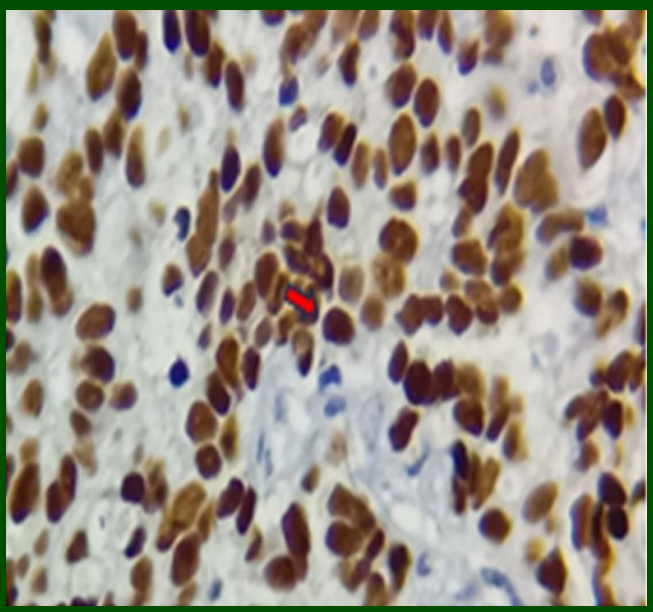
DOAJ DIRECTORY OF OPEN ACCESS JOURNALS

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE
Vol. 33 No. 1 April 2025



Strong intensity of PAX8 expression observed under the microscope at 400x magnification

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

Vol. 32 No. 3 December 2024

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

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

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Vol. 33 No. 1 April 2025

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

CONTENT

Cover :
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AUTHOR GUIDELINES

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Case series highlights important innovations with wide applicability or previously unpublished complications of new techniques or medications. The authors must confirm in the manuscript that they have obtained **written permission** of those whose case is being presented. The manuscript should be approximately 3500 words. Total number of tables and figures are limited, advisably not more than five, and references are minimally 20 from the last 10 years before the date of submission. The text consists of **Abstract, Introduction, Case Series, Discussion, Conclusion,** and **Disclosures**. The Disclosures consist of **Acknowledgment, Conflict of Interest, Patient Consent for Publication, Funding,** and **Authors Contribution**.

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1. Journal

Up to three authors, list all the authors.

Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347(4):284-7.

More than three authors, list the first three authors, followed by et al.

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.

Chapter of an edited book

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Translated book

Luria AR. The mind of a mnemonist. Solotaroff L, translator. New York: Avon Books; 1969.

Electronic book/E-book

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Darwin C. On the origin of species by means of natural selection or the preservation of favoured races in the struggle for life [Internet]. London: John Murray; 1859. Chapter 5, Laws of variation. [cited 2010 Apr 22]. Available from: http://www.talkorigins. org/faqs/origin/ chapter5.html

Full text electronic book

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Offline proceeding

Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

Online proceeding

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/ csli publicationsSta/cslipublications/HPSG/2003/toc.shtml

Thesis/dissertation

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Kay JG. Intracellular cytokine trafficking and phagocytosis in macrophages [dissertation]. St Lucia, Qld: University of Queensland; 2007

Online thesis/dissertation

Pahl KM. Preventing anxiety and promoting social and emotional strength in early childhood: an investigation of risk factors [dissertation on the Internet]. St Lucia, Qld: University of Queensland; 2009 [cited 2017 Nov 22]. Available from: https://espace.library.uq.edu.au/view/UQ:178027

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Diabetes Australia. Gestational diabetes [Internet]. Canberra (ACT): Diabetes Australia; 2015 [updated 2015; cited 2017 Nov 23]. Available from: https://www.diabetesaustralia.com.au/gestational-diabetes

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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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As the general rule, the reference numbers:

- should be placed outside full stops and commas
- the citation number can be place next to the author name where emphasis is place on the author eg. Smith[2]
- 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".[1]
Numerous studies[20-22] have.....
Smith's research .....[21]
Smith and Jones'[22] research .....

Up to 3 authors eg. Smith, Jones and McDonald reported that .....[23]

More than 3 authors eg. Smith et al.[24] reports.

ORIGINAL RESEARCH

The expression of immunohistochemical biomarkers PAX8 and CD117 in platinum resistant ovarian cancer at Saiful Anwar General Hospital, Malang, Indonesia

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Article Info
Received May 18, 2024
Revised Aug 5, 2024
Accepted Aug 9, 2024
Published Apr 1, 2025

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Keywords:
Ovarian cancer
PAX8
CD117
Platinum resistance
Maternal health

ABSTRACT

Objective: Ovarian cancer, a prevalent gynecologic malignancy, frequently presents challenges due to platinum therapy resistance. This study aims to investigate a monitoring approach for post-operative ovarian carcinoma and evaluate the immunohistochemical expression of PAX8 and CD117 in ovarian cancer tissues, assessing their association with platinum resistance development.

Materials and Methods: Employing a cross-sectional observational analytical design, this study utilized consecutive sampling of patients meeting predefined inclusion and exclusion criteria. Tissue samples, obtained from biopsy or surgical procedures and processed into representative paraffin blocks, underwent immunohistochemical analysis at the Anatomical Pathology Department of Saiful Anwar Hospital, Malang, Indonesia. Expressions of PAX8 and CD117 were evaluated using immunohistochemistry. Diagnostic performance was assessed through receiver operating characteristic (ROC) curves and Youden index calculations to determine sensitivity and specificity.

Results: The study findings revealed that the area under the curve (AUC) for PAX8 and CD117 was 0.785 and 0.809, respectively. PAX8 expression exhibited a positive predictive value of 53.125%, negative predictive value of 87.50%, sensitivity of 18.75%, specificity of 51.85%, and accuracy of 60.0%. For CD117 expression, the corresponding values were 71.4%, 72.73%, 70%, 72.73%, and 70% for positive predictive value, negative predictive value, sensitivity, specificity, and accuracy, respectively.

Conclusion: The immunohistochemical expression of PAX8 and CD117 in ovarian cancer tissues may serve as prognostic biomarkers for platinum resistance. Despite these findings, the study acknowledges several limitations that warrant refinement in future research.

How to cite: Widodo RR, Nurseta T, Mustofa E, et al. The expression of immunohistochemical biomarkers PAX8 and CD117 in platinum resistant ovarian cancer at Saiful Anwar General Hospital, Malang, Indonesia. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):1-10. doi: 10.20473/mog.V33I12025.1-10.

Highlights:

1. Ovarian cancer, a prevalent gynecologic malignancy affecting women, poses a significant challenge due to the development of resistance to platinum-based therapy in its management.
2. PAX8 and CD117 have demonstrated potential as predictive biomarkers for platinum resistance in ovarian cancer; however, studies exploring their immunohistochemical expression in relation to platinum resistance in ovarian cancer patients remain limited.
3. This study aims to evaluate the immunohistochemical expression of CD117 and PAX8 in ovarian cancer tissues and investigate their association with the emergence of platinum resistance.

INTRODUCTION

Ovarian cancer, a significant gynecologic malignancy, ranks fourth among the most prevalent gynecological cancers globally, following cervical, breast, colorectal, and endometrial cancers. It is a major contributor to mortality, accounting for 47% of deaths related to gynecological malignancies.[1] Ovarian cancer is the fifth leading cause of cancer-related mortality among women, representing approximately 3% of all female malignancies. It predominantly affects older, post-menopausal women, with nearly 80% of cases diagnosed in individuals over 50 years of age.[2] In Indonesia, the precise prevalence and incidence of ovarian cancer remain uncertain. However, data from Dharmais Cancer Hospital in Jakarta, based on estimates from 2010 to 2013, indicate that ovarian cancer ranks as the fourth most common malignancy after breast, cervical, and lung cancers, with approximately 537 new cases and 126 reported deaths during that period.[3]

Alterations in the tumor microenvironment—including changes in extracellular matrix composition, matrix stiffness, hypervascularization, hypoxia, and paracrine signaling—are closely associated with cancer progression. Chemoresistance, a hallmark of aggressive malignancies, enables cancer cells to survive and adapt to chemotherapy. Components of the extracellular matrix may contribute to this resistance by activating signaling pathways that modify gene expression and protein activity, ultimately promoting therapeutic resistance. Understanding and overcoming chemoresistance remains a central goal of oncology research, as it is defined by the capacity of cancer cells to evade or withstand therapeutic interventions.[4]

PAX8 is recognized as a highly sensitive and specific immunohistochemical marker for identifying cancers originating from the ovary or fallopian tube. Its expression may provide valuable diagnostic and prognostic information, particularly in advanced-stage ovarian cancer, and may inform therapeutic strategies prior to neoadjuvant treatment.[5] Similarly, CD117 (c-Kit) is a transmembrane tyrosine kinase receptor essential for the development of several cell types, including melanocytes, germ cells, mast cells, erythrocytes, and interstitial cells.[6] CD117 plays a pathological role in various malignancies, including ovarian cancer. Recent studies have demonstrated that CD117 expression may influence responsiveness to targeted therapies such as imatinib, a tyrosine kinase inhibitor, thereby highlighting its potential clinical significance.[7]

Given this background, the present study aims to investigate a postoperative monitoring approach for ovarian carcinoma by evaluating the immunohistochemical expression of PAX8 and CD117 as potential predictive markers of platinum resistance in ovarian cancer patients at Saiful Anwar General Hospital, Malang, Indonesia.

MATERIALS AND METHODS

An analytical observational design with a cross-sectional study methodology was employed in this investigation. The research was conducted at the Gynecologic Oncology Outpatient Clinic, Medical Records Department, and the Anatomical Pathology Laboratory of Saiful Anwar General Hospital in Malang, Indonesia. The study period spanned from November 2022 to October 2023.

The sampling technique used in this study was non-probability sampling, specifically consecutive sampling, and adhered to the established inclusion and exclusion criteria. Tissue specimens obtained from biopsy or surgical procedures were processed into paraffin blocks, followed by immunohistochemical analysis at the Anatomical Pathology Department of Saiful Anwar General Hospital in Malang. Inclusion criteria comprised patients diagnosed with ovarian carcinoma by clinicians in the Obstetrics and Gynecology Department, who had received platinum-based chemotherapy and experienced recurrence within six months of their last chemotherapy session; patients who had undergone laparotomy for confirmation of clinical examination findings; and patients with paraffin blocks of ovarian cancer tissue available at the Anatomical Pathology Laboratory of Saiful Anwar General Hospital in Malang. Exclusion criteria included patients with adnexal masses not originating from the ovaries, those diagnosed with other malignancies, and those with infected adnexal masses.

The expressions of PAX8 and CD117 were evaluated from five distinct perspectives. Strong intensity of PAX8 and CD117 expression was identified under 400x magnification as dark brown nuclear staining. Moderate expression intensity was characterized by a lighter brown hue in the nuclei at the same magnification. In contrast, weak intensity was evidenced by a pale brown nuclear coloration under 400x magnification.

The expressions of CD117 and PAX8 were analyzed descriptively. Cut-off values for CD117 and PAX8 expression were determined by identifying the optimal threshold between sensitivity and specificity. This was accomplished through Receiver Operating Characteristic (ROC) curve analysis, supplemented by calculation of the Youden index. The cut-off corresponding to the

highest Youden index was selected as the optimal threshold. Subsequently, specificity, sensitivity, positive predictive value, and negative predictive value were calculated using the established cut-off values. Statistical analysis of the data was performed using the SPSS software program, with a p-value of < 0.05 considered statistically significant.

This research received ethical approval from the Health Research Ethics Commission of Saiful Anwar General Hospital, Malang, Indonesia, under registration number 400/228/K.3/102.7/2022, issued on 21 September 2022.

RESULTS AND DISCUSSION

Figure 1 and 2 display the features of the results obtained from the immunohistochemistry staining of PAX8 and CD117, respectively.

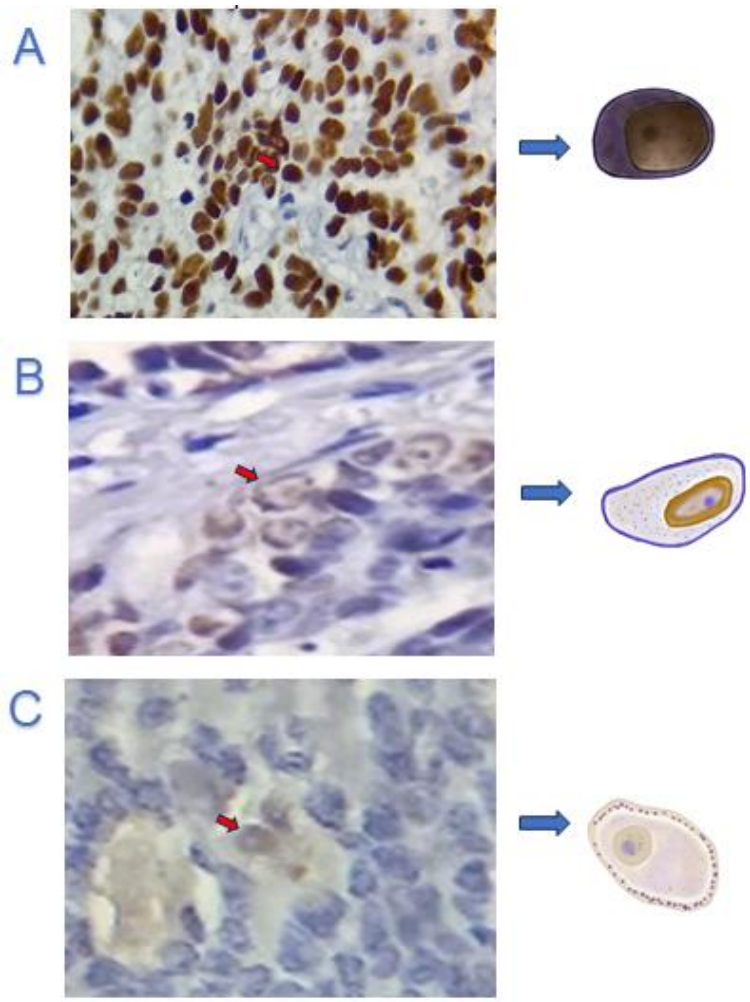

Figure 1. Immunohistochemical staining of PAX8 under the microscope. (A) Strong intensity of PAX8 expression observed under the microscope at 400x magnification; (B) Moderate intensity of PAX8 expression observed under the microscope at 400x magnification; (C) Weak intensity of PAX8 expression observed under the microscope at 400x magnification.

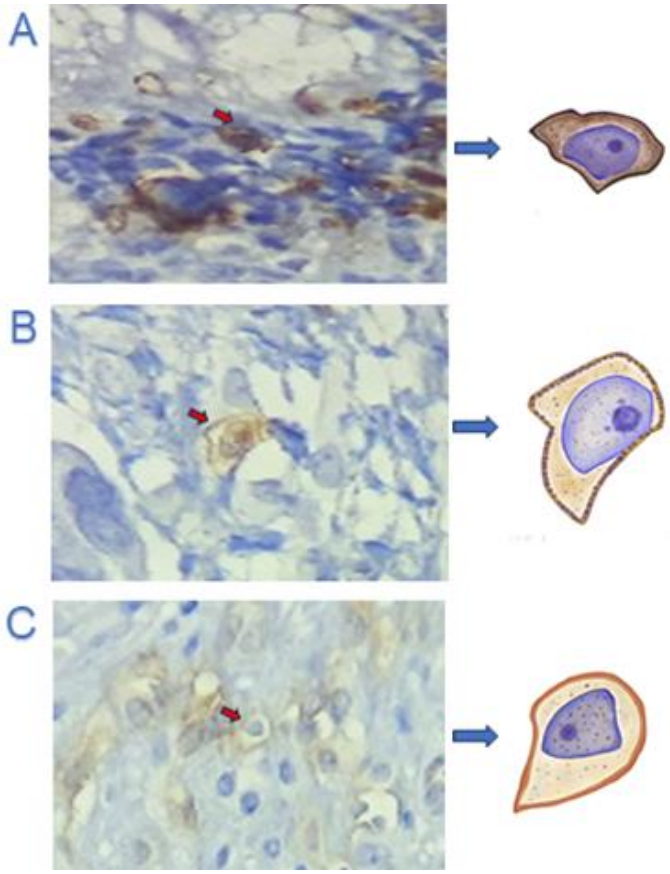

Figure 2. Immunohistochemical staining of CD117 under the microscope. (A) Strong intensity of CD117 expression observed under the microscope at 400x magnification; (B) Moderate intensity of CD117 expression observed under the microscope at 400x magnification; (C) Weak intensity of CD117 expression observed under the microscope at 400x magnification.

In this study, quantitative assessments were also performed in the form of percentage calculations based on the number of tumor cells exhibiting immunohistochemical staining for PAX8 and CD117 antibodies. A total of 32 samples were analyzed, divided into two groups consisting of 16 platinum-resistant samples and 16 platinum-sensitive samples for comparative purposes (Figure 3).

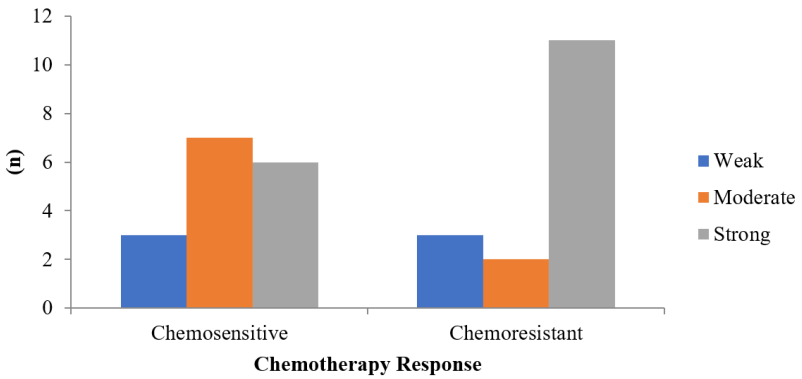

Figure 3. Distribution of PAX8 expression in relation to the occurrence of platinum resistance.

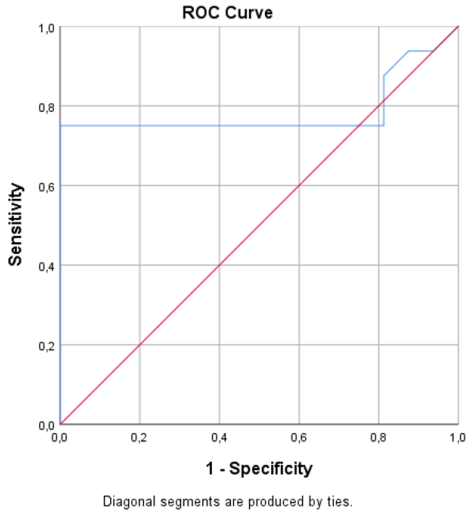

Figure 4. ROC curve of PAX8 expression in relation to the incidence of platinum resistance.

Table 1. Area under the curve for PAX8 expression and incidence of resistance

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.785	.096	.006	.598	.973

The test result variable(s): PAX_Num has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Based on Table 1, it is evident that PAX8 expression can be significantly utilized as a predictor of platinum resistance incidence ($p = 0.006$; $p < 0.05$). The area under the PAX8 expression curve is 0.785, with an upper confidence limit of 0.973 and a lower limit of 0.598. The Youden index indicates that a PAX8 expression level ≥ 3.5 yields a sensitivity of 0.875. This cutoff point is selected because its sensitivity closely approximates the area under the curve for PAX8 expression. The results obtained from this cutoff point are subsequently subjected to sensitivity, specificity, positive predictive value, and negative predictive value testing (Figure 4). The outcomes of these diagnostic evaluations are presented in Table 2. Based on the calculations in this table, the overall accuracy is determined to be 53.125%, with a sensitivity of 87.50% and a specificity of 18.75%. The positive predictive value and negative predictive value are 51.85% and 60.0%, respectively. These findings suggest that PAX8 expression is more suitable for screening purposes due to its higher sensitivity relative to its specificity.

Table 2. Diagnostic test of PAX8 expression for platinum resistance

PAX8 Expression	Platinum resistance		Total
	Yes	No	
PAX8 ≥ 3.5	14	13	27
PAX8 < 3.5	2	3	5
Total	16	16	32

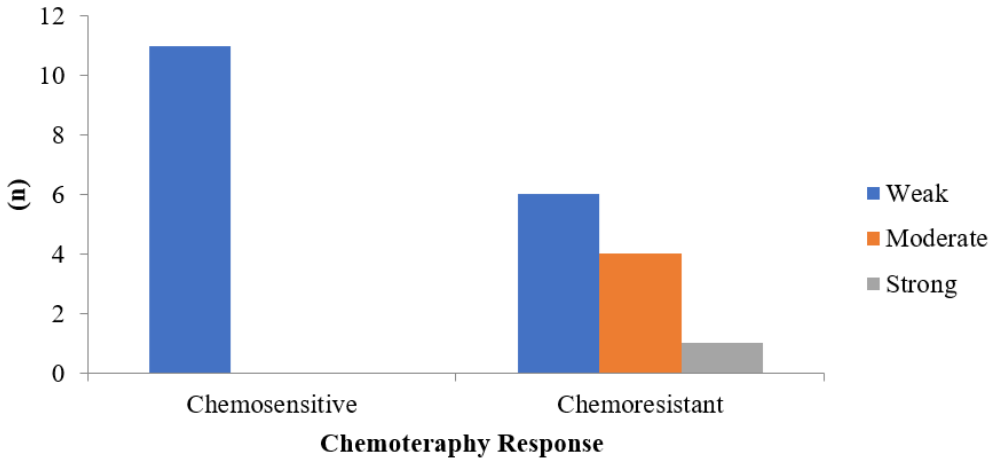

Figure 5. Distribution of CD117 expression in relation to the occurrence of platinum resistance.

Based on Figure 5, the distribution of CD117 expression in relation to the occurrence of platinum resistance is illustrated. Strong CD117 expression is observed in a small proportion of ovarian cancer patients exhibiting chemoresistance. In contrast, weak CD117 expression is more commonly found in ovarian cancer patients who are chemosensitive. According to the ROC curve analysis between CD117 expression and the occurrence of platinum resistance, it is evident that the sensitivity area is lower compared to the 1-specificity area (Figure 6).

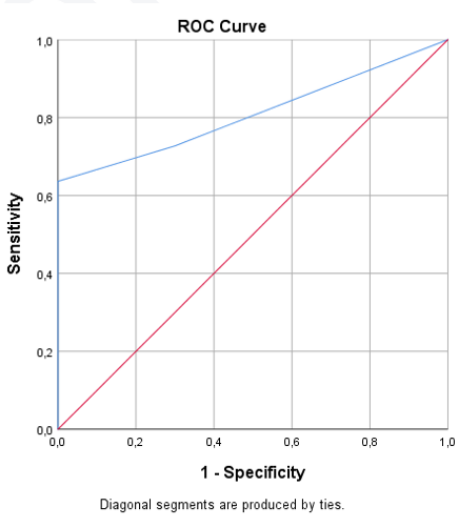

Figure 6. ROC curve of CD117 expression in relation to the incidence of platinum resistance

Table 3: Area under the curve for CD117 expression and incidence of resistance

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.809	.100	.017	.613	1.000

The test result variable(s): CD17_Num has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

Table 4. Diagnostic test of CD117 expression for platinum resistance

CD117 expression	Platinum resistance		Total
	Yes	No	
CD117 ≥ 0.55	8	3	11
CD117 < 0.55	3	7	10
Total	11	10	21

As shown in Table 3, CD117 expression demonstrates significant potential as a predictive marker for the incidence of platinum resistance ($p = 0.017$; $p < 0.05$). The area under the receiver operating characteristic (ROC) curve for CD117 expression is 0.809, with a maximum value of 1.000 and a minimum of 0.613.

According to the Youden index, a CD117 expression threshold of ≥ 0.55 yields a sensitivity of 0.827. This cutoff point was selected because its sensitivity closely approximates the area under the CD117 curve. This selected cutoff was then evaluated for its sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The detailed outcomes of these analyses are presented in Table 4.

From the diagnostic assessment in Table 4, the calculated accuracy is 71.4%, with a sensitivity of 72.73% and a specificity of 70%. The values for the positive predictive and negative predictive tests are 72.73% and 70%, respectively. These results indicate that CD117 expression may be better suited for screening applications due to its relatively higher sensitivity compared to specificity.

The entirety of this study was conducted at Saiful Anwar General Hospital, Malang. Patient samples were collected from cases diagnosed with ovarian cancer at the Gynecologic Oncology Outpatient Clinic and through the Medical Records Department of the same hospital. A blind sampling method was employed to mitigate research bias. The identity information labeled on paraffin-embedded tissue blocks remained concealed from the investigator. The investigator subsequently evaluated PAX8 and CD117 expression levels in the coded specimens and documented the corresponding results.

This investigation reveals that PAX8 expression is elevated in platinum-resistant ovarian cancer. PAX8 is a well-established biomarker in high-grade serous ovarian carcinomas (HGSC), being expressed in nearly 90% of these cases. Di Palma (2022) found that reducing PAX8 expression in HGSC cells leads to apoptosis, and inhibits both migration and invasion. The depletion of PAX8 also downregulates critical extracellular matrix components and lowers the secretion of TGFbeta, a cytokine pivotal to tumor microenvironment re-modeling. Internally, loss of PAX8 compromises spheroid cohesion and diminishes extracellular matrix protein levels.[8]

The work by Adler (2017) aimed to clarify the function of the transcription factor PAX8 in epithelial ovarian cancer (EOC) pathogenesis. Their results showed that PAX8 is commonly overexpressed in primary EOC, supporting its potential role as an oncogene. Knockdown of PAX8 significantly reduced cellular proliferation and tumorigenic potential.

Despite its cell-type-specific expression, the study also identified novel therapeutic avenues for EOC by examining downstream genes and molecular partners regulated by PAX8.[9] Additionally, PAX8 contributes significantly to cell migration and adhesion in both uterine epithelial and ovarian cancer cells. Pharmacological inhibition of PAX8 leads to reduced motility and adhesion, particularly on extracellular matrix substrates such as fibronectin and collagen.[10]

In our own study involving 32 female patients diagnosed with ovarian carcinoma at Saiful Anwar General Hospital, Malang, the ROC analysis demonstrated that PAX8 expression is associated with platinum resistance, with a statistically significant p-value of less than 0.006 ($p < 0.05$). Analysis using the contingency coefficient revealed an accuracy of 53.125%, with a positive predictive value of 51.85% and a negative predictive value of 60%.

These findings confirm the utility of PAX8 expression as a potential marker for predicting platinum resistance in ovarian cancer. This is consistent with earlier literature. Chai (2017) reported that the positive predictive value of PAX8 for identifying primary epithelial ovarian carcinoma was 92%, while for benign ovarian tumors, it was 85%. Moreover, prior studies have also indicated that elevated PAX8 expression is associated with increased mortality.[11] Therefore, besides evaluating resistance, increased PAX8 expression may also serve as a prognostic indicator of patient survival.

Based on the study findings, we conducted research involving 32 women diagnosed with ovarian carcinoma at Saiful Anwar General Hospital, Malang. The ROC curve demonstrates the association between CD117 expression and the presence of platinum resistance, with a p-value of less than 0.017 ($p < 0.05$). Analysis using the contingency coefficient to evaluate the relationship between CD117 expression and resistance yielded an accuracy of 71.4%, with a negative predictive value (NPV) of 70% and a positive predictive value (PPV) of 72.73%.

This investigation also indicates that CD117 is a detectable biomarker that can be utilized to predict platinum resistance. These findings are in alignment with earlier studies. Research by Shnaider (2023) explored the relationship between CD117 expression and histological tumor subtypes in ovarian cancer cell lines and extracellular vesicles obtained from patients. Shnaider's study (2023) reported that elevated CD117 expression in both cells and extracellular vesicles was positively correlated with tumor grade and resistance to therapy. Furthermore, the study found that recurrent ovarian cancer exhibited a significantly greater increase in CD117 expression compared to primary tumors.[12] Another investigation revealed that CD117 expression is associated with residual tumor presence, therapeutic decisions, and survival outcomes, which vary based on the ovarian cancer subtype, with the poorest prognosis found in mucinous and endometrioid histologies. [7]

The findings of this study are referred previous meta-analyses. These analyses identified a significant correlation between CD117 expression and patient age, disease stage, tumor differentiation status, and histolo-gical subtype. In patients with epithelial ovarian cancer (EOC), high CD117 expression was consistently associated with poorer overall survival outcomes. [13]

Determination of the cut-off points for PAX8 and CD117 expression in predicting platinum resistance in ovarian carcinoma can be guided by analyzing their respective sensitivity and specificity. Based on these measures, the optimal cut-off point for PAX8 expression appears to be 3.5, providing a sensitivity of 0.875 and specificity of 0.813. In comparison, the optimal cut-off for CD117 expression is 0.55, yielding a sensitivity of 0.827 and specificity of 0.300. At these thresholds, the PPV and NPV for PAX8 are 51.85% and 60.0%, respectively, whereas CD117 shows a PPV of 72.73% and an NPV of 70.0%. These findings suggest that CD117 has a stronger predictive capacity compared to PAX8. A PPV of 72.73% implies that out of 100 individuals identified as positive, approximately 73 truly experienced platinum resistance. Conversely, an NPV of 70% indicates that out of 100 individuals identified as negative, approximately 70 were correctly classified as not experiencing resistance.

Evaluation of the cut-off points described above also incorporates the sensitivity and specificity values of PAX8 and CD117 as predictors of platinum resistance in ovarian carcinoma. This study demonstrates that the sensitivity values of PAX8 and CD117 expression are 87.50% and 72.73%, respectively, while their specificity values are lower, at 18.75% and 70%, respectively. These data indicate that both PAX8 and CD117 possess potential as screening biomarkers for platinum-resistant ovarian cancer.

Immunohistochemical markers such as PAX8 and CD117 may support clinicians in assessing the likelihood of ovarian cancer patients developing resistance to platinum-based chemotherapy. This predictive capability may serve as a basis for tailoring individualized treatment strategies aimed at improving clinical outcomes.[14-16] Several alternative therapies are available for patients with platinum-resistant ovarian cancer, including taxanes (paclitaxel), poly (ADP-ribose) polymerase (PARP) inhibitors (niraparib), and the anti-angiogenic agent bevacizumab (Avastin). [17-20]

This study presents several limitations. First, the clinical characteristics of the patients were not included in the analysis. Second, the research was conducted at a single institution, thereby warranting validation through multicenter studies. Third, the study did not evaluate patient survival, limiting its ability to draw conclusions regarding prognosis in platinum-resistant ovarian carcinoma.

CONCLUSION

When PAX8 is expressed in ovarian cancer patients, it may function as a screening marker for platinum resistance, with corresponding values for accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 53.125%, 87.50%, 18.75%, 51.85%, and 60.0%, respectively. Similarly, CD117 expression may also be employed as a screening marker to predict platinum resistance in ovarian cancer patients, demonstrating accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of 71.4%, 72.73%, 70%, 72.73%, and 70%, respectively.

DISCLOSURES

Acknowledgment

The authors would like to show gratitude for supervisors of the Obstetrics and Gynecology, Faculty of Medicine, Brawijaya University, Malang, Indonesia 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

COVID-19 in pregnancy: Maternal and perinatal outcomes at Dr. Mohammad Hoesin Hospital, Palembang, Indonesia

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Article Info
Received Jun 3, 2024
Revised Aug 19, 2024
Accepted Aug 23, 2024
Published Apr 1, 2025

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Keywords:
COVID-19
Maternal mortality
Pregnancy
Maternal outcome
Perinatal outcome
Maternal health

ABSTRACT

Objective: The objective of this study was to analyze the maternal and perinatal outcomes of COVID-19 in pregnancy at Dr. Mohammad Hoesin Hospital, Palembang, Indonesia.

Materials and Methods: This retrospective cohort study was carried using medical records of pregnant mothers who delivered at Dr. Mohammad Hoesin Hospital Palembang from March 2020 to August 2021. The subjects were into two groups: pregnant women with and without COVID-19. Pearson Chi-Square test was used for bivariate analysis to determine the associations between COVID-19 and maternal as well as neonatal outcomes. The data were analysed using the Stata 15 statistical software. Multivariate analysis was done using the cox regression test to determine whether maternal characteristics affected those associations. P-value of < 0.05 were considered statistically significant.

Results: The study analyzed 220 subjects, including 62 COVID-19-positive (28.18%) and 158 COVID-19-negative (71.82%) patients. Among expectant mothers with COVID-19, caesarean sections were the most common maternal outcome (82.26%), while fetal distress was the most frequent perinatal outcome (12.13%). Significant associations were found between COVID-19 and maternal outcomes, including pneumonia (RR = 12.76), caesarean section (RR = 2.74), and ICU hospitalization (RR = 6.90). These associations remained significant after adjusting for maternal characteristics. However, no significant association was found between COVID-19 and perinatal outcomes.

Conclusion: COVID-19 increases the likelihood of adverse maternal outcomes throughout pregnancy.

How to cite: Martadiansyah A, Mirani P, Ridwan MR, et al. COVID-19 in pregnancy. Maternal and perinatal outcomes at Dr. Mohammad Hoesin Hospital, Palembang, Indonesia. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):11-20. doi: 10.20473/mog.V33I12024.11-20.

Highlights:

1. COVID-19 increases the likelihood of adverse maternal outcomes throughout pregnancy, including pneumonia, cesarean section, and ICU admission. Prompt diagnosis and treatment of COVID-19 may improve maternal outcomes.
2. COVID-19 does not increase the likelihood of adverse perinatal outcomes. Reassurance can be provided to expectant mothers.

INTRODUCTION

Initially found in Wuhan, China, coronavirus disease 2019 (COVID-19) is an infectious respiratory disease suspected to come from a bat. COVID-19 rapidly spread around the world and then is set as a pandemic by March 9th, 2020.[1] A country in Southeast Asia, Thailand, became the first country outside China who report a case, followed by Japan and South Korea. World Health Organization (WHO) data reported a total of 213.050.725 people in the world had been infected by the date August 24th, 2021.[2] Indonesia has a cumulative count of 4.026.837 individuals who have been tested positive for COVID-19. In South Sumatera, 56.525 people had been diagnosed COVID-19 at a similar time, and Palembang holds the number 29.458 of confirmed COVID-19 cases.[3]

Patients of all age groups from neonates to older adults had been screened positive for COVID-19. Pregnant women become one of the most susceptible groups based on the data from the Ministry of Health Republic Indonesia. From April 2020 to April 2021, 35.099 pregnant women had been confirmed to have COVID-19. Pregnancy induces physiological alterations that result in decreased immune function.[4] Indonesian Society of Obstetrics and Gynecology reported that 51.9% of the pregnant mother were asymptomatic and most of it was detected at 37 weeks of pregnancy.[5]

Each patient exhibited different manifestations of COVID-19. The most commonly observed symptoms include fever, cough, fatigue, sputum production, and dyspnea.[6] However, it is also possible for positive patients to be asymptomatic. Pregnant women who test positive for COVID-19 generally exhibit the same manifestation of COVID-19. In their study, Yan et al.[7] examined 116 laboratory-confirmed COVID-19 pregnant women. They observed that pregnant women with COVID-19 is mostly asymptomatic or showed symptoms i.e. fever, cough, and fatigue.

COVID-19 in pregnancy may increase the risk of maternal and perinatal adverse outcomes. Allotey et al.[8] reported that pregnant women with COVID-19 had a higher likelihood of maternal death and admission to the Intensive Care Unit (ICU) compared to those without. Another study also reported an increased risk of preeclampsia, ICU admission, and maternal death in the COVID-19 group. Out of 706 neonates born to COVID-19 positive mothers, 13% of the neonates were also tested positive for COVID-19, 20.5% experience low birth weight, and 17% have severe perinatal morbidity and mortality index at birth requiring treatment in the Neonatal Intensive Care Unit (NICU). The risk of perinatal death has also been reported to be increased.[9]

The objective of this study was to analyze the maternal and perinatal outcomes of COVID-19 in pregnancy at Dr. Mohammad Hoesin Hospital Palembang.

MATERIALS AND METHODS

This retrospective cohort study examined medical records of all pregnant women who gave birth at Dr. Mohammad Hoesin General Hospital Palembang, Indonesia, between March 2020 and August 2021. Pregnant women with malignancy, autoimmune disease, uncontrolled hypertension, diabetes mellitus, multifetal pregnancy, congenital anomaly, and any serious pregnancy complications were excluded from the study. Characteristics data including maternal age, parity, nutritional status, educational level, work, and comorbidities were acquired, along with COVID-19 diagnosis, maternal outcomes, and perinatal outcomes. The subjects were then divided into two groups: pregnant women with and without COVID-19. COVID-19 diagnosis was confirmed by a positive real-time Polymerase Chain Reaction (PCR) test. Stata 15 statistical software (StataCorp LLC, US) was used to analyze the data. Pearson Chi-Square test was used for bivariate analysis to determine the associations between COVID-19 and maternal as well as neonatal outcomes. Multivariate analysis was done using the cox regression test to determine whether maternal characteristics affected those associations. P-value of < 0.05 were considered statistically significant. This study was approved by the Faculty of Medicine Universitas Sriwijaya Health Research Review Committee (Protocol number 227-2021).

RESULTS AND DISCUSSION

Medical records of a total of 220 pregnant women were included in the study, consisting of 62 pregnant women with COVID-19 (28.18%) and 158 pregnant women without COVID-19 (71.82%). Villar et al.[9] reported a comparable prevalence of COVID-19 (33%).

Subject characteristics

The majority of subjects were pregnant women aged 20 to 35 (91.94%) with multiparity (62.90%), no comorbidity (91.94%), overweight (51.62%), and primary education level (1.94%). Out of the total of 62 subjects, 49 (79.03%) worked from home. Except for educational level and type of work, no significant characteristic differences were found between pregnant women with and without COVID-19. The complete subjects' characteristics are displayed in Table 1.

Table 1. Subject characteristics

Subject Characteristics	COVID-19 (N=62) n (%)	Non-COVID-19 (N=158) n (%)	p value*
Age			0.070
<20	0 (0)	8 (5.06)	
20-35	57 (91.94)	127 (80.38)	
>35	5 (8.06)	23 (14.56)	
Parity			0.058
Primiparity	23 (37.10)	71 (44.94)	
Multiparity	39 (62.90)	78 (49.37)	
Grande multiparity	0 (0)	9 (5.70)	
Nutritional Status			0.712
Underweight	1 (1.61)	3 (1.90)	
Normal	29 (46.77)	67 (42.41)	
Overweight	32 (51.62)	88 (55.70)	
Educational Level			0.016
No education	3 (4.84)	0 (0)	
Primary Education	57 (91.94)	149 (94.30)	
(elementary/middle/high school)	2 (3.23)	9 (5.70)	
Diploma/bachelor's degree			
Work			0.033
Unemployed	0 (0)	10 (6.33)	
Work From Home	49 (79.03)	117 (74.05)	
Work From Outside	13 (20.97)	31 (19.62)	
Comorbidity			0.088
Yes	5 (8.06)	27 (17.09)	
No	57 (91.94)	131 (82.91)	

*Pearson's Chi-square

In this study, the majority of pregnant women with COVID-19 belonged to the age group of 20 to 35 (91.94%). Previous study in Bali by Wiyati et al.[10] reported a consistent finding that the age group between 20 and 35 exhibited the highest rate of infection. The number of infected subjects differed across age groups due to different age-specific susceptibility and contact exposures. The occupational characteristics of individuals between the ages of 20 and 35 elevate the likelihood of viral exposure.[11] From a physiological standpoint, however, advancing age leads to a decline in immunity, rendering individuals more susceptible to infectious diseases. Older patients infected by SARS-CoV-2 had a higher likelihood of experiencing catastrophic maternal outcomes, indicating that advancing age was a significant risk factor for poor maternal outcomes.[8] No significant difference was found between age groups ($p > 0.05$) in this study.

Multiparous mothers had the highest infection rate in this study, contrary to study by Yan et al.[7] which reported highest infection rate in nulliparous mothers. Multiparous mothers are generally older and therefore more susceptible to infectious diseases.[8] Also, nulliparous mothers were reported to have better access to information and better preventive behavior against COVID-19.[12] In this study, however, no significant difference was found between parity groups ($p > 0.05$).

Pregnant mothers with higher body mass index (BMI) emerged as the most heavily afflicted by COVID-19. We obtained a comparable outcome from previous study by Figueiro-Filho et al.[13] In this study, no significant difference was found between BMI groups ($p > 0.05$). However, obese patients were more likely to have catastrophic maternal outcomes.[8]

The group with a basic educational level were more susceptible to contracting COVID-19 ($p < 0.05$). A prior study indicated a correlation between educational level and the preventive behavior of COVID-19.[12] Our findings diverged from a prior study in China which indicated that the group with bachelor's degrees and higher education levels exhibited the highest infection rates.[14] The disparate outcome was attributed to the different characteristics of a sample being studied. Another study in Indonesia reported that pregnant women with basic educational level were more likely to have COVID-19 due to poorer risk perception and preventive behaviour.[15]

Table 2. Maternal outcomes

Maternal outcomes	COVID-19 (N=62) n (%)	Non-COVID-19 (N=158) n (%)
Pneumonia		
Yes	35 (56.45)	7 (4.43)
No	27 (43.55)	151 (95.57)
PROM		
Yes	18 (29.03)	45 (28.48)
No	44 (70.97)	113 (71.52)
Caesarean section		
Yes	51 (82.26)	48 (30.38)
No	11 (17.74)	110 (69.62)
ARDS		
Yes	6 (9.68)	0 (0)
No	56 (90.32)	158 (100)
Preterm labor		
Yes	6 (9.68)	22 (13.92)
No	56 (90.32)	136 (86.08)
Preeclampsia		
Yes	8 (12.90)	19 (12.03)
No	54 (87.10)	139 (87.97)
Eclampsia		
Yes	1 (1.61)	6 (3.80)
No	61 (98.39)	152 (96.20)
Maternal Mortality		
Yes	5 (8.06)	0 (0)
No	57 (91.94)	158 (100)
Sepsis		
Yes	0 (0)	1 (0.63)
No	62 (100)	157 (99.37)
ICU Admission		
Yes	6 (9.68)	4 (2.53)
No	56 (90.32)	154 (97.47)
Total	62 (100)	158 (100)

PROM: premature rupture of membrane
ARDS: acute respiratory distress syndrome
ICU: intensive care unit

Maternal jobs were also being studied in this study. Mothers who were working from home are more likely to be infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, $p < 0.05$). A prior study yielded a comparable outcome, indicating that women who worked remotely experienced the highest rate of infection.[14] Pregnant mothers who worked from home had much more time to spend to go out to places with less strict COVID-19 preventive measures compared to workplaces.[15] Previous study shared a similar result where mothers who worked from home were the most infected.[14]

Surprisingly, pregnant mothers without comorbidity became the most infected by SARS-CoV-2 in this study. This might be due to background characteristics of the study population as no significant difference of SARS-CoV-2 was found between comorbidity groups ($p > 0.05$).

Maternal and perinatal outcomes

The results of our study indicate that the majority of pregnant mothers with COVID-19 underwent caesarean section (82.26%). Most of them also had pneumonia (56.45%). The incidence of other comorbidity was lower i.e. premature rupture of membrane (PROM, 29.03%), and preeclampsia (12.90%). Additionally, we identified cases of Acute Respiratory Distress Syndrome (ARDS), preterm labor, hospitalization to the Intensive Care Unit (ICU), eclampsia, and maternal death among pregnant mothers with COVID-19. No case of sepsis was observed among pregnant women with COVID-19 in our study (Table 2).

The study findings indicated a higher prevalence of pneumonia, premature rupture of membranes (PROM), caesarean section, acute respiratory distress syndrome (ARDS), preeclampsia, maternal mortality, and intensive care unit (ICU) admission in the COVID-19

group. The predominant maternal outcome seen was caesarean delivery, accounting for 82.26% of cases. Other studies similarly reported a high prevalence of caesarean section.[9,10] Prior study has indicated that respiratory problems were among the factors that warranted a caesarean section delivery.[16] Pneumonia was the second most common maternal consequence observed. Out of the expectant mothers with COVID-19 under investigation, 56.45% had x-ray findings indicative of pneumonia. Previous study in China also reported that 94% of individuals diagnosed with COVID-19 had developed pneumonia.[17] Out of the total number of expectant mothers with COVID-19, 18 cases (29.03%) were diagnosed with PROM. This result confirmed that PROM was higher on COVID-19 cases even there was only a slight difference with the non-COVID-19 cases. Consistent with a prior study,[18] infection with SARS-CoV-2 increased the likelihood of PROM. Other maternal outcomes yielded comparable findings. The incidence of ARDS was higher in the COVID-19 group, supporting the hypothesis that severe cases can result in ARDS.[19,20] We have identified five cases of maternal mortality, the majority of which occurred while the patients were receiving treatment in the Intensive Care Unit (ICU). Previous studies affirm a correlation between COVID-19 and both maternal mortality and increased ICU admissions.[7,21]

The results of our study indicate that the majority of perinatal outcomes seen in neonates born from mother with COVID-19 were fetal distress (16.13%), followed by low birth weight (12.90%) and preterm birth (9.68%). However, the incidence of low birth weight was higher in the non-COVID-19 group. No case of stillbirth or NICU hospitalization were identified in this study (Table 3).

Our research revealed a higher incidence of preterm labor, eclampsia, and sepsis in the non-COVID-19 group. It diverged from the result of prior multinational cohort study with 1.320 subjects. The discrepancy arose due to the huge difference in the sample size.[9,18] The perinatal outcomes observed in neonates born to pregnant mothers with COVID-19 included fetal distress (16.13%), preterm birth (9.68%), and COVID-19 positive neonates (4.84%). Previous study reported similar results.[9] COVID-19 was hypothesized to be a potential risk factor for fetal distress and preterm birth.

Table 3. Perinatal outcomes

Perinatal outcomes	COVID-19 (N=62) n (%)	Non-COVID-19 (N=158) n (%)
Preterm birth		
Yes	6 (9.68)	8 (5.06)
No	56 (90.32)	150 (94.94)
Low birth weight		
Yes	8 (12.90)	27 (17.09)
No	54 (87.10)	131 (82.91)
Stillbirth		
Yes	0 (0)	3 (1.90)
No	62 (100)	155 (98.10)
Neonatal death		
Yes	-	1 (0.63)
No	-	157 (99.37)
IUFD		
Yes	2 (3.23)	7 (4.43)
No	60 (96.77)	151 (95.57)
Fetal distress		
Yes	10 (16.13)	15 (9.49)
No	52 (83.87)	143 (90.51)
NICU Admission		
Yes	0 (0)	1 (0.63)
No	62 (100)	157 (99.37)
COVID-19		
Yes	3 (4.84)	0 (0)
No	59 (95.16)	158 (100)
Total	62 (100)	158 (100)

IUFD: intrauterine fetal death
NICU: neonatal intensive care unit
COVID-19: coronavirus disease 2019

Table 4. The association between COVID-19 infection with maternal and perinatal outcomes

COVID-19	RR	SE	P value	95% CI
Maternal Outcomes				
Pneumonia	12.74	5.27	<0.001	5.66-28.69
PROM	1.02	0.28	0.945	0.59-1.76
Caesarean section	2.71	0.54	<0.001	1.83-4.02
ARDS			1.000	
Preterm labor	0.69	0.32	0.430	0.28-1.71
Preeclampsia	1.07	0.45	0.867	0.47-2.45
Eclampsia	0.42	0.46	0.428	0.05-3.53
Maternal mortality			1.000	
Sepsis			1.000	
ICU admission	3.82	2.47	0.038	1.08-13.54
Perinatal Outcomes				
Preterm birth	1.91	1.03	0.230	0.66-5.51
Low birth weight	0.75	0.30	0.485	0.34-1.66
Stillbirth			1.000	
Neonatal death			1.000	
IUFD	0.73	0.58	0.692	0.15-3.50
Fetal distress	1.70	0.69	0.194	0.76-3.78
NICU admission			1.000	
COVID-19			1.000	

PROM: premature rupture of membrane; ARDS: acute respiratory distress syndrome, ICU: intensive care unit; IUFD: intrauterine fetal death; NICU: neonatal intensive care unit; COVID-19: coronavirus disease 2019; RR: risk ratio; SE: standard error; 95%CI: 95% confidence interval

We observed confirmed SARS-CoV-2 positive neonates from pregnant mothers with COVID-19. Previous research reported a similar result. However, vertical transmission was infrequently observed.[22] We observed one neonatal death among the non-COVID-19 group.

The association between COVID-19 with maternal and perinatal outcomes

A statistically significant association was seen between COVID-19 and three maternal outcomes: pneumonia, caesarean section, and ICU admission ($p < 0.05$). No statistically significant association was found between COVID-19 and any other maternal outcomes. Furthermore, this research found no statistically significant correlation between COVID-19 and perinatal outcomes ($p > 0.05$). The association between COVID-19 infection with maternal and perinatal outcomes was demonstrated in Table 4.

This study identified a significant association between COVID-19 and three maternal outcomes. COVID-19 was significantly associated with pneumonia, caesarean section, and hospitalization to the ICU. Pregnant mothers who contracted SARS-CoV-2 infection were 12.74 times more likely to develop pneumonia compared to mothers who were not infected (95% CI 5.66-28.69). Viral infection may result in a cytokine storm, causing lung damage, leading to pneumonia.[6,23] Similar result was reported in previous research.[24]

Pregnant mothers who had COVID-19 were 2.71 times more likely to have a caesarean section during labour compared to pregnant mothers without COVID-19 (95% CI 1.83-4.02). A previous study reported similar outcome that pregnant mothers with COVID-19 have 1.28 times more at risk to undergo a cesarean section.[9] COVID-19 could lead to maternal hypoxia, which can undermine the reliability of fetal heart rate assessment and can lead to caesarean section.[25] Further analysis was necessary due to the fact that the clinical symptoms of COVID-19 were mild compared to SARS and MERS and was not the indication of caesarean section.[26]

Pregnant mothers with COVID-19 were 3.82 times more at risk to be treated in the ICU (95% CI 1.08-13.54). Another study yielded similar findings, indicating that expectant mothers diagnosed with COVID-19 were 5.04 times more likely to require treatment in the ICU.[9] Severe cases of COVID-19 can lead to ARDS and Multiple Organ Dysfunction Syndrome (MODS), necessitating the use of respiratory support in the ICU.[27]

The association between COVID-19 infection and maternal characteristics with maternal and perinatal outcomes

There were significant associations between mother characteristics and some maternal as well as perinatal outcomes was statistically significant (Table 5). Maternal educational level was linked with ARDS and maternal mortality. Maternal nutritional status was associated with preeclampsia. Maternal age and maternal job were associated with eclampsia. Maternal age was significantly associated with ICU admission.

Additionally, the maternal job was found to be associated with intrauterine fetal demise (IUFD).

After being adjusted with maternal characteristics (maternal age, parity, and comorbidity), there was still a significant association between COVID-19 with pneumonia, cesarean section, and ICU admission ($p < 0.05$). Pregnant mothers with COVID-19 are 12.76 times more likely to have pneumonia, 2.74 times more likely to undergo a caesarean section, and 6.90 times more likely to require treatment in the ICU. There was no significant association found between maternal factors and the occurrence of pneumonia and caesarian section (Table 6). Similar results were reported in previous study. SARS-CoV-2 infiltrates the lung, which serves as a host organ expressing ACE (Angiotensin Converting Enzyme)-2. SARS-CoV-2 triggers the activation of inflammatory mediators, resulting in damage to the lungs.[6] The caesarean section was performed due to maternal hypoxia caused by SARS-CoV-2.[25]

The study found a significant association between maternal age and admission to the ICU. The majority of admissions were in the age category of 20 to 35 years (RR = 0.06, 95% CI 0.01-0.39). In this study, maternal age is the confounding factors affecting the association between COVID-19 and ICU admission. On the other side, previous study reported a significant increase in the relationship between COVID-19 and ICU admission (RR = 1.76, 95% CI 1.49-2.08) even after adjusting to maternal age.[9] Further study with larger sample size is needed to resolve these conflicting findings.

Table 5. The adjusted association between COVID-19 infection and maternal outcomes

Maternal Outcomes	Crude RR (95% CI)	RR[a] (95% CI)	RR[b] (95% CI)	RR[c] (95% CI)
Pneumonia	12.76 (5.66-28.73)	12.11 (5.68-25.18)	13.71 (5.87-32.02)	13.01 (5.67-29.86)
Caesarean section	2.74 (1.85-4.08)	2.81 (2.12-3.74)	2.80 (2.09-3.76)	2.83 (2.10-3.80)
ICU admission	6.90 (1.40-33.99)	6.68 (1.39-32.11)	6.40 (1.30-31.55)	5.76 (1.17-28.31)

[a]Adjusted for maternal age
[b]Adjusted for maternal age and parity
[c]Adjusted for maternal age, parity, and comorbidity

Table 6. The association between maternal characteristics with maternal and perinatal outcomes

Maternal and perinatal outcomes	COVID-19 infection and mother characteristics	RR	SE	P value	95% CI
Pneumonia	COVID-19	12.76	5.28	<0.001	5.66-28.73
	Comorbidity	1.44	0.46	0.255	0.77-2.68
PROM	Parity	0.71	0.16	0.139	0.45-1.12
Caesarean section	COVID-19	2.74	0.55	<0.001	1.85-4.08
	Work	0.85	0.20	0.493	0.54-1.34
ARDS	Educational Level	0.07	0.07	0.014	0.01-0.58
Preterm labor	Work	0.48	0.20	0.078	0.21-1.09
Preeclampsia	Nutritional status	1.71	0.38	0.017	1.10-2.66
Eclampsia	Age	0.15	0.12	0.018	0.03-0.72
	Work	0.18	0.13	0.024	0.04-0.80
Maternal mortality	Educational Level	0.06	0.06	0.009	0.01-0.50
Sepsis	Nutritional status	0.23	0.39	0.388	0.01-6.53
ICU admission	COVID-19 infection	6.90	5.61	0.018	1.40-33.99
	Age	0.06	0.06	0.003	0.01-0.39
Preterm birth	Comorbidity	2.35	1.39	0.149	0.74-7.49
Low birth weight	Age	0.44	0.20	0.065	0.18-1.05
Stillbirth	Educational Level	9.42	11.49	0.066	0.86-102.76
IUFD	Work	0.17	0.12	0.009	0.04-0.65
Fetal distress	Parity	0.31	0.19	0.053	0.09-1.02
NICU admission	Nutritional status	0.23	0.39	0.388	0.01-6.53
COVID-19	Nutritional status	0.23	0.23	0.135	0.03-1.58

PROM: premature rupture of membrane; ARDS: acute respiratory distress syndrome, ICU: intensive care unit; IUFD: intrauterine fetal death; NICU: neonatal intensive care unit; COVID-19: coronavirus disease 2019; RR: risk ratio; SE: standard error; 95%CI: 95% confidence interval

Maternal characteristics also affected the rate of ARDS, preeclampsia, eclampsia, and maternal mortality. Maternal educational level become the risk factor for ARDS and maternal mortality with basic educational level as the majority group ($p < 0.05$, RR = 0.07, 95% CI 0.01-0.58, RR = 0.06, 95% CI 0.01-0.50 consecutively). The results did not match the previous study due to the sample size difference. Preeclampsia had a significant association with maternal nutritional status, where normal nutritional status was the dominant group ($p < 0.05$, RR = 1.71, 95% CI 1.10-2.66). Similar as the association between eclampsia with maternal age and a maternal job were age 20 to 35 and working from home were the majority groups ($p < 0.05$, RR = 0.15, 95% CI 0.03-0.72, RR = 0.18, 95% CI 0.04-0.80 sequentially). The results were different from previous research which stated that there was an association between COVID-19 infection with preeclampsia and eclampsia.[9] The difference happened due to the sample size difference.

The rate of ARDS, preeclampsia, eclampsia, and maternal mortality was also influenced by maternal factors. Maternal educational level has been identified as a risk factor for ARDS and maternal mortality ($p < 0.05$, RR = 0.07, 95% CI 0.01-0.58), with the majority of cases occurring among those with a basic educational level ($p < 0.05$, RR = 0.06, 95% CI 0.01-0.50). The discrepancy in results can be attributed to the disparity in sample sizes between the current and the prior study.[9] The study found a strong correlation between preeclampsia and maternal nutritional status, with the normal nutritional status group being the most prevalent ($p < 0.05$, RR = 1.71, 95% CI 1.10-2.66). The study found a significant link between eclampsia and maternal age, as well as maternal employment. Specifically, the majority of cases occurred among women aged 20 to 35 ($p < 0.05$, RR = 0.15, 95%CI 0.03-0.72) who worked from home ($p < 0.05$, RR = 0.18, 95% CI 0.04-0.80). The findings diverged from prior research that reported a correlation between COVID-19 infection and the occurrence of preeclampsia and eclampsia.[9] The discrepancy arose as a result of the disparity in sample sizes.

Even after adjusting for maternal characteristics, there was no observed association between COVID-19 and perinatal outcomes. Nevertheless, a significant correlation was found between maternal factors and intrauterine fetal demise (IUFD). Maternal job was found to have a significant relationship with IUFD (RR = 0.17, 95% CI 0.04-0.65). There was no statistically significant correlation between maternal factors and any other perinatal outcome. Prior investigations have yielded contradictory findings about the statistical correlation between COVID-19 and perinatal outcomes.[9] The discrepancy arises due to the disparity in sample sizes. We did not observe any correlation between maternal COVID-19 and neonatal COVID-19. Until now, there has been a lack of evidence about vertical transmission of COVID-19.[28,29]

This is the first study to investigate the correlation between COVID-19 and maternal and perinatal outcomes in pregnant women in Dr. Mohammad Hoesin Hospital, Palembang. Potential confounding factors from different maternal characteristics had been investigated and the adjusted OR was calculated. Due to the nature of the study, potential bias in data collecting is inevitable. Due to limited available data from medical records, potential confounders including such as COVID-19 severity and the vaccination status of the group were not investigated. Further study with prospective design, larger sample size, and more comprehensive data should be done to generalize these findings.

CONCLUSION

COVID-19 in pregnancy is associated with pneumonia, cesarean section, and ICU admission. There is no association between COVID-19 in pregnancy and perinatal outcomes.

DISCLOSURES

Acknowledgment

We express our gratitude to all the professors and colleagues from the Faculty of Medicine at Universitas Sriwijaya, Palembang, Indonesia, for the insightful discussions during this study.

Conflict of interest

All authors declare that there is no conflict of interest.

Funding

None.

Author Contribution

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

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ORIGINAL RESEARCH

Curcumin reduces inflammation process in mice model preeclampsia

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Article Info
Received Jun 20, 2024
Revised Aug 8, 2024
Accepted Aug 23, 2024
Published Apr 1, 2025

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Keywords:
Pre-eclampsia
L-NAME
Cyclooxygenase-2
Inducible nitric oxide synthase (iNOS)
Maternal health

ABSTRACT

Objective: Preeclampsia is one of the most frequently documented pregnancy complications, with a prevalence of approximately 2 to 15% of all pregnancies. Preeclampsia is a leading cause of maternal mortality. According to research in Indonesia, preeclampsia accounts for 66.8% of all cases of hypertension during pregnancy. This research aims to evaluate the impact of curcumin on serum levels of COX-2 and iNOS in a mouse model of preeclampsia.

Materials and Methods: This study employed a true experimental design with a post-test-only controlled group approach using pregnant *Rattus norvegicus* as a preeclampsia model. Curcumin was administered orally via a feeding tube after dissolving powdered tablets. Dosages were 30 mg/day, 50 mg/day, or 100 mg/day, adjusted for the rats' weight. Serum COX-2 and iNOS levels were measured using ELISA kits from Bioassay Technology Laboratory, with concentrations reported in pg/ml. Analysis was performed using SPSS for Windows 19.0.

Results: Serum COX-2 levels showed significant differences ($p < 0.05$) across groups. L-NAME treatment increased COX-2 levels compared to the negative control. Curcumin (50 and 100 mg/kgBW) reduced COX-2 levels significantly compared to the positive control, with no notable differences between curcumin doses. For iNOS levels, significant differences were also found ($p < 0.05$). Curcumin at 100 mg/kgBW significantly lowered iNOS levels compared to the positive control, with no significant differences between other treatment groups.

Conclusion: Curcumin administration effectively reduces COX-2 and iNOS levels in the serum of *Rattus norvegicus* with a preeclampsia model.

How to cite: Rahardjo B, Widyalaksono A, Baihaqi I. Curcumin reduces inflammation process in mice model preeclampsia. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):21-29. doi: 10.20473/mog.V33I12025.21-29.

Highlights:

1. Increased oxidative stress results in increased iNOS in pre-eclampsia.
2. COX-2 expression in the placenta of women suffering from preeclampsia increases and is associated with increased thromboxane production.

INTRODUCTION

Preeclampsia and eclampsia lead to over 50,000 maternal fatalities annually. Hypertensive disorders, including preeclampsia, show ethnic and racial disparities in incidence, particularly higher among African-American and Hispanic populations, accounting for roughly 26% of maternal deaths in these groups. The WHO reports that 800 pregnant women die daily from preventable causes, with 99% of these deaths occurring in developing countries, at a rate of 240 deaths per 100,000 births. Hypertensive pregnancy disorders, such as preeclampsia and eclampsia, significantly contribute to maternal mortality, especially in Africa and Asia, where they account for approximately 10% of deaths. At Befelatanana University Maternity Hospital (CHUGOB) in Antananarivo, Madagascar, the maternal mortality rate stands at 456 per 100,000 live births, with preeclampsia responsible for 41.7% of these deaths.[1] Risk factors for preeclampsia include familial history, genetic predisposition, length of sexual cohabitation, maternal smoking, parity, advanced maternal age, in vitro fertilization history, and underlying medical conditions such as pre-existing hypertension, diabetes, chronic kidney disease (CKD), and obesity.[2]

The pathogenesis of preeclampsia involves genetic, risk, and immunological factors. Key genetic factors include FLT1, SNPs, and trisomy 13. These contribute to poor placental implantation, leading to reduced placental perfusion in the first and second trimesters. During the third trimester, elevated levels of circulating sFLT1 and sENG result in vascular dysfunction, capillary leakage, and vasospasm. Additionally, COX converts arachidonic acid into prostaglandins like thromboxane (TXA2), which induces vasoconstriction and platelet aggregation.[3] Nitric oxide (NO) is synthesized by NOS in endothelial cells and platelets, with inducible NOS (iNOS) levels rising in response to inflammation and oxidative stress. In preeclampsia, iNOS is also found in the placenta, underscoring the involvement of pro-inflammatory cytokines in the condition.[4]

Turmeric (*Curcuma longa*), a plant related to the ginger family (Zingiberaceae), originates from India and is now cultivated in various regions worldwide, including Southeast Asia, China, and Latin America.[5] Turmeric is a spice commonly used in curry preparation in India and other Asian countries because of its taste and color.[6] India stands as the top producer and primary exporter of turmeric. Reports indicate that the global turmeric market, currently estimated at 1.7 million metric tons, is projected to grow substantially by 2027.[7] The global curcumin market was valued at around half a billion USD in 2016, with a projected compound annual growth rate (CAGR) of approximately 13% from 2018 to 2025. Clinical research suggests curcumin's potential anti-inflammatory benefits in treating conditions like inflammatory bowel disease, acute respiratory distress syndrome, post-operative inflammation, knee osteoarthritis, and chronic kidney disease. Although limited data exist on curcumin's use during pregnancy, phase I clinical trials have confirmed its safety for human consumption, even at high doses (up to 12 g/day).[8] Wistar and Sprague-Dawley strains of white rats (*Rattus norvegicus*) are commonly used in biomedical research, testing, and education. *Rattus norvegicus* is favored in studies due to its genetic similarities to humans, availability of various strains, and easy accessibility.[9] This study aims to examine the effect of curcumin on serum COX-2 and iNOS levels in a preeclampsia rat model, exploring its potential to influence these inflammatory markers.

MATERIALS AND METHODS

Research design

This research employed a true experimental laboratory design with an in vivo post-test-only controlled group, using preeclampsia model pregnant rats (*Rattus norvegicus*) treated with curcumin following L-NAME induction. The study's objective was to assess the impact of curcumin on serum COX-2 and iNOS levels in the preeclampsia rat model. The research process started with a 7-day acclimatization period for the rats, after which they were randomly assigned to 5 different groups: First, the negative control group, consisting of normal pregnant rat; second, the positive control group, comprising rats which received L-NAME injection (125 mg/kgBW/day) intraperitoneally on the 13th to 19th day of gestation.[10]; third, the treatment group 1, including rats which received subcutaneous injection of L-NAME (125 mg/kgBW/day) on the 13th to 19th day of gestation. Rats were also given 30 mg/kg/day of curcumin per rat on the 13th to 19th day of pregnancy; fourth, the treatment group 2, comprising rats received subcutaneous injection of L-NAME (125 mg/kgBW/day) on the 13th to 19th day of pregnancy. Rats also received 50 mg/kg/day of curcumin per rat on the 13th to the 19th day of pregnancy; and the last the treatment group 3 that included rats receiving subcutaneous injection of L-NAME (125 mg/kgBW/day) on the 13th to 19th day of pregnancy. Rats also received 100 mg/kg/day of curcumin per rat on the 13th to 19th day of pregnancy.

The experimental subjects in this study were pregnant Wistar strain *Rattus norvegicus* rats, which were obtained from the Bioscience Laboratory at Brawijaya University, Malang. The induction of L-NAME and

administration of curcumin to the rats, as well as their maintenance, were conducted at the Bioscience and Physiology Laboratory of the Faculty of Medicine, Brawijaya University. The study was carried out over a period of four months, from March to June 2023. The treatment of the experimental animals adhered to the ARRIVE guidelines (https://arriveguidelines.org/).

Inclusion and exclusion criteria

The study included pregnant female Wistar strain *Rattus norvegicus* rats aged between 10 and 15 weeks, with a body weight ranging from 150 to 200 grams. Eligible rats had no prior exposure to treatments or chemical substances and were in good health, displaying active movement and intact fur. Their systolic blood pressure ranged between 90 and 120 mmHg. Rats were excluded if they died before the treatment began, had previously been exposed to chemical treatments, or exhibited hypertension prior to the intervention. Dropout criteria for the study included giving birth during the research, death, or intrauterine fetal demise (IUFD).

Curcumin administration

Curcumin was administered by first grinding Helmig curcumin tablets into a powder, which was then dissolved and delivered orally using a feeding tube. Doses were based on the rats' estimated weight of 200 g (0.2 kg), with the following amounts administered: 6 mg/day for 30 mg dosage, 10 mg/day for 50 mg dosage, and 20 mg/day for 100 mg dosage. These doses were diluted in distilled water, resulting in 1.5 cc, 2.5 cc, and 5 cc solutions, respectively. The procedure involved loading the curcumin solution into a 5 cc syringe connected to a feeding tube, gently holding the rat's neck, and carefully inserting the tube through the rat's mouth into the esophagus. The solution was then delivered into the stomach before removing the tube and returning the rat to its cage.

COX-2 and iNOS levels examination

COX-2 and iNOS levels were measured in the serum (collected from the left cardiac blood vessels) of pregnant rats with a preeclampsia model after treatment according to their respective groups. The COX-2 and iNOS concentration was assessed using the ELISA Kit from Bioassay Technology Laboratory with an Elisa Reader, reported in pg/ml.

Statistical analysis

The data analysis was conducted in two primary steps. First, parametric assumptions were tested by assessing normality using the Shapiro-Wilk test and evaluating the homogeneity of variances. For data that were normally distributed, a One-Way ANOVA (F-test) was performed to compare means across multiple groups, using a significance level of 95% ($p < 0.05$). If the data did not meet the normality assumption, the Kruskal-Wallis test, a non-parametric alternative, was applied with the same 95% significance level. Following the ANOVA, if significant differences were found, post-hoc analysis using the Least Significant Difference (LSD) test was conducted to determine which specific group means were different. Additionally, Pearson's correlation test was applied to evaluate the linear relationship between variables when the data met the normality criteria. All statistical analyses were performed using SPSS for Windows version 19.0, and a significance level of $p < 0.05$ was maintained throughout.

Ethical clearance

This study had received ethical approval under number 400/064/K.3/102.7/2023 from the Ethics Committee of Dr. Saiful Anwar Regional General Hospital, Malang, Indonesia (March 30th, 2023).

RESULTS AND DISCUSSION

Preeclamptic model pregnant rats were induced by administering L-NAME at a dose of 125 mg/kg body weight from gestation days 13 to 19.[10] Preeclampsia is diagnosed by measuring blood pressure and urine protein levels. The condition is indicated by elevated blood pressure exceeding 140 mmHg systolic and urine protein levels of ≥ positive one (+).

Research was conducted on preeclampsia model rats to determine the effect of 30, 50 and 100 mg/KgBW/day of curcumin per rat on the 13th to 19th day of pregnancy on COX-2 and iNOS levels in preeclampsia model rats. Blood pressure and urine protein examinations were carried out at two times, namely at gestational age of 13 days (G13) and gestational age of 19 days (G19). The first examination at 13 days of gestational age was carried out to screen for symptoms of preeclampsia (hypertension and positive urine protein) before treatment. The second examination at 19 gestational age was carried out to evaluate the administration of L-NAME and curcumin.

The study revealed that the serum COX-2 level data were not normally distributed, prompting the use of one-way ANOVA for analysis. The ANOVA results indicated a significant difference ($p < 0.05$) (Table 1). Consequently, post hoc analysis was performed using the LSD test (Table 2).

Table 1. One-Way ANOVA test of serum COX-2 level.

Groups	Mean ± SD	p-value
NC	159.0 ± 18.25	
PC	591.5 ± 239.21	
T1	411.5 ± 147.73	<0.05
T2	206.5 ± 118.70	
T3	171.5 ± 95.35	

NC: Negative Control; PC: Positive Control:
T: Treatment; SD: Standard Deviation

Analysis revealed variations in serum COX-2 levels across different groups. Statistical tests indicated that L-NAME induction of preeclampsia led to significantly higher serum COX-2 levels in the positive control group compared to serum NO levels in the negative control group. Treatment groups 2 (50 mg/kg BW) and 3 (100 mg/kg BW) showed significantly lower serum COX-2 levels compared to the positive control. However, there were no significant differences in COX-2 levels among the treatment groups themselves (p >0.05).

This study showed that the serum iNOS level data had a non-normal distribution, so it was continued with one-way ANOVA analysis (Table 3). The results of analysis using one-way ANOVA showed that there were significant differences (p <0.05). Therefore, we continued using post hoc LSD analysis (Table 4).

Based on the analysis, it shows differences in serum iNOS levels for each group. The results of statistical tests show that administration of L-NAME to induce preeclampsia can cause serum iNOS levels in the positive control group to be significantly higher than serum NO levels in the negative control group. Treatment group 3 (100 mg/kgBW) had significantly lower serum iNOS levels than the positive control. iNOS levels between treatment groups 1 and 2 did not show a significant difference (p > 0.05). iNOS levels in treatment 3 were significantly lower than those in treatment 1 and treatment 2 (p < 0.05).

The results of producing preeclamptic rats showed symptoms of preeclampsia, namely increased blood pressure and urine protein. These symptoms were found in the positive control group, while the negative controls showed no symptoms. The results of this study showed an increase in blood pressure, namely >140/90 mmHg at 15 or 3 days of gestation after L-NAME injection. This is in line with research, that the positive control group also showed an increase in blood pressure that persisted until the 19th day of gestation.[11] Research by injecting L-NAME 125 mg/KgBW/day from the 13th day of gestation to the 21st day was also able to increase the systolic blood pressure of mice.[12] This condition shows success in creating a rat model of preeclampsia. Another study found that mice administered L-NAME exhibited symptoms including elevated urine protein, increased blood pressure, endothelial damage, and higher levels of sFlt-1 and PLGF.[13]

Table 2. LSD test of serum COX-2 level

	NC	PC	T1	T2	T3
NC		<0.05	<0.05	>0.05	>0.05
PC	<0.05		>0.05	<0.05	<0.05
T1	<0.05	>0.05		>0.05	>0.05
T2	>0.05	<0.05	>0.05		>0.05
T3	>0.05	<0.05	>0.05	>0.05	

NC: Negative Control; PC: Positive Control: T: Treatment

Table 3. One-Way ANOVA test of serum iNOS level.

Groups	Mean ± SD	p-value
NC	0.805 ± 0.507	
PC	5.683 ± 3.176	
T1	3.793 ± 2.591	<0.05
T2	2.817 ± 1.903	
T3	1.110 ± 0.609	

NC: Negative Control; PC: Positive Control:
T: Treatment; SD: Standard Deviation

Table 4. LSD test of serum iNOS level

	NC	PC	T1	T2	T3
NC		<0.05	<0.05	<0.05	>0.05
PC	<0.05		>0.05	>0.05	<0.05
T1	<0.05	>0.05		>0.05	<0.05
T2	<0.05	>0.05	>0.05		<0.05
T3	>0.05	<0.05	<0.05	<0.05	

NC: Negative Control; PC: Positive Control: T: Treatment

This study demonstrated that administering curcumin at a dose of 100 mg/kg BW lowered serum COX-2 levels. Preeclampsia is characterized by elevated hypoxia and inflammatory mediators, including COX-2. Increased COX-2 expression in the placenta of preeclamptic women correlates with higher thromboxane production. L-NAME (N(G)-nitro-L-arginine methyl ester) is a nitric oxide synthase (NOS) inhibitor that mimics the pathophysiological conditions of preeclampsia by reducing nitric oxide (NO) production. This reduction triggers oxidative stress, vasoconstriction, and endothelial dysfunction. In this study, curcumin demonstrated anti-inflammatory and antioxidant effects by significantly reducing serum COX-2 and iNOS levels in L-NAME-induced preeclampsia. Curcumin counters L-NAME's effects by suppressing COX-2-mediated inflammatory pathways and lowering iNOS expression, mitigating oxidative stress and vascular dysfunction. These results underscore curcumin's potential in alleviating inflammation and oxidative stress in preeclampsia models. Elevated thromboxane levels in the placenta contribute to vasoconstriction, playing a significant role in the development of pre-eclampsia.[14] COX-2 impacts the endothelium by heightening sensitivity to angiotensin II, stimulating the immune response, and elevating oxidative stress in preeclampsia.[15]

This study found that curcumin administration led to a reduction in serum iNOS levels. iNOS, an isoform of nitric oxide synthase (NOS), influences nitric oxide (NO) production.[16] NO, crucial for vascular homeo-stasis, is synthesized from L-arginine by NOS enzymes, including iNOS. Although NO levels are normally regulated, elevated NO can react with reactive oxygen species like superoxide to produce peroxynitrite. Increased oxidative stress in preeclampsia also elevates iNOS levels.[17] Increased oxidative stress in preeclamp-sia also elevates iNOS levels. This rise in iNOS can lower serum NO, leading to vasoconstriction and hypertension.[18]

These findings are consistent with previous research by Zhou et al. (2017), which demonstrated a reduction in inflammatory mediators in a preeclampsia mouse model induced by lipopolysaccharide. Similarly, Fu et al. (2014) reported a decrease in inflammatory mediators such as TLR4, NF-κB, IL-6, and MCP-1 following curcumin administration in lipopolysaccharide-induced mice. These results align with previous studies. Ben et al. (2011) found that curcumin administration enhances the degradation of iNOS, initiated by the inhibition of ERK 1/2, leading to reduced iNOS levels. Additionally, Streyczek et al. (2022) reported that curcumin lowers iNOS levels in cell cultures. Furthermore, Greish et al. (2020) demonstrated that curcumin decreases reactive oxygen species (ROS) in L-NAME-induced animals by increasing catalase activity and reducing lipid peroxidase levels.[19–23]

Preeclampsia is asymptomatic on first two trimesters pregnancy because the symptoms are widely varied. Preeclampsia frequently remained unclearly identified and thus, is dangerous. Preeclampsia depicted as a heterogenous multisystemic disturbance that may only be diagnosed during routine antenatal visit. Early indicators include high blood pressure, with systolic readings of ≥140 mmHg and diastolic readings of ≥90 mmHg, accompanied by proteinuria of ≥300 mg over 24 hours.[24] Preeclampsia is globally defined as newly developed gestational hypertension, marked by systolic blood pressure above 140 mmHg and/or diastolic pressure exceeding 90 mmHg. This condition is associated with the development of organ dysfunction, including proteinuria, maternal organ dysfunction (involving hepatic, neurological, hematologic, or renal systems), or uteroplacental dysfunction occurring after 20 weeks of gestation. Preeclampsia patients which received delayed treatment affected the mother and the carried fetus. On the mother, cerebral hemorrhage, heart failure with pulmonary edema, kidney failure and gastric reflux aspiration may occur during seizure. On the fetus, death may occur due to intrauterine hypoxia and preterm birth may also occur.

COX is essential in the synthesis of prostanoids (Figure 1). It begins by converting arachidonic acid into the intermediate prostaglandin (PG) G, which is then converted into PGH2. PGH2 is swiftly processed into thromboxane (TXA2), prostacyclin (PGI2), and other prostaglandins (PGE2, PGD2, and PGF2α) by TXA2 synthase, PGI2 synthase, and various isomerases. TXA2, primarily produced by platelets, promotes vasoconstriction, vascular remodeling, and platelet aggregation and adhesion.

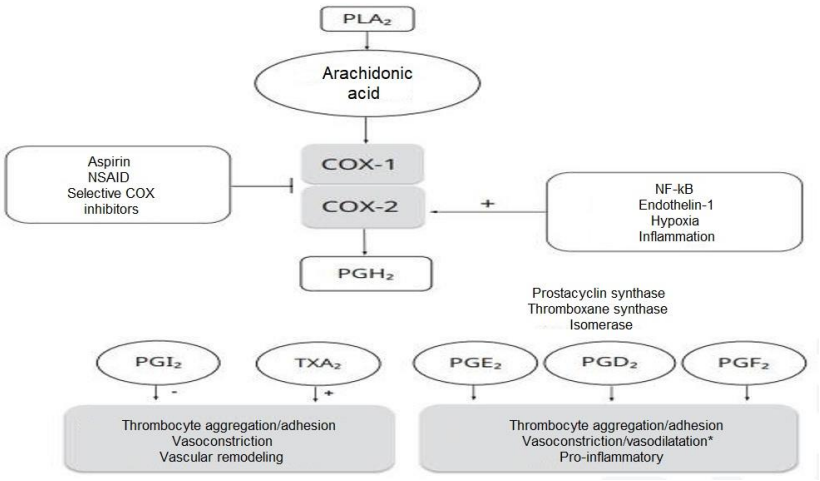

Figure 1. Aspirin and track biosynthesis prostanoids.

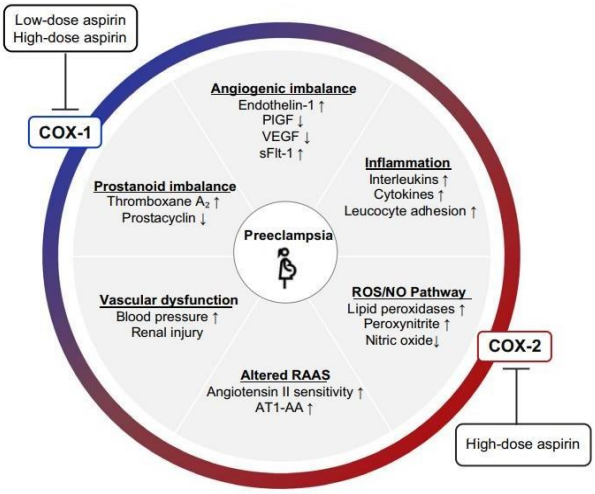

Figure 2. COX-1 mechanism and COX-2.[25]

There are two isoforms of COX: COX-1 and COX-2. COX-1 is constitutively expressed in everywhere and produce part big prostanoids during situation physio-logical. In contrast, constitutive COX-2 expression was low and mainly limited in the brain, thymus, intestines, kidneys, and placenta. Inflammatory mediators (e.g., nuclear-κB (NF-κB), hyperosmolality, endothelin (ET)-1 and hypoxia) is the main pusher to increase the regulation of inducible COX-2 (Figure 2).

Nitric oxide (NO) is produced by NO synthase (NOS) in the endothelium and platelets. Inducible NOS (iNOS) levels rise during platelet aggregation, oxidative stress, and macrophage infiltration driven by pro-inflammatory factors. iNOS is also found in the placenta of hyper-tensive and preeclamptic pregnancies. Proinflammatory cytokines are likely key in endothelial activation in preeclampsia. NO, a potent vasodilator, is crucial for blood pressure control in preeclampsia and is generated by three NOS forms: neuronal NOS (nNOS), endo-thelial NOS (eNOS), and inducible NOS (iNOS). Both iNOS and eNOS are present in the placenta. Unlike the other NOS forms, iNOS operates in-dependently of calcium or calmodulin. iNOS expression has been identified in villous mesenchymal cells using iNOS-specific monoclonal antibodies and can also be detected in vascular endothelial cells under inflamma-tory conditions. Pregnancy, even without complications, is associated with oxidative stress, where reactive oxygen species interact with NO, forming peroxynitrite during preeclampsia development. iNOS contributes to NO production, thereby participating in oxidative stress,

which may be linked to the onset of preeclampsia. Pregnancy increases iNOS expression in smooth muscle cells, indicating a possible role for iNOS in regulating uterine muscle tone.[26] N(G)-nitro-L-arginine methyl ester (L-NAME) is metabolized by cellular esterases into bioactive NG-nitro-L-arginine, which inhibits NOS activity in the vascular endothelium by displacing its usual substrate, L-arginine.[27] L-NAME has a higher affinity for eNOS and can also inhibit other NOS isoforms at elevated concentrations. Its synthetic availability makes L-NAME a common NO antagonist in animal model studies.[28]

Strengths and limitations of the study

This study provides significant insights into the impact of curcumin on COX-2 and iNOS levels in a pre-eclampsia mouse model, demonstrating a thorough evaluation of its anti-inflammatory effects. Conducted under ethical oversight, the study adheres to ethical guidelines and aligns with previous research, which reinforces its validity. The methodology, including ELISA for accurate measurement and body weight-based dosing, contributes to the study's credibility.

Nevertheless, the study has limitations. The lack of funding may have constrained resources for more extensive experiments or advanced analyses. Using only a mouse model may not fully represent the complexities of human preeclampsia. Additionally, the short study duration might not account for the long-term effects of curcumin or its impact across different preeclampsia stages. The research also focused solely on COX-2 and iNOS, without investigating other potentially relevant inflammatory mediators or pathways influenced by curcumin.

CONCLUSION

The administration of curcumin can reduce COX-2 and iNOS level in the serum of Wistar rats (*Rattus norvegicus*) a model of preeclampsia. In order to support the conclusions of this research, further research is needed to analyze peroxynitrite and iNOS levels which play a role in the mechanism of preeclampsia and to analyze the effect of combining curcumin with antihypertensives on COX-2 and iNOS levels.

DISCLOSURES

Acknowledgment

The authors wish to express their sincere appreciation to the Faculty of Medicine at Brawijaya University, Malang, Indonesia, for their extensive support and resources that facilitated the completion of this study.

Conflict of interest

The authors report no conflicts of interest.

Funding

This study did not receive any funding.

Author contribution

All authors contributed significantly to all stages of this research, including study design, data acquisition and analysis, manuscript preparation, and final approval for publication.

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ORIGINAL RESEARCH

The influence of maternal factors and residential building characteristics on infant mortality in Papua Province, Indonesia, based on secondary data analysis of the IDHS 2017

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Article Info
Received Jul 4, 2024
Revised Oct 23, 2024
Accepted Oct 25, 2024
Published Apr 1, 2025

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Keywords:
Infant mortality
Maternal and socioeconomic factors
Papua Province
IDHS 2017
Maternal health

ABSTRACT

Objective: Infant mortality remains a critical global public health concern, with 2.4 million neonates dying within the first month of life in 2020. In Indonesia, the infant mortality rate stood at 16.85 per 1,000 live births in 2022, with Papua Province reporting the highest incidence. This study seeks to examine the determinants of infant mortality in Indonesia, with a focus on maternal age, antenatal care, immunization status, delivery conditions, parity, educational attainment, maternal employment, household income, and housing characteristics.

Materials and Methods: This study utilized a quantitative cross-sectional design, analyzing secondary data from the Indonesian Demographic and Health Survey (IDHS) 2017. The sample comprised 658 women aged 15–49 years who delivered infants aged 0–11 months between 2012 and 2017 in Papua Province. The analytical approach consisted of three phases: univariate analysis to assess frequency distributions, bivariate analysis employing logistic regression ($p < 0.05$) to examine associations, and multivariate analysis using multiple logistic regression for simultaneous variable assessment. Variables with p-values < 0.25 were retained, while those exceeding 0.05 were sequentially eliminated, with emphasis on Odds Ratio (OR) variations.

Results: The analysis identified maternal education level as the most significant predictor of infant mortality, demonstrating an Adjusted Odds Ratio (AOR) of 43.579 (p-value = 0.000, 95% CI = 5.549–342.235). Mothers with only basic education were 43.57 times more likely to experience infant mortality compared to those with advanced education.

Conclusions: Maternal socioeconomic factors exert a substantial influence on infant mortality in Papua Province, and these findings can guide targeted interventions to mitigate mortality rates in the region.

How to cite: Putri SAPJ, Handayani S, Ningrum AG. The influence of maternal factors and residential building characteristics on infant mortality in Papua Province, Indonesia, based on secondary data analysis of the IDHS 2017. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):30-36. doi: 10.20473/mog.V33I12025.30-36.

Highlights:

1. This study focused on Papua, which had the highest infant mortality rate, using a multivariate approach to analyze various factors. Data from the IDHS 2017 and robust statistical analysis were expected to aid in formulating effective health policies.
2. The uniqueness of this research lies in its broader scope of variables, including education and employment, while considering the social and cultural context of Papua, providing new insights into infant health issues.

INTRODUCTION

Infant mortality persists as a critical global public health challenge. As reported by WHO (2022), approximately 2.4 million neonates died within their first month of life in 2020, equating to nearly 6,700 daily infant deaths that accounted for 47% of under-five mortality. This metric serves as a key indicator of regional and national welfare and healthcare quality. Beyond its profound psychosocial consequences for affected families, infant mortality adversely impacts socioeconomic development.[1]

The infant mortality rate (IMR) in Papua has decreased from 129 in 1971 to 38 in 2021. However, Papua still has the highest IMR in Indonesia. This requires attention from the government, health institutions, international organizations, and civil society. According to the 2020 Population Census, Papua's IMR is 38.17, meaning there are 38-39 infant deaths per 1,000 live births, more than twice the national average of 16.85.

As a sensitive population health indicator, IMR reflects healthcare system effectiveness, with lower values denoting superior service quality.[2] The Sustainable Development Goals (SDGs) target reducing IMR to ≤12 per 1,000 live births by 2030. Indonesia has implemented multifaceted interventions including facility-based deliveries attended by skilled health personnel and standardized neonatal care protocols. These measures have contributed to a 90% IMR reduction over five decades - from 26 (2010 Census) to 16.85 (2020 Census) per 1,000 live births. Expanded immunization coverage and prolonged breastfeeding duration have been key determinants of this improvement. According to Central Statistics Agency (BPS) 2022 data, Indonesia's national IMR reached 16.85, with Papua maintaining the highest regional rate (38.17).[3]

Established determinants of infant mortality encompass maternal age, antenatal care frequency, tetanus toxoid immunization status, delivery location and attendant, birth intervals, parity, maternal education, employment status, household income, residential location, and housing characteristics. Current IMR reduction strategies emphasize skilled birth attendance and standardized newborn care protocols. This study investigates the multifactorial determinants of infant mortality in Indonesia.

MATERIALS AND METHODS

This observational study employed a cross-sectional design to examine determinants of infant mortality in Papua Province. Conducted from January to March 2024, the investigation applied predetermined inclusion and exclusion criteria for participant selection. The final cohort comprised 658 female respondents (aged 15-49 years) who delivered infants between 2012-2017. Primary independent variables - maternal age, antenatal care frequency, tetanus toxoid immunization status, delivery location, and housing characteristics - were extracted from the Indonesian Demographic and Health Survey (IDHS) 2017. The study received ethical clearance from Universitas Airlangga Surabaya (Approval No. 60/EC/KEPK/FKUA/2024; February 29, 2024).

Analytical procedures progressed through three phases: Univariate analysis characterized frequency distributions for both the outcome variable (infant mortality) and predictor variables (including maternal characteristics, healthcare utilization metrics, and socioeconomic factors). Bivariate analysis assessed crude associations between independent and dependent variables through simple logistic regression (α=0.05, 95% CI). The final stage employed multiple logistic regression for multivariate modeling, incorporating variables demonstrating preliminary associations ($p<0.25$) while sequentially eliminating non-significant predictors ($p>0.05$). Model refinement continued until all retained variables achieved statistical significance ($p\leq0.05$), with monitoring of odds ratio stability throughout the elimination process.

RESULTS AND DISCUSSION

The study findings demonstrate respondent characteristics as detailed in Table 1. Potential covariates for multiple logistic regression analysis were selected from Table 2 based on a significance threshold of $p < 0.25$.[4] The qualifying variables included maternal age, antenatal care (ANC) attendance, tetanus toxoid immunization status, delivery location, and residential building characteristics.

Four hypotheses concerning infant mortality determinants were examined. Analytical outcomes revealed differential significance among these factors. First, antenatal care visits demonstrated no significant

Table 1. Characteristics of respondents

Characteristics	Frequency (n)	Percent (%)
Maternal age		
< 20 years	142	21.6
20-35 years	321	48.8
> 35 years	195	29.6
Pregnancy check-ups		
First ANC	492	74.8
Complete ANC	166	25.2
Tetanus toxoid immunization		
No	522	79.3
Yes	136	20.7
Maternity center		
No health facilities	157	23.9
Health facilities	501	76.1
Residential Building		
Not liveable	117	17.8
Liveable	541	82.2
Total	658	100.0

Table 2. Relationship of mother's age, pregnancy check-up, tetanus toxoid immunization, place of delivery, and building residence to infant mortality

Characteristics	Infant mortality				Total		ρ value n
	Die		Live				
	n	%	n	%	n	%	
Maternal age							
< 20 years	36	5.5	106	16.1	142	21.6	0.295
20-35 years	72	10.9	249	37.8	321	48.8	0.609
> 35 years	40	6.1	155	23.6	195	29.6	
Total	148	22.5	510	77.5	658	100.0	
Pregnancy check-ups							
First ANC	103	15.7	381	59.1	492	74.8	0.100
Complete ANC	45	6.8	121	18.4	166	25.2	
Total	148	22.5	510	77.5	658	100.0	
TT immunization							
No	123	18.7	399	60.6	522	79.3	0.199
Yes	25	3.8	111	16.9	136	20.7	
Total	148	22.5	510	77.5	658	100.0	
Maternity center							
No health facilities	49	7.4	108	16.4	157	23.9	0.003
Health facilities	99	15.0	402	61.1	501	76.1	
Total	148	22.5	510	77.5	658	100.0	
Residential building							
Not liveable	6	0.9	111	16.9	117	17.8	< 0.001
Liveable	142	21.9	399	60.6	541	82.2	
Total	148	22.5	510	77.5	658	100.0	

Table 3. Results of multiple logistic regression analysis variables

Variables	B	p-value	Adjusted Odds Ratio (AOR)	95% CI
Pregnancy check-up	0.135	0.548	1.144	0.738-1.775
Tetanus toxoid immunization	0.273	0.337	1.314	0.752-2.294
Maternity center	-0.660	0.003	0.517	0.333-0.803
Residential building	1.861	0.000	6.427	2.732-15.120
Constant	0.836	0.001	2.306	

association with infant mortality (p=0.548). Similarly, tetanus toxoid immunization showed no statistically significant relationship (p=0.337). However, delivery location significantly correlated with infant mortality (p=0.003), showing facility-based deliveries conferred 0.517-fold greater odds of infant survival versus non-facility deliveries. Lastly, residential conditions significantly impacted mortality (p=0.000), with substandard housing associated with 6.427-fold higher infant mortality risk (Table 3). These findings highlight the critical roles of delivery care quality and living environments in mortality reduction.

The association between maternal age and infant mortality was examined. Although the majority of respondents aged 20–35 years showed no statistically significant correlation,[5] adolescent pregnancies (<19 years) are associated with increased health risks[6] due to physiological reproductive immaturity. While maternal health status substantially affects neonatal outcomes,[7] the provision of adequate antenatal care and the presence of skilled birth attendants can substantially reduce these risks.

This study demonstrates that most pregnant women in Papua do not receive adequate antenatal care (ANC). Although previous studies have reported a link between ANC visits and infant mortality,[5] insufficient ANC visits that fail to meet established standards may elevate the risk of neonatal death.[8] Contributing factors include poor maternal nutritional status, such as Chronic Energy Deficiency (CED), and inadequate iron intake, which present critical challenges to maternal well-being in Papua.[9] Additionally, research indicates that demanding physical labor during pregnancy may delay or hinder ANC attendance, often shaped by socio-economic and cultural conditions.[9] While ANC remains vital to maternal and neonatal health, challenges in its delivery and quality—compounded by socio-economic constraints like CED and iron deficiency—continue to impede reductions in infant mortality in both Papua and Indonesia overall. Strengthened interventions are essential to enhance awareness, improve healthcare access, and elevate service quality for pregnant women.

This study further reveals that the majority of respondents received Tetanus Toxoid (TT) immunization, and prior research supports its efficacy in preventing neonatal deaths caused by tetanus infections.[10] Neonatal tetanus may arise from non-sterile delivery practices or maternal infections acquired prior to childbirth. TT immunization is a central component of the Maternal and Neonatal Tetanus Elimination (MNTE) program, aimed at ensuring hygienic and safe delivery practices.[11] According to data from the 2023 Papua Provincial Health Profile, complete basic immunization coverage plays a critical role in preventing infectious diseases that may result in infant death.[3] Although progress has been made in expanding immunization coverage in Papua, significant challenges persist in achieving full immunization among all children—highlighting the need for improved public awareness and healthcare access. Overall, TT immunization not only protects individuals from tetanus but also contributes to broader efforts to enhance maternal and child health. Greater public awareness and improved healthcare service delivery are key to reducing infant mortality due to vaccine-preventable diseases like tetanus.[12]

Most mothers in the study delivered in healthcare facilities, and the literature identifies a strong correlation between place of delivery and neonatal mortality rates.[13] This study supports evidence that births in health facilities—staffed by trained personnel and equipped with appropriate infrastructure—significantly reduce the risk of neonatal death compared to deliveries in unsterile or inadequately resourced settings. However, a study by Mogi & Anggraeni (2021) presents differing findings, suggesting that place of delivery may not independently influence infant mortality rates. Nevertheless, they emphasize that deliveries in well-equipped facilities are better positioned to manage complications that could otherwise result in neonatal death.[14] Data from the 2023 Papua Provincial Health Profile show a rising trend in the percentage of women delivering in healthcare institutions, yet persistent barriers remain in ensuring equitable access to quality care across both urban and rural areas.[15] Factors such as educational attainment, economic conditions, and maternal age further influence the decision-making process regarding place of delivery.[16]

In conclusion, although healthcare facilities provide a safer environment for childbirth, substantial efforts are still required to improve the quality and accessibility of services in order to reduce neonatal mortality in Papua Province. Ongoing strategies aimed at increasing community awareness about the benefits of facility-based deliveries and at enhancing health infrastructure are vital to improving maternal and child health outcomes.

The majority of survey participants reside in habitable housing structures, and a significant correlation has been identified between housing conditions and infant mortality rates. The health outcomes of infants are directly influenced by the physical integrity and sanitation of their living environments. Illnesses such as influenza, diarrhea, and typhoid commonly emerge in unsanitary settings, impeding infant development and

heightening the risk of neonatal mortality.[17,18] Gozali et al. (2023) demonstrated a strong association between the incidence of childhood diarrhea and the availability of proper sanitation facilities, such as functional toilets and closed waste disposal systems.[19] UNICEF Indonesia further reported that 88% of global child deaths due to diarrhea are attributable to poor sanitation and unsafe drinking water, which compromise child potential and lower overall human resource quality. The health of infants is also impacted by the structural quality of housing—specifically the building materials, architectural integrity, and overall community environment. These elements are closely tied to the household's socioeconomic status. The extent to which residential features such as walls, flooring, and roofing shield infants from environmental exposure and infectious agents significantly affects health outcomes. Notably, 83% of households in Papua with recorded infant deaths were categorized as residing in high-quality housing, whereas only 17% were in substandard housing. Low-quality homes are often characterized by inadequate heating, poor ventilation, structural deficiencies, overcrowding, and the presence of environmental health hazards such as mold, all of which exacerbate health risks among occupants.[20,21]

The study findings reveal significant associations between infant mortality and factors such as antenatal care, Tetanus Toxoid (TT) immunization, place of delivery, and the structural condition of residential housing. Among these, the quality of housing emerged as the most influential factor associated with infant mortality. The data underscore that housing conditions have a more profound impact on infant mortality compared to other variables. For example, Okech et al. (2021) assert that deficient housing—marked by poor construction and lack of essential facilities—substantially raises the risk of infant death.[22] Furthermore, Rahman et al. (2022) point out that access to high-quality prenatal services and secure living environments can markedly lower infant mortality rates.[23] Conversely, maternal age showed no statistically significant correlation with infant mortality in Papua Province, as evidenced by the 2017 Indonesia Demographic and Health Survey (SDKI). Routine antenatal visits and TT immunizations contribute to lowering infant mortality risks. Deliveries outside formal healthcare facilities remain linked to higher infant mortality rates, consistent with prior research findings.[24] The upward trend in facility-based deliveries, especially among economically advantaged mothers in urban areas, highlights the critical role of healthcare accessibility and quality services. Environmental cleanliness and structural housing conditions further influence infant well-being. Unhygienic surroundings and inadequate sanitation contribute to disease transmission, thereby hampering infant development and increasing the risk of death. This study emphasizes the importance of robust sanitation and hygiene practices in improving community well-being and reducing infant mortality. Ongoing interventions to enhance access to healthcare, improve service delivery, and upgrade housing conditions are essential to mitigating infant mortality risks, particularly within Papua Province.[5]

The research addressing infant mortality in Papua Province possesses distinct strengths and limitations. One notable strength is its high relevance, focusing on a region with the highest infant mortality rates in Indonesia, thus providing vital insights for public health advancement. The utilization of secondary data from the Indonesia Demographic and Health Survey (IDHS) ensures methodological reliability and data standardization. Moreover, the study conducts a comprehensive examination of multiple independent variables influencing infant mortality, offering a nuanced understanding of contributing factors. The results hold potential for informing effective public health policies in high-risk regions and enhancing community awareness of mortality determinants. However, the study also has certain constraints. The exclusive use of secondary data may introduce gaps in data coverage or potential biases in data collection. Establishing direct causal links between variables presents methodological challenges. Additionally, the study's geographic concentration on Papua may limit the extrapolation of findings to other regions in Indonesia. There may also be confounding or unmeasured factors influencing infant mortality that are not captured in the dataset. Lastly, the data represent conditions as of 2017 and may not fully reflect current epidemiological trends or health policy changes. Despite these limitations, the study provides valuable contributions toward strategies aimed at decreasing infant mortality rates in Papua.

CONCLUSION

This study highlights the substantial influence of residential housing quality on infant mortality rates in Papua Province. Although variables such as maternal age, antenatal care, and Tetanus Toxoid immunization are acknowledged as important, they do not demonstrate a statistically significant correlation with infant mortality. In contrast, deliveries conducted within healthcare facilities are associated with reduced infant death rates, emphasizing the critical importance of access to high-quality maternal healthcare services. Additionally, the structural integrity and sanitary conditions of residential environments emerge as key

determinants, with substandard housing conditions contributing significantly to heightened infant health risks. In conclusion, efforts to expand healthcare accessibility, improve housing quality, and strengthen maternal health education are imperative for reducing infant mortality in Papua and comparable settings.

DISCLOSURES

Acknowledgment

We sincerely appreciate researchers, healthcare professionals, and institutions whose efforts have contributed to this study. Their dedication and collaboration have been instrumental in shaping this study.

Conflict of interests

The authors declare that there are no conflicts of interest regarding this research. All authors have contributed to, reviewed, and approved the final manuscript for publication.

Funding

This research did not require or receive any funding and was solely supported by the researchers, ensuring the independence and impartiality of the research findings and conclusions. Informed consent was obtained from all participants involved in this study.

Author contributions

All authors have actively contributed to this study, each playing a distinct role in its conception, design, data collection, analysis, and manuscript preparation. Their collective efforts have been essential to the completion of this study.

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ORIGINAL RESEARCH

Placenta Accreta Spectrum in delivered women is associated with history of curettage: A case-control study at Dr. Moewardi General Hospital, Surakarta, Indonesia

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Article Info
Received Aug 25, 2024
Revised Dec 27, 2024
Accepted Jan 10, 2025
Published Apr 1, 2025

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Keywords:
Placenta accreta spectrum
History of curettage
Delivered women
Maternal health

ABSTRACT

Objective: Placenta Accreta Spectrum (PAS) involves abnormal placental adherence to the myometrium, causing severe obstetric hemorrhage and increased maternal morbidity and mortality (3,000–5,000 mL blood loss). Its global incidence has risen from 0.12% to 0.31%, linked to uterine trauma from cesarean sections or curettage. This study evaluates the association between curettage history and PAS.

Materials and Methods: This study employed an analytical observational design with a case-control approach. Purposive sampling was utilized, resulting in the inclusion of 134 participants who met the predefined criteria. The study population consisted of women who delivered and were referred to Dr. Moewardi General Hospital, Surakarta, Indonesia, between May 2022 and May 2024. Data were analyzed using IBM SPSS version 25. The Chi-square test was applied to assess the association between variables at a significance level of $p < 0.05$, while logistic regression analysis was conducted to identify the most influential variables.

Results: The study cohort comprised 67 patients diagnosed with PAS and 67 without PAS. A statistically significant association was observed between a history of curettage and PAS, as determined by the Chi-square test, with a p-value of 0.000. Logistic regression analysis further confirmed this association, yielding a p-value of 0.001 and an odds ratio (OR) of 5.769 (95% CI: 2.090–15.928) for a history of curettage.

Conclusion: A history of curettage is significantly associated with the development of PAS. Patients with a prior curettage procedure are 5.769 times more likely to develop PAS compared to those without such a history.

How to cite: Prabowo HA, Anggraini NWP, Anggraeni A, et al. Placenta Accreta Spectrum in delivered women is associated with history of curettage: A case-control study at Dr. Moewardi General Hospital, Surakarta, Indonesia. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):37-43. doi: 10.20473/mog.V33I12025.37-43.

Highlights:

1. Placenta Accreta Spectrum cases rise in proportion to the high frequency of uterine wall damage.
2. A significant association was found between curettage history and Placenta Accreta Spectrum.

INTRODUCTION

Indonesia continues to encounter a major public health challenge regarding the Maternal Mortality Rate (MMR), which remains considerably distant from achieving the Sustainable Development Goals (SDGs) target of reducing the global MMR to fewer than 70 per 100,000 live births by 2030.[1] Data from the Long Form Population Survey conducted by Badan Pusat Statistik (BPS) indicate that the MMR in Central Java is slightly below the national figure, which reached 183 per 100,000 live births as of 2020.[2] The three leading causes of maternal mortality in Indonesia include hypertensive disorders of pregnancy, hemorrhage, and infection. Hemorrhagic events contributing to maternal death are classified as either antepartum or postpartum hemorrhage.[3,4] Postpartum hemorrhage can arise from various etiologies, such as uterine atony, genital tract lacerations, coagulopathies, and more recently recognized, retained placenta.[5,6]

The term “Placenta Accreta Spectrum” (PAS) denotes a condition in which placental villi abnormally adhere directly to the myometrium, due to the absence of the decidua basalis and Nitabuch’s layer. PAS is the most frequent cause of major obstetric hemorrhage. The global incidence of PAS has increased from 0.12% to 0.31%.[7] This rising trend is attributed to the prevalence of uterine injury from procedures such as cesarean section and curettage, both of which compromise the integrity of the endometrial lining and lead to abnormal placental implantation.[8] Multiple risk factors are associated with the development of PAS, including previous cesarean section, placenta previa, uterine curettage, advanced maternal age, multiparity, and tobacco use.[9] A prospective cohort study at the University of Kobe, Japan, demonstrated that women with a history of curettage had a 2.8-fold increased risk of developing PAS.[10] Similarly, a case-control study conducted in Egypt found that women with a history of curettage were 3.996 times more likely to develop PAS compared to those without such a history.[11] Scarring from curettage, cesarean sections, or infections may lead to thinning or loss of the Nitabuch layer.[12]

Impaired wound healing can result in permanent dysregulation of myofibrous tissue, leading to inflammation, reduced connective tissue elasticity, interstitial edema, and localized hypoxia.[13] Relative hypoxia activates the Hypoxia Inducible Factor-1 (HIF-1) pathway, which signals blastocyst implantation at specific sites. Elevated HIF-1 levels promote collagen synthesis in the myometrium. However, collagen-rich healing tissue tends to be structurally weaker, less elastic, and poorly vascularized.[14] In view of this background, the present study aims to investigate the association between a history of uterine curettage and the occurrence of PAS, particularly as there has been no prior investigation into PAS risk factors at Dr. Moewardi General Hospital, Surakarta, Indonesia.

MATERIALS AND METHODS

This study adopted an analytical observational design with a case-control approach, comparing two groups: women who delivered with Placenta Accreta Spectrum (PAS) complications and those without PAS complications. In this context, "complications" denotes PAS, encompassing placenta accreta, increta, and percreta, based on the extent of villous invasion. The control group, defined as "without PAS complications," included cases without PAS.

Placenta previa was selected as a control due to shared risk factors with PAS, such as endometrial disruption, scarring from intrauterine or intraoperative procedures, and manual placental removal.[3,4] The definitive diagnosis of PAS was confirmed through histopathological examination and intraoperative findings. Medical records from May 2022 to May 2024 were collected for this study. A total of 134 patients were included using purposive sampling.[15] The inclusion criteria were: (1) women delivering with or without PAS complications, (2) a confirmed PAS diagnosis via histopathological verification, and (3) women with or without a history of curettage.

The independent variable was a history of curettage, categorized into two groups: those with prior curettage and those without. The dependent variable, Placenta Accreta Spectrum, was divided into PAS and non-PAS groups. Confounding variables, including prior cesarean section, maternal age, previous placenta previa, and parity, were analyzed to minimize bias. Bivariate analysis employed the Chi-square or Fisher test for nonparametric comparative hypotheses, while multivariate logistic regression identified the most influential variables. A significance level of $\alpha = 0.05$ (95% confidence interval) was applied. The hypothesis was accepted if $p < 0.05$, indicating a significant association between tested variables. Variables with a p-value < 0.25 in bivariate analysis were included in the logistic regression. Ethical approval was obtained from the Health Research Ethics Commission, Dr. Moewardi General Hospital, Surakarta, Indonesia, under Number: 677/III/HREC/2024 prior to data collection. Data were analyzed using SPSS 25, developed by IBM in New York.

RESULTS AND DISCUSSION

The number of samples obtained in accordance with the large sample formula and meeting the inclusion criteria amounted to 134, with a 1:1 allocation ratio between the case and control groups, resulting in 67 samples for each group. Among the 67 patients, more than half of the women diagnosed with PAS (64.2%) had no history of curettage, while only 24 individuals (35.8%) reported a history of the procedure. A notably higher incidence of cesarean section (CS) was observed in the PAS group, with at least two previous CS in 52.2% of cases. In contrast, the majority of women in the non-PAS group had either no CS history or fewer than two cesarean deliveries (83.6%). The occurrence of placenta previa in prior pregnancies was relatively low in both groups; only 9 women (13.4%) in the PAS group and 7 women (10.4%) in the non-PAS group reported such history. Most women who delivered with PAS were either multiparous or grand multiparous (98.5%), with only one woman classified as primiparous. Among women with PAS, 42 (62.7%) were under 35 years of age, while the distribution of age categories <35 and ≥35 years in the non-PAS group was nearly equivalent (Table 1).

The bivariate analysis presented in Table 1 assesses the association between a history of curettage and the occurrence of PAS using the Chi-square test. The resulting p-value was $p = 0.000$, signifying a statistically significant association between a curettage history and PAS ($p < 0.05$). No significant associations were observed between PAS and previous placenta previa ($p = 0.594$; Chi-square test), maternal age ($p = 0.221$; Chi-square test), or parity ($p = 0.062$; Fisher's exact test), based on the bivariate analysis of potential confounders—all demonstrating p-values > 0.05. Table 2 outlines the PAS risk factors, with the strength of association ranked from highest to lowest: previous CS ($p = 0.000$; OR = 7.549), history of curettage ($p = 0.001$; OR = 5.769), and maternal age ($p = 0.041$; OR = 0.418). Individuals with a history of curettage were found to be 5.769 times more likely to develop PAS compared to those without such a history.

Table 1. Basic characteristics of research samples and bivariant analysis of PAS risk factors

Variables	Placenta Accreta Spectrum		p-value
	No	Yes	
History of curettage (n, %)			
No	60 (89.6)	43 (64.2)	0.000[a]
Yes	7 (10.4)	24 (35.8)	
Total	67 (100.0)	67 (100.0)	
Previous CS (n, %)			
Never and <2 times	56 (83.6)	32 (47.8)	0.000[a]
≥2 times	11 (16.4)	35 (52.2)	
Total	67 (100.0)	67 (100.0)	
Previous PP (n, %)			
No	60 (89.6)	58 (86.6)	0.594[a]
Yes	7 (10.4)	9 (13.4)	
Total	67 (100.0)	67 (100.0)	
Mother's age (n, %)			
<35	35 (52.2)	42 (62.7)	0.221[a]
≥35	32 (47.8)	25 (37.3)	
Total	67 (100.0)	67 (100.0)	
Parity (n, %)			
Primiparous	7 (10.4)	1 (1.5)	0.062[b]
Multiparous and grand multiparous	60 (89.6)	66 (98.5)	
Total	67 (100.0)	67 (100.0)	

CS = cesarean section
PP = placenta previa
[a] Chi-square test
[b] Fisher test

Table 2. Multivariate logistic regression of history of curettage, previous CS, and mother's age

Variables	p-value	OR	CI 95%	
			Min	Max
History of curettage	0.001	5.769	2.090	15.928
Previous CS	0.000	7.549	3.060	18.624
Mother's age	0.041	0.418	0.181	0.965

This investigation identified a significant association (p = 0.000; Chi-square test, Table 1) between prior curettage and Placenta Accreta Spectrum (PAS) in women delivering at Dr. Moewardi General Hospital, Surakarta. Multivariate logistic regression analysis (Table 2) established that a history of curettage is the second most significant risk factor for PAS, following prior cesarean section (p = 0.001; OR = 5.769; 95% CI 2.090–15.928). Women with a history of curettage exhibited a 5.769-fold increased risk of developing PAS compared to those without such a history. These findings align with a case-control study conducted in China between 2015 and 2021, which reported a significant association in bivariate analysis (p < 0.001) between curettage and PAS, with multivariate analysis indicating an odds ratio of 2.54 for a single curettage procedure.[16] Baldwin et al.[17] observed that women with a history of curettage had a 2.1-fold higher risk of PAS compared to those without. Similarly, a prospective cohort study at Kobe University found a 2.8-fold increased risk of PAS among women with prior curettage.[10] A case-control study in Egypt demonstrated that women with a history of curettage had a 3.996-fold higher risk of PAS compared to those without.[11] Experimental studies in the United States identified disruptions in myometrial integrity and deeper trophoblastic invasion in mice with surgical scars from curettage, mirroring the histological characteristics of PAS.[18]

In contrast, a retrospective study evaluating the Placenta Accreta Index Score found no significant association between prior curettage and PAS (p = 0.82).[19] Similarly, a study at Dr. M. Djamil General Hospital, Padang, reported no significant association (p = 0.114).[20] In addition, a study conducted in Iran by Kasraeian et al.[21] in Iran found a non-significant association in bivariate analysis between prior curettage and PAS (p = 0.381). A retrospective study in Italy from 2014 to 2019 concluded no significant association (p = 0.357).[22] Additionally, a cohort study in Japan from 2011 to 2014 determined that prior curettage was not a risk factor for PAS (p = 0.468).[23]

Curettage compromises endometrial tissue, leading to abnormal placental attachment. Ineffective wound healing disrupts myofiber regulation, resulting in inflammation, tissue edema, loss of connective tissue elasticity, and relative hypoxia.[13] Hypoxia Inducible Factor-1 (HIF-1), activated by hypoxic conditions, promotes blastocyst implantation in scarred areas. Healing tissues with elevated collagen content are weaker, less elastic, and exhibit reduced vascularization, allowing trophoblasts and chorionic villi to invade deeply into the myometrium to fulfill fetal nutritional demands. Women with prior curettage experience diminished uterine blood flow and increased vascular resistance. Poor vascularization contributes to focal myometrial degeneration, impeding re-epithelialization and decidualization in affected areas.[14] The thinning of the decidua basalis and Nitabuch layer around the curettage site, which normally separates chorionic villi from the myometrium, facilitates trophoblastic invasion into the myometrium under hypoxic conditions.[24] Repeated curettage impairs the endometrial architecture by removing uterine tissue, leading to niche formation and uncontrolled invasion by extravillous trophoblasts (EVT). The absence of the Nitabuch layer, combined with elevated HIF-1 activity, promotes angiogenesis without regulation by inhibitory factors, further exacerbating the risk of PAS.[25]

The study findings demonstrated a statistically significant association between a history of cesarean section (CS) and the occurrence of PAS among women delivering at Dr. Moewardi General Hospital (p = 0.000; Chi-square test in Table 1). As presented in Table 2, logistic regression analysis identified prior CS as the most significant risk factor for PAS (p = 0.000; OR = 7.549; CI95% 3.060–18.624). Patients with a previous history of CS were found to have 7.549 times higher odds of developing PAS compared to those without such a history. These findings align with a study conducted in France from 2013 to 2015, which demonstrated a significant association between previous CS and PAS, as indicated by a p-value of less than 0.001.[26] In that study, the highest frequency of CS for both PAS and non-PAS patients was one prior CS, with 216 and 50 cases, respectively. In contrast, a study conducted in Utah, United States, found that the majority of PAS cases had a history of at least two cesarean deliveries, with 99 (50.5%) out of 196 patients reporting this. Multivariate analysis in that study indicated that having undergone two cesarean sections

increased the likelihood of developing PAS by 4.61 times.[27]

The pathophysiological basis of PAS involves the formation of uterine scar tissue. A cross-sectional study on maternal hemodynamics and fetoplacental circulation in Norway revealed that following CS, average uterine vascular resistance significantly increased ($p = 0.026$), while endometrial blood flow significantly decreased ($p = 0.038$).[28] This disruption in blood flow impairs vascularization of the scar tissue, which in turn contributes to permanent myometrial degeneration and interferes with key physiological processes such as decidualization and re-epithelialization.[12]

Nevertheless, this study has certain limitations. One of the major constraints is the absence of analysis for other known risk factors that may influence PAS, such as maternal Body Mass Index, use of In-Vitro Fertilization, multiple gestations, tobacco use, and uterine anomalies, among others.[16,23,29–34] The omission of these variables could introduce potential bias due to the presence of uncontrolled confounding factors. Furthermore, this study was conducted exclusively at Dr. Moewardi General Hospital, Surakarta, which limits the generalizability of the findings and may not adequately represent the broader population. To obtain more robust and representative results, future studies should be conducted across multiple centers using broader population samples and study designs that better account for confounding variables.

CONCLUSION

A significant association was identified between a history of curettage and the occurrence of PAS. Patients with a history of curettage were more likely to develop PAS compared to those without such a history. Based on these findings, the researchers recommend further studies involving larger populations and alternative methodologies to better investigate the relationship and potential causality between prior curettage and PAS.

DISCLOSURES

Acknowledgment

The authors of this paper would like to thank Dr. Moewardi General Hospital Surakarta for giving research permission.

Conflict of interest

All of the authors do not have any conflicts of interest.

Funding

No outside funds were obtained.

Author contribution

HAP: develops a research proposal and study design, collects data, analyzes data, and writes manuscript. NWPA & AA: develops a research proposal and writes manuscript. SS: analyzes data and writes manuscript. All authors gave contributions to the article and also provided approval to the submitted version.

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META-ANALYSIS

Breaking the cycle of infertility with clomiphene citrate and letrozole for successful ovulation induction for obese women with PCOS

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Article Info
Received Sep 23, 2024
Revised Dec 24, 2024
Accepted Jan 10, 2025
Published Apr 1, 2025

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Keywords:
Clomiphene citrate
Letrozole
PCOS
Obese
Overweight
Ovulation induction
Maternal health

ABSTRACT

Objective: Indonesia has a higher prevalence of PCOS, a common endocrine disorder that affects 4% to 8% of women who are of reproductive age. Obesity, insulin resistance, and anovulatory infertility are all linked to PCOS. The ability of letrozole and clomiphene citrate (CC) to induce ovulation in overweight or obese PCOS patients was examined in this meta-analysis.
Materials and Methods: PRISMA criteria were followed when conducting a systematic literature search utilizing PubMed, Google Scholar, Cochrane Library, and ScienceDirect. Keywords included PCOS, obesity, clomiphene, and letrozole. Studies published between 2000 and 2024 in English, with full-text accessibility, were included. The search yielded 260 studies, of which nine were selected for quantitative synthesis.
Results: Letrozole showed a 12% increase in ovulation and a 33% increase in pregnancy rates compared to clomiphene citrate (CC). There was no discernible difference in the two groups' endometrial thickness. This meta-analysis finds that letrozole is more successful than CC in triggering ovulation and achieving conception in overweight or obese PCOS patients.
Conclusion: In women with PCOS who are overweight or obese, letrozole works better than clomiphene citrate (CC) to induce ovulation. Because it is accessible and reasonably priced, CC is still the first-line treatment, even if its efficacy is lesser. As a second-line therapy, letrozole is advised for women who are resistant to or do not react to CC.

How to cite: Permadi IGNW, Prasetyaji IMNW. Breaking the cycle of infertility with clomiphene citrate and letrozole for successful ovulation induction for obese women with PCOS. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):44-52. doi: 10.20473/mog.V33I12024.44-52.

Highlights:

1. Polycystic ovarian syndrome (PCOS) is a hyperandrogenous state with oligo-anovulation.
2. Letrozole is more efficient than CC in promoting ovulation and facilitating pregnancy in women with PCOS who are overweight or obese.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a hyper-androgenous state with oligo-anovulation that cannot be explained by another disorder.[1,2] It affects about 1 in 10 women before menopause and struggles with its complications.[3] PCOS is a common endocrinopathy that affects 4%-8% of women of childbearing age, with Indonesia reporting 5-10% prevalence.[4,5] The exact etiology and pathophysiology of PCOS remain largely unknown. However, data points to several internal and external factors, such as genetics, epigenetics, environmental factors, insulin resistance, and hyper-androgenism.[6]

Letrozole, compared with clomiphene citrate, demonstrated a higher live birth rate in overweight and obese PCOS patients. Letrozole's ability to gradually reduce estrogen levels causes an increase in follicle-stimulating hormone (FSH). Compared with clomiphene citrate, which is associated with an increased incidence of thin endometrium, this mechanism increases the ovulation rate and endometrial receptivity. In addition, letrozole showed better performance in cases of clomiphene resistance by improving ovulation and pregnancy. In a randomized controlled trial, letrozole increased ovulation rates by 75% in clomiphene-resistant women, surpassing the performance of other alternative therapies. Letrozole also has milder side effects, such as hot flashes and mood changes, which makes it a safer choice for long-term use.

To overcome PCOS, the most crucial step is to lose at least 5% of body weight, which can be achieved through regular exercise, a fat and sugar-free diet, or using complementary and alternative medicine strategies.[7,8] Cardiometabolic dysfunction is associated with most comorbidities connected to obesity, such as type 2 diabetes, hypertension, and other symptoms of metabolic syndrome.[7,9] Insulin resistance, compensatory hyperinsulinemia, and underlying cardiometabolic dysfunction are also linked to obesity-related cancers, including endometrial carcinoma.[10]

Clomiphene citrate (CC) and letrozole help induce ovulation in PCOS patients. CC is adequate for most drugs, but letrozole shows a higher success rate, especially in clomiphene-resistant patients. Letrozole also has fewer side effects and better results, making it a safer and more practical choice for women with PCOS.

One of the main complaints that most patients see a health professional is a complaint related to infertility.[11] About 25% of couples have infertility due to ovulation disorders, and PCOS is the primary cause of an-ovulatory infertility, which accounts for over 70% of all instances.[12,13] Several endocrine and metabolic traits, including an elevated risk of cardiovascular disease, type 2 diabetes mellitus, dyslipidemia, obesity, insulin resistance, and hyperinsulinism, are also associated with PCOS. Additionally, miscarriages and pregnancy problems like gestational diabetes may be more common in women with PCOS.[14]

For PCOS patients, ovulation induction is the primary treatment option for anovulatory infertility.[15] Clomiphene citrate, an effective selective modulator of estrogen receptors, is used in infertile PCOS patients.[15,16] However, only 18-20% of women who use clomiphene citrate become pregnant, and ovulation rates range from 60-85%.[17,18] Women with PCOS who are overweight and obese often show more severe insulin resistance and hyperandrogenism compared with lean PCOS cases, which can affect ovulation and fertility outcomes. Body weight is essential in transmitting the effectiveness of treatment for these metabolic and hormonal problems. In addition, obesity-induced inflammation and altered adipokine profiles may impair endometrial receptivity and its response to ovulation induction therapy. Therefore, paying special attention to women who are overweight or obese makes it possible to launch treatment methods that are more targeted and adapted to their specific problems.

Letrozole, an aromatase inhibitor, has been used as a backup medication option for PCOS patients, particularly those who become resistant to clomiphene.[19] This meta-analysis aims to analyze and compare the efficacy of clomiphene citrate and letrozole regarding infertility in overweight and obese PCOS patients.

MATERIALS AND METHODS

Search strategy

The 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) standards were followed in conducting and presenting this meta-analysis. The literature was thoroughly searched using PubMed, Google Scholar, Cochrane Library, and ScienceDirect. "(PCOS OR Polycystic Ovary Syndrome) AND (Obese OR Obesity OR Overweight) AND (Clomiphene OR Clomiphene citrate) AND (Aromatase Inhibitor OR Letrozole)" were the predefined keywords used to perform the literature search. Papers with pertinent titles and abstracts will be considered for further qualitative and quantitative analysis and full-text evaluation throughout this process. Studies that were published between 2000 and 2024, written in English, and had full-text accessibility are

included in this study. The specifics of the study search method are displayed in Figure 1.

Inclusion and exclusion criteria

Finding studies that provide specific information on the reproductive result of obese or overweight PCOS patients taking letrozole or clomiphene citrate was the main objective of the research selection criteria. Only studies that met these requirements were taken into consideration for inclusion to guarantee a thorough examination of the relative effectiveness of letrozole vs. clomiphene citrate for obese or overweight PCOS patients. To ensure the authenticity and dependability of the findings, the following exclusion criteria were used: 1) research that did not provide significant findings; 2) publications with full texts that are no longer accessible.

Data extraction and risk of bias assessment

The study's design, ovulation and pregnancy rates, treatment strategies, endometrial thickness, author name, and year of publication were all retrieved. After that, we took data out of the publications we had chosen. CONSORT (Consolidated Standards of Reporting Trials) was another tool used to evaluate the quality of articles about randomized-controlled trials. Every reviewer worked together to analyze the quality until an agreement was achieved.

Outcome measure

The key outcome indicators are the comparisons between ovulation rate, pregnancy rate, and endometrial thickness in each group. Relative risk (RR) and mean difference (MD) were computed with 95% confidence intervals to evaluate these results and thoroughly compare the two interventions.

Data analysis

Data analysis was performed using SPSS to ensure accuracy and reliability. A random-effects model based on the DerSimonian and Laird technique was used since the study populations can differ. There were two phases in the analysis. All continuous variables were first calculated for the mean difference (MD), RR, and 95% confidence interval (CI). The standard errors (SE) of the pertinent SMDs were then computed. A forest plot was used to graphically represent each study's MDs, RRs, and 95% CIs, giving researchers a thorough understanding of effect sizes and variability. The forest plot also includes the pooled MD, RR, and 95% confidence interval from the random-effects model to summarize the total effect estimate overall included trials. Using the Higgins I-squared (I2) statistical model, heterogeneity was investigated. The findings of the heterogeneity test were classified as minimal (0-25%), low (25%-50%), moderate (50-75%), or high (<75%).

RESULTS AND DISCUSSION

Included studies

The initial search turned up 260 studies from all databases. As many as 236 of the abstracts and titles were rejected after screening. Furthermore, four of them were eliminated because they were duplicates. Eleven further studies were eliminated since their findings had nothing to do with the review. Nine papers were ultimately considered for quantitative synthesis. The results of the qualitative synthesis of every study that was included are displayed in Table 1.

Study characteristics and outcomes

Table 1 displays the key characteristics of the included papers in this systematic review. Out of all the included research, the study with the lowest determined CONSORT score (19.00/25.00) had the lowest risk assessment. This suggests that more than two-thirds of the criteria were met by all the included studies, indicating a decreased chance of bias and generally excellent quality.

Ovulation rate

Figure 2 presented the relative risk of the ovulation rate between the CC and letrozole groups. We found that the RR of the ovulation rate in the letrozole group was significantly higher, specifically, 12% higher overall in comparison to the CC group with an RR of 0.88 (95% CI 0.84-0.93; $p < 0.0001$) with low heterogenicity showed by an I2 of 49%.

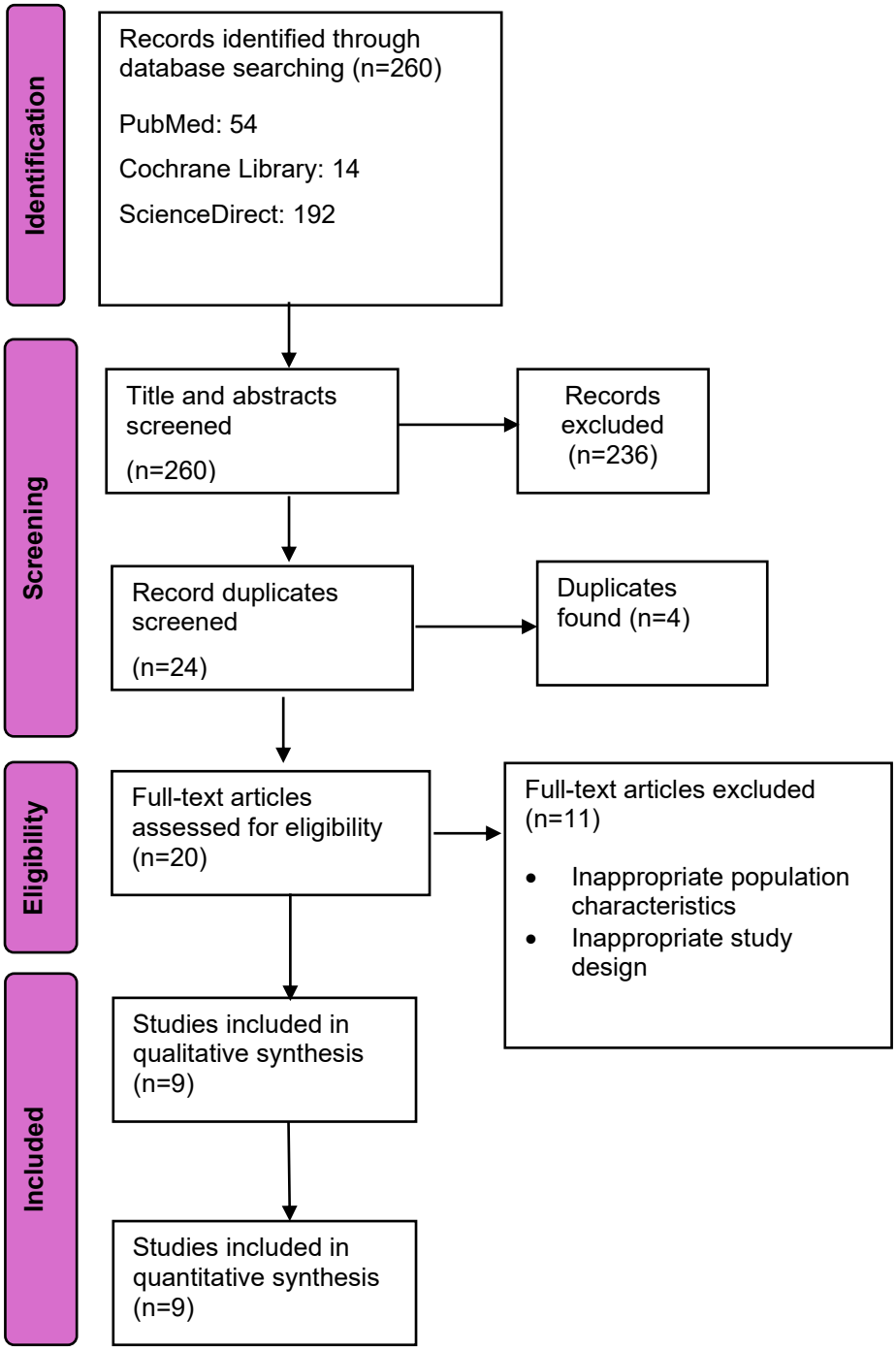

Figure 1. Flow diagram of literature search strategy for this meta-analysis

Table 1. Study characteristics

Authors	Year	Study design	CC group (n)	Letrozole group (n)	Clomiphen citrate group	Letrozole group	Ovulation		Pregnancy		Endometrial thickness	
							CC	Letrozole	CC	Letrozole	CC	Letrozole
Ray, et al.[19]	2012	RCT	78	69	100 mg	2.5 mg	48	60	14	20	8.78 ± 1.16	8.72 ± 1.41
Basakarod, et al.[20]	2023	RCT	40	40	50 mg	2.5 mg	16	22	3	8	8.45 ± 1.53	9.85 ± 2.32
Roy, et al.[21]	2012	RCT	106	98	50 mg	2.5 mg	72	65	28	43	6.3 ± 1.1	9.1 ± 0.3
Kar, et al.[22]	2012	RCT	51	52	100 mg	5 mg	31	38	4	12	7.65 ± 2.1	7.61 ± 1.96
Nambiar, et al.[23]	2018	RCT	96	104	100 mg	2.5 mg	89	102	51	57	10.53 ± 3.27	10.52 ± 2.79
Legro, et al.[24]	2014	RCT	376	374	50 mg	2.5 mg	288	331	81	117	10.1 ± 3.7	9.2 ± 3.8
Bigawy, et al.[25]	2008	RCT	34	30	150 mg	2.5 mg	25	24	5	5	6.43 ± 1.85	9.44 ± 1.81
Arya, et al.[26]	2021	RCT	313	314	50 mg	2.5 mg	Not reported		51	81	Not reported	
Wasiim, et al.[27]	2024	RCT	110	110	50 mg	2,5 mg	70	75	17	32	Not reported	

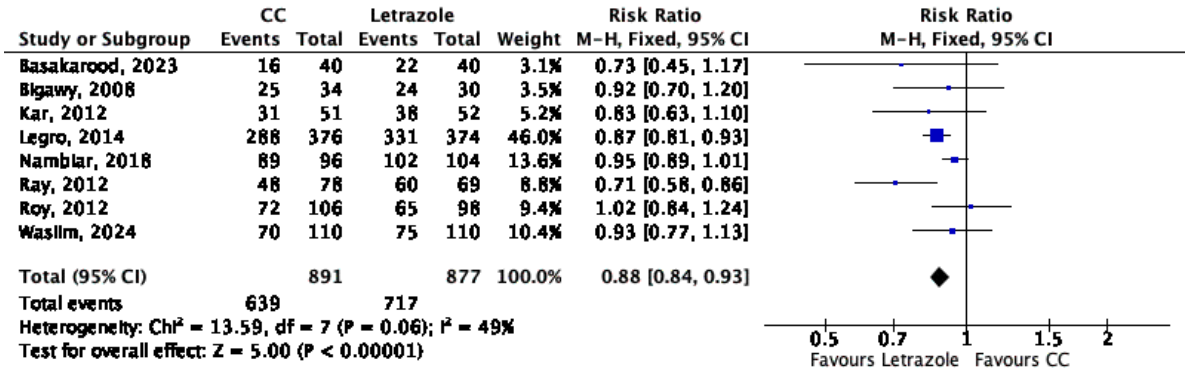

Figure 2. Pooled result of ovulation rate between CC vs letrozole

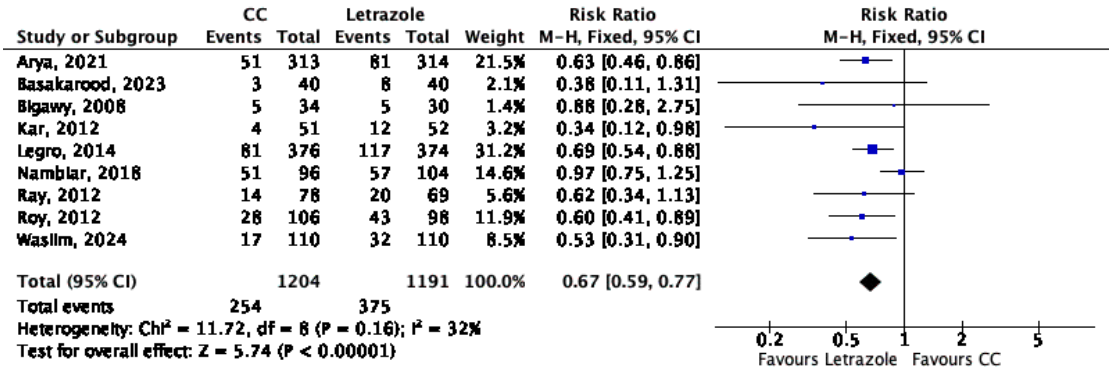

Figure 3. Pooled result of pregnancy rate between CC vs letrozole

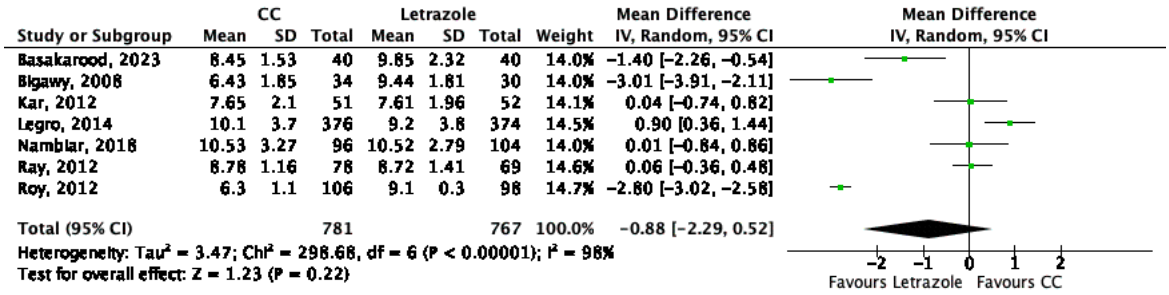

Figure 4. Pooled result of endometrial thickness between CC vs letrozole

Pregnancy rate

Figure 3 presented the relative risk of the pregnancy rate between the CC and letrozole groups. We found that the RR of the pregnancy rate in the letrozole group was significantly higher, specifically, 33% higher overall in comparison to the CC group with an RR of 0.67 (95% CI 0.59-0.77; p < 0.0001) with low heterogenicity showed by an I2 of 32%.

Endometrial thickness

Figure 4 presented the mean difference in endometrial thickness between the CC and letrozole groups. We found that the MD of the endometrial thickness between both groups was not significantly different with an MD of -0.88 (95% CI -2.29 - 0.52; p = 0.22) with high heterogenicity showed by an I2 of 98%.

According to our meta-analysis, letrozole was the best medication for ovulation induction in overweight or obese women with PCOS who were infertile or subfertile in terms of ovulation and pregnancy rate. However, there was no discernible difference between the two groups' endometrial thicknesses.

To induce ovulation, clomiphene citrate (CC) remains the main medication for infertile women with PCOS.[28] By inhibiting the brain's estrogen receptors via a negative feedback mechanism, CC, an anti-estrogen therapy, promotes the growth of follicles. By blocking the hypothalamic estrogen receptors, CC acts as an anti-estrogen, increasing the amplitude of pulses that release gonadotropin-releasing hormone (GnRH). The anterior pituitary's (LH) enhanced synthesis of follicle-stimulating hormone (FSH) and luteinizing hormone helps the follicles reach their final maturity. Using ultrasound and endocrine blood tests, CC administration should be monitored to determine the day of ovulation and prevent multiple pregnancies (risk rate of 11%).[19] As a monitoring technique, an ultrasound examination is performed on days 11 to 14, and measurements of follicular growth and endometrial thickness are also taken.[29]

The anti-estrogenic actions may also impact the endometrium and cervical mucus, which may reduce endometrial growth and impede implantation. Hot flushes, nausea, breast soreness, dizziness, and impaired vision are among the side effects of CC. Starting on days 2 through 5 of a cycle, the standard course of therapy is a daily dosage of 50 mg. Pregnancy rates are

only 30% to 40%, even though 70% to 90% of patients experience ovulation induction with CC.[30] Because twin and triplet pregnancies with CC are rising (5%–7% and 0.3%, respectively), ultrasonographic surveillance should be carried out to identify multi follicular development. Kafy and Tulandi noted this.[31] To increase ovulation and conception rates, women with PCOS who have anovulatory infertility and no other infertility problems should consider using CC as a second-line treatment (conditional recommendation based on evidence, lower quality of evidence).[32]

Letrozole is an aromatase inhibitor. Aromatase inhibitors produce lower levels of E2. This dramatically reduces the likelihood that many follicles will grow. Among CCs, this is one of the key benefits of letrozole. Letrozole also has the advantage of not interfering with endometrial estrogen receptors, which means it has no detrimental effects on cervical mucus or endometrial thickness. Letrozole may increase ovulation rates, as shown by Mejia et al. However, there is no proof that this medication increases the likelihood of getting pregnant. Letrozole is still advised as a second-line therapy for women with CC resistance or failure when no other reproductive problems are present.[33]

Letrozole's effectiveness in inducing ovulation in women who did not react well to CC was first shown by Mitwally and Casper in 2001.[33] In a recent review by Cochrane, Franik et al. discovered that letrozole showed a greater live birth rate than CC, according to evidence of moderate quality. Based on high-quality data, they also found that letrozole and CC had comparable rates of ovarian hyperstimulation syndrome (OHSS) and no differences in miscarriages or multiple pregnancies. Furthermore, letrozole seemed to reduce the chance of multiple pregnancies in comparison to CC, which had the most significant incidence of mono-follicular development.[16]

Typically, patients get 2.5 mg daily for five days, from day two to day five of the cycle (either naturally occurring or caused by progesterone). Follicle tracking with ultrasonography is used to track ovulation. Human chorionic gonadotropin (hCG) can induce ovulation and timed sexual activity when the leading follicle reaches a minimum of 18 mm. The estimated time frame for ovulation is 36 to 48 hours following stimulation. It is advisable to counsel couples who have more than two mature follicles to refrain from unprotected sexual activity. The dose may be increased by twice in the following cycle if ovulation is not achieved.[34]

Letrozole's ability to successfully induce ovulation has been explored in assisted reproduction, including intrauterine insemination (IUI) and in vitro fertilization methods.[31] In addition to causing ovulation in cases of anovulatory infertility, patients with unexplained infertility undergoing superovulation and IUI found that a prolonged letrozole regimen was more effective than clomiphene citrate.[32] To facilitate ovulation in women diagnosed with PCOS, letrozole has been compared to recombinant FSH and has proven to be an appropriate and affordable inducing drug. Based on prior research and the findings of this investigation, letrozole appears to be a viable substitute for clomiphene citrate in overweight or obese PCOS patients with anovulation-related infertility. It can be taken as a first-line medication to treat anovulation and stimulate the ovaries.

CONCLUSION

According to these results, letrozole is more efficient than CC in promoting ovulation and facilitating pregnancy in women with PCOS who are overweight or obese. However, it is important also to note that CC remains the first-line ovulation induction drug for PCOS patients due to its affordability, accessibility, and oral administration. For women who have either acquired resistance to clomiphene citrate (CC) or have not reacted to it, letrozole is recommended as a second-line treatment.

DISCLOSURES

Acknowledgment

We express our highest gratitude to all authors and our alma mater that has been supporting us conducting this meta-analysis.

Conflict of interest

We have no conflict of interest to declare

Funding

No funding was received during the making of this meta-analysis

Author contribution

The authors contributed equally as first authors, involving in 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

Determinants of interprofessional collaboration in implementing Basic Emergency Obstetric and Neonatal Care (BEmONC) services

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Article Info
Received Mar 15, 2024
Revised Sep 12, 2024
Accepted Sep 20, 2024
Published Apr 1, 2025

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Keywords:
BEmONC
Interprofessional collaboration
Referral
Primary healthcare
Maternal health

ABSTRACT

Objective: Maternal and infant mortality is a global challenge due to limited healthcare access. The WHO's BEmONC program in Indonesia aims to reduce MMR and IMR, but its effectiveness is suboptimal due to service-related issues. This study identified factors affecting essential obstetric and neonatal service implementation in primary healthcare facilities.

Materials and Methods: A literature review was conducted using a descriptive analysis approach, supported by Mendeley and Biblioshiny in R-Studio. Sixteen peer-reviewed articles were selected from four online databases, based on predefined inclusion criteria.

Results: The study identified three critical domains for improving and evaluating the performance of BEmONC teams. These domains include optimizing team efficacy through factors such as healthcare personnel, infrastructure, collaboration, and targeted training. Furthermore, effective BEmONC management is essential, encompassing policy formulation, communication strategies, operational improvements, and robust leadership. Lastly, evaluating the implementation of BEmONC requires consideration of factors such as self-efficacy, healthcare workforce capacity, and societal trust, confidence, and recognition. Key contributors to the success of BEmONC include efficient collaboration, streamlined administration, and focused evaluation. Enhancing maternal and newborn health service delivery can be achieved by addressing infrastructure deficiencies, improving healthcare worker performance, and fostering community trust.

Conclusion: Effective teamwork, robust management, and community confidence are pivotal in improving maternal and newborn health outcomes within BEmONC services.

How to cite: Ersianti YL, Fernandez V, Aulia R, et al. Determinants of interprofessional collaboration in implementing Basic Emergency Obstetric and Neonatal Care (BEmONC) services. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):53-64. doi: 10.20473/mog.V33I12025.53-64.

Highlights:

1. BEmONC has been proven to diminish both newborn and mother death rates and morbidity.
2. The study identified three main areas for improving and assessing the determinants of interprofessional collaboration (IPC) in the implementation of BEmONC services: team performance, management, and BEmONC evaluation.

INTRODUCTION

Maternal and child health services are critical indicators of a nation's development, necessitating government focus.[1] In resource-constrained settings, up to 94% of maternal deaths result from postpartum hemorrhage, infection, and pre-eclampsia, while neonatal deaths are primarily attributed to birth asphyxia, preterm delivery complications, and sepsis.[2] The Sustainable Development Goals aim to reduce maternal mortality to below 70 deaths per 100,000 live births between 2015 and 2030, requiring enhanced access to antenatal care services.[3]

Elevated maternal mortality ratios stem from inadequate access to high-quality healthcare and delays in care due to delayed recognition of danger signs and decision-making processes.[1] Additional factors impacting intrapartum care in developing nations include deficient health infrastructure, limited collaboration among healthcare teams, ineffective patient communication, and suboptimal referral systems for obstetric emergencies.[2] The World Health Organization (WHO) introduced a global policy to reduce maternal and infant mortality rates through the Basic Emergency Obstetric and Neonatal Care (BEmONC) program.[4] In Indonesia, interprofessional collaboration (IPC) has been implemented to enhance the quality of healthcare services, effectively reducing MMR and IMR.[5]

Basic Emergency Obstetric and Neonatal Care, known in Indonesia as *Pelayanan Obstetri dan Neonatal Darurat Dasar*, provides 24-hour emergency services at primary care facilities, such as *puskesmas*.[5] BEmONC encompasses treatment and referral for: 1) asphyxia; 2) infant feeding issues, low birth weight, jaundice, hyperbilirubinemia, hypoglycemia, hypothermia; 3) postpartum hemorrhage; 4) puerperal infection; 5) shoulder dystocia and vacuum extraction; 6) hypertensive disorders in pregnancy; 7) infants with respiratory distress; 8) infants with seizures; 9) infants with infections; 10) general preparation; 11) pregnancy monitoring.[1]

For optimal healthcare delivery, each district/city should maintain at least four BEmONC-capable *puskesmas* and Comprehensive Emergency Obstetric and Neonatal Care (CEmONC) services in hospitals for referrals. Collaboration with advanced referral healthcare facilities significantly reduces maternal mortality and morbidity.[6] Understanding factors associated with interprofessional collaboration in BEmONC may enhance knowledge on designing effective community programs to improve health service quality and reduce maternal and neonatal mortality. This study aimed to investigate factors associated with interprofessional collaboration in the implementation of BEmONC services.

MATERIALS AND METHODS

This study utilized a systematic literature review design, adhering to the PRISMA checklist through sequential stages of identification, screening, eligibility, and inclusion. A systematic literature review methodically collects and critically evaluates core findings from prior research and expert-authored texts within the primary manuscript. This approach elucidates sources of knowledge advancement and policy development, stimulates innovative concepts, and serves as a guiding framework for subsequent investigations in a specific domain. A descriptive analysis approach was employed to delineate factual aspects of a phenomenon without hypothesis testing.[7] Sixteen articles were selected following a rigorous screening process, employing keywords including “Interprofessional,” “Collaborative,” “Emergency,” “Obstetric,” “Neonatal Care,” and “Primary Health Care” across four databases: Google Scholar, Science Direct, SINTA, and EBSCO. Boolean operators, such as AND, were strategically applied to refine search queries (e.g., “Interprofessional Collaborative AND Emergency Obstetric AND Neonatal Care AND Primary Health Care”). Duplicate articles were removed using Mendeley software. Furthermore, keywords, titles, and abstracts pertinent to the study’s objectives were meticulously assessed to ensure relevance. Data analysis was performed using Biblioshiny in R-Studio, generating a comprehensive overview of key articles, authors, journals, institutions, and countries, while also mapping the co-occurrence network among the selected publications to highlight interconnections.

Inclusion criteria for article selection were: 1) Original research studies, excluding literature reviews; 2) Articles fully accessible and not sourced from repositories; 3) Studies utilizing quantitative or qualitative methodologies; 4) Articles published within the decade spanning 2013 to 2023. Exclusion criteria comprised: 1) Articles published prior to 2013; 2) Articles in the form of books, theses, or reviews; 3) Articles lacking full-text access; and 4) Articles addressing interprofessional collaboration but not specifically related to BEmONC. To structure the review’s focus and search strategy, the PEO framework (Population, Exposure, Outcome, and study design) was employed. The PEO framework (Table 1) and a flowchart (Figure 1) illustrate the systematic process of literature search and selection undertaken in this study, ensuring methodological rigor and transparency..

Table 1. PEOs Framework

P (Population)	E (Exposure)	O (Outcome)	S (Study Design)
All individuals involved with BEmONC, including healthcare providers (doctors, midwives, nurses, and other health workers), were included.	Interprofessional collaboration	BEmONC implementation	All publications original research regarding interventions in Interprofessional Collaboration concerning the implementation of BEmONC (Basic Obstetric and Neonatal Emergency Care) were reviewed.

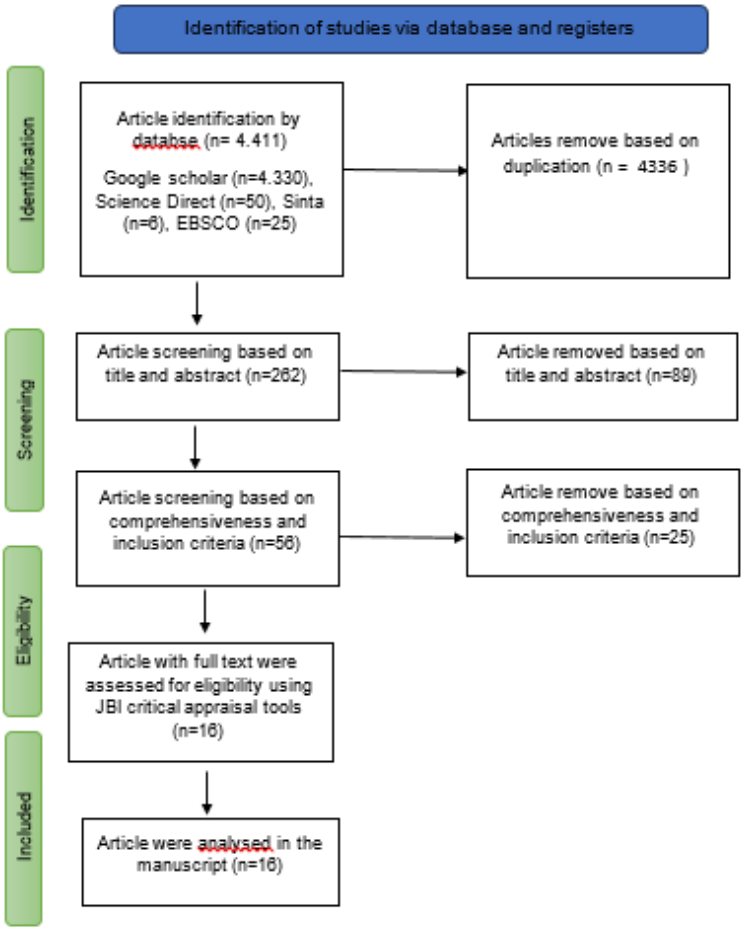

Figure 1. Prisma flow-chart

RESULTS AND DISCUSSION

Articles fulfilling the inclusion criteria were extracted, categorized, and summarized based on journal bibliography, population, intervention, comparison, results, outcomes, and study duration. These articles were subsequently synthesized into tabular format, encompassing article titles, findings, study designs, methodologies, and outcomes. The 16 selected articles have been synthesized, as presented in Table 2.

Table 2. Synthesized data of the article reviews

No	Authors	Outcome	Research design and method	Result
1.	Zhong et al., 2021	Participants get better performance in both teams and individually, as well as increased confidence to handle emergencies in the future.[2]	In South India, a qualitative descriptive study was conducted with 125 health workers, including medical and nursing staff and other health workers, using pre and post-workshops. Workshop one-Simulation approach using realistic scenarios and simulation.[2]	Participants highlighted patient relationships, support from other health professionals, perceived gaps in knowledge and experience, and a lack of resources as variables influencing their experience with obstetric emergencies. Participants' learning centered on increasing team and individual performance, as well as gaining confidence in dealing with future emergencies.[2]
2.	Susanti et al. 2019	Evaluate the implementation of BEmONC at *Puskesmas* Bangetayu Semarang and identify factors that promote and hinder the success of the program.[1]	Descriptive qualitative research using interviews with informants selected using purposive sampling technique. Informants included representatives from the Semarang City Health Office, Bangetayu Community Health Centre (*Puskesmas* Bangetayu), and the program's target communities.[1]	Studies show that implementation of BEmONC is less effective. This is due to the lack of health resources in terms of quantity and quality. In addition, health workers did not receive BEmONC training. This was exacerbated by inadequate facilities and infrastructure. BEmONC implementation is influenced by the communication process between organizations and the community's socialization process, both of which are not ideal.[1]
3.	Haider et al., 2019	To improve maternal and neonatal care in Bahawalnagar district, barriers to the provision of emergency obstetric and neonatal services should be removed.[3]	A sequential exploratory mixed methods design study in Pakistan. Participant interviews were used to acquire qualitative data, which was guided by key informants. Quantitative data were acquired from the same subjects through a rank-order survey. In the Bahawalnagar district's primary health unit, 79 healthcare professionals provided 24-hour BEmONC services.[3]	Interpersonal challenges include a lack of teamwork, dispute resolution, communication, and an imbalance of power. Job instability, a lack of organizational culture, challenges with human resource placement, and a lack of role clarity are all significant organizational impediments. At the system level, important challenges included a lack of target management, a lack of resource availability, homework requirements, and difficulty with dual practice.[3]
4.	Edward et al., 2019	Research will assist in a uniform continuing professional development program to assure its relevance and integrity, and to catalyze the ongoing development of interprofessional education programs, independent of organizational size or location.[8]	A mixed-method study with 114 participants from Australia. The survey consisted of sixty (60) questions, and although the majority of the questions were closed, three (3) asked respondents to make further remarks, and twenty-five (25) questions had an 'Other (Please specify)' option. The open-ended questions in this poll provide qualitative data.[8]	The results showed an association between special education departments (DEDs) and the quality of maternal care offered.[8]
5.	Kumar et al. 2021	The training applied to their daily practice, and their eagerness to learn how to handle complex births demonstrated the ongoing importance of obstetric and neonatal emergency simulation training. [4]	A semi-structured one-on-one interview strategy was utilized in this qualitative study conducted in India. All doctors, midwives, nurses, and health workers who participated in the ONE-Sim program, N=48.[4]	The interviews revealed five themes: comparing simulation to clinical practice, learning and working in teams, thinking retention and sustainability, integrating Simulation-Based Education into the role, and managing leadership.[4]
6.	Kost et al., 2019	Nurses, midwives and doctors on duty were given the opportunity to train in two significant obstetric crises in a realistic simulated environment that matched the actual situation.[9]	Pre and post simulation quantitative research study in Philadelphia. This quality improvement intervention adopted a blended curriculum approach, widely used in simulation research and proven superior to traditional in-service training. The program involved 30 registered nurses (75% of the unit's nurses) and 13 obstetric clinicians (59% of	The objectives of this assignment are: The objectives of this assignment are: 1) to enhance the team's perception of environmental safety in patient care, 2) to improve the effectiveness of team collaboration in managing obstetric crisis events, 3) to improve compliance with the best practice list for addressing postpartum haemorrhage (PPH) and shoulder

			obstetricians or nurse midwives).[9]	dystocia (SD) occurrences, 4) to enhance the self-efficacy of obstetric personnel in managing obstetric crisis events, 5) address any potential system or process affecting patient care, 6) Use simulation training to improve obstetric staff satisfaction, and 7) Increase the effectiveness of post-simulation briefings.[9]
7.	Berg et al., 2023	The utilization of a structured model of process-oriented group reflection for healthcare practitioners on labor and birth care proved to be a crucial part of the training intervention, as it supplemented the information gained through theory- and simulation-based education. The three-pillar training intervention enhances care routines that promote healthy birth and the management of problems.[10]	Qualitative research in Congo with an interview approach by 131 health care providers.[10]	Group reflection contributes valuable information to the other components of the three-pillar training intervention. Sharing and analysing care circumstances helps healthcare personnel build self-awareness, tools for implementing regulated and safe care routines, and teamwork.[10]
8.	Mselle et al., 2023	Investigate how health professionals, management, and communities viewed the introduction of a comprehensive obstetric and neonatal emergency training program in rural Tanzania.[11]	Qualitative research design with FGDs in five (5) healthcare facilities In rural Tanzania, enrolling in a thorough emergency obstetric and neonatal training program Twenty-four (24) focus group discussions comprising health management board teams, health facility managers, staff receiving training, and community members.[11]	Participants discussed the acquisition of skills required for quality and safe obstetric and neonatal care. The study revealed five themes: 1) Competent and confident health teams, 2) Increased commitment to teamwork, 3) Community trust and confidence in the health team, 4) Mentoring as a vital success factor, and 5) Improved training and practice. These five emerging themes reflect greater community confidence and trust, as well as better health-care team competency in supporting mothers during pregnancy and labor at the health center.[11]
9.	Kumar et al., 2019	The provision of BEmONC and CEmONC services in Pakistan continues to pose a significant challenge, particularly in light of the substantial burden of maternal and neonatal mortality. The objective of the study was to evaluate the accessibility of emergency obstetric and newborn care within Sindh Province, Pakistan.[12]	A cross-sectional study of 12 districts selected in Sindh Province, Pakistan for their child and maternal health considerations. Data were collected from 63 public sector health facilities, including district-level hospitals, Taluka (sub-district) central hospitals, and rural health clinics. BEmONC and CEmONC services were evaluated via direct observation and interviews with facility directors, managers, and employees.[12]	BEmONC is available but does not meet WHO requirements. Seven components of basic emergency obstetric and neonatal services revealed that 92% of health facilities had parenteral antibiotics, 90% had oxytocin, 92% had manual placenta services, 87% had staff capable of removing the remaining products of conception, 82% had normal birth facilities, and 80% had neonatal resuscitation services available.[12]
10.	Tria et al., 2019	The dominant variable that has a relationship to referral requirements and preparation with standard operating procedures.[13]	Quantitative analytic study with survey method in Aceh, Indonesia with BEmONC teams from 18 health centers totaling 72 people (total sampling).[13]	SOPs in preparation and referral requirements have not been met and feedback from CEmONC-BEmONC is difficult to work with. Staff lack BEmONC standards and training. There is also no referral infrastructure. Insufficient facilities are available in the ambulance. Communication between BEmONC-CEmONC is one-way, SOPs are incomplete and placement of SOPs is not ergonomic so they are not easily seen by health workers.[13]
11	Sulistyaningsih et al., 2022	Other studies show evidence that Interprofessional teamwork can boost health-care quality and reduce medical errors. The goal of this project is to create a	Qualitative design with single case study with holistic case design in Bantul, Yogyakarta, Indonesia. Researchers collected data by observation followed by in-depth	The study identified four themes: work culture mechanisms, environ-mental mechanisms, practices in interprofessional collaboration, and institutional support mechanisms.

		model of BEmONC Inter-professional Collab-oration Practice (ICP) at health centers.[5]	interviews and then ending with documentation. The informants were 19 members of BEmONC. Supporting informants were two patients and their families [5]	These mechanisms are interrelated, influencing the effectiveness of interprofessional collaboration and the quality of BEmONC.[5]
12	Ernawati et al., 2023	The implementation of BEmONC *puskesmas* has not been optimal, as evidenced by the MMR, IMR, and under-five mortality rate. Support from the local government and related parties is needed with the hope of being able to meet resource needs in the context of organizing BEmONC primary health facilities.[6]	Qualitative research using a descriptive approach. In the Solok district of Indonesia, data was collected through interviews, document analysis, and observation. A total of 7 informants, including the field manager, MCH manager, program subdivision, 4 BEmONC *puskesmas*.[6]	The implementation of BEmONC capable health centers has not been optimal due to the unavailability of resources, infrastructure, equipment, medicines and provision of BEmONC team. In addition, the process of commitment, communication, and community interaction among stakeholders has not been optimized. The implementation of the BEmONC program requires coordination with local government support through awareness of budget determination, coordination as well as involvement between stakeholders in the hospital environment, professional associations, NGOs, local communities and CEmONC as a unified referral system.[6]
13	Yamuragiye et al., 2023	To optimize MCH, policymakers, professional health educators, and clinicians must identify measures for improving interprofessional interactions and contributing to the quality of obstetric and neonatal care.[14]	A semi-structured interview was used to perform a descriptive qualitative study at five Northern Rwanda public hospitals. The study included 25 health workers, including nurses, midwives, doctors, and non-physician anaesthetists who worked in maternity wards.[14]	Some of the benefits of effective interprofessional collaboration include reducing child and maternal mortality and morbidity, and optimizing quality care. However, there are challenges related to communication and competition in interprofessional collaboration, stressful work environment and lack of resources.[14]
14	Cornthwaite et al., 2013	The primary objective of the training is to enhance maternity care. Therefore, participants should receive positive feedback, but formal assessment should be avoided. However, monitoring outcomes is still essential to ensure the safety and quality of care. It is essential to remember that the training's effectiveness should be assessed by the safety of both mothers and babies, not only exam scores.[15]	Quantitative research study with a pre and post training experimental approach in the UK with practical midwifery multiprofessional respondents.[15]	This study recommends formal evaluation of training programs with a focus on clinical needs and outcomes, rather than participants' exam scores. Research highlights the importance of good team communication and coordination to reduce risks to mothers and babies. The analysis revealed variations in team management. Optimal teamwork is defined as effective action toward a common goal. Effective leadership is developed through internal and evidence-based training, as well as clinical practice. Simulation, inter-professional training, and leadership training are essential for enhancing teamwork and leadership in labor emergencies. This can be achieved by focusing on situation awareness, structured communication, and evidence-based learning.[15]
15	Walker et al., 2015	PRONTO training was effective in strengthening obstetric and neonatal care professionals' knowledge and confidence, resulting in improved clinical practice.[16]	Quantitative study with pre and post-test simulation training in obstetric and neonatal care providers in 15 clinics in the country of Guatemala.[16]	Knowledge and self-efficacy scores rose significantly across all instructional areas. At the end of the program, scores were connected across all topics. More than 60% of the objectives established for improving clinic function and emergency treatment were met. No predictors of goal achievement were found. These positive results confirm the positive impact of PRONTO training in the context of neonatal and obstetric care in a limited-resource

				environment.[16]
16	Tanjung et al., 2016	The study evaluated the implementation of the BEmONC Program at *Puskesmas* Tegal with a focus on context, input, process, and product (CIPP).[17]	A qualitative study using in-depth interviews, observation, and document review in Indonesia. A total of 10 key informants were selected for this study, including the head of *Puskesmas*, the head of the Family Health and Nutrition Division of the Tegal Regency Health Office, the midwife in charge of the BEmONC operation, and mothers with severe pre-eclampsia.[17]	The results of the evaluation showed that BEMONC in Tegal Health Center managed to implement the program well, although there are still some areas that need to be improved, such as nurse involvement, resource allocation, and some constraining factors. The evaluation results showed that the number of health workers was deemed adequate, yet nurses were not entirely involved (context). In addition, there is no specific funding for the operation of the BEMONC health center. Training for emergency services and efforts to improve facilities were well implemented (input). BEMONC services and health workers are performing well (process). Intersectoral cooperation is working well. Constraining factors include the slow processing of BPJS claims and low public awareness. The results show a high level of patient satisfaction with BEMONC services (product).[17]

Table 3. Country distribution of the articles

Countries	Freq.	Countries	Freq.
Australia	1	England	1
Congo	1	Pakistan	2
Guatemala	1	Philadelphia (US)	1
India	2	Rwanda	1
Indonesia	5	Tanzania	1

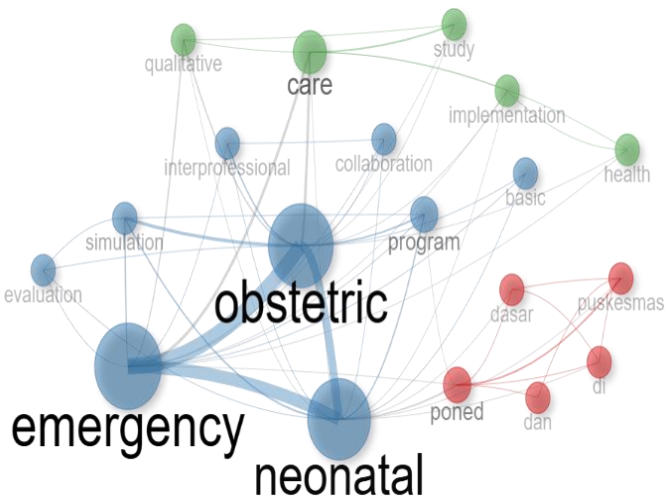

Figure 2. Co-occurence network of the articles

Table 4. Articles' summary

No	Theme	Subject matter
A	Team Performance of BEmONC	a. Health workers [2, 3, 9, 13] b. Infrastucture [2 and 10] c. Teamwork [1, 3, 5, 6, 8, 11, and 16] d. Aappropriate training [1, 5, 6, 7, and 8]
B	BEmONC management	a. BEmONC impelemtation policy [10 and 12] b. Professional and community communication [2, 10, 12, and 13] c. Fixed management issues [3,6, and 11] d. Leadership [5] e. Support and assistance from the BEMONC team [4, 8, 11, and 12]
C	Evaluation of BEmONC Implementation	a. Self-efficacy of health workers [1, 6, 8, and 15] b. Public satisfaction, confidence and trust in health workers [6, 8, and 14]

Characteristics

A total of 16 articles were identified based on the search results and alignment with the research keywords. The review included studies conducted in both developed and developing countries. The developing countries represented in the articles include India, Indonesia, Pakistan, the Democratic Republic of the Congo, and Tanzania. Articles from developed countries were conducted in Australia, the United Kingdom, Guatemala, Philadelphia (USA), and Northern Rwanda (Africa). The countries featured in these articles served as the primary research settings.

This review explores interprofessional collaboration in BEmONC services within healthcare facilities. The primary focus of the reviewed articles includes team performance, management practices, and the evaluation of BEmONC implementation. The selected studies comprised original research employing qualitative,[1,2,5,7,8,11,12,13,16] quantitative,[6,9,10,14,15] and mixed-methods[3,4] research designs.

Thematic analysis

According to the Indonesian Ministry of Health (2016), BEmONC has been shown to significantly reduce both maternal and neonatal mortality and morbidity.[6] The article review identified multiple variables influencing the effectiveness of BEmONC services, which were grouped into key themes and subtopics, as presented in Table 4.

To ensure the quality of care, referral implementation must be executed with adequate and timely preparation to promote service delivery that is both effective and efficient. A major barrier to referral system functionality is the shortage of trained personnel and the absence of blood transfusion units across all districts. Critical success factors for effective referrals include healthcare personnel, transportation availability, interprofessional teamwork, facility readiness, standard operating procedures, and communication. Strengthening the healthcare referral system is essential to address existing challenges in BEmONC services, particularly in facilitating timely referrals from *puskesmas* to hospitals.[13]

Team Performance of BEmONC

Health workers

Research indicates that the availability of resources plays a pivotal role in effectively managing obstetric and neonatal emergencies.[2] Resource-related barriers are predominantly experienced at the organizational level, encompassing issues such as the absence of a supportive organizational culture, unclear role delineation, ineffective human resource allocation, and job insecurity.[3] The quality of healthcare services and supporting infrastructure contributes to overall service quality in both independent and combined capacities. Setyawan asserts that the standard of healthcare delivery is directly influenced by the quality of human resources, supporting facilities, and infrastructure.[18]

Infrastructure

Several reviewed articles reported that certain BEmONC facilities were operating with inadequate infrastructure and insufficient resources.[2,10]. Conversely, the adequacy of healthcare facilities and infrastructure significantly determines access to health services.[19] The presence of well-equipped facilities, adherence to referral standard operating procedures, the availability of competent personnel, established communication networks between BEmONC health centers and CEmONC hospitals, and compliance with referral requirements and preparatory standards all contribute to the delivery of accurate, timely, safe, and optimal referrals. These conditions ultimately enhance the management of maternal and neonatal emergency cases.[13]

Teamwork

A study conducted at the Tegal Community Health Center in 2017[16] found that nurses were not fully engaged within the BEmONC team, which typically comprises physicians, nurses, and midwives who collaborate in addressing obstetric and neonatal emergencies at the primary care level.[17]

Interprofessional teamwork is critical to the successful implementation of BEmONC services at puskesmas.[1,3,5,6,8,11] Evidence suggests that the effectiveness of health services is closely linked to health workers' job satisfaction and their capacity for teamwork.[20] To enhance service quality, it is essential to conduct biannual evaluations and prioritize patient satisfaction through targeted training and team-based collaboration.[21]

Relevant training

According to Bloom's taxonomy, behavior is shaped by the integration of knowledge, skills, and attitudes. Human knowledge is classified into six cognitive levels: knowledge, comprehension, application, analysis, synthesis, and evaluation.[22,23] Evidence suggests that training in Normal Childbirth Care (Asuhan Persalinan Normal or APN) significantly influences midwives' behavioral outcomes.[22] To deliver evidence-based care in obstetric and neonatal emergencies, it is essential to enhance competencies across knowledge, perception, practical skills, and clinical experience.[1,5-8] The BEmONC simulation-based training is designed to enable healthcare professionals to critically reflect on their clinical practice by comparing simulated scenarios with real-life situations. This training promotes collaborative learning and team functioning, improves retention and sustainability, bridges contextual relevance and professional roles, and strengthens leadership capacities.[12]

BEmONC management

BEmONC implementation policy

Research conducted on BEmONC-designated health centers in the Solok District Health Office area revealed inadequacies in policy execution. The local health authority holds the responsibility for implementing BEmONC-related policies, including the designation of capable facilities and ensuring the availability of essential resources such as infrastructure, trained teams, medications, equipment, and medical supplies.[6] Tria et al.'s review highlighted that referral protocols and preparatory requirements remain insufficient.[13] Furthermore, communication from CEmONC hospitals back to BEmONC-level *puskesmas* is problematic, often functioning in a one-directional manner. Standard operating procedures (SOPs) are reported to be incomplete and poorly placed in non-ergonomic locations, thereby reducing visibility and accessibility for health personnel.

Professional and community communication

Studies indicate that the communication between BEmONC and CEmONC levels is inadequately supportive.[13] Other studies also demonstrate that stakeholder engagement, community involvement, and program socialization are not optimally executed. Successful BEmONC implementation requires coordinated efforts supported by budgetary planning, active collaboration among local government bodies, hospital-based stakeholders, professional associations, non-governmental organizations (NGOs), local communities, and the critical involvement of CEmONC hospitals as part of an integrated referral framework.[6]

Persistent management issues

Implementation of the BEmONC program continues to encounter managerial challenges, particularly in areas such as conflict resolution and unequal distribution of authority. There is a clear need to apply core management functions to foster an effective work culture and build responsive organizational systems. Health center-level management practices typically involve a phased approach: initial systematic planning (P1), followed by mobilization and execution of managerial operations (P2), and concluding with continuous monitoring, program supervision, and evaluation (P3).[24]

Leadership

A review article highlighted that leadership within BEmONC teams is associated with peer-to-peer teaching among team members, a progressive approach to management, and the delegation of leadership roles when appropriate.[4] Leadership plays a pivotal role in determining the success of organizational functions. Future development initiatives at *puskesmas* will prioritize programs tailored to the local context, community conditions, and needs within the facility's catchment area. Emphasis will also be placed on establishing environmental conservation initiatives and enhancing the overall quality of healthcare services. Furthermore, regional *puskesmas* aim to become financially self-sustaining, while simultaneously empowering and engaging communities in health-related activities.[24]

Support and assistance from the BEmONC team

Effective BEmONC implementation requires robust institutional support encompassing management, resources, and policy. A well-structured organizational culture facilitates collaborative work environments, promotes effective communication, and fosters interpersonal skills development. Supportive environmental mechanisms should be established to nurture a productive workplace, support the integration of advanced information and communication technologies, and stimulate the development of health information systems.[5]

Evaluation of BEmONC Implementation

Self-efficacy of health workers

As proposed by Bandura (1997), self-efficacy arises from the interaction of individual attributes, behavioral patterns, and environmental contexts.[25] The self-efficacy of health workers is not solely determined by their technical competencies, but by their perception and confidence in their own abilities.[25] Emergency obstetric training programs such as PROMPT have demonstrated improvements in clinical practice, patient outcomes, and healthcare workers' confidence in managing obstetric emergencies.[8] Training initiatives designed to assess evidence-based knowledge and enhance self-efficacy can be effectively delivered through simulation-based, team-oriented programs for providers of maternal and neonatal care. Findings indicate that 60% of participants reported improved knowledge and enhanced self-confidence following participation in emergency response training for maternal and neonatal cases.[16]

Public satisfaction, confidence and trust in health workers

Inadequate team collaboration has been shown to negatively affect maternal and neonatal outcomes, thereby diminishing public trust in healthcare personnel. Poorly managed maternal emergencies contribute to dissatisfaction among approximately 20% of mothers, particularly when considering subsequent childbirth experiences. Substandard care may affect maternal psychological well-being, disrupt breastfeeding, and impair the maternal–infant bond, despite the initial trust placed in healthcare providers. Effective communication among healthcare staff can help rebuild trust and foster a positive perception of the services provided.[15]

The study's results demonstrated that responsiveness, provider characteristics, patient safety, empathy, and reliability influence patient satisfaction, with responsiveness being the most influential variable.[26] Greater success among healthcare workers in delivering quality services correlates with increased community acceptance, as reflected in the growing number of women opting to deliver at primary healthcare centers. To maintain and strengthen public trust, strategies must be implemented to enhance emergency obstetric and neonatal skills and ensure active community involvement in the intervention process.[11]

CONCLUSIONS

Based on the analysis of the data, it can be concluded that interprofessional collaboration within the BEmONC team contributes positively to the reduction of maternal and neonatal morbidity and mortality rates. The effective cooperation among BEmONC team members—including physicians, nurses, and midwives—combined with strategic management and targeted evaluation, represents a fundamental determinant for the successful implementation of obstetric and neonatal care services in primary healthcare settings. Despite the identification of several barriers, such as inadequate infrastructure and insufficient communication practices, strengthening the self-efficacy of healthcare providers and increasing community satisfaction with maternal and neonatal services can contribute to improved outcomes. Ongoing research is warranted to further refine and assess the influence of BEmONC team collaboration on clinical practices and maternal and neonatal health indicators within the framework of primary care.

DISCLOSURES

Acknowledgment

The researcher wishes to recognize the Indonesia Endowment Fund for Education (LPDP) of the Ministry of Finance of the Republic of Indonesia for their scholarship funding. The researcher also would like to thank Universitas Padjadjaran, the supervisors and all those who supported and played a role for supporting this research.

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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SYSTEMATIC REVIEW

The impact of micronutrient supplementation on the outcome of In Vitro Fertilization: A comprehensive systematic review of current studies

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Article Info
Received Apr 5, 2024
Revised Sep 9, 2024
Accepted Sep 20, 2024
Published Apr 1, 2025

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Keywords:
Fertility
Micronutrients
IVF treatment
Female infertility
Good health and well-being
Maternal health

ABSTRACT

Objective: In vitro fertilization is the most common form of assisted reproductive and fertility technology. However, it is important to note the success rates of IVF generally decrease as a person gets older. Identifying modifiable factors affecting human fertility, including diet, is significant for clinical and community wellness. This systematic review investigates the role of micronutrients supplementation in fertility and its potential impact on in vitro fertilization (IVF) outcomes.

Materials and Methods: A systematic search in multiple databases using specific keywords related to in vitro fertilization, micronutrient supplementation, and outcome measures.

Results: Out of 1462 retrieved studies, 8 were included in the systematic review. These studies covered a range of micronutrients and their effects on different IVF outcomes. Findings indicated potential benefits of vitamin D3 supplementation. Vitamin D3 supplementation was associated with a significant improvement in implantation rates ($p < 0.05$) in two studies, while no significant effect was observed in clinical pregnancy rates in other micronutrients. The systematic review highlights the diverse effects of various micronutrient supplements on IVF outcomes. While some supplements showed potential benefits, others did not significantly improve pregnancy rates. Further research with larger cohorts is necessary to establish conclusive evidence. Keywords: micronutrient supplements, IVF outcomes, pregnancy rates.

Conclusion: In conclusion, this systematic review sheds light on the impact of micronutrients on IVF outcomes. Some studies suggested potential benefits of vitamin D3 supplementation >20 ng/ml, further research is needed to provide more definitive conclusions. Understanding the function of micronutrients in fertility could have significant implications for IVF treatment and female infertility management.

How to cite: Abdullah MRT, Suryoadji KA, Fakhri A, et al. The impact of micronutrient supplementation on the outcome of In Vitro Fertilization: A comprehensive systematic review of current studies. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):65-73. doi: 10.20473/mog.V33I12025.65-73.

Highlights:

1. Potential benefits of vitamin D3 supplementation >20 ng/ml, along with myo-inositol, folic acid, and melatonin, on implantation rates.
2. Subsequent studies revealed no substantial enhancement in pregnancy rates when specific supplements were used.
3. Further research is needed to provide more definitive conclusions.

INTRODUCTION

In-vitro fertilization (IVF) is the predominant method of assisted reproductive and fertility technology and is employed to assist patients experiencing difficulties in achieving conception. As per the Society for Reproductive Technology (SART), 55.6% of successful births through in vitro fertilization (IVF) happen in women who are younger than 35 years old. Additionally, 41.4% of initial embryo transfers lead to live births. The birth rate following embryo transfer is approximately 47%. For women between the ages of 38 and 40, the success rate is 26.8%, which represents a notable decline compared to the age range of 35 to 37. Women over the age of 42 have a success rate of only 3.9%. As a woman ages, both the number and quality of her eggs typically decrease. This may result in suboptimal embryo quality, thereby diminishing the probability of a successful uterine implantation. Recent scientific discussions have sparked an interest in the role of micronutrients in fertility.[1]

The correlation between maintaining a nutritious diet and fertility has been consistently and recently proven.[1,2] Micronutrients refer to crucial micro-nutrients that are necessary in small amounts as essential components of the diet. There is a scarcity of research conducted on humans, resulting in limited knowledge regarding the impact of micronutrient levels on female fertility. Nevertheless, micronutrients fulfill significant functions at different stages of the reproductive process. For example, the quality, maturation, fertilization, and implantation of oocytes rely on appropriate levels of folate. While these micronutrients do not contribute to the energy supply, they are important for both anabolic and catabolic processes. Micronutrients must be acquired from external sources.[3] A prospective study found that women who followed the dietary recommendations in the Netherlands had a higher probability of achieving pregnancy when undergoing in-vitro fertilization procedure or intracytoplasmic sperm injection.[4]

Assessing the influence of micronutrient deficiency on female infertility is difficult because it involves various crucial cofactors, such as salpingitis and sexually transmitted diseases, which can lead to infertility. Moreover, in a recent evaluation, specific scientists have emphasized the potential impact of micronutrients on female reproductive ability, yet have not been able to offer precise overall suggestions.[1] This highlights the imperative need for additional investigation on this topic. In order to assess the influence of potential micronutrient supplementation on female infertility, we performed a comprehensive analysis to examine the consequences of micronutrient supplementation on the results of in vitro fertilization.

MATERIALS AND METHODS

Research protocol and registration

Prior to writing this review, we submitted a protocol that was officially registered in the International PROSPERO on February 7th, 2024 (CRD4202 4507137).

Eligibility criteria

The strengths of this review encompass the assessment of an extensive range of international literature, conducted in accordance with a peer-reviewed protocol. This approach involved a stringent critical evaluation of dietary assessment methodologies and overall study quality, ensuring the inclusion of only reliable research. The inclusion standards for the study were based on the following criteria: the study had to be an original research study; the topic had to be suitable, specifically focusing on micronutrient supplementation in in vitro fertilization patients; the study had to include one control group and one exposure group; and a transparent extraction and statistical analysis method had to be used. The exclusion criteria was studies focusing on male infertility or lacking a control group to ensure that the results specifically reflect the impact of micronutrients on female fertility. We also excluded the studies with absence of a complete text version and the study of languages other than English. This approach was intended to minimize confounding factors and enhance the specificity of the findings

Search strategy

This study employed the PRISMA guidelines. We performed a comprehensive literature search using the latest editions of PubMed, ScienceDirect, Scopus, Embase, and the Cochrane Library up to May 20th 2024. The search included articles published in the last 10 years, focusing on studies examining micronutrient supplementation and IVF outcomes. The systematic search covered articles published between January 2014 and December 2023 to ensure the relevance and novelty of the findings.

Data extraction and study selection

In this review, four researchers independently reviewed the title and abstract of the studies and excluded those that were not relevant. The studies that were ultimately obtained were examined for any duplicate entries and

then systematically assessed based on the predetermined criteria for inclusion and exclusion. The researchers evaluated the subject characteristics (patients undergoing in vitro fertilization), the intervention used in the study (supplementation with micronutrients), the outcome of the study (in vitro fertilization outcomes), and any other pertinent information. This systematic review was analyzed using Microsoft Excel software.

Risk of bias assessment

The quality of the included studies was assessed using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (RCTs) and the Newcastle-Ottawa Scale for observational studies. Two independent reviewers evaluated each study for potential biases in selection, performance, detection, and attrition. Discrepancies were resolved through discussion or by consulting a third reviewer. Furthermore, sensitivity analyses were conducted to determine the impact of excluding studies with a high risk of bias.

RESULTS AND DISCUSSION

A combined total of 1462 studies were obtained by searching the databases PubMed/Medline (n = 64), Science Direct (n = 681), Scopus (697), Embase (13), and Cochrane Library (n = 7) using the specified keywords. Following the evaluation of abstracts and titles, a total of 1450 studies were eliminated. The studies were then compared for duplicates, and no studies were excluded. Out of the remaining 10 studies, they were evaluated based on the inclusion and exclusion criteria, and two of them were excluded. After the final screening, 8 studies were found to fulfill the inclusion and exclusion criteria. The flowchart illustrating the process of study selection is presented in Figure 1.

This systematic review obtained the results of 8 studies that met the inclusion criteria. The search results can be observed in Table 1.

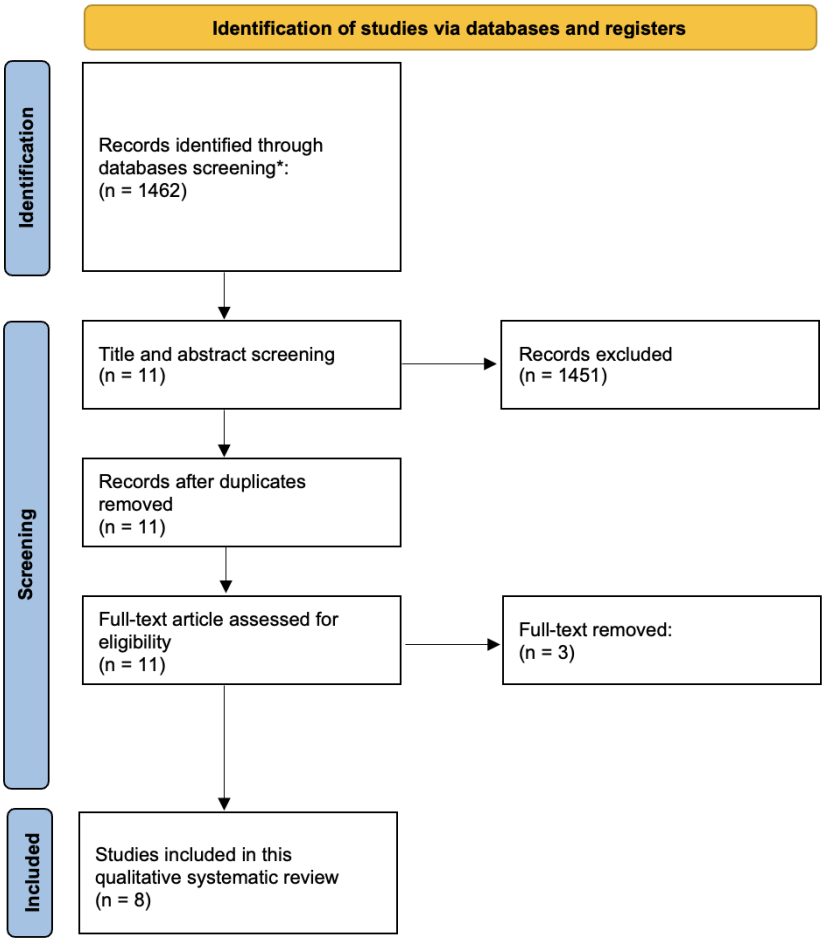

Figure 1. Article search and selection flowchart

Table 1. Search results[5-13]

Author and Year	Research design	Study population	Results
Espinola MSB et al, 2021	RCT	Population: Infertile women undergoing in vitro fertilization procedure Intervention: Oral vitamin D3, folic acid, myo-inositol, and melatonin Comparison: Oral myo-inositol, folic acid, and alpha-lactalbumin Outcome: Implantation rate	The research discovered that the addition of vitamin D supplementation, along with folic acid, myo-inositol, and melatonin, resulted in higher levels of vitamin D3 and showed a positive relationship with success rate of implantation in invitro fertilization (IVF). Larger cohorts of patients need to confirm these findings.
Somigliana E et al, 2021	RCT	Population: Women aged 18-39 years with low level of vitamin D undergoing IVF procedure Intervention: Single dose oral 600,000 IU of vitamin D3 Comparison: Placebo group Outcome: Rate of clinical pregnancy per cycle	The study concluded that administering oral vitamin D3 supplements didn't enhance the clinical pregnancy rate in women with preserved ovarian reserve, normal weight, and low levels of vitamin D who were undergoing invitro fertilization.
Makieva S et al, 2021	RCT	Population: Women with Vitamin D deficiency undergoing IVF Intervention: Oral vitamin D Comparison: Placebo group Outcome: Gene expression in granulosa cells and hormone levels in follicular fluid	The study found vitamin D resulted in a transcriptomic signature in luteinized granulosa cells. However, it did not alter hormone levels in follicular fluid.
Murto T et al, 2014	Case control	Population: Woman with unexplained infertility Intervention: Folic acid supplementation Comparison: None mentioned Outcome: IVF pregnancy outcome	The study found that woman with unexplained infertility had a higher consumption of folic acid supplements and a greater overall intake of folic acid compared to fertile women in the control group. Women who had infertility without a known cause had higher levels of folate in their blood and lower levels of homocysteine. Nevertheless, there was no correlation found between the supplementation of folic acid and the status of folate, and the outcome of pregnancy in women with unexplained infertility.
Lu X et al, 2018	RCT	Population: Patients with endometriosis undergoing IVF-ET Intervention: Vitamin C supplementation Comparison: VitC non-treatment group Outcome: IVF-ET outcomes	The study revealed that individuals with endometriosis exhibited diminished levels of vitamin C, superoxide dismutase (SOD), and total antioxidant capacity (TAC) in comparison to control group. Following a 2-month vitamin C treatment, there was a notable increase in serum vitamin C levels, while oxidative stress markers remained unchanged. The study concluded that oral vitamin C supplementation improved vitamin C levels but didn't affect the markers of oxidative stress in patients with endometriosis. A total of 245 patients with endometriosis and 132 patients without endometriosis underwent successful in vitro fertilization and embryo transfer (IVF-ET) and were followed up.
Polzikov M et al, 2022	RCT	Population: Normogonadotropic women undergoing fresh in vitro fertilization cycles Intervention: Serum level of total magnesium, folate, and calcium before ovarian stimulation Comparison: None mentioned Outcome: IVF cycle outcomes	Women with elevated folate levels in their bloodstream exhibited a reduced quantity of retrieved eggs and diminished probabilities of attaining a clinical pregnancy and live birth, in contrast to women with lower folate levels. Women with an elevated Ca/Mg ratio exhibited greater odds ratios for biochemical pregnancy, clinical pregnancy, and live birth in comparison to women with a lower Ca/Mg ratio. The study indicated that increased levels of folate in the blood and a higher ratio of calcium to magnesium were linked to poorer outcomes in in vitro fertilization (IVF) procedures among women with normal levels of gonadotropins.

Nouri K et al, 2017	RCT	Population: Women undergoing IVF/ICSI Intervention: PROfertil® female (micronutrient supplementation) Comparison: Folic acid supplementation Outcome: Embryo quality, clinical pregnancy rate	The study utilized a multinutrient supplementation called PROfertil ®, which consisted of selenium, folic acid, catechins, glycyrrhizin, vitamin E, damiana, diosgenin, and omega-3-fatty acids. The findings indicated that women who received multinutrient supplementation exhibited a greater proportion of high-quality embryos (embryos with a minimum of 6 cells and a fragmentation rate below 20%) in comparison to those who received folic acid supplementation. The clinical pregnancy rate was excluded. The study concluded that the provision of micronutrient supplementation had a beneficial effect on the quality of embryos in in vitro fertilization (IVF) procedures.
Youssef MAFM et al, 2015	RCT	Population: Women with unexplained infertility undergoing in vitro fertilization or ICSI Intervention: Oral antioxidants supplementation (multivitamins and minerals) Comparison: No antioxidant supplementation Outcome: The quantity of mature metaphase II (MII) oocytes and the rate of successful pregnancies.	The study revealed that the addition of oral multivitamins and minerals supplementation didn't have a significant impact on the quantity of mature metaphase II oocytes or the success rate of clinical pregnancies who were undergoing ICSI/IVF treatment. There were no notable disparities between the group that received antioxidant supplementation and the control group in terms of age, BMI, number of metaphase II oocytes, and rate of clinical pregnancy.

The systematic review analyzed eight relevant research studies that investigated the impact of different micronutrient supplements on the outcomes of in vitro fertilization (IVF). These studies covered a wide variety of micronutrients and their effects on various aspects of IVF treatment. It emphasizes the lack of published studies that investigate the effects of micronutrient supplementation on clinical outcomes in couples undergoing IVF treatment and subsequent follow-up. Although the eight studies that fulfilled the inclusion criteria showed significant differences in clinical outcomes and varied in their research methods, conducting a meta-analysis was not feasible.

Prior research has primarily focused on investigating the effects of antioxidants, such as vitamins A, B, C, D, E, and coenzyme Q10, as dietary micronutrient supplements in assisted reproductive techniques. Research has demonstrated that antioxidants can decrease the amount of reactive oxygen species in males, safeguarding semen from oxidative harm and enhancing sperm characteristics like motility.[13,14] However, there is limited clinical evidence regarding the impact of antioxidants on female infertility.

Espinola et al. (2021) investigated the effects of vitamin D3 supplementation, along with myo-inositol, folic acid, and melatonin, on the implantation rate of embryos in women who are experiencing infertility and undergoing in vitro fertilization (IVF) treatment. This demonstrated a statistically significant improvement in implantation rates with vitamin D3 supplementation ($p < 0.05$). However, the small sample size ($n = 23$) limits the generalizability of the findings. The study revealed a clear correlation between vitamin D3 levels and the rate of successful attachment of an implanted embryo to the uterus, suggesting potential benefits for in vitro fertilization (IVF) outcomes. However, it is imperative to have larger cohorts of participants to validate and establish the veracity of these findings.[5] In contrast, Somigliana et al. (2021) reported no significant difference in clinical pregnancy rates, indicating the potential role of other factors such as baseline vitamin D status, dosage, and timing of supplementation. Somigliana et al. (2021) conducted a retrospective cohort study on women undergoing in vitro fertilization (IVF) with deficient levels of vitamin D. Women with normal body weight, preserved ovarian reserve, and low level of vitamin D did not experience any improvement in the clinical pregnancy rate after receiving a single oral dose of 600,000 IU of vitamin D3 supplementation.[6] Makieva et al. (2021) examined the effects of administering Vitamin D orally to women with Vitamin D deficiency who were undergoing in vitro fertilization (IVF). The study discovered that vitamin D supplementation induced a distinct gene expression pattern in luteinized granulosa cells, but had no impact on hormone levels in the fluid surrounding the ovarian follicles.[7]

Murto et al. (2014) conducted a case-control study that specifically investigated the impact of folic acid supplementation on women with unexplained infertility. The study found that women with unexplained infertility had a greater consumption of folic acid supplements and showed increased levels of folate in

their blood plasma. Nevertheless, there was no evident association between the administration of folic acid and the results of pregnancy.[8] Lu et al. (2018) conducted a retrospective cohort study on individuals diagnosed with endometriosis who were undergoing in vitro fertilization and embryo transfer (IVF-ET) and receiving vitamin C supplementation. The follicular fluid's microenvironment significantly affects multiple parameters of in vitro fertilization (IVF) outcomes, such as oocyte quality, fertilization rate, and the production of high-grade embryos. It is essential to maintain a precise balance between the amount of reactive oxygen species (ROS) and the capacity of antioxidants in the follicular fluid in order to achieve high-quality oocytes and embryos during in vitro fertilization (IVF) treatment. The study showed that the administration of vitamin C increased vitamin C levels, but it did not affect oxidative stress markers in individuals diagnosed with endometriosis.[9] Polzikov et al. (2022) investigated the relationship between serum folate, total magnesium (Mg), and calcium (Ca) levels before ovarian stimulation and the results of IVF cycles in normogonadotropic women. The study found a link between elevated levels of folate in the bloodstream and a greater calcium to magnesium ratio, as well as adverse outcomes in in vitro fertilization (IVF).[10] Nouri et al. (2017) conducted a study comparing the effects of multinutrient supplementation (PROfertil® female) and folic acid supplementation in women undergoing IVF/ICSI. The study found that women who were given multinutrient supplementation had a higher occurrence of high-quality embryos.[11] In their study, Youssef et al. (2015) provided women with unexplained infertility who were undergoing ICSI/IVF with oral antioxidant supplementation, which included multivitamins and minerals. Nevertheless, they did not detect any substantial improvements in pregnancy rates.[12]

The most promising micronutrient supplementation for improving in vitro fertilization outcomes is vitamin D. According to a study by Hasan et al. (2023), it was shown that the level of 25(OH)D in the mother's blood before conception can be used to predict the outcome of in vitro fertilization (IVF) treatment during pregnancy. A preconception serum level of 25(OH)D greater than 50 nmol/L is linked to a higher probability of achieving a successful pregnancy outcome after undergoing IVF treatment. According to the current guidelines from the Institute of Medicine, our study found that 19% of women had a vitamin D deficiency (less than 30 nmol/L) and 69% had a vitamin D insufficiency (between 30-50 nmol/L).[15] Maternal serum 25(OH)D is likely responsible for controlling the expression and release of hCG, as well as promoting the production of estrogen and progesterone in trophoblasts. These processes ultimately support the successful implantation and maintenance of a healthy pregnancy. Nevertheless, there is disagreement among researchers regarding the specific function of maternal 25(OH)D in enhancing pregnancy outcomes. Some studies have found no correlation between the level of maternal serum 25(OH)D and the fertilization rate or indicators of embryo quality.[16] Evaluating the impact of vitamin D supplementation and addressing vitamin D deficiency/insufficiency before IVF treatment is crucial for understanding its effects on pregnancy outcomes.

Despite the growing number of studies in recent years investigating the impact of micronutrient supplementation on in vitro fertilization (IVF), the inconsistencies and the absence of supportive studies specifically focused on female IVF prevent definitive conclusions regarding the use of micronutrients in clinical practice. Furthermore, there is a lack of information regarding which specific group would derive greater benefits from supplementation. Although there may be certain advantages to taking micronutrient supplements, the existing evidence is inadequate to support this assertion. Hence, it is imperative to conduct extensive clinical trials that focus on the administration of micronutrient supplementation, either individually or in conjunction with other treatments, to assess their potential impact on the clinical outcomes of couples undergoing IVF therapy.

Modifying one's diet and lifestyle has been the primary method used to achieve natural conception in cases of unexplained infertility.[17] Although quitting smoking[18] and controlling obesity[19] have a significant positive impact on natural conception, the use of micronutrient supplementation has been a subject of debate. Supplementing with vitamins and anti-oxidants enhances the quality of semen, while women tend to exhibit diverse results. Nevertheless, according to our findings, we suggest that micro-nutrients may have positive effects on both males and females.[20]

Given the potential benefits of vitamin D3 supplementation observed in some studies, clinicians should consider assessing and optimizing vitamin D status in women undergoing IVF, particularly those with known deficiencies. However, the current evidence is insufficient to recommend routine micronutrient supplementation for all IVF patients. Personalized supplementation strategies, based on individual nutritional status and reproductive history, should be explored in future research. Future research should focus on large-scale, multicenter RCTs with standardized micronutrient supplementation protocols and homogenous patient populations. Studies should aim to elucidate the optimal dosage, duration, and combination of micronutrient supplements to improve IVF outcomes. Additionally,

investigating the potential mechanisms by which micro-nutrients influence reproductive processes could provide valuable insights into their role in fertility treatment. Subgroup analyses based on factors such as age, BMI, baseline micro-nutrient status, and infertility etiology could provide more nuanced insights into which patient populations are most likely to benefit from specific micronutrient supplementation. Such analyses would help tailor individualized supplementation strategies in clinical practice.

Strength and limitations

The primary strength of the review lies in its comprehensive search strategy and methodical approaches employed to identify relevant data. To include articles that met the review's eligibility or inclusion criteria, we utilized the PRISMA checklist. Eight studies fulfilled the criteria for providing relevant information on the impact of micronutrients supplementation on in vitro fertilization (IVF) outcomes. This study includes its utilization of research sources with a high level of evidence-based practices, notably RCTs, as the most common source of study. As RCTs are considered the most appropriate study design for intervention research, they are included in various micronutrients in IVF outcomes, as reviewed in this systematic review. Additionally, the study benefits from only using recent research, with a limit of including only primary studies conducted within the last 10 years, thus maintaining credibility. Furthermore, the study adheres to the PRISMA checklist, providing a methodo-logical guide for systematic review writing.

Limitations might be the fact that a high level of heterogeneity was observed among studies. This could be due to the differences in research methods used, micronutrient supplementation given, and outcomes studied in each study. Moreover, other associated factors such as supplementation doses, history of infertility, and comorbidities were not clearly reported in several studies. While this systematic review included only eight studies, the limited sample size necessitates cautious interpretation of the findings. To strengthen the conclusions, future research should include a more detailed meta-analysis involving larger cohorts of patients. This study lies in the diverse range of included research types, making it unable to differentiate between various studies on the same micronutrients with the same IVF assessment outcomes, thus precluding meta-analysis. The high heterogeneity observed among the included studies, primarily due to varying research methods, micronutrient supplementation protocols, and outcome measures, hampers the ability to derive definitive conclusions. The variability in micronutrient supplementation protocols (e.g., dosage, duration, and combination of supplements) across the included studies poses a significant limitation. Furthermore, differences in patient populations, such as baseline micronutrient status and underlying causes of infertility, may have influenced the outcomes. The lack of standardized outcome measures for IVF success, including live birth rates and embryo quality, further complicates the interpretation of the results. Therefore, further randomized controlled trials with standardized supplementation protocols and homogeneous patient populations are essential to establish stronger evidence on the effects of micronutrient supplementation on IVF outcomes. However, this weakness does not diminish the usefulness of the information that can be derived from this systematic review.

CONCLUSION

In conclusion, this systematic review examined eight studies on micronutrient supplementation's impact on in vitro fertilization (IVF) outcomes. Some studies suggested potential benefits of vitamin D3 supplementation >20 ng/ml, while others found no significant improvement in pregnancy rates with certain supplements. Further research with larger cohorts is needed to establish conclusive evidence in this area.

DISCLOSURES

Acknowledgment

Not applicable.

Conflict of interest

The authors declare there are no conflicts of interest.

Funding

This manuscript was prepared without the use of any external funding.

Author contribution

All authors have made substantial contributions to all aspects of this research, including the preparation, collection, and analysis of data, drafting of the manuscript, and approval for its publication.

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SYSTEMATIC REVIEW

The effectiveness of pregnancy exercises for a smooth childbirth process

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Article Info
Received May 23, 2024
Revised Aug 8, 2024
Accepted Aug 23, 2024
Published Apr 1, 2025

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Keywords:
Pregnancy exercises
Childbirth process
Third trimester
Maternal health

ABSTRACT

Objective: Childbirth is the process of delivering the fetus, placenta, and membranes from the uterus through the birth canal. It requires both physical and psychological preparation to ensure a safe and smooth delivery. This study examined the effectiveness of pregnancy exercises in facilitating a smoother labor process.

Materials and Methods: This study employed a systematic review method, utilizing databases such as PubMed, ScienceDirect, ProQuest, Wiley Online Library, and EBSCO. Article selection followed the PICO framework, using keywords like "Prenatal Exercise" OR "pregnant* exercise" AND ("Length of labor" OR "stage* of childbirth") to identify relevant research.

Results: Out of 821 articles, 35 were identified as potentially relevant. Various study designs, including retrospective, observational, and experimental studies with control groups, indicated that prenatal exercise can not only facilitate a faster labor process but also accelerate postpartum involution and positively impact maternal and infant health. However, some cohort studies reported conflicting findings, showing no significant relationship between prenatal exercise and labor outcomes. These discrepancies may be attributed to factors such as maternal health status, prior childbirth experience, and the type and intensity of prenatal exercise performed.

Conclusion: The reviewed articles indicate that prenatal exercise significantly facilitates and optimizes the labor process. Therefore, it is essential to encourage pregnant women to engage in regular prenatal exercise starting in the third trimester, ensuring it is conducted safely and comfortably to maximize its benefits for both mother and baby.

How to cite: Islami T, Ismarwati. The effectiveness of pregnancy exercises for a smooth childbirth process. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):74-82. doi: 10.20473/mog.V33I12025.74-82.

Highlights:

1. Pregnant women are prone to experiencing labor jams and tears during childbirth
2. Regular pregnancy exercises during the third trimester of pregnancy can help the delivery process run smoothly and reduce the occurrence of birth canal tears.

INTRODUCTION

Labor is the physiological process through which the fetus, placenta, and membranes are expelled from the uterus via the birth canal.[1] The mother's physical endurance and the progression of labor can be influenced by psychological factors. Approximately 97% of labor occurs naturally; however, maternal anxiety can lead to increased tension in smooth muscles and blood vessels, resulting in cervical rigidity and uterine hypoxia. Consequently, pain impulses travel to the cerebral cortex via the thalamo-limbic pathway, heightening fear and further inhibiting uterine contractions. This may prolong the second stage of labor and increase the likelihood of cesarean delivery.[2,3]

In Indonesia, there are approximately 5,082,537 pregnant women. Among those experiencing pregnancy and childbirth complications, 11% are attributed to prolonged labor. Pregnant women who engage in regular prenatal exercise, particularly during the last trimester, tend to experience reduced labor pain compared to those who do not participate in such activities. This reduction in pain is associated with increased levels of endorphins, which serve as natural analgesics.[4]

Prenatal exercise is widely recommended as part of antenatal care to prepare women for childbirth. While numerous studies have demonstrated its benefits in enhancing maternal fitness and alleviating pregnancy discomfort, its role in facilitating labor remains a subject of debate. This controversy stems from variations in research methodology, sample sizes, and differing definitions of labor ease.[4] Some studies suggest that excessive physical activity may lead to pregnancy-related complications, whereas others highlight that consistent prenatal exercise can mitigate such complications.[5,6] This study aims to evaluate the effectiveness of pregnancy exercises in promoting a smoother labor process.

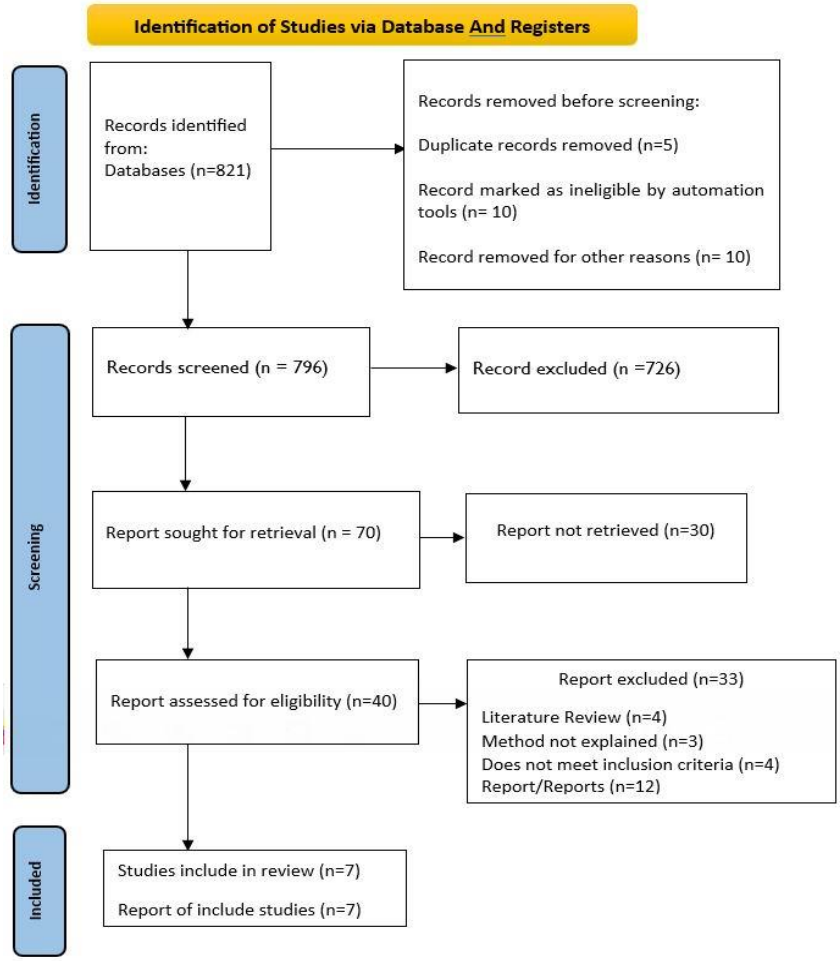

Figure 1. PRISMA flow chart

MATERIALS AND METHODS

This study was a systematic review by using databases for article search: PubMed, Science Direct, ProQuest, Wiley Online Library, EBSCO, Google Scholar. The keywords used in the article search are compiled based on the PICO framework, ((Prenatal Exercise) OR (pregnant* exercise)) AND (Length of labor)) OR (stage* of childbirth)).

The inclusion criteria for this study were as follows: articles published within the last five years, written in either English or Indonesian, original research articles, and studies specifically examining the impact of pregnancy exercises on the labor process. The exclusion criteria included literature reviews, books, reports, and articles unrelated to the research topic.

This scoping review identified a total of 821 articles from various databases: PubMed (107 articles), Wiley Online Library (141 articles), ScienceDirect (500 articles), ProQuest (38 articles), and EBSCO (35 articles). These articles were imported into Covidence software, where five duplicate articles were detected and subsequently removed. Following this, a systematic screening process was conducted by reviewing titles and abstracts to determine relevance based on the predefined inclusion and exclusion criteria. During this phase, 10 articles were identified as non-research studies, while 11 articles were inaccessible. After filtering the remaining 796 articles by title and abstract, 70 articles were selected for further evaluation based on completeness and relevance, while 726 articles were excluded for not meeting the criteria. Among the 70 selected articles, 40 had full-text availability. However, 33 of these were excluded as they did not directly address the research question. Ultimately, seven articles met all inclusion criteria and were included in this study.

A critical appraisal was conducted to systematically evaluate the quality and validity of the selected articles. The Joanna Briggs Institute (JBI) critical appraisal tool was used for this assessment, which was performed independently by two reviewers (Author One and Author Two). Each article was carefully examined to determine its suitability for inclusion as a reference for further research. The quality of the articles was graded using A, B, and C classifications, with final assessments presented in Table 1. This thorough evaluation ensured the inclusion of high-quality studies that directly contributed to the research objectives.

Table 1. Summary of journal literature search results

No	Titles	Countries	Aims	Data collection	Type of research	Participants/ Sample Size	Results	Grades
A1	The effectiveness of a Pilates exercise program during pregnancy on childbirth outcomes: a randomized controlled clinical trial.[7]	Iran	To find out the effectiveness of the pilates gymnastics program during pregnancy and during childbirth.	The instruments used to collect data were a two-part checklist, RPE, VAS and mackey birth satisfaction assessment scale.	Randomized Clinical Trial	This clinical study involved 110 primipara women in the intervention group (n = 55) and control (n = 55).	The results showed that doing pilates exercises during pregnancy significantly reduced the intensity of labor pain, the duration of the active phase, and the second phase of labor.	A
A2	Pregnancy exercise to smooth delivery process for maternal.[8]	Indonesia	To find out the relationship between pregnancy gymnastics and the delivery process in maternity at PMB Budi Ariani Siregar 2021	Data collection using questionnaires .	Cross sectional	The study involved 30 respondents, of which 15 of them did pregnancy exercises and 15 did not.	The results showed a significant relationship between Ahamil gymnastics and the delivery process of maternity at PBM Budi Ariani Siregar STR. Keb	A
A3	The effectiveness of pregnancy exercises on the smooth delivery of	Indonesia	To determine the effectiveness of pregnancy exercises on the smooth	Primary data using observation sheets.	Cross sectional	The respondents in this study were 35 people.	The results showed that there was a significant correlation between pregnancy exercises and smooth delivery	A

	phase II in inpartu mothers at the Bulupoddo Health Center, Sinjai Regency. [9]		delivery of phase II in inpartu mothers at the Bulupoddo Health Center, Sinjai Regency.				in the second trimester of inpartu mothers	
A4	Influence of a Water-Based Exercise Program in the Rate of Spontaneous Birth: A Randomized Clinical Trial.[10]	USA	To evaluate the prevalence of spontaneous birth among women participating in a water-based physical exercise program	Participant data was collected at health centers. Recruitment of participants began in the first half of April 2016, when the ultrasound examination was performed at the 12th week of pregnancy, and ended at six weeks	Randomized Clinical Trial	The respondents in this study were 129 people.	The results showed that women who participated in water-based exercise programs experienced weight loss during pregnancy.	B
A5	The Effectiveness of Pregnancy Gymnastics Exercises on the Childbirth Process at the Pancoran Mas Depok Health Center.[11]	Indonesia	To find out the effectiveness of pregnancy gymnastics exercises on the delivery process at the Pancoran Mas Depok Health Center	Data were collected using primary data.	Quasi experimental	The respondents in this study were 50 respondents	The results of the bivariate study showed a P value of 0.003; OR = 9.333 (p0.05) and has no chance of process quality	A
A6	The effect of the combination of prenatal yoga and pregnancy exercises on the level of anxiety and the duration of labor in the first trimester of pregnancy in pregnant women in the third trimester.[12]	Indonesia	To find out the effect of the combination of prenatal yoga and pregnancy exercises on the level of anxiety and the duration of labor in the first trimester of pregnant women	Data collection using primary data	Quasi experimental	The respondents in this study were 30 pregnant women in the third trimester	The results of the study showed that the combination of prenatal yoga and pregnancy exercises had an impact on the anxiety of pregnant women in the third trimester when facing childbirth.	A
A7	The Effect Of Pregnancy Exercise On Third Trimester Primigravida Anxiety In Dealing With Childbirth.[13]	Indonesia	This study analyzes the effect of pregnancy exercises on primigravida anxiety in the third trimester in facing childbirth.	This study uses the Hamilton Rating Scale Anxiety (HRS-A) Instrument which will be studied for respondents' anxiety.	Design of quasi-experiments with nonrandomized pretest-postest control groups	The respondents in this study were 34 respondents	The results of this study show that in the third trimester, pregnancy exercises have an impact on pregnant women's anxiety.	A

RESULTS AND DISCUSSION

As outlined in Table 1, a total of seven articles were analyzed, comprising two cross-sectional studies, two randomized controlled trials (RCTs), and three quasi-experimental studies. The findings from these studies identified several benefits of prenatal exercise in facilitating the labor process. These benefits include improved maternal and fetal health, enhanced physical preparedness for childbirth, better management of labor discomfort and associated health risks, reduced anxiety levels, improved maternal psychological well-being, strengthened pelvic muscle function, and support for the postpartum involution process.

Among the initial 821 articles reviewed, 35 were regarded potentially relevant. Various study designs, including retrospective, observational, and experimental studies with control groups, demonstrated that prenatal exercise not only facilitates a smoother labor process but also accelerates postpartum uterine involution. Additionally, prenatal exercise has been shown to have a positive impact on maternal and neonatal health following delivery. However, findings from cohort studies yielded conflicting results, indicating no significant association between prenatal exercise and labor outcomes. These discrepancies may be attributed to multiple influencing factors, such as maternal health status, prior childbirth experience, as well as the type and intensity of prenatal exercise performed.

To ensure a structured analysis, the selected articles were categorized based on their original characteristics, including research methodology, study design, and country-specific factors such as healthcare infrastructure and maternal care practices. This scoping review encompasses studies from the United States, representing developed countries with advanced healthcare systems, and from Indonesia and Iran, representing developing nations where maternal health programs and access to prenatal care may differ significantly. By including studies from diverse healthcare settings, this review provides a broader perspective on the impact of prenatal exercise across different socioeconomic and medical environments.

The findings from this review indicate that prenatal exercise is significantly effective in promoting a smoother labor process. Engaging in prenatal exercise has been associated with reduced labor pain, shorter labor duration, and increased maternal satisfaction with the childbirth experience. The seven selected articles provide various perspectives on the benefits of prenatal exercise, reinforcing its importance in maternal health. These findings align with research conducted by Rahayu & Fitria (2019), which highlights prenatal exercise as a method for maintaining or enhancing maternal physical stability. It is a form of exercise therapy recommended from 28 weeks of gestation until delivery, aiming to facilitate a safe, efficient, and less painful labor process. The recommended frequency for prenatal exercise is two to three times per week to maximize its benefits.[14]

Prenatal exercise plays a crucial role in promoting maternal health and reducing the risk of complications associated with postural changes during pregnancy. However, for optimal benefits, prenatal exercise should follow a structured and systematic approach. Properly regulated prenatal exercise is essential for maintaining smooth blood circulation, which is critical for both maternal and fetal well-being. Midwives and healthcare providers can incorporate prenatal exercise into routine prenatal care by educating pregnant women on its benefits and guiding them through safe and effective exercise routines. Regular prenatal exercise helps expectant mothers prepare physically for childbirth while also alleviating labor pain.[15-17]

The childbirth process requires both mental and physical preparedness from the mother to ensure a safe and smooth delivery. Engaging in regular pregnancy exercises is an effective strategy to enhance physical endurance, improve mental resilience, reduce stress levels, promote relaxation, and facilitate a smoother and more efficient labor experience.[18]

Prenatal exercise has been shown to provide significant health benefits for both the mother and fetus. When a baby begins to breathe independently at birth, oxygen transfer occurs through the placenta from the maternal bloodstream to the fetal circulation. Pregnancy exercises improve maternal oxygenation, thereby enhancing oxygen supply to the fetus via the placenta.[19] Additionally, prenatal exercise strengthens and maintains the elasticity of key muscle groups involved in labor, including the abdominal wall, ligaments, and pelvic floor muscles. One of the common complications during childbirth is perineal rupture or tearing. Pregnancy exercises, particularly those targeting the pelvic floor, may reduce the likelihood of such injuries. Beyond its physiological benefits, prenatal exercise helps alleviate common pregnancy discomforts and prepares women both physically and mentally for labor.[20]

Findings from this review also highlight that participation in prenatal exercise enhances self-confidence, positively influencing the overall childbirth experience. This is consistent with research by Nikmah et al. (2021),[20] which emphasizes that prenatal exercise strengthens core muscles, improves physical endurance, and fosters a sense of comfort and confidence. By

reducing pregnancy-related complaints and anxiety, prenatal exercise contributes to a more positive and manageable labor experience.[21]

The World Health Organization (WHO) recommends that adults aged 18 to 64 engage in at least 150 minutes of moderate-intensity physical activity or 75 minutes of high-intensity physical activity per week. A sedentary lifestyle is a significant risk factor for major global causes of mortality, including cardiovascular disease, stroke, and diabetes mellitus. Reduced physical activity contributes to these conditions, underscoring the importance of maintaining an active lifestyle.[22-25]

Prenatal exercise offers numerous benefits for pregnant women, including alleviating common pregnancy-related discomforts such as aches, pains, and muscle tension. It also improves cardiovascular and respiratory function, enhances muscle tone, and promotes better sleep. Engaging in relaxation exercises during pregnancy aids in deep breathing techniques, helping expectant mothers maintain overall health and prepare for a smoother childbirth experience. Pregnant women who incorporate regular physical activity into their routine, along with increased awareness and mental preparedness, tend to experience greater comfort, calmness, and a positive outlook during pregnancy.[26] Although 85% of deliveries occur without complications, approximately 15% require medical intervention. Proper antenatal care, including prenatal exercise, can significantly reduce the risk of labor complications. In contrast, physical inactivity during pregnancy may lead to increased fatigue, heightened pain perception, and prolonged labor, particularly in the second stage, which elevates the risk of fetal distress.[27] Therefore, adequate physical preparation for childbirth is essential to optimize maternal and fetal outcomes.[28]

Anxiety disorders are common during pregnancy, with affected women frequently experiencing excessive worry, whether minor or significant. This persistent anxiety can manifest as restlessness, fatigue, difficulty concentrating, irritability, muscle tension, tremors, heightened startle responses, sleep disturbances, excessive sweating, nausea, diarrhea, shortness of breath, or tachycardia. To break the cycle of prenatal anxiety, relaxation techniques such as yoga and pregnancy exercises have been identified as effective interventions. Pregnancy gymnastics, in particular, exerts a calming effect, reducing stress and promoting emotional well-being.[29]

A study conducted by Aktas et al. (2021)[30] demonstrated that pregnancy exercises not only alleviate pain in the final stages of pregnancy but also improve uterine blood flow through pelvic muscle relaxation. The use of birth ball exercises enhances maternal comfort by facilitating proper pelvic positioning and reducing pain perception. Additionally, these exercises promote flexibility and strengthen the core muscles, further aiding in labor preparation. By focusing on movement and posture, pregnant women can divert attention from discomfort, enhance body awareness, and improve their overall labor experience, leading to a more positive childbirth outcome.

For low-risk pregnancies, pregnancy exercises are recommended due to their positive impact on cervical readiness and Bishop's score, increasing the likelihood of spontaneous labor while decreasing the need for labor induction or cesarean section. These exercises allow pregnant women to regulate their body movements and breathing, effectively managing anxiety and tension.[31] When performed consistently and correctly, prenatal exercise strengthens uterine contractions, enhances pelvic floor and abdominal muscle endurance, and facilitates a shorter, more natural labor process. Thus, pregnancy exercises play a crucial role in promoting maternal well-being and optimizing birth outcomes.[8]

Prenatal exercises play a crucial role in strengthening and preserving the elasticity of the abdominal wall muscles, ligaments, and pelvic floor, all of which are essential for the labor process. Engaging in these exercises regularly, at least once a week for a minimum of 30 minutes, yields optimal benefits and contributes to a more positive childbirth experience for expectant mothers. Fundamentally, prenatal exercises are designed to enhance muscle strength and maintain flexibility, particularly in the abdominal wall, pelvic muscles, and pelvic floor. Pregnant women who do not engage in such exercises are more susceptible to both emotional and physical stress, which can result in muscle stiffness and joint discomfort.[9]

During the second stage of labor, prenatal exercises aid in relaxation, breathing control, and contraction regulation, while also strengthening the abdominal wall and pelvic floor muscles to facilitate a smoother delivery. Additionally, during the third and fourth stages of labor, these exercises help in reducing excessive postpartum bleeding and contribute to a normal labor duration. A structured regimen of pregnancy exercises is essential in preparing expectant mothers physically by maintaining the condition of muscles and joints critical to the childbirth process, while also fostering mental readiness and boosting maternal confidence. Studies have identified a correlation between regular prenatal exercise and timely, uncomplicated deliveries.[32]

Prenatal exercise provides numerous benefits, including alleviating labor-related pain and reinforcing the

strength of the abdominal and pelvic floor muscles, both of which are essential during childbirth. For a more comprehensive approach, prenatal exercises are often combined with prenatal yoga. Prenatal yoga integrates elements of traditional yoga into a specialized regimen tailored for pregnancy. It represents a holistic approach encompassing physical, mental, and spiritual well-being through muscle stretching, breathing techniques, and meditative practices aimed at enhancing maternal health and emotional balance.[33]

The findings of this study strongly support the integration of pregnancy exercises into antenatal care programs to promote a smoother and more positive birthing experience. Based on the review of seven selected studies, it is evident that prenatal exercise is a highly beneficial intervention that should be widely encouraged among pregnant women. Special emphasis should be placed on its promotion in remote areas, where access to structured antenatal programs may be limited, ensuring that expectant mothers in all regions receive the necessary preparation for childbirth.

Strength and limitations

This study provides a comprehensive review of prenatal exercise, incorporating diverse research methodologies and evidence from both developed and developing countries. An important strength is its focus on various prenatal exercises, including pregnancy gymnastics, birth ball exercises, and prenatal yoga, highlighting their physical and psychological benefits for maternal well-being and labor outcomes.

However, limitations exist. Variability in study designs and sample sizes introduces inconsistencies, and some findings rely on self-reported data, which may be biased. Additionally, conflicting results from cohort studies suggest that maternal health, previous childbirth experience, and exercise intensity influence labor outcomes. The study primarily focuses on low-risk pregnancies, limiting its applicability to high-risk cases. Lastly, differences in exercise frequency and adherence make it challenging to define a standardized prenatal exercise regimen. Future research should focus on large-scale trials to establish more definitive guidelines for prenatal exercise benefits.

CONCLUSION

Pregnancy gymnastics has been shown to not only facilitate the labor process but also accelerate postpartum involution, contributing to improved maternal and neonatal health. Considering these advantages, it is essential to encourage pregnant women to engage in regular pregnancy gymnastics, particularly from the third trimester onward. Emphasis should be placed on ensuring that exercises are performed safely, comfortably, and under appropriate guidance to maximize their effectiveness.

DISCLOSURE

Acknowledgment

We would like to thank the entire academic community of the Faculty of Health Sciences, University of 'Aisyiyah Yogyakarta, especially the Master of Midwifery Study Program, for the opportunity to collaborate in the preparation of this systematic review.

Conflict of interest

There is no conflict of interest in this systematic review.

Funding

This systematic review study was not funded by any party.

Author contributions

All authors have contributed to all of this systematic review process, including the preparation, data collection and data analysis, as well as the preparation and approval of this publication.

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CASE REPORT

The application of Mississippi Protocol in superimposed pre-eclampsia patients with class 2 hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome

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Article Info
Received Jul 20, 2024
Revised Oct 23, 2024
Accepted Oct 25, 2024
Published Apr 1, 2025

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Keywords:
Corticosteroids
HELLP syndrome
Mississippi Protocol
Placental abruption
Superimposed pre-eclampsia
Maternal health

ABSTRACT

Objective: To describe the implementation of the Mississippi Protocol (MP) in a case of superimposed pre-eclampsia complicated by class 2 HELLP syndrome.

Case Report: The patient initially received conservative treatment, including anticonvulsant prophylaxis, antihypertensive agents, and high-dose corticosteroids, in accordance with the MP. However, during observation, placental abruption and fetal distress were noted. Consequently, an emergency (green code) Caesarean section was performed. Placental abruption is a known complication associated with pre-eclampsia. The neonatal outcome following pregnancy termination was premature birth, low birth weight, and respiratory distress. Following delivery, laboratory parameters gradually improved. MP therapy was continued for 4 days post-delivery until clinical and laboratory indicators normalized. The administration of high-dose corticosteroids in HELLP syndrome is based on its characteristic excessive inflammatory response, which represents the distinctive feature of this case. Corticosteroid therapy is intended to reduce maternal morbidity and mortality and to enhance neonatal outcomes.

Conclusion: Careful monitoring and comprehensive management are essential when applying the MP in such cases. The definitive treatment for both pre-eclampsia and HELLP syndrome remains the termination of pregnancy. Further research is required to assess the effectiveness of MP in emergency or complicated scenarios.

How to cite: Kusuma AANJ. The application of Mississippi Protocol in superimposed pre-eclampsia patients with class 2 hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2025;33(1):83-88. doi: 10.20473/mog.V33I12025.83-88.

Highlights:

1. The neonatal outcome following pregnancy termination was preterm birth, accompanied by low birth weight and respiratory distress.
2. Following pregnancy termination, laboratory parameters gradually demonstrated improvement over time.
3. Mississippi Protocol therapy was maintained for 4 days after pregnancy termination until both clinical status and laboratory values showed improvement.

INTRODUCTION

Pre-eclampsia is a form of gestational hypertension. This condition is defined by an elevation in systolic blood pressure to 140 mmHg and diastolic blood pressure to 90 mmHg, accompanied by proteinuria of 30 mg/dL or dysfunction of maternal or uteroplacental organs. Maternal organ dysfunction includes renal, hepatic, neurological, and hematological impairment. When this condition develops in a patient with a history of chronic hypertension prior to 20 weeks of gestation, it is classified as superimposed pre-eclampsia.[1]

The global burden of pre-eclampsia affects approximately 39 million pregnancies, with an estimated incidence of 4.6%.[2] Each year, it accounts for around 63,000 maternal deaths.[3] This corresponds to 20 deaths per 100,000 pregnancies and a case fatality rate of approximately 0.8%.[4] The mortality associated with pre-eclampsia is disproportionately higher in low- and middle-income countries. In developing nations, pre-eclampsia and eclampsia are responsible for approximately 30% of all maternal deaths.[3]

HELLP syndrome—characterized by hemolysis, elevated liver enzymes, and low platelet count—represents a more severe variant of pre-eclampsia. Approximately 20–30% of pre-eclampsia cases progress to HELLP syndrome.[5] About 30% of HELLP syndrome cases develop in the postpartum period, typically within 48 hours.[6] Although the syndrome most frequently occurs in the third trimester, a minority of cases may arise between 22 and 24 weeks of gestation, with postpartum occurrence accounting for up to 30%.[5] HELLP syndrome affects approximately 5% of patients with pre-eclampsia and 10–20% of those with severe pre-eclampsia. It carries a maternal mortality rate of 1.1% and is associated with serious complications, including disseminated intravascular coagulation, hepatic hematoma, liver failure, and renal failure. The reported perinatal mortality rate ranges from 6% to 17%.[7]

HELLP syndrome shares a common pathophysiological mechanism with pre-eclampsia, particularly abnormalities in placental development and spiral artery remodeling.[3] These placental anomalies arise due to imbalances in antiangiogenic factors such as soluble FMS-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF), and endoglin.[8,9] Accordingly, corticosteroid therapy is incorporated into the Mississippi Protocol.[5] This report aimed to present the application of the Mississippi Protocol (MP) in a case of superimposed pre-eclampsia with class 2 HELLP syndrome.

CASE REPORT

A 43-year-old woman was referred from a community health center at 30 weeks' gestation with gestational hypertension, blood pressure of 200/110 mmHg, and proteinuria (+2). At Prof. Dr. I.G.N.G Ngoerah Hospital, she had no abdominal pain, dyspnea, or visual/epigastric symptoms. Her medical history included uncontrolled hypertension and hepatitis B diagnosed during antenatal care. At the referring center, she received a 4-gram IV bolus of 40% magnesium sulfate (MgSO4), a 6-gram maintenance dose, and 10 mg of oral nifedipine prior to hospital admission.

Physical examination

Upon hospital admission, the patient's blood pressure was 160/110 mmHg, with a Mean Arterial Pressure (MAP) of 126 mmHg, pulse rate of 98 beats per minute, respiratory rate of 20 breaths per minute, and axillary temperature of 36.5°C. General physical examination findings were unremarkable. Obstetric examination revealed a uterine fundal height midway between the xiphoid process and umbilicus, no uterine contractions, a fetal heart rate (FHR) of 158 beats per minute, and cephalic presentation.

Additional examination

Laboratory results are presented in Table 1. Ultrasonographic evaluation revealed a single, viable fetus with a positive FHR and fetal movement, corresponding to a gestational age of 27 weeks and 3 days, with an estimated fetal weight of 1107 grams.

Assessment and management

The patient was diagnosed with G4P2012 at 30 weeks and 1 day, with a single viable fetus, superimposed pre-eclampsia with severe features, class 3 HELLP syndrome, chronic hepatitis B infection, and hypokalemia. Conservative management included administration of 6 grams of 40% MgSO4, dexamethasone 6 mg intramuscularly every 12 hours for 2 days to promote fetal lung maturation, and nifedipine 10 mg intraorally every 8 hours if MAP exceeded 125 mmHg. On the second day of hospitalization, the patient's condition deteriorated, with blood pressure escalating to 200/120 mmHg. Laboratory findings indicated a platelet count of 79.45/µL, elevated lactate dehydrogenase (LDH) of 940 U/L, proteinuria (+3), and evidence of a urinary tract infection. The worsening laboratory parameters prompted reclassification of the HELLP syndrome to class 2.

Table 1. Laboratory examination

Components	Results	References	Unit
WBC	12.3	4.1 – 11.0	10^3/µL
HGB	12.89	13.5 – 17.5	mg/dL
PLT	106.5	150 – 440	10^3/µL
LDH	765	125 - 220	U/L
SGOT	33.2	<34	U/L
SGPT	27	<55	U/L
Albumin	3.1	3.40 – 4.80	g/dL
BUN	8,4	8.4 – 25.7	mg/dL
Creatinine	0.74	0.72 – 1.25	mg/dL
Potassium	2.95	3.6 – 5.2	mmol/L
Proteinuria	(+3)		
HbSAg	reactive		

WBC = white blood cells, HGB = hemoglobin, PLT = platelet, LDH = lactate dehydrogenase, SGOT = Serum Glutamic-Oxaloacetic Transaminase Test, SGPT = Serum Glutamic Pyruvic Transaminase, BUN = blood urea nitrogen, HbsAg = hepatitis B surface antigen

The patient was subsequently managed in accordance with the Mississippi Protocol (MP), receiving intravenous dexamethasone 10 milligrams every 12 hours and intravenous cefoperazone 1 gram every 12 hours to treat the urinary tract infection. During observation, the patient's blood pressure remained persistently elevated; therefore, a continuous infusion of nicardipine at 5 milligrams per hour was initiated. Following dexamethasone administration under the MP, laboratory values improved, with platelet counts rising to 111.7 /µL and 122.7 /µL on the third and fourth days of treatment, respectively. However, on day four, the patient experienced sudden, intermittent abdominal pain with uterine contractions occurring four times in ten minutes, lasting 30–35 seconds each, and a fetal heart rate of 140 beats per minute. Abdominal examination revealed increased uterine tone. Cardiotocography indicated a category 3 pattern (sinusoidal), raising suspicion of placental abruption and fetal distress. An emergency Caesarean section (green code) was therefore performed.

Outcome

The newborn delivered via Caesarean section was diagnosed with very low birth weight (1,000 grams), severe asphyxia, and respiratory distress. Postoperatively, the mother received an oxytocin infusion of 20 IU, 6 grams of 40% $MgSO_4$ for 24 hours, and nifedipine 10 milligrams every 8 hours if MAP exceeded 125 mmHg. Dexamethasone was continued at 10 milligrams every 12 hours on the first postoperative day and tapered to 5 milligrams every 12 hours thereafter. During follow-up, laboratory evaluation revealed normalization of the platelet count by the second day post-termination, while LDH levels remained elevated. By the fourth day, LDH showed a downward trend, suggesting a reduction in systemic inflammation. The patient was discharged on nifedipine and methyldopa. No adverse events related to MP administration were reported by the patient.

DISCUSSION

The diagnosis of pre-eclampsia is established by the presence of hypertension in conjunction with proteinuria, clinical maternal organ dysfunction, or uteroplacental dysfunction.[1] In this case, all diagnostic criteria were fulfilled, complicated by HELLP syndrome, a severe variant of pre-eclampsia. Organ dysfunction in HELLP syndrome involves the hematological system, including thrombocytopenia, hemolysis, and elevated liver enzymes. Numerous risk factors contribute to pre-eclampsia, including chronic renal disease, autoimmune conditions, diabetes mellitus, chronic hypertension, and a history of hypertensive disorders in prior pregnancies. Additional moderate-risk factors include nulliparity, maternal age over 40 years, body mass index (BMI) exceeding 35 kg/m², multiparity, or interpregnancy intervals greater than 10 years.[10] In this case, the patient exhibited risk factors of advanced maternal age (over 35 years) and chronic hypertension, consistent with a diagnosis of superimposed pre-eclampsia. A detailed clinical history is essential for timely identification of such risk profiles.

The primary therapeutic goals of the Mississippi Protocol (MP) are to prevent disease progression from class 2, class 3, or partial HELLP syndrome to class 1, reduce the incidence of major maternal morbidity, prevent maternal mortality, shorten disease duration and treatment time, and minimize perinatal morbidity and mortality.[11] According to the Mississippi criteria, HELLP syndrome is classified into three categories

based on platelet count. When only one or two of the three diagnostic criteria are met, the condition is termed partial HELLP syndrome.[12] In this case, the patient initially presented with an LDH level of 765 IU/L and a platelet count of 106.5 /µL, consistent with class 3 HELLP syndrome. On the second day of MP-based treatment, laboratory findings demonstrated a decline in platelets to 79,450 /µL and a rise in LDH to 940 IU/L, prompting reclassification to class 2 HELLP syndrome. The dynamic changes in laboratory values highlight the importance of close monitoring during the acute management phase.

HELLP syndrome typically develops between 27 and 37 weeks of gestation; likewise, this case manifested at 30 weeks. The syndrome is associated with a more intense inflammatory response than standard pre-eclampsia. Endothelial injury leads to red blood cell fragmentation as they traverse damaged vessels, producing schizocytes and burr cells. This intravascular hemolysis causes anemia and elevated LDH levels. Hemolysis also activates the coagulation cascade, increasing the risk of disseminated intravascular coagulation (DIC). Concentrations of FasL in both trophoblastic villi and maternal circulation are reported to be higher in HELLP syndrome compared to pre-eclampsia without HELLP features.[13]

The heightened inflammatory state in HELLP syndrome is marked by elevated levels of C-reactive protein, interleukin-6, and TNF-alpha, along with increased white blood cell counts.[13] This enhanced inflammatory response provides the rationale for high-dose corticosteroid therapy under the MP. The MP management of HELLP syndrome includes the administration of magnesium sulfate ($MgSO_4$) for seizure prophylaxis and to reduce systemic vascular resistance, the use of oral or intravenous anti-hypertensive agents, and intravenous dexamethasone 10 milligrams every 12 hours for 48–72 hours, continued until platelet counts trend toward normalization (≥100,000/µL).[5]

The definitive treatment for pre-eclampsia is pregnancy termination; however, the timing of intervention—whether immediate or delayed—depends on multiple factors, including gestational age, the severity of maternal illness, and fetal condition. Nonetheless, any decision to terminate must carefully weigh both maternal and fetal status.[14] The likelihood of disease progression can be assessed by measuring plasma levels of proangiogenic and antiangiogenic factors produced by the placenta, which is the primary source of the disorder.[15] Immediate control of maternal hypertension remains the cornerstone of emergency management in severe pre-eclampsia. Magnesium sulfate ($MgSO_4$) acts as the principal prophylactic agent against eclampsia but should not take precedence over achieving effective blood pressure control. Research into emerging adjuvant therapies may enable prolonged gestation, improved perinatal outcomes, and enhanced maternal safety.[16]

The efficacy of corticosteroid therapy has been conclusively validated. One of the most impactful advances in perinatal medicine has been the antenatal administration of corticosteroids to women in the mid to late stages of pregnancy to mitigate complications associated with preterm birth. The broad acceptance of this intervention is supported by substantial evidence demonstrating enhanced neonatal outcomes, particularly through corticosteroid-facilitated maturation of fetal lungs.[17] Supporting this, a study by Chawla (2022) found that administration of a complete course of antenatal corticosteroids at a gestational age of 22 6/7 weeks or less was independently associated with improved survival and survival without major morbidity among neonates delivered between 22 0/7 and 23 6/7 weeks who received intensive care.[18] The Mississippi steroid protocol emphasizes the first 24 hours following steroid initiation and employs high-dose dexamethasone. In patients with HELLP syndrome, prednisolone has been shown to reduce maternal IL-6 levels, though it does not significantly affect IL-1, IL-10, or soluble IL-6 receptor levels. The pathophysiology of pre-eclampsia is also associated with neutrophil activation, which involves neutrophil adhesion and transmigration across the endothelium.[19]

Both maternal and fetal complications are frequently observed in HELLP syndrome. Damaged maternal endothelium has been implicated in the pathogenesis of maternal morbidity associated with severe pre-eclampsia. Moreover, endothelial dysfunction may persist for years after the initial presentation, reflecting long-term vascular compromise.[20] In this case, the neonatal outcome following Caesarean section was very low birth weight (1,000 grams), severe asphyxia, and respiratory distress. Despite 7 days of intensive treatment, the infant's condition deteriorated, and death occurred due to septic shock and complications of prematurity. Prematurity continues to pose a significant challenge in the management of perinatal HELLP syndrome. Therefore, involvement of a dedicated neonatal care team and the availability of comprehensive healthcare infrastructure are critical to reducing neonatal morbidity and mortality.[21] Limitations of this study include the absence of a control group and uncertainty regarding the temporal relationship between exposure and health outcomes. Additionally, specific laboratory indicators of inflammation, such as interleukins, were not evaluated in the patient. However, the observed downward trend

in clinical markers may serve as a surrogate indicator of reduced systemic inflammation.

CONCLUSION

Continuous monitoring and appropriate management are essential when implementing the Mississippi Protocol (MP) in clinical practice. The definitive treatment for both pre-eclampsia and HELLP syndrome remains pregnancy termination. However, premature termination may adversely affect fetal outcomes, whereas delayed intervention increases the risk of maternal organ dysfunction and mortality. Further research is warranted to assess the efficacy of MP implementation in emergency settings or complex clinical scenarios.

DISCLOSURES

Acknowledgment

Prof. Dr. I.G.N.G. Ngoerah Hospital's Maternal Fetal Medicine Division, Obstetrics and Gynecology Department, is acknowledged for their assistance.

Conflict of interest

The author has no conflict of interest.

Patient's consent for publication

The patient had signed the informed consent form and consented to the publication of this case report.

Funding

There is no external funding for this study.

Author contribution

The author has carried out all phases of this research, including preparation, data collection and analysis, drafting of the article.

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