 patients, 21 (7.9%) patients met maternal morbidity criteria with MEOWS modality sensitivity of 85.7% (95% CI 63.7 – 97%) and specificity of 67.9% (95% CI 61.7 – 73.7%). Severe PE and eclampsia were the most common outcomes in 16 maternal patients (76.2%) of all patients who met the maternal morbidity criteria.<sup>22</sup> Ryan et al. (2017) obtained data from several maternal and ICU units. From their study of MEOWS parameters, 46 patients were admitted to the ICU and 138 were not. With MEOWS chart triggers between all triggers  $\geq 1$  red and or  $\geq 2$  yellow, and  $\geq 2$  red obtained significant results ( $p < 0.0001$ ).<sup>30</sup>

In this systematic review, we discussed in detail the benefits of NLR and MEOWS modalities for predicting PE events. From the results of the systemic search and review, several articles were obtained that discussed the two modalities. The entire article explains that NLR and MEOWS can be used as predictors of PE, especially when applied to facilities with limited resources. However, it must be admitted that there are limitations of this study. This systematic review was carried out on a small scale and it is expected that in the future systematic reviews and meta-analyses will be carried out to a larger number of articles so that the results obtained will better clearly illustrate the benefits of NLR and MEOWS.

## CONCLUSION

The results of the overall research presented in this systematic review suggest that the combination of NLR and MEOWS can be used as a potential modality to detect and predict PE events. Another benefit is that the

modality can be used simply and applied to facilities with limited resource conditions.

## DISCLOSURES

### Acknowledgment

None.

### Conflict of interest

There was no conflict of interest among all authors in this study.

### Funding

There was no sponsorship of the study, and the entire cost came from private funds.

### Author contribution

RS, MM, dan YT have contributed to the overall process of this study starting from data collection, processing, analysis, and completion process to publication of the study.

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## SYSTEMATIC REVIEW

### Stress exposure due to the COVID-19 pandemic on menstrual abnormalities: A systematic review


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Article Info	ABSTRACT
<p>Received Jun 20, 2023 Revised Sep 15, 2023 Accepted Sep 22, 2023 Published Dec 1, 2023</p> <p><b>*Corresponding author:</b> Budi Utomo budiutomo@fk.unair.ac.id</p> <p><b>Keywords:</b> Menstrual abnormalities Stress COVID-19 pandemic Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p><b>Objective:</b> COVID-19 pandemic had caused a considerable increase in stress level due to reduced human mobility, interaction, and activity. High stress levels are often associated with an adverse health outcome. Stress influences female reproduction systems, where it is an important indicator of female health. This systematic review aimed to analyze the relationship between stress levels due to the COVID-19 pandemic and the incidence of abnormal menstruation.</p> <p><b>Materials and Methods:</b> This systematic review was registered in PROSPERO international database (CRD42023433296). Literature search was conducted across four databases, Pubmed, Web of Science, Science Direct, and Google Scholar, with boolean AND and OR operators as keyword search assistants. Literature was searched and limited to journals published during the pandemic (2019-2023), written in English, an open access article, and meet the keywords. Literature not a research study, duplicated and limited access were not included. Inclusion to the journal was carried out by screening using PRISMA flowchart and EPHPP Assessment Tool for Quantitative Studies for the quality assessment.</p> <p><b>Results:</b> Nine out of 1150 journals were eligible for review. Seven studies revealed that there was a significant relationship between stress and anxiety due to the COVID-19 pandemic and the incidence of menstrual abnormalities. However, one study revealed that these changes were not significant.</p> <p><b>Conclusion:</b> There is a significant relationship between stress during the COVID-19 pandemic and the incidence of menstrual abnormalities.</p>

**How to cite:** Nugroho SB, Utomo B, Frety EE, et al. Stress exposure due to the COVID-19 pandemic on menstrual abnormalities: A systematic review. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science)*. 2023;31(3):150-156. doi: 10.20473/mog.V31I32023.150-156.

#### Highlights:

1. There is a significant higher level of stress during COVID-19 pandemic.
2. The highest menstrual abnormalities during pandemic cases were found in premenstrual syndrome and dysmenorrhea, and the lowest was found in menstrual cycle disorders (polygomenorrhea, oligomenorrhea, amenorrhoea).

## INTRODUCTION

Menstrual cycle is one of vital sign on women's health.<sup>1</sup> Women under 30 continue to experience problems related to hormones and menstruation, especially abnormal menstruation.<sup>2</sup> Abnormal menstruation not only causes discomfort for women and interferes women's quality of life, it is also associated with poor health outcomes, such as an increased risk of coronary heart disease, type 2 diabetes mellitus, and cardio-metabolic diseases.<sup>3</sup> On the other hand, menstrual cycle has become one indicator of overall women health, although sometimes it is overlooked by several health practitioners.<sup>1</sup> Abnormalities in menstruation that commonly occurs are dysmenorrhea, premenstrual symptoms, menorrhagia, polymenorrhea, abnormal vaginal bleeding, amenorrhea, oligomenorrhea, and irregular menstruation.<sup>4</sup>

High levels of stress are often associated with adverse health outcomes. Stress can cause or exacerbate significant health problems, including cardiovascular disease, obesity, sexual dysfunction, digestive problems, and mental health conditions.<sup>1</sup> Stress also influences female reproduction, where stress involves the hormonal system as a system that plays a significant role. Several studies were found a relation between stress and menstrual abnormalities.<sup>4</sup>

COVID-19 pandemic has caused a relatively high increase in stress levels due to reduced mobility, interaction, and human activity. This situation tend to be stressful for some individuals.<sup>5</sup> During COVID-19 pandemic, prevalence rate of stress in general population was found to be higher, especially in women and younger age groups.<sup>6</sup> High levels of anxiety and stress have led to the emergence of other studies regarding the relationship between the pandemic and abnormal menstruation or disruption of the menstrual cycle. The prevalence of population experienced severe dysmenorrhea during the pandemic were higher than before pandemic occurred.<sup>7</sup> Based on this background, further exploration was needed in regard with the relationship between exposure to stress due to the COVID-19 pandemic and the incidence of abnormal menstruation.

## MATERIALS AND METHODS

This systematic review was registered in PROSPERO international database (CRD42023433296). The research was started by determining research questions,

PICO, quality assessment, data extraction, and reporting.

Table 1. PICO Question

Population	Women of childbearing age
Intervention	Stres during COVID-19 pandemic
Comparison	Stres before COVID-19 pandemic
Outcome	Menstrual abnormalities

We performed the literature search using the AND and OR boolean operators. Literature was searched and limited to journals published during the pandemic (2019-2023), written in English, an open access article, and meet the keywords. Article not a research study, duplicated and limited access were not included. Literature screening was based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) search flow (Figure 1). Literature that has been screened through the PRISMA method was further screened through the EPHPP Quality Assessment Tool for Quantitative Studies.

## RESULTS AND DISCUSSION

We found relationship between exposure to stress due to the COVID 19 pandemic and menstrual abnormalities. The relationship was analyzed through five cross-sectional, two observational, and two retrospective study. Eight studies revealed a significant relationship between stress due to the COVID 19 pandemic and the occurrence of abnormal menstruation, and one study revealed that these changes were not significant.

### Stress during the COVID-19 pandemic

COVID-19 pandemic has causes stress and generates negative emotions such as fear, anxiety, and depression for everyone, regardless of age, gender, or socioeconomic status.<sup>8</sup> COVID-19 pandemic also have more significant impact on women than men, both as a front liners such as doctors, nurses, midwives, as well as women who work and do not work at home.<sup>9</sup> Based on research that has been filtered, all respondents experienced an increase in stress levels during the COVID-19 pandemic. Decreased mood, higher anxiety, sleeping difficulty, increased stress, loneliness, and lack of concentration were found during COVID-19 pandemic.<sup>10,11</sup> Women also tend to experienced one to more than one new symptoms and worsening mental health changes during COVID-19 pandemic.<sup>12-14</sup>



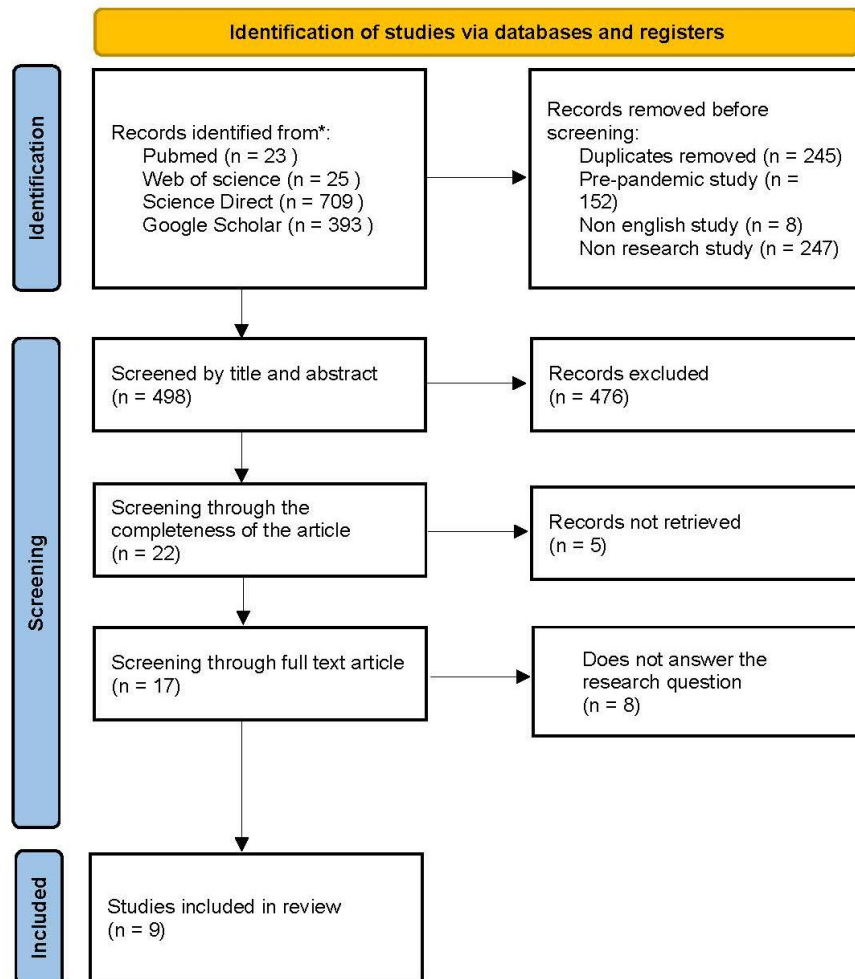


Figure 1. PRISMA Method

Table 2. Data Extraction

Author	Aims	Study criteria	Characteristics	Results
Takmaz et al., (2021)	Knowing the relationship between menstrual cycle regularity and anxiety, depression, and stress related to the COVID-19 pandemic in medical personnel.	Type: Cross-sectional Location: Turkey Sample: 925 Instrument: Questionnaire	Medical personnel with an age range of 18 to 40 years, had regular menstrual cycles for 1 year up to more before the pandemic.	Medical personnel with an age range of 18 to 40 years had regular menstrual cycles for one year up to more before the pandemic. Relationship was found between menstrual cycle regularity and anxiety, depression, and stress related to the COVID-19 pandemic in medical personnel with higher CSS and DASS-21 results compared to the group with regular menstruation (p<0.001).
Samo et al., (2021)	Knowing the relationship between mental health during the COVID-19 pandemic and menstrual abnormalities in female students.	Type: Cross-sectional Location: Pakistan Sample: 400 Instrument: Questionnaire	Female students aged 17-25 years have no gynecological problems and are not married.	A relationship was found between mental health during the COVID-19 pandemic and menstrual abnormalities in female students with the results 59.75% of students felt their mental health was affected by COVID-19 and 25.75% of female students felt that their menstrual cycle was affected.
Phelan et al., (2021)	Knowing the relationship between the menstrual cycle, libido and lifestyle changes to the pandemic.	Type: Observational Location: Ireland, UK, other countries Sample: 1031 Instrument: Questionnaire	Women of childbearing age aged 15-54 years	A relationship was found between the menstrual cycle during the pandemic with the result that 46% of women experienced changes in their menstrual cycle during the COVID-19 pandemic.

Payne et al., (2023)	Knowing the relationship between COVID-related stress and menstrual variables (menstrual pain, number and severity of menstrual symptoms, and menstrual pain disorders)	Type: Observational Location: USA Sample: 223 Instrument: Questionnaire	Women of childbearing age aged 18-55 years, experienced 1x menstruation in the last 3 months, did a self-report in the last 12 months.	Results showed that COVID-related stress was associated with higher rates of menstrual pain, more frequent and more severe menstrual symptoms, and greater menstrual pain disturbances.
Nguyen et al., (2021)	To determine whether the COVID pandemic is affecting ovulation and menstruation	Type: Retrospective cohort Location: UK, USA, Sweden Sample: 18076 Instrument: Questionnaire	Women who entered menstrual data from March to September 2019 and March to September 202	The results showed that fewer menstrual abnormalities occurred during the pandemic than before the pandemic. There was no independent relationship between stress and cycle disorders. However, more abnormal cycles were found in women over 45 years of age, which may indicate stress-related sensitivity during the perimenopausal state.
Medina Perucha et al., (2022)	To determine whether the COVID pandemic is affecting the menstrual cycle	Type: Cross-sectional Location: Spain Sample: 17455 Instrument: Questionnaire	Women aged 18-55 years	39.4% experienced menstrual changes since the start of the pandemic.
Maher et al., (2022)	To determine whether the COVID pandemic is affecting the menstrual cycle	Type: Cross-sectional Location: Ireland, UK, other countries Sample: 1335 Instrument: Questionnaire	Women of childbearing age and are not breastfeeding and experience amenorrhea due to pregnancy, intrauterine disorders, and implants	Results showed that there has been an increase in anxiety and the prevalence of pain during menstruation and worsening of pre-menstrual symptoms during the pandemic.
Aolymat et al., (2022)	To find relationship between dysmenorrhea, PMS, and health of the reproductive tract on anxiety, depression, and stress related to COVID-19	Type: Cross-sectional Location: Jordan Sample: 385 Instrument: Questionnaire	Medical students in Jordan over the age of 18 and unmarried	Results showed a positive Pearson correlation between mental health disorders related to COVID-19 and the severity of dysmenorrhea, PMS and reproductive health disorders (p <0.05).
Garcia de leon et al., (2023)	To evaluate female reproductive and mental health on the 1 <sup>st</sup> year of COVID-19 pandemic	Type: Retrospective survey Location: Columbia, Canada Sample: 4171 Instrument: Questionnaire	Women aged 25-69 years	Results found 27.8% of the respondent reported menstrual cycle disturbances, especially on respondent with higher perceived stress, depression and anxiety scales.

## Menstrual abnormalities during the pandemic

### Menorrhagia

The incidence of menorrhagia during the pandemic was found in four studies. Medina-Perucha et al.<sup>15</sup> found 7.2% of their respondents experienced an increase in bleeding. This finding was in line with a study by Samo et al.<sup>13</sup> which found that 15% of the respondents experienced heavy bleeding during the COVID-19 pandemic, and also in line with the research by Phelan et al.<sup>11</sup> who also mentioned that 28% of the respondents had menstruation for more than eight days. Higher percentage was found on a study by Maher et al.<sup>12</sup> which stated that 50% of their respondents felt that their menstrual volume during the pandemic had also increased.

### Hypomenorrhea

Hypomenorrhea was also found during the COVID-19 pandemic. The incidence of hypomenorrhea was found in four studies. Takmaz et al.<sup>10</sup> found that 2.5% of their respondents experienced reduced blood volume during menstruation. This was in line with a study by Maher et al.<sup>12</sup> which 5.1% of their respondents experienced a reduction in menstrual days, and 5% experienced a reduction in menstrual volume. Samo et al.<sup>13</sup> also revealed a decrease in menstrual volume in 16.75% of

their respondents. Phelan et al.<sup>11</sup> on their studies also revealed that 29% of their respondents experienced menstruation in under two days.

### Amenorrhea

Cases of secondary amenorrhea during the pandemic were also found in three studies. Medina-Perucha et al.<sup>15</sup> revealed that their respondents did not get menstruation for at least one cycle during the pandemic. This confirmed a study of Phelan et al.<sup>11</sup> which found their respondents did not experience their periods during the pandemic. Research conducted by Samo et al. also found that 16% of the respondents experienced amenorrhea during the pandemic.<sup>13-20</sup> Higher percentage were found in a study by Garcia de Leon et al.<sup>21</sup>, which found that 23.7% of their respondents, specifically 13.1% of their under 40s respondent having fewer periods than before.

### Dysmenorrhea

Dysmenorrhea is one of the most common findings during the pandemic. Six studies were found talking about dysmenorrhea. Medina-Perucha et al.<sup>15</sup> revealed an increase in menstrual pain out 12.6% of the respondents. A study conducted by Aolymat et al.<sup>16</sup> also found that during the pandemic, there was an increase in



severe dysmenorrhea by 13% compared to before the pandemic. Payne et al.<sup>10</sup> also revealed that the increase in stress and distress due to COVID has a relationship with more significant menstrual pain disorders. Samo et al.<sup>13</sup> also found that respondents to their study experienced dysmenorrhea. Higher percentage were found in these following latest studies: Garcia de Leon et al.<sup>21</sup> found that 44.3% of their respondents indicated more symptomatic on their periods, specifically 52.7% of their under 40s respondents. Phelan et al.<sup>11</sup> found that 49% of their respondents experienced higher dysmenorrhea than before the pandemic, and Maher et al.<sup>12</sup> also revealed that 59% of their research respondents experienced dysmenorrhea during the pandemic.

### Premenstrual Syndrome

Cases of premenstrual syndrome were also found in some of these studies. Phelan et al.<sup>11</sup> revealed that 53% of respondents experienced premenstrual syndrome worse than before the pandemic. Payne et al.<sup>17</sup> also revealed that increased stress and distress due to COVID were related to more frequent and severe menstrual symptoms. In other research, Maher et al.<sup>12</sup> revealed that 68% of respondents experienced more severe premenstrual syndrome symptoms than before the pandemic. This study was in line with the study conducted by Aolyamat et al.<sup>16</sup> which also found an increase in the frequency of premenstrual syndrome

### Polyhoamenorrhea

Polygoamenorrhea or shortened menstrual cycles have been found in four studies during COVID-19 pandemic. Samo et al.<sup>13</sup> revealed that 3% of the respondents in this study experienced a decrease in the length of the menstrual cycle. In another study, Medina-Perucha et al.<sup>15</sup> stated that 10% of respondents experienced shorter menstrual cycles. Higher percentage was found on Garcia de Leon et al.'s<sup>21</sup> study which stated that 15.7% of their respondents, specifically among 19% of them who were under 40s, had shorter periods than before. However, research conducted by Phelan et al.<sup>11</sup> and Nguyen et al.<sup>14</sup> showed no significant changes in the average cycle and duration of menstruation.

### Oligomenorrhea

Oligomenorrhea had also been found in five studies. Samo et al.<sup>13</sup> revealed that 7.2% of their respondents experienced a cycle extension. Takmaz et al.<sup>10</sup> found that 12.9% of female medical personnel experienced menstrual cycle lengthening during the pandemic. In another research, Maher et al.<sup>12</sup> also revealed that 12.5% of their respondents experienced longer menstrual cycles. Garcia de Leon et al.<sup>21</sup> also found that 25.4% of

their respondents, specifically 32.1% of them under 40s, indicated longer periods than before. However, less significant changes in mean cycle and menstrual length were found by Takmaz et al.<sup>10</sup> and Maher et al.<sup>12</sup>, which remained at 28 days, but there was wider variability in minimum and maximum cycle length.

### Menstrual abnormalities in COVID-19 pandemic

The difference in results related to abnormal menstruation can be attributed to the stress level experienced by the respondents. Eight of nine journals in this systematic review stated that higher levels of depression, anxiety, and stress were associated with menstrual abnormalities. Phelan et al.<sup>11</sup> stated that respondents with low mood, anxiety, and/or stress had a higher prevalence of changes in their menstrual cycle, worsening premenstrual symptoms, dysmenorrhea, and reduced libido. Garcia de Leon et al.<sup>21</sup> also stated that their analysis showed there were twice as many respondents who indicated changes in symptoms due to the pandemic control measures. In line with the research by Payne et al.<sup>17</sup>, stress during the pandemic was associated with an increase in menstrual pain, the number and severity of premenstrual syndrome, as well as menstrual pain disorders. These menstrual abnormalities can also disturb a woman's quality of life.<sup>18</sup>

Broke down of the supply chains in the world, shutdown of retail stores, and mandated restrictions of movement during COVID-19 lockdowns had given negative affect of menstruators physical and mental health.<sup>22,23</sup> The stress response is based on the hypothalamus-pituitary-adrenal (HPA) axis. Exposure to physical, social, and environmental stressors causes the secretion of various hormones and dysregulation of HPA axis activity.<sup>19</sup> The HPA axis is activated during stress, which results in CRH secretion from the hypothalamus. CRH acts on the pituitary, facilitating the release of adrenocorticotrophic hormone (ACTH), which interacts with the adrenal cortex and stimulates the release of cortisol. Chronic stress will produce an irregular HPA axis, as shown by glucocorticoids inhibiting the action of gonadotropin-releasing neurons (GnRH), gonadotrophs, and gonads. Excessive CRH levels can also cause inhibition of the hypothalamic-pituitary-gonadal (HPG) axis. Other obstacles that can occur include decreased pituitary response to GnRH, resulting in decreased secretion of luteinizing hormone (LH), giving direct inhibitory effects of glucocorticoids on sex hormone secretion, glucocorticoid-induced resistance to gonadal steroids in target tissues, and direct catecholaminergic inhibition of FSH, LH secretion, and prolactin.<sup>10</sup>

Contrasting to the stress levels, a study conducted by Nguyen et al.<sup>14</sup> states that the absence of this

relationship may be related to the sociodemographic of the respondents. This study was conducted on women with a college education in their 30s and in relationships. These criteria have been considered in several studies to be able to adapt well during the COVID-19 pandemic. This statement is supported by research by Kwak et al.<sup>20</sup> and Andiarna<sup>23</sup> which states that abnormal menstruation is commonly found in women with lower socioeconomic status and education. Significantly, seven out of eight studies concluded that there was a link between stress during the pandemic and abnormal menstruation. The highest cases were found in premenstrual syndrome and dysmenorrhea, and the lowest was found in menstrual cycle disorders (polygomenorrhea, oligomenorrhea, amenorrhoea).

Limitations of this study were in the choice of language, the difference in the use of questionnaires in each study, in which some studies did not include the results of their validity, and the lack of sources, which limited to open access study. These limitations reduced the diversity of information which could have been included in this systematic review.

## CONCLUSION

There is a significant relationship between stress during the COVID-19 pandemic and the incidence of menstrual abnormalities. Future researchers are expected to be able to study further on the effect of stress during the COVID-19 pandemic on menstrual disorders.

## DISCLOSURES

### Acknowledgment

None

### Conflict of interest

There are no conflicts of interest in this study's content among all authors

### Funding

This research has received no external funding.

### Author Contribution

All authors have contributed to all processes in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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## CASE REPORT

### The effectiveness of McDonald Transvaginal Cerclage in preventing preterm labor

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Article Info	ABSTRACT
<p>Received Mar 9, 2023 Revised Jun 9, 2023 Accepted Jun 16, 2023 Published Dec 1, 2023</p> <p><b>*Corresponding author:</b> Adhi Pribadi priana1001@gmail.com</p> <p><b>Keywords:</b> Cervix incompetence Premature birth Cervical cerclage Tocolytic agents Silk Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p><b>Objective:</b> To determine the success and effectiveness of the use of McDonald's transvaginal cerclage techniques and the thread material used to prevent premature labor in cases of uterine cervical incompetence.</p> <p><b>Case Report:</b> This was a retrospective study. Data for 13 patients were taken from the medical records of Dr. Hasan Sadikin Hospital, Bandung, Indonesia, and private clinics from the years of 2009 to 2021. The procedure used was a McDonald's cerclage technique with material suture using silk no. 1 and mersilene tape thread. Indications were used based on a previous history of obstetrics preterm, abortion beyond 13 weeks or based on cervical length. The criterion for cerclage success was achieving pregnancy at 36 weeks. Adjuvant therapy using tocolytics was administered intermittently in all patients. The patient was advised to douch the vagina using an antiseptic if there was excessive vaginal discharge. According to the success criteria, 92% of elective McDonald cerclages were able to maintain a pregnancy well up to 36 weeks. A total of 11 elective cases used silk no. 1, while mersilene was used in 1 case. The silk no. 1 thread material was used in the elective cases with 91% success. One case using mersilene tape was able to maintain pregnancy until delivery by cesarean section at 38 weeks of age with bicornuate uterine pathology. One case of emergency cerclage with silk no. 1 failed to maintain pregnancy until 36 weeks.</p> <p><b>Conclusion:</b> The use of cerclage in conjunction with adjuvant therapy and antiseptic douching efforts has resulted in good success in maintaining pregnancy in cases of cervix incompetence with a history of obstetric preterm and recurrent abortus. When there is no tape-shaped thread material suture, the use of silk thread or other monofilament threads with a larger diameter can be considered.</p>

**How to cite:** Pribadi A. The effectiveness of McDonald Transvaginal Cerclage in preventing preterm labor. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science)*. 2023;31(3):157-161. doi: 10.20473/mog.V31I32023.157-161.

#### Highlights:

1. Cervical cerclage is effective to prevent preterm birth.
2. The use of silk thread (monofilament) or ribbon for suture material is successful in maintaining pregnancy.

#### INTRODUCTION

Cerclage or suturing of the uterine cervix is a way to reduce the risk of preterm labor or delivery in the second trimester.<sup>1</sup> The incidence of preterm labor is determined by factors such as multiple pregnancies, uterine anomalies, history of cervical trauma due to

destructive procedures or dilatation during curettage, and size of the cervix. A short cervix is mainly detected on transvaginal ultrasound examination.<sup>2</sup> There are 2 transvaginal suturing techniques, the Shirodkar technique and the McDonald technique (and its modifications). The cerclage technique has been used in singleton pregnancies or multiple pregnancies.<sup>3</sup>





Most cerclage techniques are currently performed transvaginally. However, if transvaginal surgery is problematic, it can be performed transabdominally.<sup>4</sup> The success rate of transvaginal cerclage varies greatly between studies. Zakkia found a success rate of 73.<sup>3</sup> percent, while Waloch found a success rate of 90.8 percent.<sup>5,6</sup> The use of monofilament and thin thread material is ideal because it reduces the risk of infection.<sup>7</sup> Although it has several advantages, the use of tape-shaped thread is not more effective than monofilament thread.<sup>8</sup> The purpose of this study was to determine the success and effectiveness of the McDonald's transvaginal cerclage technique, as well as the thread material used.

### CASE REPORT

From 2009 to 2021, data were collected retrospectively from the medical records of Dr. Hasan Sadikin Hospital in Bandung, Indonesia, as well as from private clinics in the same town. The procedure used was a McDonald's cerclage technique, with the types of thread available for use were silk no. 1 and Mersilene. Indications used were based on previous obstetric history, such as preterm delivery at least once, repeated abortions beyond 13 weeks, or based on cervical length using a transvaginal ultrasound device. After the cerclage, the patient was advised to douch the vagina using an antiseptic if there was excessive vaginal discharge. Adjuvant therapy using tocolytics, given intermittently in all patients, was recommended to be consumed if

there were uterine contractions. The tocolytics used were  $\beta_2$  agonists or isoxsuprine. Subsequent pregnancy control was carried out according to the general antenatal care schedule. The criteria for the success of cerclage is when the pregnancy reaches 36 weeks (when the sutures are opened) and is accompanied by good fetal condition based on clinical evaluation and ultrasound.

After collecting the data, there were 13 cases that met the criteria, and a cerclage was taken. There were some cases where they met the criteria for cerclage but refused to do the procedure. A total of 6 cases (46%) of deliveries were directly monitored because the patient was pregnant again and had a second cerclage sutured or gave birth in a hospital that was recommended, especially by cesarean section. In some cases, vaginal delivery after 36 weeks may be required.

In 54% of cases, women gave birth in several medical service sites or other hospitals with no information, so that the time of delivery was unknown. However, according to the success criteria, a total of 11 elective cases used silk no. 1 with 91% success rate. One case of emergency cerclage with silk no. 1 failed to maintain pregnancy until 36 weeks. Meanwhile, one case using mersilene tape was able to maintain pregnancy until delivery by cesarean section at 38 weeks of age with bicornuate uterine pathology. The complete cases can be seen in Table 1.

Table 1. Number of cases that underwent cerclage

No	Living baby	Cervical length	Cerclage (Weeks)		Delivery time (weeks)	Thread Types	Obstetrics history	
			Start	Off				
1	G2P1A0	0	2.5 cm	24	36	No data	Silk	1 preterm
2,3 <sup>A</sup>	(2)G3P0A2	0	1.5 cm	17	36	Aterm	Silk	2 abortion*
	(3)G4P1A2	1	2.2 cm	15	36	Aterm	Silk	2 abortion*
4	G3P2A0	0	Not measured	20	Aterm	No data	Silk	2 preterm
5	G4P3A0	1	Not measured	16	36	No data	Silk	3 preterm
6 <sup>B</sup>	G4P3A0	0	Not measured	25	35	35	Silk	3 preterm
7,8 <sup>A</sup>	(7)G5P4A0	0	Not measured	16	36	Aterm	Silk	4 preterm
	(8)G6P5A0	1	Not measured	14	36	Aterm	Silk	4 preterm
9	G3P2A0	0	3.0 cm	16	36	No data	Silk	2 preterm
10 <sup>C</sup>	G3P2A0	0	3.0 cm	14	38(CS)	38	Mersilene	2 preterm
11	G3P0A2	0	3.0 cm	14	38(CS)	38	Silk	2 abortion*
12	G3P0A2	0	3.4 cm	14	37	No data	Silk	2 abortion*
13 <sup>D</sup>	G2P1A0	1	1.5 cm	30	30	30	Silk	-

Notes: A: 2 times cerclage; B: Midwife, living baby 2300 grams; C: Bicornuate uterus, D: Hospital, living baby 1440 grams, \*Beyond 13 weeks, EMG: Emergency, CS: Cesarean Section.



## DISCUSSION

Elective cerclage, according to Table 1, can maintain pregnancy up to 36 weeks, almost the same as that obtained by Waloch.<sup>6</sup> The majority of cerclage suturing used silk sutures with a combination of intermittent administration of tocolytic  $\beta_2$  agonist or isoxsuprine. Combination therapy can be done by tocolytics so that contractions are reduced or lost and the pressure on the threads decreases, thereby reducing the risk of labor.<sup>2</sup> Tocolytics are used in varying doses with the main aim of making contractions disappear. The average number of preterms before cerclage in this study was 2.6 times.

The technique used in all cases was McDonald's, which was relatively easier to do than Shirodkar's technique, with no difference in the success rate of the procedure.<sup>10</sup> The thread material used was silk no. 1. In the majority of cases, it could maintain pregnancy for up to 36 weeks. Thus, the use of silk no. 1 suture may be considered in the absence of other types of suture, although combination therapy with tocolytics may increase the success of cerclage.<sup>11</sup> In Arora's study, the comparison of the use of silk and nylon did not differ in terms of the success rate or the degree of fibrosis that occurred.<sup>12</sup>

Douching is recommended in all patients only when there is excessive vaginal discharge to reduce the potential for infection. Douching is not recommended to be done routinely because it will reduce the balance of the vaginal atmosphere, so that in the long term it will reduce health.<sup>13</sup> Silk or mersilene is a foreign object in the vagina so that it increases the risk of infection. So, whatever type of thread is chosen, the possibility of infection must always be considered and addressed at the cerclage procedure.

Case no. 10 is a unique case with the cause of preterm labor being a bicornuate uterus with 2 lethal preterm deliveries. Bicornuate uterus is one of the causes of abortus or recurrent preterm labor because it has a shorter cervical length when compared to pregnancy with normal uterus.<sup>14</sup> Based on the research, it was decided to use a tape-shaped thread (mersilene) in this case because the tape form is stronger in resisting contraction than monofilament although it is not more effective. Pregnancy care in case no. 10 went well and an elective cesarean section was performed at 38 weeks with the fetus in a transverse position. The cerclage was then opened after a cesarean section.

Case no. 13 was an emergency case at 30 weeks of gestation with a cervical shortening of 1.5 cm and strong uterine contractions. After that, the cerclage was carried out with silk no. 1 because tape-shaped was not

available. Uterine contractions were abolished by titrating  $\beta_2$ -agonist tocolytics, but 2-day treatment tended to not disappear completely, and cervical shortening continued. On the second day of treatment, it was decided to remove the cerclage because it was not effective. Shortly after being released, there was labor. The success of emergency cerclage tends to be lower than when performed at the early of the 2nd trimester or without contractions.<sup>15</sup>

There were 4 cases of cerclage with an indication of a history of abortion beyond 13 weeks. Cervical length was measured in all of these abortion cases, with an average of 2.4 cm. Procedure using silk thread with a 100% success rate of pregnancy can be maintained until at least 36 weeks. Cases 2 and 3 are the same person with a very short cervical length below 2.5 cm. Cerclage efforts are very helpful in cases of abortion, especially in cases of incompetent cervix, such as this one with indication short cervical length.<sup>16</sup>

Cases 7 and 8 are examples of cerclage cases with repeated preterm indications, with a history of four preterms and no living children. After a successful 5th pregnancy, the patient was then pregnant again (6th) and a second cerclage procedure was performed. The second cerclage procedure had made it to 36 weeks of gestation. The indication in this case was repeated preterm.<sup>17</sup> As there was no clear evidence of a difference between using an obstetric history indication or a short cervix for cerclage, so clinical indications such as the number of preterm deliveries or ultrasound measurement of cervical length can still be used.<sup>18</sup> The outcome of pregnancy of the two babies from this patient was good and the babies survive.

Delivery after cerclage can still be done vaginally.<sup>19</sup> The opening of the cerclage is at 36-37 weeks of gestation.<sup>6</sup> Delivery interval after cerclage removal was 9.3 days, and only 20% were delivered within 48 hours.<sup>20</sup> It is expected that after entering 37 weeks, term labor is the best time for labour. Cerclage is not an indication for cesarean section.<sup>21</sup> Obstetric indications continue to be the best choice for mode of delivery following cerclage.

The limitations in this study were the minimal number of patients, limited transvaginal ultrasound equipment, and delivery that was not fully monitored after the cerclage was opened. So, it is necessary to collect more cases with better diagnostic procedures and delivery management at the recommended place, so that the conclusions drawn are more precise, especially regarding the success of the procedure.

## CONCLUSION



The use of a combination of cerclage with adjuvant therapy and antiseptic douching efforts has good success in maintaining pregnancy in cases of uterine cervical incompetence. When there is no tape-shaped thread material suture, the use of silk threads no 1 or larger diameter can be considered.

## DISCLOSURE

### Acknowledgment

Gratitude is expressed to the Maternal-Fetal Medicine Division, Department of Obstetrics and Gynecology Padjadjaran University, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia.

### Conflict of interest

No conflict of interest

### Funding

This research has received no external funding.

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## CASE REPORT

### Complicated vivax malaria in pregnancy: A case report in rural area of Indonesia

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Article Info	ABSTRACT
<p>Received May 11, 2023 Revised Aug 2, 2023 Accepted Aug 11, 2023 Published Dec 1, 2023</p> <p><b>*Corresponding author:</b> Yudianto Budi Saroyo yudibs@gmail.com</p> <p><b>Keywords:</b> Vivax malaria Complication Education Anemia Pregnancy Maternal health</p> <p>This is an open access article under the CC BY-NC-SA license (<a href="https://creativecommons.org/licenses/by-nc-sa/4.0/">https://creativecommons.org/licenses/by-nc-sa/4.0/</a>)</p> 	<p><b>Objective:</b> This study aimed to report a preterm delivery and anemia as part of <i>P. vivax</i> malaria infection complications in a pregnant woman in Timor Tengah Selatan regency, East Nusa Tenggara, Indonesia.</p> <p><b>Case report:</b> A 42-year-old pregnant woman, gravida 6 para 5, 36-week of gestational age pregnant woman came with complaints of water breaking since one day before admission. She had fever with chills for three days, especially at night along with muscle, headache, joint soreness, dizziness, and palpitations. Rapid diagnostic test for malaria showed positive result. Peripheral blood smear examination revealed microcytic hypochromic due to iron deficiency or chronic infection and presence of trophozoites-ring form of <i>P. vivax</i> with 4,235 parasitemia. A baby boy was born with weight of 2,470 grams (percentile 28%), fetal head 31 cm (percentile 13%), birth length 43 cm (percentile 4%), and Apgar Score (AS) 8 and 9 at 1 and 5 minutes, respectively. The treatment was provided according to anti-malarial guideline in Indonesia using dihydroartemisinin 120 mg and piperazine phosphate 960 mg fixed dose as DHP for 3 days and primaquine 15 mg for 14 days.</p> <p><b>Conclusion:</b> Anemia as part of vivax malaria complication in pregnancy contributes to preterm delivery.</p>

**How to cite:** Surya R, Manurung ES, Saroyo YB. Complicated vivax malaria in pregnancy: A case report in rural area of Indonesia. *Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science)*. 2023;31(3):162-166. doi: 10.20473/mog.V31I32023.162-166.

#### Highlights:

1. In malaria endemic area, pregnant women are highly prone to suffer from malaria infection.
2. Vivax malaria in pregnancy can contribute to anemia and preterm delivery.

#### INTRODUCTION

World Health Organization (WHO) reported there were 247 million cases of malaria with 619,000 death cases in 2021.<sup>1</sup> Around 90% of the population at risk of *Plasmodium vivax* (*P. vivax*) infection lives in the Asia

and Pacific regions.<sup>2</sup> In Indonesia, the prevalence of diagnosed and treated malaria in pregnant women was 2,650 cases.<sup>3</sup> *P. vivax* infection in pregnancy is associated with stillbirth, preterm delivery, low birthweight, and anemia.<sup>4-6</sup> However, this infection is

less severe than *P. falciparum* because it infects only reticulocytes; thus, there are parasites densities.<sup>7</sup>

In endemic area of malaria, pregnant women are highly prone to suffer from malaria infection.<sup>8</sup> *P. vivax* infection in pregnancy is associated with maternal anemia and hepatic dysfunction, miscarriage, congenital malaria, preterm delivery, and development to severe disease.<sup>6,9,10</sup> A significant burden and impact of *P. vivax* infection in pregnancy needs a strategy to prevent and control the spread of the infection. Unfortunately, *P. vivax* and *P. ovale* are the only malaria species which have the ability to relapse because of the dormant liver stages known as hypnozoites. In acute stage of vivax malaria, schizontocidal agent chloroquine (CHQ) is the key of treatment and it is also safe for pregnancy.<sup>11</sup> To prevent the occurrence of relapse, both 8-aminoquinolines prima-quine (PMQ) or tafenoquine (TQ) are active against hypnozoites stage of *P. vivax*. However, it is contraindicated in pregnancy because the glucose-6-phosphate dehydrogenase (G6PD) status of the fetus cannot be determined antenatally in most malaria endemic settings.<sup>11,12</sup>

Therefore, this study aimed to report a preterm delivery and anemia as part of *P. vivax* malaria infection complications in a pregnant woman in endemic areas of malaria in Indonesia, the Timor Tengah Selatan regency, East Nusa Tenggara.

## CASE REPORT

A 42-year-old pregnant woman, gravida 6 para 5, 36-week of gestational age pregnant woman was admitted to a rural hospital in SoE, East Nusa Tenggara, Indonesia with complaints of water breaking in the past one day before admission. She had fever with chills for three days, especially at night along with muscle, headache, joint soreness, dizziness, and palpitations. No history of malaria infection before. The patient had a BP of 110/70 mmHg, pulse 105 bpm, RR 20 bpm, temperature 102<sup>0</sup>F, and saturation of 98% without oxygen support. Physical examination revealed normal range. On obstetrical status, there was head presentation at station -1 and 2 cm dilatation without intact membrane. Ultrasound examination showed oligohydramnios with estimated fetal weight (EFW) of 2,500 grams.

The patient had Hb 8.3 g/dL, leucocyte 12,400/uL, platelet 229,000/uL, mean corpuscular volume (MCV) 76/um, mean corpuscular hemoglobin (MCH) 25 pg, granulocyte 69%, lymphocyte 23%, monocyte 8%, random blood glucose (RBG) 112 mg/dL, aspartate aminotransferase (AST) 28 U/L, alanine aminotrans-

ferase (ALT) 24 U/L, urea 13 mg/dL, creatinine 0.4 mg/dL. Rapid diagnostic test for malaria showed positive result. Peripheral blood smear examination revealed microcytic hypochromic due to iron deficiency or chronic infection and presence of trophozoites-ring form of *P. vivax*. Malaria smear showed 4,235 *P. vivax* parasitemia with trophozoite-ring form stage of the parasite present (Figure 1).



Figure 1. Trophozoite-ring form stage of *P. vivax* parasitemia.

After observation for 12 hours, a baby boy was born with a weight of 2,470 grams (percentile 28%), fetal head 31 cm (percentile 13%), birth length 43 cm (percentile 4%), and Apgar Score (AS) 8 and 9 at 1 and 5 minutes, respectively. Examination on the Fenton growth curve revealed that it was still appropriate for gestational age (AGA). Neonatal and cord blood smears were negative for malaria parasites.

The treatment was in line with anti-malarial guideline in Indonesia using dihydroartemisinin 120 mg and piperazine phosphate 960 mg fixed dose as DHP for 3 days and PMQ 15 mg for 14 days. Paracetamol in divided doses was given to control the fever. The fever clearance time was 12 hours, and the clinical symptoms was resolved after day 1. The patient was hospitalized for three days to obtain DHP administration. The patient was well and she was to be discharged. Evaluation after 7, 14, and 21 days of treatment revealed no *P. vivax* on peripheral blood smear (Figure 2).

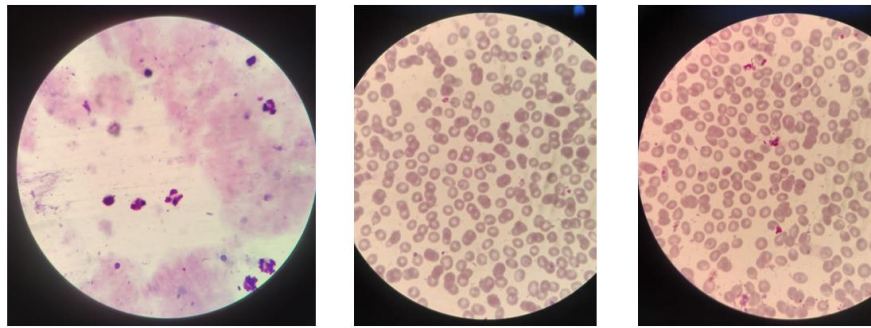


Figure 2. Blood smear evaluation after 7 (left), 14 (center), and 21 (right) days of treatment with no *P. vivax* parasitemia found.

## DISCUSSION

The classic *P. vivax* malaria symptoms consist of fever, headache, and chills which usually occur after 10-15 days after getting bitten by an infected mosquito.<sup>1</sup> The high frequency of headache combined with fever in *P. vivax* infection requires the malarial rapid diagnostic test at antenatal check-up, especially in endemic area.<sup>13</sup> In our case, a woman came with fever and headache so that the midwives performed malarial rapid diagnostic test. *P. vivax* microscopic mono-infection is defined as the presence of asexual *P. vivax* parasites of any densities and no other of Plasmodium species found on the blood smear. Congenital malaria is defined as the presence of asexual Plasmodium parasites in the peripheral of neonates or cord blood at delivery without regarding the clinical symptoms and signs.<sup>6</sup>

In Asia, infection of both *P. falciparum* and *P. vivax* in pregnancy are prevalent, while *P. vivax* infection is considered to be benign and results in less morbidity than *P. falciparum*.<sup>14</sup> A study in Papua showed that high drug-resistant malaria and the ability to relapse of *P. vivax* infection caused 34% of infections in pregnancy,<sup>8</sup> which was higher than that reported in a study from Thailand with the prevalence of 17%.<sup>15</sup> The higher transmission rate might be supported by good immunity to suppress both symptoms and parasitemia, resulted in persistent infection, whether it is undetected and untreated. In addition, lower parasitemia density in *P. vivax* infection, as compared to infection with *P. falciparum*, results in less symptom presentations. Therefore, women who search for treatment are less.<sup>8</sup> In our case, the woman came to the health facility due to obstetrics reason with suspicious symptoms of malaria. She underwent rapid positive malarial test and was continued with *P. vivax* infection on peripheral blood smear. There was 4,235 *P. vivax* parasitemia, higher than that in a study in Papua which showed lower

average of *P. vivax* parasitemia (632 parasites/uL). Thus, our patient revealed classic symptoms of malaria corresponding to higher parasitemia level.<sup>8</sup>

The risk of anemia, small for gestational age (SGA), and preterm delivery is increasing along with *P. vivax* infection. A study by Bardaji et al.<sup>6</sup> revealed that clinical *P. vivax* infection increased the risk of maternal anemia (OR 5.48; 95% CI 1.83-16.41; p=0.009). Meanwhile, another study in Venezuela stated that 84.6% of women with malaria came with mild to severe anemia, where the severe anemia as the most frequent complication of around 23%, which was corresponding to some studies in Brazil.<sup>16,17</sup> Vivax malaria infection is associated with the increased of SGA (OR 1.27; 95% CI 1.21-1.33).<sup>18</sup> Meanwhile, vivax malaria infection at each gestational age is related to preterm birth (OR 1.23-1.79).<sup>18</sup> In our case, the woman suffered from vivax malaria at 36 weeks of gestational age with clinical symptoms of microcytic hypochromic anemia, AGA, and preterm delivery due to obstetrical indication of water breaking. On peripheral blood smear, we found microcytic hypo-chromic smear due to iron deficiency or chronic infection or malaria infection. Whether *P. vivax* infection causes preterm birth or SGA is still debatable. There are some evidences that *P. vivax* is able to sequester in the placenta, regardless of placental inflammation as one of factors contributing to preterm birth.<sup>18</sup> In *P. vivax* infection, systemic inflammation is more common than local placental inflammation which is proved by modest placental pathology and absent of sequestration.<sup>19</sup> In our case, the history of malaria infection was unknown. The possibility of preterm birth in our case might be caused by maternal anemia impacting to vivax-associated SGA.<sup>18</sup> Besides, anemia in malaria is often normocytic and normochromic without spherocytes or schistocytes. However, microcytic hypochromic anemia in our case was related to malaria is because of high frequencies of hemoglobin-

opathies and iron deficiency in endemic countries. Therefore, malaria infection combined with iron deficiency anemia is the most common problem in pregnancy, resulting in preterm birth through preterm premature rupture of membrane.

In endemic areas of malaria, routine screening at antenatal visit and optical microscopy should be used for case detection of malaria infection.<sup>20</sup> WHO recommends all suspected cases of malaria having to be confirmed by diagnostic testing using parasite-based microscopy or rapid diagnostic test. The treatment of malaria needs multiple medicines based on type of malaria, drug-resistance, weight or age of infected person with malaria, and pregnancy status.<sup>1</sup> In *P. vivax* infection, dormant hypnozoites leading to relapses weeks or months later, prevention of relapses is the most important strategy for disrupting transmission.<sup>21</sup> PMQ is the only drug licensed for prevention of relapses. However, it is contraindicated in pregnancy due to safety reasons. It imposes to higher risk of clinical relapses.<sup>22</sup> Pregnant woman often serve as asymptomatic parasite reservoirs so that it limits for effective malaria control and elimination. Fortunately, our patient delivered after 12 hours of observation and she was administered with PMQ after delivery. Before PMQ administration, a mother should have been tested for G6PD deficiency. Side effects such as abdominal pain and risk of drug-induced hemolysis are part of complications in G6PD-deficient individuals.<sup>22,23</sup> WHO conditionally recommends for radical cure postpartum after 6 months of age.<sup>24</sup>

This study was conducted in an endemic area of malaria in Indonesia. Thus, the analysis both in hospital and primary health care was used to examine malaria through peripheral blood smear. Besides, this study depicted the classical symptoms of malaria in pregnancy as well as the complication of the pregnancy. However, due to the limitation of laboratory tests in remote area, there was no availability of iron profile test such as serum iron, ferritin, transferrin, and total iron binding capacity (TIBC) and hemoglobin electrophoresis to rule out the differential diagnosis of microcytic hypochromic anemia.

## CONCLUSION

Anemia as one of vivax malaria complications in pregnancy contributes to preterm delivery. PMQ is the drug for preventing relapses in vivax malaria. However, it is contraindicated in pregnancy.

## DISCLOSURES

### Acknowledgment

Thank you to all parties involved in this research.

### Conflict of interest

All authors have no conflict of interest.

### Patient consent for publication

The patient has agreed that her case is to be published in a case report.

### Funding

This research has received no external funding.

### Author contribution

All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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**MAJALAH OBSTETRI & GINEKOLOGI****INDEX****Volume 31, April, August, December 2023****AUTHORS**

Achmad, L	3:123-128	Lubis, AD	1:30-35
Agustina, VL	1:52-60	Lubis, IK	1:45-51
Ambari, E	3:123-128	Lumbanraja, SN	2:86-91
Andrina, H	3:129-138	Manurung, ES	3:162-166
Ardiansyah, E	2:86-91	Mardiyana, NE	2:75-79
Arif, M	1:45-51	Maskasoni	2:61-67
Armanza, F	2:68-74	Melinawati, E	1:11-16
Ashar, H	1:45-51	Mirani, P	3:129-138
Budihastuti, UR	1:11-16	Murwani, A	1:45-51
Darto	1:11-16	Musoddaq	1:45-51
Dewantiningrum, J	2:61-67	Nainggolan, PAS	1:30-35
Dewi, MS	3:117-122	Nooryanto, M	2:92-96
Dwiningsih, SR	1:52-60	Nugroho, SB	3:150-156
Dwiyan, RK	1:11-16	Pangestu, M	1:11-16
Dzikrifishofa, M	2:92-96	Prakosa, T	1:11-16
Edianto, D	3:117-122	Pribadi, A	3:157-161
Effendi, IH	2:86-91	Purnamasari, NDA	1:36-44
Ernawati	2:80-85, 2:103-109	Puspita, IM	2:75-79
Ernawati, M	3:110-116	Putra, VGE	3:123-128
Eyanoer, P	2:86-91	Qonitatillah, J	2:103-109
Fachryandini, N	2:80-85	Rahajeng	2:92-96
Fadhdy, M	3:117-122	Rahman, MA	2:80-85
Faizal, TR	3:123-128	Ratnasari, AA	1:11-16
Faradina, D	1:30-35	Rozifa, AW	2:75-79
Fatin, FN	1:23-29	Rusda, M	1:30-35
Fauziyah, S	3:150-156	Sa'adi, A	3:150-156
Frety, EE	3:150-156	Samsudin, M	1:45-51
Hadi, C	1:11-16	Saroyo, YB	3:162-166
Halim, KS	2:68-74	Senewe, FP	1:45-51
Hardianto, G	1:23-29	Shabrina, A	1:17-22
Hidayat, T	2:80-85	Simanjuntak, RY	3:117-122
Hidayati, HB	1:17-22	Singgih, R	3:139-149
Iskandar, TM	3:123-128	Siregar, MFG	2:86-91
Izzati, D	1:23-29	Siswanto, T	3:110-116
Jatiningtyas, AZ	1:11-16	Sitepu, M	3:117-122
Kesty, C	3:129-138	Sudewo, Y	2:86-91
Khaerunnisa, S	1:52-60	Sukmawati, M	1:11-16
Khoiri, MA	2:86-91	Sulistyo, A	2:103-109
Kristiawan, EC	3:123-128	Supadmi, S	1:45-51
Kurniasari, N	1:17-22, 1:36-44	Surya, R	3:162-166
Kusrini, I	1:45-51	Susanto, L	1:11-16
Kusuma, AANJ	2:97-102	Susilowati, T	1:45-51
Kusumawardani, HD	1:45-51	Tamara, Y	3:139-149
Kwary, MMI	3:139-149	Tjokroprawiro, BA	1:36-44, 1:17-22
Laqif, A	1:11-16	Tristiarti, AM	1:11-16
Legiran	3:129-138	Triyawati, L	1:1-10
Lintang, LS	3:117-122	Utomo, B	1:36-44

Utomo, B	3:150-156	Yunitawati, D	1:45-51
Waluyo, ST	2:68-74	Yuseran, H	2:68-74
Yuliani, E	1:1-10		

## SUBJECTS

Abnormal Uterine Bleeding	1:30-35	Leiomyoma	1:30-35
Anemia	3:110-116, 3:162-166	Malaria, vivax	3:162-166
Attitude	3:110-116	Malignancy	1:17-22
$\beta$ -hCG	1:17-22	Menopause, duration	2:86-91
Bishop score	2:61-67	Menstrual abnormalities	3:150-156
Body Mass Index	2:80-85	Mental health	1:23-29
Cancer	2:68-74	Micronutrient	2:92-96
Cervical cancer	1:36-44, 3:123-128	Midwife	2:75-79
Cervical cerclage	3:157-161	Midwifery service	2:75-79
~ ripening	2:61-67	Misoprostol, oral	2:61-67
Cervix incompetence	3:157-161	Misoprostol, vaginal	2:61-67
Cesarean section	1:45-51	MMP-1	2:92-96
Chemotherapy	1:17-22	Modified Obstetric Early Warning Systems (MEOWS)	3:139-149
Chronic Energy Deficiency	1:1-10	Monochorionic Monoamniotic	2:103-109
Collagen, type-1	2:92-96	Neutrophil Lymphocyte Ratio	3:117-122
Complementary therapies	2:75-79	Neutrophil-to-lymphocyte Ratio (NLR)	3:139-149
Complication	3:162-166	Obstetrics	3:129-138
Complications, obstetrics	1:45-51	Ovarian cancer	3:117-122
Congenital Heart Disease	2:80-85	~ cyst	3:117-122
COVID-19	1:23-29, 2:68-74	Pain	1:52-60
COVID-19	2:97-102, 3:150-156	PALM-COEIN	1:30-35
Delivery management	2:103-109	Parity	1:36-44
Delivery method	1:45-51	Parity	3:110-116
DNA fragmentation index	1:11-16	Pelvic Organ Prolapse	2:92-96
Dysmenorrhea	1:52-60	Placenta	2:97-102
Education	1:1-10, 3:162-166	Platelet Lymphocyte Ratio	3:117-122
Female Sexual Function Index	2:86-91	Preeclampsia	3:139-149
Fennel	1:52-60	Pregnancy	1:23-29, 2:97-102
First complaint	1:36-44		3:162-166
Gestational Trophoblastic Neoplasia	1:17-22	Pregnancy factors	3:110-116
Ginger	1:52-60	~ outcomes	1:23-29
Gynecology	3:129-138	~ rate	1:11-16
Gynecology oncology	2:68-74	Premature birth	3:157-161
Health services	2:68-74	Pre-pregnancy	2:80-85
Histopathology	1:36-44, 2:97-102	Radiation proctitis	3:123-128
Hydatidiform mole	1:17-22	Radiation therapy	3:123-128
Incubator	1:11-16	Regional origin	1:36-44
Infertility, male	1:11-16	Sexual function	2:86-91
Informative Support	1:1-10	Silk	3:157-161
Insemination, intrauterine	1:11-16	Sperm morphology	1:11-16
Instrument Support	1:1-10	~ motility	1:11-16
Intrauterine insemination	1:11-16	Stage	1:36-44
Knowledge	1:1-10, 3:110-116	Stem cells, amniotic	3:129-138

Stem cells, bone marrow	3:129-138	Testosterone	2:86-91
~ mesenchymal	3:129-138	Tocolytic agents	3:157-161
Stress	3:150-156, 1:23-29	Twin pregnancy	2:103-109
Swim-up method	1:11-16	Vitamin D	2:92-96

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