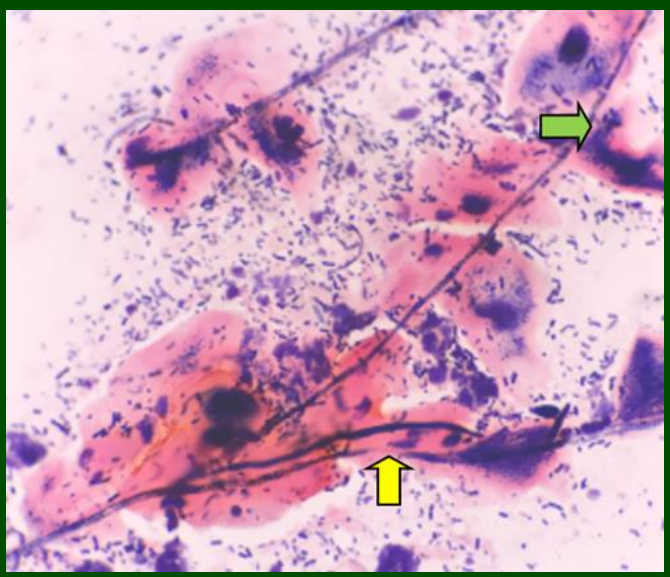
DOAJ DIRECTORY OF OPEN ACCESS JOURNALS

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE
Vol. 30 No. 2 August 2022



Yeast cell (green arrow) and pseudohyphae (yellow arrow) of *Candida spp.* appearance on microscopic examination in vulvovaginal candidiasis.

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. 30 No. 2 August 2022

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

EDITORIAL TEAM

Address

Department of Obstetrics and Gynecology
Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital
Jl. Mayjen Prof dr Moestopo no. 6 – 8, Surabaya 60286, Indonesia. Phone: 62-31-5501185, Facs: 62-31-5037733
https://e-journal.unair.ac.id/MOG/
Email: mog@journal.unair.ac.id, mog.obgsby@gmail.com

Vol. 30 No. 2 August 2022

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

CONTENT

Cover :
Yeast cell (green arrow) and pseudohyphae (yellow arrow) of *Candida spp*. appearance on microscopic examination in vulvovaginal candidiasis.

This edition page 74

AUTHOR GUIDELINES

Majalah Obstetri & Ginekologi publishes original articles on all aspects of obstetrics and gynecology. Articles can be classified as original research, case report/case series, review article, systematic review, meta-analysis, and opinion that keep the readers informed of current issues, innovative thinking in obstetrics and gynecology. Articles are considered for publication with the condition that they have not been published, submitted, or being under consideration for publication elsewhere. Manuscript must be written in American English with proper grammar, while the Abstract will be published in English and Indonesian. Authors should follow the **Author Guidelines** and the manuscript is arranged according to the **Manuscript Template**. Manuscript must be submitted through online submission by registered users. Authors can register themselves in the journal system. For further question contact us at: mog@journal.unair.ac.id.

General Principles

The manuscript must be free of typing errors and have a proportional length. The length of each manuscript is 5-10 pages of A4 size paper (1.5 spaces, Times New Roman font size 12, with normal margins page layout of 2.54 cm on each side). The recommended references are the updated ones in the last ten (10) years from the date of current submission (minimal of 20 references), unless in a special case accepted by the editors due to scientific reasons.

Total number of tables and figures should be limited, advisably no more than five. Tables should be numbered with Arabic numbers, and the title of each table should be written center-aligned at the top of the table, in normal Times New Roman, font size 12. Text within tables should be written in 1 space, normal Times New Roman font size 10 or less. Figures (including graphs, diagrams, charts, drawings, and photographs) should be produced at least 300 dpi in jpg, jpeg, or png format, have clear legends, numbered with Arabic numerals, and the title of each figure should be written center-aligned at the bottom of the figure, in normal Times New Roman, font size 12. All words in Latin must be written in italics. The use of abbreviations is generally agreed upon, and an extension must be given in the first mention of the abbreviation. Decimal numbers are marked with points (.).

All types of manuscripts must consist of:

- **Title**, which must be concise, specific, and informative. The title must consist of no more than 30 words, written on the top line with bold Gill Sans MT font size 12, left-aligned, and in sentence case. Latin name is italicized (italic).
- **The author's name(s)** is complete (without title) and the home institutions of the authors are written with an initial capital letter for each word in Gill Sans MT font, size 10, left-aligned, without ending points. If there is more than 1 author, all is written, separated by commas. Numeric code in superscript is added behind the author's name. The author's home institution is written under the author's name beginning with a numeric code (superscript). The name of the institution is followed by the name of the city and the country where the institution is located. At least one of the authors is required to add their **ORCID IDs** listed on https://orcid.org/. The link should be embedded on the ORCID logo after the authors' names. At least 1 of the authors must include external (more than 1, if necessary) affiliation(s) outside the Majalah Obstetri & Ginekologi publisher.
- **Abstract** must be arranged with a brief description (containing no more than 250 words). The abstract is written in English.
  a. Abstract of original research report, systematic review or meta-analysis must consist of objective, materials and methods, results, and conclusion each written as one paragraph.
  b. Abstract of narrative review article must consist narration summarizing the content of the manuscript, written in one paragraph.
  c. Abstract of case report or case series must consist of background, objective, case(s), and conclusion, each written in one paragraph.
- **Keywords** consist of 3-5 words and/or phrases, written under abstract as seen in the template, in English, started with a capital letter (sentence case), separated with semi-colon, and without an ending point. Keywords should apply terms present in **Medical Subject Headings (MeSH)**. The keywords must contain at least one keyword of **Sustainable Development Goals (SDGs)**.
- **Running title** (short version of full title or abbreviated title) must be written as a header of the manuscript on the right side.
- **Correspondence** is written under the keywords including the name, full address, and email address of one of the authors responsible as corresponding author.
- **Highlights** of the manuscript, which consist of minimally two keypoints representing the novel contributions of the study and must not be the copy-paste and/or repetition of sentences of any other

parts of the manuscript. These two highlights should be written before the introduction using number bullets (see template).

Article Types

The journal accepts the following types of articles:

a. Original research

Original research reports a substantial body of laboratory or clinical work, presenting the outcome of a large trial, case control, observational or retrospective study. The authors must confirm in the manuscript that they have ethical clearance for the conduct of the reported research. The procedure in the research should be in accordance with the **Declaration of Helsinki 2013**. The ethical clearance should be submitted along with the manuscript. 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, Materials and Methods, Results and Discussion, Conclusion,** and **Disclosures**. The Disclosures consist of **Acknowledgment, Conflict of Interest, Funding, and Authors Contribution**.

b. Case report/case series

Case report 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 Report/Case Series, Discussion, Conclusion,** and **Disclosures**. The Disclosures consist of **Acknowledgment, Conflict of Interest, Patient Consent for Publication, Funding,** and **Authors Contribution**.

c. Review article

Review article is a survey of previously published research on a topic. It should give an overview of current thinking on the topic. 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, any subheadings as needed by the author(s), Conclusion,** and **Disclosures**. The Disclosures consist of **Acknowledgment, Conflict of Interest, Funding,** and **Authors Contribution**.

d. Systematic review

Systematic review is a synthesis of the evidence on a clearly presented topic using critical methods to identify, define and assess research on the topic, extracting and interpreting data from published studies on the topic, then analyzing, describing, and summarizing interpretations into a refined conclusion. Appropriate methodology should be followed, such as PROSPERO, the online international register for systematic reviews. 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, Materials and Methods, Results and Discussion, Conclusion,** and **Disclosures**. The Disclosures consist of **Acknowledgment, Conflict of Interest, Funding,** and **Authors Contribution**.

e. Meta-analysis

Meta-analysis is a statistical analysis combining the results of multiple scientific studies, analyzing multiple scientific studies addressing the same question, with each individual study reporting measurements that are expected to have some degree of error. 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, Materials and Methods, Results and Discussion, Conclusion,** and **Disclosures**. The Disclosures consist of **Acknowledgment, Conflict of Interest, Funding,** and **Authors Contribution**.

f. Opinion

Opinion is commentaries on subjects reflecting new concepts or controversies in research, education, healthcare organization or clinical practice. The word count is a maximum of 1800 words with a maximum of 10 references. Abstract is not required and subheadings or boxed of keypoints are optional. Tables and figures should not exceed three (3).

Authors must also supply the **Author Statement and Copyright Transfer Agreement** issued by Majalah Obstetri & Ginekologi. The form can be downloaded from the website of the journal. The statement should be submitted along with the submission of the manuscript.

References

Number of references depends on each types of article (see "Article types") and should in general be limited to ten years before the date of submission. References must be numbered in the order in which they are mentioned in the text. Use the style of the examples below, which are based on the **International Committee of Medical Journal Editors (ICMJE)** Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References. Avoid using abstracts as references. Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" with written permission from the source. Papers accepted but not yet published may be included as references; designate the journal and add "Forthcoming". Avoid citing "personal communication" unless it provides essential information not available publically, name the person and date of communication, obtain written permission and confirmation of accuracy from the source of a personal communication. Authors is recommended to use reference management software, in writing the citations and references such as: Mendeley®, Zotero®, EndNote®, and Reference Manager®.

Here are some examples of the references:

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

Chapter from an electronic book

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

Macdonald S. editor. Maye's midwifery 14th ed. [eBook]. Edinburgh: Bailliere Tindall; 2011 [cited 2012 Aug 26]. Available from: Ebrary.

Proceeding book

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

Offline thesis/dissertation

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

3. Website

With author

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

No author

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

CITATION WRITING

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]).
- Do not use a hyphen if there are no citation numbers in between that support your statement e.g. ([1-2]). Use instead ([1,2])

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 performance of midwives in early detection of cervical cancer using visual inspection test with acetic acid

Deviati Juwita Sari[1], Pudji Lestari[2]*, Pungky Mulawardhana[3]
[1]Midwifery Education Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [2]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [3]Department of Obstetrics and Gynecology, Faculty of Medicine, Dr. Soetomo Academic Hospital, Surabaya, Indonesia.

ABSTRACT

Objective: This study examined the association between service period, knowledge, and attitudes toward the performance of midwives in the early detection of cervical cancer using the Visual Inspection with Acetic Acid (VIA) method in Banjarmasin, Indonesia.
Materials and Methods: This is a cross-sectional study done in 26 Public Health Centers in Banjarmasin, Indonesia, from March to November 2020 involving 172 respondents. Samples were purposively selected using a non-probability sampling technique. Data collection instruments were questionnaire and Health Service reports. Data analysis was done computerized.
Results: Out of 172 respondents, 67.4% of which had > 10 years of service period, 67.4% had inadequate knowledge and 86% showed a positive attitude about early detection of cervical cancer using the IVA method, and 79.9% had poor performance in conducting early detection of cervical cancer using the IVA method. Results of Chi-square test showed the associations between the service period (P = 0.005), knowledge (P = 0.0001), and attitude (P = 0.005) with the performance of midwives in early detection of cervical cancer using the VIA method.
Conclusion: Service period, knowledge, and attitudes were associated with the performance of midwives in the early detection of cervical cancer using the VIA method in Banjarmasin, Indonesia. Professional training programs should be taken into consideration in improving the performance of midwives in cervical cancer detection.

Keywords: Cervical cancer; early detection; performance of midwives; VIA

ABSTRAK

Tujuan: Penelitian ini menganalisis hubungan antara lama kerja, pengetahuan, dan sikap dengan kinerja bidan dalam deteksi dini kanker serviks menggunakan metode Inspeksi Visual Asam Asetat (IVA) di Banjarmasin, Indonesia.
Bahan dan Metode: Penelitian ini menggunakan pendekatan *cross-sectional* yang dilaksanakan di 26 Puskesmas di Kota Banjarmasin, Indonesia, pada bulan Maret – November 2020 dengan jumlah sampel sebanyak 172 responden. Pengambilan sampel secara purposive sampling menggunakan teknik non-probability sampling. Instrumen penelitian berupa kuesioner dan laporan Dinas Kesehatan. Analisis data dilakukan secara komputerisasi.
Hasil: Hasil penelitian menunjukkan bahwa dari 172 responden didapatkan 67.4% memiliki lama kerja > 10 tahun, 67.4% memiliki pengetahuan kurang dan 86% memiliki sikap positif tentang deteksi dini kanker serviks dengan menggunakan IVA, dan 79.9% memiliki kinerja tidak baik dalam melakukan deteksi dini kanker serviks dengan menggunakan metode IVA. Hasil analisis statistik Chi-square menyatakan ada hubungan antara lama kerja (P = 0.005), pengetahuan (P = 0.0001), dan sikap (P = 0.005) dengan kinerja bidan dalam deteksi dini kanker serviks dengan menggunakan metode IVA.
Simpulan: Terdapat hubungan antara lama kerja, pengetahuan dan sikap dengan kinerja bidan dalam deteksi dini kanker serviks menggunakan metode IVA di Kota Banjarmasin, Indonesia. Pelatihan merupakan salah satu langkah yang menjadi pertimbangan dalam meningkatkan kinerja bidan dalam deteksi kanker serviks.

Kata kunci: Kanker serviks; deteksi dini; kinerja bidan; IVA

***Correspondence:** Pudji Lestari, Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, email: pudjilestari70@fk.unair.ac.id

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.52-57
● Maj Obs Gin. 2022;30:52-57 ● Received 5 Oct 2021 ● Revised 15 Jan 2022 ● Accepted 28 Jan 2022 ● Published 1 Aug 2022

INTRODUCTION

Cervical cancer has the highest prevalence and it is the fourth leading cause of death from all cancers, as well as the leading cause of death for women from cancer in 42 countries.[1-3] The Global Burden Cancer (GLOBOCAN) reported that there were approximately 32,469 cervical cancer cases in Indonesia in 2018, cervical cancer prevalence ranked second in Indonesia after breast cancer.[3] The Health Office of South Kalimantan Province reported in 2019 that the number of women experiencing cervical cancer symptoms or pre-cervical cancer reached 461 people or 1.9% of the 33,000 women who had undergone VIA screening. Furthermore, the Maternity report of Ulin Regional Hospital of Banjarmasin, Indonesia, mentioned that 128 women were positively diagnosed with cervical cancer and most of them were in stage II and III.

Cervical cancer generally does not show symptoms at early stage, making it difficult to detect without performing screening or early detection.[4] VIA (Visual Inspection of Acetic Acid) is a cervical cancer screening method that is widely used in Indonesia as an early detection of pre-cervical cancer lesions through visual observation by applying 3-5% acetic acid in the cervix to see any presence of thickened white plaque (acetowhite epithelium). This procedure can be carried out by general practitioner, trained midwife or paramedic.[5]

Unfortunately, as mentioned in Basic Health Research of Indonesia in 2013 the high prevalence of cervical and breast cancer in Indonesia is not yet followed by higher number of healthcare providers (general practitioners and midwives) to conduct the screening.[6] Banjarmasin City currently had a team of trainer consisting of one general practitioner and 21 providers consisting of 10 general practitioners and 11 midwives from 10 Health Centers. There were 26 Public Health Centers in Banjarmasin City that were required to carry out VIA services on daily basis. The number of trained midwife providers was still lacking as it is equal to 5.9% of the total number of midwives (185 people in 2019), whereas midwives were front liners in providing VIA services.

Interviews done in the preliminary study with VIA and BSE coordinators at two Public Health Centers in Banjarmasin, Indonesia, revealed that the implementation of the IVA program at the Public Health Centers was mostly delegated to midwives whose duties were concurrently as providers of maternal, child and family planning health services at the Maternal and Child Health Polyclinic (KIA) with only 1-2 midwives on duty per day. This condition has made the IVA services to WUS (women of childbearing age) less optimal. In addition, they also lacked confidence to carry out VIA examinations independently because they had never attended VIA examination training.

The target for early detection of cervical cancer using the VIA method and breast cancer using the Breast Self-Examination (BSE) method set by the Ministry of Health of the Republic of Indonesia includes women aged 20 years and older, but the priority target of the program from 2015 to 2019 is set for women aged 30-50 who make up to 50% of the total target.[7] As reported by the Health Office of Banjarmasin, Indonesia (2019), the number of women who tested for VIA in five years from 2015 - 2019 only reached 16,295 people (15.5%) which is far below the target of 105,346 people.[8]

The performance of a midwife is defined as the extent to which she carries out the duties and functions, including main duties as well as administrative, development, and others activities at work. Several variables affect the performance of a midwife, including personal variables (training, knowledge, and length of work), organizational variables (leadership and rewards), and psychological variables (attitudes and motivation). Midwives play an important role in providing clear information to the community, particularly to women. Better performance of midwives is associated with better knowledge and attitudes of the community which eventually results in better behavior of the community.[9]

Tran et al. (2011), Kress et al. (2015) and Cham (2018) stated that the problem that hinders cervical cancer screening is the inadequate knowledge of health workers (midwives) in providing services or facilities regarding VIA screening.[10–12] According to Tchounga et al. (2014), midwives who have previously screened for cervical cancer either through pap smears or IVA will recommend routine cervical cancer screening to patients.[13]

The increase in the coverage rate for early detection of cervical cancer is also influenced by the performance of health workers, especially midwives as the front-line service providers of maternal reproductive healthcare for women. The result of this study is expected to provide an insight for the advocacy and government planning, especially in Banjarmasin, in order to improve midwives' competence and capacity in performing early detection of cervical cancer using the VIA method. Based on this description, the study was performed to examine the association between service period, knowledge, and attitudes of midwives with their performance in performing early detection of cervical cancer using the VIA method in Banjarmasin.

MATERIALS AND METHODS

This observational analytic study was performed using a cross-sectional approach. This study took place in 26 Public Health Centers in Banjarmasin, Indonesia, from March to November 2020. The population in this study consisted of all 190 midwives at the health centers from which 172 samples were selected using a non-probability and purposive sampling techniques based on predetermined inclusion criteria; midwives in Public Health Centers in Banjarmasin, Indonesia, midwives are civil servants/non-civil servants, and willing to participate in this study as respondent.

The independent variables included midwives' service period, knowledge, and attitudes toward early detection of cervical cancer using the VIA method, while the dependent variable was the performance of midwives on early detection of cervical cancer using the VIA method. Midwives' attitude reflects their readiness which includes their thoughts, feelings, and attention to the early detection of cervical cancer using the VIA method,[14] while the performance of the midwife is the result of the work of the midwife which is a combination of personal characteristics and organization which was measured based on the applicable standards for carrying out early detection of cervical cancer using the VIA method.[9]

A set of questionnaires was employed to obtain primary data, while Health Office reports of Banjarmasin were used to obtain secondary data. All data were then analyzed to measure the distribution of frequency and percentage of each variable. The association between the independent variable and the dependent variable was measured in the Chi-square statistics test with a significance level of 95 % ($\alpha = 0.05$).

RESULTS AND DISCUSSIONS

The data distribution and the percentage of each variable are shown in Table 1. Most of the respondents had service period 10 years (67.4%), and 67.4% of them had inadequate knowledge on VIA, while only 2.3% of them had adequate knowledge in this matter. The results showed that the majority of the respondents had positive attitudes about early detection of cervical cancer using the VIA method with 86%, yet most of them showed poor performance in early detection of cervical cancer using the VIA method (79.7%).

Table 1. Data on midwives' service period, knowledge, attitudes, and performance in early detection of cervical cancer using the VIA method at 26 public health centers in Banjarmasin, Indonesia.

Variable	Category	Frequency (person)	Percentage (%)
Work Period of Services	< 10 years	56	32.6
	≥ 10 years	116	67.4
Knowledge	Poor	116	67.4
	Sufficient	52	30.2
	Good	4	2.3
Attitude	Negative	24	14.0
	Positive	148	86.0
Performance	Poor	137	79.7
	Good	35	20.3

Table 2. The association between midwives' service period, knowledge, and attitudes with their performance in early detection of cervical cancer using the VIA method at 26 health centers in Banjarmasin, Indonesia.

Variables	Category	Performance		Total	p value
		Poor	Good		
		f (%)	f (%)	f (%)	
Work Period of Services	< 10 years	52 (92.9)	4 (7.1)	56 (100)	0.005
	≥ 10 years	85 (73.3)	31 (26.7)	116 (100)	
Knowledge	Poor	110 (94.8)	6 (5.2)	116 (100)	0.0001
	Sufficient + Good	27 (48.2)	29 (51.8)	56 (100)	
Attitude	Negative	24 (100)	0 (0)	24 (100)	0.005
	Positive	113 (76.4)	35 (23.6)	148 (100)	

Table 2 presents the relationship between midwives' service period and their performance. Most of the respondents with service period < 10 years mostly show poor performance (92.2%). The results of this study go in line with research on the evaluation of the quality of the VIA screening examination for officers in Kediri City which stated that the length of work > 10 years correlated to higher experience in performing examination, performance level and compliance with procedures compared to those who had worked less than 10 years.[15] The Chi-square analysis indicated an association between the service period and midwives' performance in the early detection of cervical cancer using the VIA method (P = 0.005). Similar results were found in several studies on the practice of VIA screening by midwives in West Kalimantan Province, Indonesia, and Cote d'Ivoire, West Africa, where service period correlated with the performance of midwives in conducting VIA screening using the VIA method.[13,16]

Table 2 also describes the relationship between midwives' knowledge and performance. The results show that inadequate knowledge associates with poor performance (94.8%). A person's compliance with standard procedures is also influenced by the individual's knowledge; therefore, higher knowledge is likely followed by higher the adherence to the applicable standard procedures.[17] Research on VIA screening practices by midwives in West Kalimantan Province, Indonesia, stated that the lack of knowledge and skills of midwives and nurses as health service providers associated with the low performance of midwives and nurses in performing clinical practice.[16] The Chi-square statistical tests indicated an association between knowledge and performance of midwives in the early detection of cervical cancer using the VIA method (P = 0.0001). Similar results were also found in prior studies involving female health workers in conducting cervical cancer screening in Iran which asserted that there was a correlation between the level of knowledge and occupation of health care providers and there was a correlation between knowledge and attitude, in which adequate knowledge would affect the attitude of midwives in providing cervical cancer screening recommendations. Health service providers in this context include doctors and midwives.[18]

In addition, obstacles in cervical cancer management programs include the negative attitudes of service providers due to lack of competence in carrying out screening for cervical cancer, leading to dependencies in providing services.[19] The results of the study show that knowledge is one of the factors that can affect the performance of a midwife in conducting early detection of cervical cancer using the IVA method.

Table 2 also presents the relationship between midwives' attitude and performance. The results showed that most of the respondents had negative attitudes and all respondents (100%) showed poor performance. The Chi-square analysis indicated that there was a relationship between attitudes and the performance of midwives in the early detection of cervical cancer using the VIA method (P = 0.005). Similarly, at Public Health Centers in Kendal Regency, Indonesia, midwives' attitudes affected their practical skills in VIA counseling. Better attitudes lead to better practice and counseling skills.[20]

Cervical cancer prevention programs should consider the issues regarding patients, health service providers, and health system. An important step to significantly increase the achievement of prevention programs and reduce the incidence of cervical cancer is to improve the knowledge, shift the negative attitudes, address socio-cultural challenges, enhance cross-sector collaboration and coordination, and improve the cross-program management, financing, and competence of healthcare workers, especially midwives.[19]

Ease of access to good information needs to be provided through seminars and or training for midwives in all types of health facilities in order to increase the proportion of midwives with adequate knowledge and good attitudes about cervical cancer screening.[13] Midwives who had good knowledge and positive attitudes showed better performance in carrying out early detection of cervical cancer using the IVA method compared to midwives who had a negative attitude. Hence, more trainings are required to change negative attitude of midwives toward the IVA program.

Midwives affect the behavior of women of childbearing age in carrying out VIA examinations.[21] Support and positive attitudes of health workers will affect the behavior and visits of women of childbearing age in carrying out screening for VIA examinations in health services.[21–23] The support and positive attitude of the midwife can be in the form of providing information, invitations, and motivation personally or in groups (counseling) in promoting VIA examinations.[23,24]

CONCLUSION

The results of this research showed that most respondents had service period of 10 years, poor knowledge and negative attitudes regarding early detection of cervical cancer using the VIA method which then associated to their poor performance in early detection of cervical cancer using the VIA method. The service period, knowledge, and attitudes were found

correlated to the performance of midwives in early detection of cervical cancer using the VIA method in Banjarmasin, Indonesia. The importance of increasing the capacity and competence of midwives in early detection of cervical cancer. Providing training for midwives in this program is an important step to take in order to improve midwives' knowledge, attitude and performance in conducting cervical cancer detection.

DISCLOSURE

Acknowledgment

Gratitude is expressed to the Center of Human Resources Development of Ministry of Health that has funded this study through Professional Scholarship.

Conflict of Interest

All authors have no conflict of interest.

Funding Disclosure

This research has received no external funding.

Author Contribution

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

REFERENCES

1. Basu P, Mittal S, Bhadra Vale D, Chami Kharaji Y. Secondary prevention of cervical cancer. Best Pract Res Clin Obstet Gynaecol. 2018;47:73-85. doi: 10.1016/j.bpobgyn.2017.08.012. Epub 2017 Sep 6. PMID: 28988647.
2. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6):394-424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020 Jul;70(4):313. PMID: 30207593..
3. WHO. Cancer Today - World. Int Agency Res Cancer [Internet]. 2019;876:2018–9. Available from: https://gco.iarc.fr/today/data/factsheets/ populations/ 900-world-fact-sheets.pdf
4. YKI. Melantun kebersamaan berantas kanker [Together eradicating cancer]. Yayasan Kanker Indonesia. Harapan Terpadu [Internet]. 2017;1–403. Available from: yayasankankerindonesia.org
5. Titisari I, Yanuarini TA, Antono SD. Faktor-faktor yang mempengaruhi sikap pasangan usia subur (PUS) melakukan skrining kanker serviks dengan Metode IVA di Wilayah Kerja Puskesmas Wilayah Utara Kota Kediri [Factors affecting attitude of fertile age couples for cervical cancer screening with VIA method]. J Ilmu Kesehat. 2017;5(2):74–83.
6. Ministry of Health, Republic of Indonesia. Situasi penyakit kanker Indonesia [Cancer situation in Indonesia]. Pus Data dan Inf Kemenkes RI. 2015;2:31–3.
7. Ministry of Health, Republic of Indonesia. Program nasional gerakan pencegahan dan deteksi dini kanker leher rahim dan kanker payudara [National program on prevention and early detection of cervical and breast cancer]. 2015. p. 1–47.
8. Health Office, Banjarmasin City. Laporan IVA test Dinas Kesehatan Kota Banjarmasin tahun 2019 [IVA test report, Health Office, Banjarmasin]. Banjarmasin; 2019.
9. Panjaitan N. Faktor-faktor yang memengaruhi rendahnya kinerja bidan dalam pelaksanaan program keluarga berencana di Puskesmas Aek Kanopan Kabupaten Labuhanbatu Utara [Factors affecting midwifes' low performance in family planning implementation in Aek Kanopan Health Center] [Internet]. Universitas Sumatera Utara; 2018. Available from: http://repositori.usu.ac.id/ handle/123456789/1741%0D
10. Cham B. Knowledge, practice and acceptability of cervical cancer screening among midwives in the Gambia. Womens Heal Sci J. 2018;2(3):123–6.
11. Kress CM, Sharling L, Owen-Smith AA, et al. Knowledge, attitudes, and practices regarding cervical cancer and screening among Ethiopian health care workers. Int J Womens Health. 2015;7:765-72. doi: 10.2147/IJWH.S85138. PMID: 26261427; PMCID: PMC4527576.
12. Tran NT, Choe SI, Taylor R, et al. Knowledge, attitude and practice (KAP) concerning cervical cancer and screening among rural and urban women in six provinces of the Democratic People's Republic of Korea. Asian Pac J Cancer Prev. 2011;12(11):3029-33. PMID: 22393985.
13. Tchounga BK, Jaquet A, Coffie PA, et al. Cervical cancer prevention in reproductive health services: knowledge, attitudes and practices of midwives in Côte d'Ivoire, West Africa. BMC Health Serv Res. 2014;14:165. doi: 10.1186/1472-6963-14-165. PMID: 24721621; PMCID: PMC4012470.
14. Notoatmodjo S. Ilmu Perilaku Kesehatan [Health Behavior Science] [Internet]. PT Rineka Cipta. Jakarta: Rineka Cipta; 2014. 1–174 p.
15. Sismiarti. Evaluasi kualitas pemeriksaan skrining IVA (inspeksi visual asam asetat) bagi petugas

yang telah mendapatkan pelatihan khusus dan yang belum di Puskemas kota Kediri tahun 2010 [IVA screening evaluation for trained and untrained officers in Health Offices Kediri]. Program Pasca Sarjana Ilmu Kesehatan Masyarakat Universitas Gajah Mada. Vol. 2. Universitas Gajah Mada; 2011.

16. Mardiana M, Dasuki D, Pradjatmo H. Pengetahuan dan keterampilan bidan untuk skrining kanker serviks dengan metode Inspeksi Visual Asam Asetat (IVA) di Kalimantan Barat [Midwife knowledge and skill for cervical cancer screening with VIA method in West Kalimantan]. J Kesehat Reproduksi. 2015;2(1):1–11.
17. Jia Y, Li S, Yang R, et al. Knowledge about cervical cancer and barriers of screening program among women in Wufeng County, a high-incidence region of cervical cancer in China. PLoS One. 2013;8(7):2–8.
18. Mohammadi S, Rejali M, Mostajeran M, et al. The study of relationship between risk factors for cervical cancer and knowledge and attitude of health workers toward pap smear in Isfahan and its comparison with Chaharmahal and Bakhtiari Province, Iran. Int J Cancer Manag. 2019;12(4).
19. Bayrami R, Taghipour A, Ebrahimipour H. Challenges of providing cervical cancer prevention programs in Iran: a qualitative study. Asian Pac J Cancer Prev. 2014;15(23):10071-7. doi: 10.7314/apjcp.2014.15.23.10071. PMID: 25556428.
20. Rochwati S, Jati SP, Suryoputro A. Pengetahuan bidan mempengaruhi praktik bidan dalam konseling pemeriksaan IVA pada wanita usia subur [Midwives' knowledge affects their practice in VIA conseling]. J Promosi Kesehat Indones. 2016;11(2):84.
21. Eka NM, Wahyono B. Determinan kunjungan inspeksi visual asam asetat di Puskesmas Kota Semarang [Determinant of visit for VIA inspection in Health Center, Semarang]. Higeia J Public Heal Res Dev. 2018;2(1):33–44.
22. Indriyani S, Wahyono B. Penyedia layanan terhadap implementasi program inspeksi visual dengan asam [Provider for implementing VIA inspection program]. Higeia J Public Heal Res Dev. 2019;3(1):1–11.
23. Citra SA, Ismarwati I. Hubungan dukungan petugas kesehatan dengan perilaku WUS (Wanita Usia Subur) dalam pemeriksaan IVA [Correlation between health office support and behavior in VIA inspection]. Midwifery JJ Kebidanan UM Mataram. 2019;4(2):46.
24. Yuliastanti T, Rismawati. Hubungan peran bidan dengan perilaku periksa Inspeksi Visual Asam Asetat (IVA) [Midwife role and behavior in VIA inspection]. J Kebidanan Stikes Estu Utomo. 2019;XI(01):96–104.

ORIGINAL RESEARCH

Factors in infertility score on referral and non-referral cases who underwent In Vitro Fertilization (IVF) treatment at a fertility clinic in Surabaya, Indonesia

Nadhif Rashesa Brahmana[1]*, Ashon Sa'adi[2], Rina Yudiwati[3]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, [2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [3]Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

ABSTRACT

Objectives: To examine the factors used in infertility score on referral and non-referral cases who underwent IVF treatment at Fertility Clinic of Graha Amerta, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2014-2016
Materials and Methods: This research was a descriptive analytic retrospective study using secondary data from medical records at Fertility Clinic of Graha Amerta in 2014-2016. With a total sampling technique, total of 342 referral and non-referral infertility cases were obtained. The variables of this study were the factors used in infertility score.
Results: From total of 342 cases, 44% had a wife's age in the range of 30-35 years, 80.1% had an infertile duration of $\geq$ 3 years, and 54.7% had one type of pelvic pain, 68.4% still had regular menstrual cycles, and about 76% did not have a history of pelvic infection. On sperm analysis factor, there were 27.5% of men who fell into the severe category according to infertility score. There was a significant difference from the duration of infertility and sperm morphology in referral and non-referral cases.
Conclusion: Infertility score can be useful because each case has its own infertility factors with different degrees of severity, which leads to infertility.

Keywords: Infertility; infertility score; In Vitro Fertilization (IVF); maternal health.

ABSTRAK

Tujuan: Mengkaji gambaran faktor dalam skor infertilitas pada kasus rujukan dan non rujukan yang menjalani tindakan IVF di Klinik Fertilitas Graha Amerta RSUD Dr. Soetomo, Surabaya, Indonesia, periode 2014-2016.
Bahan dan Metode: Penelitian ini merupakan deskriptif analitik retrospektif dengan menggunakan data sekunder dari rekam medis di Klinik Fertilitas Graha Amerta tahun 2014-2016. Dengan teknik total sampling didapatkan total 342 kasus infertilitas rujukan dan non rujukan. Variabel penelitian ini adalah faktor-faktor yang dipakai dalam skor infertilitas
Hasil: Dari total 342 kasus, sebanyak 44% memiliki umur istri dalam rentang 30-35 tahun, 80.1% memiliki lama infertil $\geq$ 3 tahun, dan 54.7% memiliki satu macam nyeri, 68.4% masih mempunyai siklus haid teratur dan sekitar 76% kasus tidak memiliki riwayat infeksi panggul. Pada faktor analisa sperma, didapatkan 27.5% dari pria yang masuk dalam kategori berat menurut skor infertilitas. Didapatkan perbedaan yang signifikan dari lama menikah dan morfologi sperma pada kasus rujukan dan non-rujukan.
Simpulan: Skor infertilitas dapat bermanfaat karena setiap kasus memiliki faktor infertilitasnya masing-masing dan dengan derajat keparahan yang berbeda-beda sehingga menyebabkan terjadinya infertilitas.

Kata kunci: Infertilitas; skor infertilitas; Fertilisasi In Vitro (FIV); kesehatan ibu.

***Correspondence:** Nadhif Rashesa Brahmana, Medical Program, Faculty of Medicine, Universitas Airlangga, Jalan Prof Dr Moestopo 47, Surabaya 60131, Indonesia. E-mail: nadhifrb@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.58-65
● Maj Obs Gin. 2022;30:58-65 ● Received 15 Nov 2021 ● Revised 3 Mar 2022 ● Accepted 18 Mar 2022 ● Published 1 Aug 2022

INTRODUCTION

Infertility is a complex problem that can often be found especially in married couples who desire to have children. It can have a big impact on many aspects of our lives, such as medically, psychologically, or even economically. It is necessary to know that there are actually many factors from both partners that can affect this condition. The incidence of infertility also increases over time. In 2010, it was estimated about 48.5 million couples around the world has infertility, of which 14.4 million of them came from Asia.[1] Likewise in Indonesia, it was stated the incidence rate of infertility in Indonesia is around 10-22% of the total reproductive age couples.[2]

There are also several obstacles of treating infertility in Indonesia, such as its vast and archipelagic geographic condition, the lack of health service capabilities and the uneven distribution of socioeconomic, educational and cultural conditions. Therefore, a fast, structured, and targeted infertility service system is needed. If they're late to be treated, it will increase the likelihood of complications in infertile patients, especially those related to their aging process.

To overcome this, an instrument was made by a professor of Obstetrics and Gynecology from Airlangga University, which can help medical personnel to detect infertility quickly, namely through the scoring system of infertile patients. This infertility score can be used as an initial screening, making it easier for health workers in their work field to differentiate which infertile couples are classified as mild, moderate, or severe, and also the appropriate level of health service for each score. The factors assessed in the score are a combination of female and male factors, including wife's age, menstrual cycle, sperm analysis, and others.[3] After counting the score, the next step is to the treatment itself, ranging from just giving information and education about fertility, until treatment that requires careful calculation and special skills, such as by in vitro fertilization (IVF).

Several studies on IVF have been conducted before, but there is not much about this infertility score, specifically discussing each factor that is being used in it. It's important to know more about these factors, so hopefully health workers can easily differentiate infertility cases, based on each factor that are being used. Therefore, the researcher wanted to know and study the description of the factors in the infertility score in referral and referral cases who underwent IVF at the Graha Amerta Fertility Clinic, Dr. Soetomo Hospital, Surabaya, for the period 2014-2016.

MATERIALS AND METHODS

The design of this study was a descriptive analytical study, which is intended to provide a complete and clear picture of the variables to be studied. The data of this study is from secondary data, which was gained specifically from the medical record. Incomplete medical records were excluded from this study. This research was conducted in Graha Amerta Fertility Clinic, Dr. Soetomo General Academic Hospital, Surabaya, from January – June 2020. The population of this research is all infertile cases at Graha Amerta Fertility Clinic. Sample of the research is all infertile cases (referral and non-referral) who underwent IVF treatment at Graha Amerta Fertility Clinic. Incomplete medical records were excluded from this study. Total sampling method is used in this study.

Variables of this study are factors that are being used to calculate the infertility score, which are wife's age, duration of infertility, menstrual cycle, pelvic pain, history of pelvic infection and Intrauterine Device (IUD), and sperm analysis which include concentration, motility, and morphology of the sperm. The type of data used in this study is secondary data, which were obtained from the medical records of Graha Amerta Fertility Clinic. The data collected will be processed and analyzed by using SPSS software, then will be described in the discussion.

RESULTS AND DISCUSSION

There were total of 342 infertility cases that were included in this study from all cases available from 2014-2016 at the Graha Amerta Fertility Clinic in Surabaya. Among those cases, there were 183 referral cases and 159 non-referral cases. Table 1 shows the characteristics of those cases based on factors used to calculate the infertility score. Each factor has their own parameter or certain value that can later be categorized as mild, moderate, and severe. Most of the factors are from the women such as their age, menstrual cycle, and others. The only male factor is sperm analysis, which includes concentration, motility, and morphology of the sperm. The final result of the score is obtained after taking into account all factors from both women and men. Based on the result of this study, it was found that there are only two factors from the infertility score , which is significantly different between referral and non-referral cases, which are the duration of infertility (P = 0.014) and the sperm morphology (0 = 0.038).

Table 1. Infertile cases characteristics based on factors in infertility score

Characteristics based on the Infertility Score	Number of referral cases (%)	Number of non-referral cases (%)	Total cases (%)
Wife's age			
< 30 years	45 (24.6)	43 (27)	88 (25.7)
30-35 years	86 (47)	64 (40.3)	150 (43.9)
> 35 years	52 (28.4)	52 (32.7)	104 (30.4)
Duration of infertility			
1-2 years	11 (6)	14 (8.8)	25 (7.3)
> 2 years	15 (8.2)	28 (17.6)	43 (12.6)
≥ 3 years	157 (85.8)	117 (73.6)	274 (80.1)
Menstrual cycle			
Normal	119 (65)	115 (72.3)	234 (68.4)
Oligomenorrhea	61 (33.3)	42 (26.4)	103 (30.1)
Amenorrhea	3 (1.6)	2 (1.3)	5 (1.5)
Pelvic pain			
Negative	89 (48.6)	71 (44.7)	160 (46.8)
1 type of pain	93 (50.8)	87 (54.7)	180 (52.6)
≥ 2 types of pain/adnexal mass	1 (0.5)	1 (0.6)	2 (0.6)
History of pelvic infection & IUD			
Negative	142 (77.6)	118 (74.2)	260 (76)
Once/IUD	34 (18.6)	36 (22.6)	70 (20.5)
≥ 2 times	7 (3.8)	5 (3.1)	12 (3.5)
Sperm concentration			
≥ 20 million/ml	141 (77)	137 (86.2)	278 (81.3)
10-20 million/ml	14 (7.7)	5 (3.1)	19 (5.6)
< 10 million/ml	28 (15.3)	17 (10.7)	45 (13.2)
Sperm motility (a+b)			
≥ 50 %	131 (71.6)	129 (81.1)	260 (76)
25-50 %	16 (8.7)	6 (3.8)	22 (6.4)
< 25 %	36 (19.7)	24 (15.1)	60 (17.5)
Sperm morphology (normal)			
≥ 15 %	122 (66.7)	125 (78.6)	247 (72.2)
5-15 %	24 (13.1)	16 (10.1)	40 (11.7)
< 5 %	37 (20.2)	18 (11.3)	55 (16.1)

Wife's age

Wife's age is the first factor in infertility score. From the analysis, it was found that from all 342 infertile cases, most of the them are 30-35 years old, which is 150 women (43.9%), followed by 104 women (30.4%) who are more than 35 years old and 88 women (25.7%) who are less than 30 years old. When viewed based on the type of referral, the results of the Chi-square statistical test showed that there was no significant difference between the ages of the wives of referral and non-referral cases (P = 0.450). From the data obtained, it is true that the age of the wife in referral and non-referral cases is not much different, most of them are 30-35 years old, which is in the moderate category according to infertility score.

This study is similar to several studies that have been conducted before. A study in 2015 at the fertility clinic of Putri Hospital, Surabaya, found that, out of 83 infertile cases, more than half (57.8%) were between 26-35 years old.[4] Another study on a total of 212 infertile women in three different fertility clinics in three major cities of Indonesia (Jakarta, Surabaya, Bali) found 40% of those aged 30-35 years.[5]

Infertility is closely related to age, especially in women or wives. According to theory, as a woman gets older her fertility will decrease due to several reasons. Unlike men, who will continue to produce sperm throughout their lives, women are born with all the follicles they will have throughout their lives, so it can be said that the number will only gradually decrease as they get older. At birth there are about 1 million follicles, at puberty it will decrease to about 300 thousand follicles, and among them only about 300 will be released at ovulation during their reproductive period.

The quality of the ova also decreases with age. An important change in the quality of the ovum is the

frequency of the genetic abnormality of aneuploidy, which is an insufficient or too many chromosome counts in the ovum. This will decreases the likelihood that women can get pregnant and also increases the likelihood of miscarriage in older women.[6] It is also said that women's fecundity decreases gradually but significantly starting from the age of 32 years and decreases more rapidly after the age of 37 years. This is due to the decreasing quality of the ovum and also, with age, the risk of diseases that can affect fertility, such as leiomyoma, tubal disease, and endometriosis also increases.[7] The trend of infertility cases where many are found at the productive age (<35 years) is not only because the physiology of the body decreases with age, but is also influenced by several other factors such as lifestyle, behavior, level of stress, diet, work and daily activities. It can also have effect to the body as a whole and to fertility conditions.

Duration of infertility

The second factor in infertility score, which is the duration of infertility, also plays a big role in determining the degree of infertility. From the analysis, it was found that from all 342 cases, most of them have been infertile for three years or more, which is 274 cases (80.1%), and only 25 cases (7.3%) that have duration of 1-2 year. There was also found one case with the duration of 20 years.

The duration of infertility is high in relation to the first factor, which is wife's age. The longer the duration of infertility in women, the more their age will be. One study suggests that the length of marriage affects the causes of infertility. In couples with length of marriage less than five years, the causes of PCOS and tubal factors due to sexually transmitted diseases are common. Whereas in couples with a length of marriage more than five years, what is often encountered is idiopathic infertility and male infertility. This is related to the increasing age of both partner which results in decreased quality and quantity of both ovum and sperm.[8]

This duration of infertility factor is also important to be considered in treating infertility. It has been said that the age of the woman and the duration of infertility are important factors in determining specific therapy for partners, where the age of more than 35 years and also long duration of infertility are suitable candidates for IVF treatment.[9]

When viewed based on the type of referral or non-referral cases, there was a significant difference between the duration of infertility for referral and non-referral cases (P = 0.014). Duration of ≥ 3 years, which is the severe category according to infertility score, was more prevalent in referral cases (85.8%). Meanwhile, the duration of 1-2 years, or the mild category according to the infertility score, was found more in non-referral cases (8.8%). This difference could happen due to the referral cases usually tend to have more complicated conditions than non-referral cases, which may result in longer or shorter duration of infertility.

Menstrual cycle

Menstrual cycle was chosen as the third factor in infertility score because of its high relation to ovulation disorders, which may affect fertility. From the analysis, it was found that from all 324 cases, 234 of them (68.4%) still have a regular or normal menstrual cycle, and only five cases (1.5%) have amenorrhea. When viewed based on the type of referral or non-referral case, there was no significant difference between the menstrual cycle for referral and non-referral cases (P = 0.350), most of them still have regular menstrual cycles, which is in the mild category according to the infertility score.

The average duration of a menstrual cycle is 28 days, with the most common occurring between 25-30 days. If the menstrual cycle is more than 35 days, it is called oligomenorrhea. And if there is no menstruation after three or more cycle, it is called amenorrhea.[3] Irregular menstrual cycles often occur when women are in the early and late stages of reproductive age (menarche and menopause) due to anovulation and inadequate follicular development.

Several studies also found an association between menstrual cycle duration and fecundity. A study stated that short menstrual cycles, menarche at a young age, and heavy menstrual bleeding are associated with reduced fecundity. So in this case it indicates that the characteristics of the menstrual cycle can be used as a marker of potential fertility in those planning a pregnancy.[10] Apart from physiological factors, irregular menstrual cycles can also be caused by lifestyle. A study conducted in Korea found that factors such as stress, obesity, and smoking were significantly associated with menstrual irregularities in pre-menopausal women, which can lead to infertility itself.[11]

Pelvic pain

Pelvic pain is the fourth factor that is used to calculate the infertility score. Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that out of a total of 342 cases, 180 cases (52.6%) had one type of pain, 160 cases (46.8%) no

pain, and only two cases (0.6%) had ≥ 2 kinds of pain/adnexal mass. When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was no significant difference between pelvic pain in referral and non-referral cases (P = 0.762), both of them mostly have one kind of pain, which is in the moderate category according to the infertility score.

In calculating the infertility score, types of pelvic pain include menstrual pain, intercourse pain, and spontaneous pelvic pain. According to research by Samsulhadi, these three types of pain are the clinical effects of endometriosis in general. Endometriosis has an incidence of 10% in the general population, and about 50% in infertile women.[3]

Endometriosis is closely related to infertility and fecundity. The prevalence of endometriosis increases dramatically to 25-50% in infertile women. The fecundity rate in women with endometriosis is estimated to be 2-10% wherein normal women the range is 15-20%.[12] Endometriosis is also associated with the management of infertility, one of which is IVF. Several studies have described the relationship of endometriosis with the outcome of IVF, where the pregnancy rate that can be obtained from IVF is inversely related to the severity of the endometriosis.[13]

History of pelvic infection & IUD

It's the last women factor that is used to calculate the infertility score. Based on the analysis, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that, out of a total of 342 cases, most of them had no history of pelvic pain or IUD, which is 260 cases (76%), and only a small proportion had a history of ≥ 2 times, which is only 12 cases (3.5%). When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was no significant difference between the history of pelvic infection and IUD in referral and non-referral cases (P = 0.629). From the data obtained, both of them mostly have no history of pelvic infection or IUD use, which is in the mild category according to the infertility score.

According to the literature by Samsulhadi, history of pelvic infection and IUD are related to the tubes and peritoneum, where residual defects after pelvic infection and also a history of IUD use can cause abnormalities in the tubes and peritoneum.[3] A history of pelvic infection is often referred to as Pelvic Inflammatory Disease (PID), which is defined as inflammation of the female genital tract due to infection. The effect of PID on fertility can be very significant, with several studies showing a 5-fold increase in infertility in women with a history of PID. Not only that, PID can also lead to ectopic pregnancy due to damage to the fallopian tubes.[14]

The intrauterine device (IUD) also has a value in the infertility score, where patients who have a history of IUD use will be included in the moderate category. This is because the IUD can also cause pelvic infections.[3] Based on a study from the WHO, it was found that the risk of PID from IUD users is low, but the incidence of PID that increases during the first month indicates that infection may be due to the insertion process of the IUD itself.[15]

Sperm analysis

It is the last and also the only male-acquired factor in the infertility score. The European Association of Urology (EAU) states there are several things that can cause infertility in men, including congenital, acquired, or idiopathic factors. To date, several methods have been found to assess male infertility, including semen/sperm analysis, hormonal tests, and testicular biopsy. Sperm analysis includes both macroscopic and microscopic examinations. The examination can be carried out from the first five minutes and if the sample is frozen it can be done at a later date. Microscopic counts were performed manually under a microscope with a magnification of 200-400 x. After that, observations were made on volume, concentration, motility, and others.[16]

Sperm concentration

Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that of a total of 342 cases, most of them had a concentration of ≥ 20 million/ml, namely 278 people (81.3%), followed by concentration <10 million/ml for 45 people (13.2%), and a concentration of 10-20 million/ml for 19 people (5.6%). When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was no significant difference between the sperm concentration of referral and non-referral cases (P = 0.069). From the data obtained, both of them mostly have sperm concentrations of ≥ 20 million/ml, which is in the mild category according to the infertility score.

The WHO states that the standard reference value for sperm concentration is ≥ 15 million/ml. If it is lower than this value, it is called oligozoospermia, and if there is no sperm in the ejaculate, it is called azoospermia. A study says that 90% of male infertility is related to

sperm count, and there is a positive relationship between abnormal semen parameters and sperm count.[17] A decrease in sperm concentration/number is found in many cases of infertility, especially those caused by male factors. A 2013 study was conducted on a total of 396 men who came to a fertility clinic in Lahore, Pakistan. The results found that as many as 44 people (11.1%) experienced oligozoospermia and 59 people (14.9%) experienced azoospermia.[18]

Sperm motility

Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that, out of a total of 342 cases, most had ≥ 50% progressive motile sperm, namely 260 people (76%), followed by those who had <25% of progressive motile sperm, which is 60 people (17.5%), and the rest had 25-50% progressive motile sperm, namely as many as 22 people (6.4%).When viewed based on the type of referral or non-referral case, the results of the Chi-square statistical test showed that there was no significant difference between sperm motility in referral and non-referral cases (P = 0.071). From the data obtained, both of them mostly have ≥ 50% progressive motile sperm, which is included in the mild category according to the infertility score.

The classification of sperm motility according to the WHO is progressive motility, non-progressive motility, and also non-motile. Progressive motile sperm can move actively (linear or circular) regardless of the speed. Meanwhile, non-progressive motile sperm has a movement pattern but there is no progression, such as moving only in a small circle, or only movement in the flagellum is observed. It is said that non-motile sperm do not get any movement at all. The WHO also sets the lowest reference value for progressive motile total sperm, which is 32%, if less than that it is called asthenozoospermia.[16]

A study says that motile spermatozoa tend to make propulsive, linear and progressive movements when penetrating the cervical border. Therefore, several specific movement attributes (speed, straightness and amplitude of sperm head movement) assisted by other sperm analysis criteria (concentration and morphology) are characteristics of sperm quality that can facilitate the penetration process.[19] This is supported by other studies which say that the concentration of motile sperm is the most significant parameter to predict the likelihood of fertilization. Several factors that can affect sperm motility include oxidative stress, mitochondrial disorders, male age, and certain proteins.[20]

Sperm morphology

Based on the analysis of frequency distribution, the characteristics of infertility cases at the Graha Amerta Fertility Clinic for the period 2014-2016, it was found that out of a total of 342 cases, most of them had ≥ 15% normal morphological sperm, namely 247 people (72.2%), followed by those 55 people (16.1%) who had <5% normal morphological sperm, and 40 people (11.7%) who had 5-15% normal morphological sperm.

The WHO states that the lowest standard reference value for sperm morphology (normal) is 4%, and if less then it is called teratozoospermia. In the process of analyzing sperm morphology, the semen sample obtained was stained first and then observed with a 1000x magnification using immersion oil.[16] The cause of abnormalities in sperm morphology is still not known with certainty, but some sperm morphological abnormalities can be related to abnormalities in their function such as chromatin condensation, abnormalities in acrosome reactions, and disturbances in tail motility. There are also some disorders associated with genetic abnormalities such as globozoospermia, sperm macrocephaly syndrome, and others.[21]

When viewed based on the type of referral or non-referral cases, the results of the Chi-square statistical test showed that there was a significant difference between sperm morphology in referral and non-referral cases (P = 0.038). Normal morphological sperm of <5%, or severe category according to the infertility score, was more common in referral cases (20.2%). Meanwhile, normal morphological sperm of ≥ 15%, or the mild category according to the infertility score, was more common in non-referral cases (78.6%).

CONCLUSION

This study shows that there are many factors from both men and women that can affect fertility. The result of this study suggests that the degree of severity of each factor varies widely among those cases. Some factors can be used to identify infertile patients. It was found that the duration of infertility and sperm morphology were significantly different between referral and non-referral cases. Therefore, this infertility score can be useful as an initial screening, by calculating some important infertility factor from both partners, and it also helps doctors and general practitioners to decide whether to treat them or to refer them to the gynecologist for further management. It is also necessary for health workers to provide information and education about infertility for couples, so that they are

more aware of their respective reproductive health conditions.

DISCLOSURES

Acknowledgment

The authors thank all the staff of the Faculty of Medicine, Universitas Airlangga, who gave permission and helped facilitate this research, and to all staff of the medical records section at the Fertility Clinic of Graha Amerta, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, who gave help to obtain the data for this research.

Conflict of Interest

The authors declare there is no conflict of interest.

Funding Disclosure

This research has received no external funding.

Author Contribution

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

REFERENCES

1. Mascarenhas MN, Flaxman SR, Boerma T, et al. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med. 2012;9(12):e1001356. doi: 10.1371/journal.pmed.1001356. Epub 2012 Dec 18. PMID: 23271957; PMCID: PMC3525527.
2. Harzif AK, Santawi VPA, Wijaya S. Discrepancy in perception of infertility and attitude towards treatment options: Indonesian urban and rural area. Reprod Health. 2019;16(1):126. doi: 10.1186/s12978-019-0792-8. PMID: 31426818; PMCID: PMC6700767.
3. Samsulhadi. Sistem rujukan kasus infertilitas (berdasarkan faktor risiko) [Infertility case referral system (based on the risk factors)]. Indonesian Journal of Obstetrics and Gynecology. 2007;31(1): 49-56.
4. Sa'adah N, Purnomo W. Karakteristik dan perilaku berisiko pasangan infertil di Klinik Fertilitas dan Bayi Tabung Tiara Cita, Rumah Sakit Putri Surabaya [Characteristics and risky behavior of infertile couples]. Jurnal Biometrika dan Kependudukan. 2017;5(1): 61.
5. Bennett LR, Wiweko B, Bell L, et al. Reproductive knowledge and patient education needs among Indonesian women infertility patients attending three fertility clinics. Patient Educ Couns. 2015;98(3):364-9. doi: 10.1016/j.pec.2014.11.016. Epub 2014 Nov 24. PMID: 25477052.
6. Cimadomo D, Fabozzi G, Vaiarelli A, et al. Impact of maternal age on oocyte and embryo competence. Front Endocrinol (Lausanne). 2018;9:327. doi: 10.3389/fendo.2018.00327. PMID: 30008696; PMCID: PMC6033961.
7. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice and Practice Committee. Female age-related fertility decline. Committee Opinion No. 589. Fertility and Sterility. 2014;101(3): 633-4.
8. Deshpande PS, Gupta AS. Causes and Prevalence of Factors Causing Infertility in a Public Health Facility. J Hum Reprod Sci. 2019;12(4):287-93. doi: 10.4103/jhrs.JHRS_140_18. Epub 2019 Dec 17. PMID: 32038077; PMCID: PMC6937760.
9. Sadeghi MR. Unexplained infertility, the controversial matter in management of infertile couples. J Reprod Infertil. 2015;16(1):1-2. PMID: 25717428; PMCID: PMC4322174.
10. Wesselink AK, Wise LA, Hatch EE, et al. Menstrual cycle characteristics and fecundability in a North American preconception cohort. Ann Epidemiol. 2016;26(7):482-7.e1. doi: 10.1016/j.annepidem.2016.05.006. Epub 2016 May 31. PMID: 27449569; PMCID: PMC4964792.
11. Bae J, Park S, Kwon JW. Factors associated with menstrual cycle irregularity and menopause. BMC Womens Health. 2018;18(1):36. doi: 10.1186/s12905-018-0528-x. PMID: 29409520; PMCID: PMC5801702.
12. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am. 2012;39(4):535-49. doi: 10.1016/j.ogc.2012.10.002. PMID: 23182559; PMCID: PMC3538128.
13. Vassilopoulou L, Matalliotakis M, Zervou MI, et al Endometriosis and in vitro fertilisation. Exp Ther Med. 2018;16(2):1043-51. doi: 10.3892/etm.2018.6307. Epub 2018 Jun 13. PMID: 30116357; PMCID: PMC6090275.
14. Jennings LK, Krywko DM. Pelvic Inflammatory Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 –. PMID: 29763134.
15. Hubacher D. Intrauterine devices & infection: review of the literature. Indian J Med Res.

2014;140 Suppl(Suppl 1):S53-7. PMID: 25673543; PMCID: PMC4345753.
16. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: World Health Organization; 2010.p. 9-102
17. Kumar N, Singh AK. Trends of male factor infertility, an important cause of infertility: A review of literature. J Hum Reprod Sci. 2015;8(4):191-6. doi: 10.4103/0974-1208.170370. PMID: 26752853; PMCID: PMC4691969.
18. Butt F, Akram N. Semen analysis parameters: experiences and insight into male infertility at a tertiary care hospital in Punjab. J Pak Med Assoc. 2013;63(5):558-62. PMID: 23757979.
19. Khatun A, Rahman MS, Pang MG. Clinical assessment of the male fertility. Obstet Gynecol Sci. 2018;61(2):179-91. doi: 10.5468/ogs.2018.61.2.179. Epub 2018 Mar 5. PMID: 29564308; PMCID: PMC5854897.
20. Sati L, Huszar G. Sperm motility and viability: Overview of the cellular and physiological aspects that support these functions. European Medical Journal. 2015;1(1): 74-80.
21. Gatimel N, Moreau J, Parinaud J, et al. Sperm morphology: assessment, pathophysiology, clinical relevance, and state of the art in 2017. Andrology. 2017;5(5):845-862. doi: 10.1111/andr.12389. Epub 2017 Jul 10. PMID: 28692759.

ORIGINAL RESEARCH

Inflammatory markers in lean Polycystic Ovary Syndrome subjects are not associated with the spectrum of dyslipidemia

Elisia Atnil[1], Andon Hestiantoro[1,2]*, Oki Riayati[2], Ririn Rahmala Febri[2], Naylah Muna[2]
[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[2]Human Reproductive, Infertility and Family Planning Research Centre, Indonesia Medical Education and Research Institute (IMERI), Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

ABSTRACT

Objectives: This study aimed to address the detailed lipid profile in lean woman with PCOS and investigate the relationship between chronic low grade inflammation (using NLR, PLR, and monocyte/HDL ratio) and dyslipidemia (defined as total cholesterol level > 190 mg/dL).
Materials and Methods: This study was a cross-sectional study conducted from June – December 2020 at the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia, involving 45 women aged 18 – 35 years old, diagnosed as having PCOS with normal BMI (18.5 – 22.9 kg/m^2). To compare quantitative variables, data analysis was carried out using the t-test or Mann-Whitney U test as appropriate; whereas, to compare categorical variables, the Chi-square test was used.
Results: We found that although the median BMI was within normal limits at 21.48 kg/m^2, the mean values of the lipid profiles were found to be either abnormal or borderline, indicating the high possibility of dyslipidemia. No statistically association between NLR, PLR and MHR with dyslipidemia.
Conclusion: Dyslipidemia and chronic low-grade inflammation were found in lean PCOS subjects, but there was no significant association between inflammation markers (NLR, PLR and MHR) and dyslipidemia. Further studies should investigate other factors that cause the inflammation.

Keywords: dyslipidemia; inflammation; lean PCOS; maternal health

ABSTRAK

Tujuan: Tujuan dari penelitian ini adalah untuk mengetahui profil lipid pada pasien SOPK non obesitas dan mencari tahu hubungan antara inflamasi kronis derajat rendah (RNL, RPL, rasio monosit/HDL) dan dislipdemia (kadar kolesterol > 190 mg/dL)
Bahan dan Metode: Studi *cross sectional* dilakukan dari Juni – Desember 2020 di Departemen Obstetri Ginekologi Fakultas Kedokteran Universitas Indonesia, Jakarta, Indonesia, melibatkan 45 wanita berusia 18-35 tahun yang terdiagnosis SOPK dengan IMT normal (18.5 – 22.9 kg/m^2). Data kuantitatif dihitung dengan menggunakan uji T dan uji Mann-Whitney U sedangkan data kategorik menggunakan uji Chi-square.
Hasil: Meskipun IMT dalam batas normal, rata-rata kadar lipid pada pasien ditemukan abnormal atau batas tinggi, yang menunjukkan adanya kemungkinan dislipidemia. Tidak ditemukan adanya hubungan signifikan antara NRL, PLR, dan MHR dengan dislipidemia.
Simpulan: Dislipidemia dan inflamasi kronis derajat rendah ditemukan pada pasien SOPK non-obesitas, tetapi tidak ditemukan hubungan signifikan antara marka inflamasi (NLR, PLR, dan MHR) dengan dislipidemia. Penelitian selanjutnya diperlukan untuk mengetahui faktor lain yang terkait kondisi inflamasi kronis derajat rendah.

Kata kunci: dislipidemia; inflamasi; SOPK non-obes; kesehatan ibu

***Correspondence:** Andon Hestiantoro, Jl. Salemba Raya No.6, RW.5, Kenari, Kec. Senen, Kota Jakarta Pusat, Daerah Khusus Ibukota Jakarta 10430, Indonesia. Email: hestiantoro@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.66-71
● Maj Obs Gin. 2022;30:66-71 ● Received 30 Nov 2021 ● Revised 4 Apr 2022 ● Accepted 8 Apr 2022 ● Published 1 Aug 2022

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine problem mostly seen in reproductive age women, around 5 to 10% as concluded from the European Society for Human Reproduction and Embryology/ American Society for Reproductive Medicine (ESHRE/ASRM) in 2004.[1] PCOS patients have abnormal anthropometry profile, more than 80% have obesity body mass index (50-80%), however the disease can also be found in women with normal body mass index (20-50%). PCOS contributes to the quality of life that can change the endocrine and metabolic body process. Factors associated with this syndrome include glucose intolerance, abnormal blood lipid levels, insulin resistance, oxidative stress and other metabolic abnormalities, and among these abnormalities, dyslipidemia is one of the most common phenomena observed in women with PCOS.[2,3] In most cases, dyslipidemia indicates an abnormal serum lipid component (at least one component) (i.e. high total cholesterol (> 190 mg/dL), high triglycerides, high Low Density Lipoprotein (LDL), and low High Density Lipoprotein (HDL)).[4]

Until now, it is not yet known the exact etiology and pathogenesis of ovarian polycystic syndrome both in obesity group or non-obesity group, the differences between those groups also have not been classified. One of the theories says that ovarian polycystic syndrome is a condition of chronic inflammation in low degree.[5] There are several markers that can be used to measure inflammation, including CRP, Neutrophil to Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), and monocyte/HDL ratio. Complete blood count is an inexpensive, routine, and feasible test that may provide information regarding the red blood cells, white blood cells, and platelets. Proinflammatory mediators (chemokines and cytokines) can be released by platelet, and, when activated, platelets can stimulate thrombus formation. The activation of platelets plays a crucial role in cardiovascular events and coronary artery disease as inflammation marker.[6,7] However, the data about PLR, NLR, and monocyte/HDL ratio and its association with inflammation and their correlation with dyslipidemia are lacking in PCOS patients. Therefore, this study aims to address the detailed lipid profile in lean woman with PCOS and investigate the relationship between chronic low grade inflammation (using NLR, PLR, and monocyte/HDL ratio) and dyslipidemia (defined as total cholesterol level > 190 mg/dL).

MATERIALS AND METHODS

This study was a comparative, observational, and cross-sectional study. The study was conducted from June until December 2020 at the Departments of Obstetrics and Gynecology of Universitas Indonesia and Human Reproductive, Infertility and Family Planning Research Centre, Indonesia Medical Education and Research Institute (IMERI), Faculty of Medicine Universitas Indonesia. Forty five women aged 18 – 35 years old, diagnosed as having PCOS with normal BMI (18.5 – 22.9 kg/m^2) were enrolled after giving informed consent. All the subjects enrolled in the study were in good health, had no chronic or acute disease, and for at least three months had not been taking any medication known to affect lipid profile.

For the basis of PCOS diagnosis, we used the revised Rotterdam criteria, in which that at least two of the these three features are required: (1) oligo-ovulation or anovulation (< 6 menstrual periods per year); (2) clinical and/or biochemical signs of hyperandrogenism, including hirsutism (Ferriman-Gallwey score > 8), severe persistent acne, and/ or total testosterone level > 0.8 ng/mL); and (3) sonographic evidence of PCOS (i.e., at least one ovary containing 12 or more peripheral follicles measuring 2–9 mm in diameter and/or ovarian volume of at least 10 mL).

Exclusion criteria were patients with acute infection, history of cancer, autoimmune disease, hematologic disease, chronic disorders (diabetes mellitus, renal, heart or liver disorder), patients who have endocrine disorders (hyperprolactinemia, nonclassical congenital adrenal hyperplasia), use of any antidiabetic, antiobesity, anti-inflammatory and hormonal drugs (oral contraceptives, glucocorticoids, antiandrogens, ovulation induction agents) within the previous two months.

We performed a detailed medical history taking and full clinical examination for all participants. The data that we recorded included age, menstrual pattern, and history of significant metabolic or cardiac disease. For physical examination, we measured the weight, height, and blood pressure as well as the body mass index (BMI, calculated as weight in kilograms divided height in meters squared). Waist circumference was defined as the obtained minimum circumference value of the iliac crest and lateral costal margin.

For the measurement of total cholesterol, high and low density lipoprotein (HDL and LDL), fasting blood glucose, and triglycerides levels, the blood samples were taken between 7 a.m. – 10 a.m. with an overnight fasting. Lipid levels measurement was carried out using enzymatic assay kits. The glucose oxidase method was performed to measure the glucose level.

Based on World Health Organization (WHO) estimates in 2008, dyslipidemia is defined as total cholesterol blood levels of > 5 mmol/L (190 mg/dL) in the

Southeast Asia. Patients were then divided into two group based on total cholesterol level.

The data were reported as mean ± SD or number and percentage. The t-test or Mann-Whitney U test was used to compare of quantitative variables. For the comparison of categorical variables, we performed the Chi-Square test (except for a less than 5 frequency, in which we used the exact test). A P value of ≤ 0.05 was considered significant. Data analysis was carried out using the Statistical Package for the Social Sciences, version 15 (SPSS, Chicago, IL, USA).

RESULTS AND DISCUSSION

In this study, 45 lean PCOS women were included. Table 1 shows the clinical and biochemical characteristics of lean women diagnosed with PCOS. We found that although the median BMI was within normal limits at 21.48 kg/m^2, the mean values of the lipid profiles were found to be either abnormal or borderline, indicating the high possibility of dyslipidemia. Furthermore, we found that there is no significant association between changes in the inflammation markers (NLR, PLR and Monocyte/HDL ratio) and dyslipidemia ($p > 0.05$) as shown in Table 2.

In this study, despite the lean women having a normal body mass index, the lipid profiles of the women were either abnormal or borderline with mean HDL cholesterol 52.88 mg/dL, LDL cholesterol 121.71 mg/dL and total cholesterol 196.73 mg/dL. This finding is consistent with the National Cholesterol Education Program guidelines which suggest that about 70% of women with PCOS exhibit borderline or high lipid levels. According to the same guideline, criteria for metabolic syndrome includes the low level of HDL <50 mg/dL showing that our finding suggests a borderline low level of HDL of 52.88 mg/dL. This result is consistent with most previous studies showing a reduced level of HDL in women with PCOS.[8,9] The findings on our study showed a relatively higher HDL compared to other studies possibly due to the exclusion of obese PCOS in our study, unlike many others which included both obese and lean patients. The exact mechanism behind reduction of HDL in women is poorly understood. However, one hypothesis suggests that the reduction in HDL occurs due the underlying insulin resistance and hyperandrogenemia, which are thought to enhance the activity of hepatic lipase, removing lipid from HDL, consequently reducing the number of HDL particles.[10]

Table 1. The clinical and biochemical characteristics of lean women with PCOS (n=45).

Variable	Mean ± SD	Median (range)
Age	28.60 ± 3.68	
Weight (kg)	53.61 ± 4.96	
Height (cm)	159.7 ± 5.46	
BMI (kg/m^2)		21.48 (17.97 – 22.72)
Fasting blood glucose		87.9 (70.2 – 151)
HDL cholesterol	52.88 ± 10.39	
LDL cholesterol	121.71 ± 32.78	
Total cholesterol	196.73 ± 39.42	

Table 2. The association between changes in inflammation markers (NLR, PLR and Monocyte/HDL ratio) and dyslipidemia (total cholesterol > 190 mg/dL).

Inflammation Marker	Dyslipidemia	No Dyslipidemia	Total	P value
NLR				
High (≥ 1.60)	12 (52.2)	13 (61.9)	25 (56.8)	0.515[a]
Low (<1.60)	11 (47.8)	8 (38.1)	19 (43.2)	
PLR				
High (≥ 11.50)	2 (8.3)	3 (14.3)	5 (11.1)	0.526[a]
Low (<11.50)	22 (91.7)	18 (85.7)	40 (88.9)	
Monocyte/HDL ratio				
High (≥ 11.46)	4 (16.7)	6 (28.6)	10 (22.2)	0.338[a]
Low (<11.46)	20 (83.3)	15 (71.4)	35 (77.8)	

Values are presented in number (percentage), [a]Chi-square

In terms of LDL, our study showed an increased level of LDL at borderline level. This finding is in line with previous studies which have also shown marked increase in LDL amongst women with PCOS, even in lean patients.[11] A retrospective study in Rome also reported a non-significant difference in LDL levels between obese and lean women diagnosed with PCOS, showing that an increased level of LDL seems to be a common finding in women with PCOS regardless of their BMI.[12] In contrast, a study in Korea found that no significant change was found in the level of LDL in non-obese Korean patients.[11] The differences in the these findings of lipid profile may be explained by differing phenotypes of the PCOS, which we did not take into account in this study. This phenomenon is supported by a study by Spalkowsa et al. who suggested that different lipid profiles may be found in PCOS based on its phenotypes and androgens' levels.[13] It is also worth noting that, aside from LDL quantity, recent studies have also suggested that the quality of LDL is affected in PCOS. In PCOS, smaller and denser LDL particles, which are more atherogenic, are more commonly found.[10,14-17]

As for total cholesterol, our study has also shown that, even in lean patients, there seems to be an increased level of total cholesterol. This is in agreement with a previous Danish study which has also found increased median values of total cholesterol in PCOS subjects.[18] In lean patients, increased level of cholesterol is still possible due to intraabdominal visceral fat accumulation, hyperandrogenemia, and insulin resistance, all of which result in abnormalities in lipid metabolism. Interestingly, another study also found that family history of dyslipidemia results in higher values of total cholesterol.[10] This genetic component can potentially be a confounding variable, which was not taken into consideration in this study.

The presence of dyslipidemia found in this study prompts further question regarding its association with low grade, chronic inflammation as its possible underlying cause in lean PCOS patients. Chronic low-grade inflammation has been thought to be one of the pathological mechanisms affecting women with PCOS. The inflammation is likely to be associated with insulin resistance, endothelial dysfunction and atherosclerosis, caused by increased visceral adiposity, which appears to occur regardless of BMI.[19] However, this study has also found that there is no significant association between changes in the inflammation markers (NLR, PLR and Monocyte/HDL ratio) and dyslipidemia in the patients ($p > 0.05$). This finding is not in line with previous studies which found their association with PCOS patients. A study by Cakiroglu et al. has shown that both NLR and PLR were significantly increased in all PCOS patients.[20] Another study by Pergialiotis et al. found that NLR and PLR were not affected by obesity, hence similar results should be produced even with lean women populations.[21] Nevertheless, the study by Cakiroglu et al. did not investigate the correlation between NLR and PLR with lipid profile indices.[20] In fact, the study by Pergialiotis et al. found weak correlation ($r = -0.171$), between NLR and HDL values.[21]

Similarly, in terms of monocyte/HDL ratio (MHR), our finding is not in agreement with prior study by Usta et al. in 124 women which found that MHR may be a novel and useful predictor of the presence of PCOS ($P = 0.0018$). The study also recommended the use of MHR as a low-cost, reproducible marker to detect cardiovascular risk in PCOS patients. However, in this study, it was not clear if MHR had any direct correlation with dyslipidemia (measured by cholesterol), although it was indicated that there was a significant difference in total cholesterol level between their PCOS subjects and non-PCOS subject ($P = 0.022$).[22] The differences between our findings and the previous study may be attributed to the small number of samples used in our study. Moreover, our study involved only lean patients who are thought to suffer less severe hormonal and metabolic derangements compared to their obese counterparts.[4]

The strength of our study is that this is the first study investigating direct association between inflammation markers NLR, PLR and MHR with dyslipidemia in PCOS patients. Our limitation is the small number of subjects enrolled in this study. Further investigation with larger number of subjects is encouraged.

CONCLUSION

In lean PCOS subjects, we found that there are dyslipidemia and chronic low grade inflammation. In this study, we failed to find significant association between the inflammation markers (NLR, PLR and MHR) and dyslipidemia in our subjects, but we cannot rule out low-grade chronic inflammation as the probable cause of metabolic syndrome in lean PCOS women. We speculated that there might be other factors that can cause inflammatory condition, such as sedentary life style, poor nutrition, and dysbiosis of gut microbiota, so screening these women for metabolic abnormality like insulin resistance is recomm ended.

DISCLOSURES

Acknowledgment

The authors thank to colleagues and staffs of Human Reproduction, Infertility, and Family Planning who had

supported for helping, gathering, and compiling data for this paper.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding Disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Author Contribution

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

REFERENCES

1. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;6:1-13. doi: 10.2147/CLEP.S37559. PMID: 24379699; PMCID: PMC3872139.
2. Tehrani FR, Rashidi H, Khomami MB, et al The prevalence of metabolic disorders in various phenotypes of polycystic ovary syndrome: a community based study in Southwest of Iran. Reprod Biol Endocrinol. 2014;12:89. doi: 10.1186/1477-7827-12-89. PMID: 25224635; PMCID: PMC4180586.
3. Macut D, Bjekić-Macut J, Savić-Radojević A. Dyslipidemia and oxidative stress in PCOS. Front Horm Res. 2013;40:51-63. doi: 10.1159/ 000341683. Epub 2012 Oct 18. PMID: 24002405.
4. Lin C-F, Chang Y-H, Chien S-C, Lin Y-H, Yeh H-Y. Epidemiology of dyslipidemia in the Asia Pacific region. International Journal of Gerontology. 2018;12(1):2-6.
5. Hestiantoro A, Kapnosa Hasani RD, Shadrina A, et al. Body fat percentage is a better marker than body mass index for determining inflammation status in polycystic ovary syndrome. Int J Reprod Biomed. 2018;16(10):623-628. PMID: 30643854; PMCID: PMC6314644.
6. Balta S, Ozturk C. The platelet-lymphocyte ratio: A simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets. 2015;26(7):680-1. doi: 10.3109/09537104.2014.979340. Epub 2014 Dec 30. PMID: 25549287.
7. Turkmen K, Erdur FM, Ozcicek F, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17(3):391-6. doi: 10.1111/hdi.12040. Epub 2013 Mar 24. PMID: 23522328.
8. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 17;106(25):3143-421. PMID: 12485966.
9. Kim JJ, Choi YM. Dyslipidemia in women with polycystic ovary syndrome. Obstet Gynecol Sci. 2013;56(3):137-42. doi: 10.5468/ogs.2013.56.3.137. Epub 2013 May 16. PMID: 24327994; PMCID: PMC3784112.
10. Diamanti-Kandarakis E, Papavassiliou AG, Kandarakis SA, et al. Pathophysiology and types of dyslipidemia in PCOS. Trends Endocrinol Metab. 2007;18(7):280-5. doi: 10.1016/j.tem.2007.07.004. Epub 2007 Aug 10. PMID: 17692530.
11. Toosy S, Sodi R, Pappachan JM. Lean polycystic ovary syndrome (PCOS): an evidence-based practical approach. J Diabetes Metab Disord. 2018;17(2):277-285. doi: 10.1007/s40200-018-0371-5. PMID: 30918863; PMCID: PMC6405408.
12. Morciano A, Romani F, Sagnella F, et al. Assessment of insulin resistance in lean women with polycystic ovary syndrome. Fertil Steril. 2014;102(1):250-256.e3. doi: 10.1016/j.fertnstert.2014.04.004. Epub 2014 May 10. PMID: 24825420.
13. Spałkowska M, Mrozińska S, Gałuszka-Bednarczyk A, et al. The PCOS Patients differ in Lipid Profile According to their Phenotypes. Exp Clin Endocrinol Diabetes. 2018;126(7):437-444. doi: 10.1055/s-0043-121264. Epub 2018 Jan 31. PMID: 29388179.
14. Mondal K, Chakraborty P, Kabir SN. Hyperhomocysteinemia and hyperandrogenemia share PCSK9-LDLR pathway to disrupt lipid homeostasis in PCOS. Biochem Biophys Res Commun. 2018;503(1):8-13. doi: 10.1016/j.bbrc.2018.04.078. Epub 2018 Jun 18. PMID: 29660344.
15. Gourgari E, Lodish M, Shamburek R, et al. Lipoprotein particles in adolescents and young women with PCOS provide insights into their cardiovascular risk. J Clin Endocrinol Metab. 2015;100(11):4291-8. doi: 10.1210/jc.2015-2566. Epub 2015 Sep 15. PMID: 26371381; PMCID: PMC4702461.

16. Sam S, Scoccia B, Yalamanchi S, et al. Metabolic dysfunction in obese Hispanic women with polycystic ovary syndrome. Hum Reprod. 2015;30(6):1358-64. doi: 10.1093/humrep/dev073. Epub 2015 Apr 8. PMID: 25857311; PMCID: PMC4498223.
17. Dokras A, Playford M, Kris-Etherton PM, et al Impact of hormonal contraception and weight loss on high-density lipoprotein cholesterol efflux and lipoprotein particles in women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 2017;86(5):739-746. doi: 10.1111/cen.13310. Epub 2017 Mar 9. PMID: 28199736; PMCID: PMC5651984.
18. Glintborg D, Mumm H, Hougaard D, et al. Ethnic differences in Rotterdam criteria and metabolic risk factors in a multiethnic group of women with PCOS studied in Denmark. Clin Endocrinol (Oxf). 2010;73(6):732-8. doi: 10.1111/j.1365-2265.2010.03873.x. PMID: 20846294.
19. Duleba AJ, Dokras A. Is PCOS an inflammatory process? Fertil Steril. 2012;97(1):7-12. doi: 10.1016/j.fertnstert.2011.11.023. PMID: 22192135; PMCID: PMC3245829.
20. Çakıroğlu Y, Vural F, Vural B. The inflammatory markers in polycystic ovary syndrome: association with obesity and IVF outcomes. Journal of endocrinological investigation. 2016;39(8):899-907.
21. Pergialiotis V, Trakakis E, Parthenis C, et al Correlation of platelet to lymphocyte and neutrophil to lymphocyte ratio with hormonal and metabolic parameters in women with PCOS. Horm Mol Biol Clin Investig. 2018;34(3):/j/hmbci.2018.34.issue-3/hmbci-2017-0073/hmbci-2017-0073.xml. doi: 10.1515/hmbci-2017-0073. PMID: 29694329.
22. Usta A, Avci E, Bulbul CB, et al. The monocyte counts to HDL cholesterol ratio in obese and lean patients with polycystic ovary syndrome. Reprod Biol Endocrinol. 2018;16(1):34. doi: 10.1186/s12958-018-0351-0. PMID: 29631598; PMCID: PMC5891948.

ORIGINAL RESEARCH

Increased vulvovaginal candidiasis incidence risk in various gestational ages at a private midwifery practice in Surabaya, Indonesia

Regina Martina Cilik[1], Willy Sandhika[2]*, Zakiyatul Faizah[1]
[1]Midwifery Education Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [2]Department of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, [3]Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

ABSTRACT

Objectives: This study aimed to analyze whether there was an increase in the incidence risk of vulvovaginal candidiasis at various gestational ages.
Materials and Methods: A study examined vaginal smears of pregnant women at a private midwifery practice Farida Hadjri, Surabaya, Indonesia. A total sample of 96 patients was taken by the consecutive sampling method, consisting of 32 patients each from the 1st, 2nd, and 3rd trimester of pregnancy.y The smear was examined using Gram stain at *Balai Besar Laboratorium Kesehatan Daerah Jawa Timur* to detect the presence of fungi elements. Data were analyzed using Chi-square test with 95% confidence interval to investigate whether there was an increased risk of vulvovaginal candidiasis and gestational age.
Results: There was an increased risk of vulvovaginal candidiasis and increased gestational age ($p < 0.05$). This result was related to the hormonal status of pregnant women. An increase in estrogen level during pregnancy leads to an increase in glycogen production by vaginal epithelial cells, which cause the vaginal environment to become more susceptible to fungal growth.
Conclusion: There was increased vulvovaginal candidiasis incidence risk along with gestational age. Pregnancy is one of the predisposing factors for candida infection.

Keywords: Vulvovaginal candidiasis; pregnancy; gestational age; maternal health

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk menganalisis adanya peningkatan resiko kejadian vulvovaginal candidiasis pada berbagai usia kehamilan
Bahan dan Metode: Penelitian dilakukan dengan pemeriksaan apus vagina ibu hamil pada Bidan Praktek Swasta Farida Hadjri, Surabaya, Indonesia. Sampel diperoleh dengan teknik konsekutif sampling dengan jumlah total sampel 96 pasien yang terdiri atas masing-masing 32 pasien untuk kehamilan trimester 1,2 dan 3. Spesimen diperiksa dengan pewarnaan Gram di Balai Besar Laboratorium Kesehatan Daerah Jawa Timur untuk mendeteksi adanya elemen jamur. Analisis data menggunakan tes Chi-square dengan tingkat kesahihan 95% untuk membuktikan adanya peningkatan risiko kejadian kandidiasis vulvovaginal seiring dengan bertambahnya usia kehamilan.
Hasil: Didapatkan peningkatan risiko kandidiasis vulvovaginal seiring dengan bertambahnya usia kehamilan ($p < 0,05$). Hasil ini terkait dengan status hormonal ibu hamil. Peningkatan kadar estrogen selama kehamilan menginduksi peningkatan produksi glikogen oleh sel epitel vagina yang menyebabkan lingkungan vagina menjadi lebih rentan terhadap pertumbuhan jamur.
Simpulan: Terjadi peningkatan resiko kejadian kandidiasis vulvovaginal seiring dengan bertambahnya usia kehamilan. Kehamilan merupakan salah satu faktor predisposisi terjadinya infeksi kandida.

Kata kunci: kandidiasis vulvovaginal; kehamilan; usia kehamilan; kesehatan ibu

***Correspondence:** Willy Sandhika, Departement of Anatomic Pathology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jalan Prof Dr Moestopo 47, Surabaya 60131, Indonesia. E-mail : willysand@fk.unair.ac.id

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.72-77
● Maj Obs Gin. 2022;30:72-77 ● Received 20 Dec 2021 ● Revised 23 Mar 2022 ● Accepted 18 Mar 2022 ● Published 1 Aug 2022

INTRODUCTION

Vulvovaginal candidiasis is the second most common infection found in pregnancy after bacterial vaginosis. *Candida spp*. infection commonly found in pregnant women of reproductive age. Pregnancy is the first risk factors that support vulvovaginal candidiasis due to hormonal changes during pregnancy.[1] The study on pregnant women in Ghana, explained that pregnancy is a predisposing factor for vulvovaginal candidiasis.[2] New York prevalence study suggested that candida species colonize the vagina of at least 20% of all women and increase to 30% in pregnancy, most are asymptomatic. Pregnant women are more likely to experience it than non-pregnant women.[3]

Based on a research report by the Health Research and Development Agency (Ministry of Health of the Republic of Indonesia) in 2016, a study of the prevalence of reproductive tract infections in pregnant women in 3 major cities in Indonesia, namely Pekanbaru, Bandung, and Tangerang district, candidiasis vulvovaginal ranked third (13-45.6%) after trichomoniasis and bacterial vaginosis of all pregnant women sampled.[4]

Reproductive health services for antenatal care need to check for reproductive tract infections and sexually transmitted infections in all pregnant women by providing sufficient education about the importance of screening, infection prevention and treatment, especially in the third trimester of pregnancy, to prevent complications for pregnant women and their fetuses.[5]

Vulvovaginal candidiasis in pregnant women may result in labor complications such as premature membrane rupture and low birth weight. Therefore detection of vulvovaginal candidiasis in antenatal care can prevent these complications.[6]

This study aimed to analyze whether there was an increased incidence of vulvovaginal candidiasis in various trimesters at a private midwifery practice Farida Hadjri, Surabaya, Indonesia.

MATERIALS AND METHODS

Samples for this study were taken from pregnant women who did antenatal care at the private midwifery practice Farida Hadjri Surabaya from August until October 2020 (inclusion criteria of this study). There were 540 patients during this period, and the patients who refused to join the study were excluded. The sample size was calculated using Slovin's formula with a 5% error margin, and the result was 96 patients, consisting of 32 patients from each trimester of pregnancy. The samples were obtained by the consecutive sampling method (non-random sampling). This study did not separate between low-risk and high-risk pregnancies. The incidence of vulvovaginal candidiasis was assessed by finding the presence of fungi in vaginal smear stained with gram stain. The smears were examined at *Balai Besar Laboratorium Kesehatan Daerah Jawa Timur*, to assess whether there were yeast cells or pseudo hyphae in the gram-stained slide. The results of the smear examination were analyzed with the Chi-square statistic formula to obtain odd ratio at various gestational age trimesters. This study had been ethically approved by Health Research Ethic Committee, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, No.159/EC/KEPK/FKUA/2020.

RESULTS AND DISCUSSION

Ninety-six patients were enrolled in this study. Most of the samples were in the age of 20-29 years old (72.92%), and patients with multi pregnancy were more than those with first pregnancy (62.5%). Most of the patients (61.46%) had complaints such as fluor albus and itchy vulva, half of the patients had senior high school education (50%), and most (80.21%) had profession as a housewife (Table 1).

Table 1. Patients' clinical characteristics for this study.

Variables	Total	n (%)
Age		
< 20	6	6.25
20-29	70	72.92
30-40	19	19.79
>40	1	1.04
Total	96	100
Pregnancy status		
First pregnancy	36	37.5
Multi pregnancy	60	62.5
Total	96	100
Complaints experienced		
No complaints	37	38.54
Specific complaints	23	23.96
Other complaints	36	37.50
Total	96	100
Level of education		
Primary school	11	11.46
Junior high school	25	26.04
Senior high school	48	50
Faculty education	12	10.42
Total	96	100
Profession		
Housewife	77	80.21
Private employees	19	19.79
Total	96	100

Vaginal smear examination revealed 25 patients (26.04%) had *Candida spp.* infection, while 71 patients (73.96%) had no candida infection. Positive smears

were found primarily on patients aged 20-29 years (72%), patients with multi-pregnancy (80%), patients with genital complaints such as fluor albus and itchy vulva (72%), senior high school education background (56%) and housewife profession (72%). Candida infections were identified with gram stain as a cluster of fungi in the form of blastospores, hyphae or pseudo-hyphae, or a mixture of the two. Tissue cells such as epithelium, leucocytes, erythrocytes, and other microbes such as bacteria or parasites were also observable in the preparation. Fungi appeared in the form of budding yeast cells and pseudo-hyphae. *Candida albicans* was seen as a monomorphic yeast and yeast-like organism that grows well at temperatures of 25-30 ºC and 35-37 ºC (Figure 1).

This study revealed that most patients infected with candida were at the age of 20-29 years old. This result was in accordance with the previous study, which showed that vulvovaginal candidiasis rarely occurred before puberty, increased in women of childbearing age, and decreased after menopause.[7] Studies of candida in women in Saudi Arabia found a similar result that candida infection was most common in the age group of 21 to 30 years, which was of reproductive age, and their hormonal status was still active.[8] Candidiasis was found more often in patients with multi-pregnancy than the first pregnancy. This finding shows that pregnancy is a risk factor for vulvovaginal candidiasis.[9] Most women in this study had vulvovaginal symptoms such as fluor albus and itchy vulva. Pereira et al. found that 62.2% of women with candidiasis were symptomatic while 37.8% were asymptomatic.[10]

Vaginal smear examination revealed that the most candida infections (13 patients or 52%) were experienced by pregnant women in the 3rd trimester of pregnancy. Among those in 2nd trimester of pregnancy, seven patients (28%) were positive for candidiasis, and the lowest candida infection was experienced by pregnant women during the first trimester of pregnancy (five patients or 20%).

Analysis of candida infection risk had shown that infection of candida in the 2nd trimester of pregnancy did not show a significant increase of infection compared with 1st-trimester pregnancy ($p > 0.05$), while those in the third trimester had a significant increase of candida infection risk compared those in the 1st and 2nd trimester of pregnancy ($p < 0.05$). From these results, it can be concluded that the third trimester of pregnancy was associated with a higher incidence of candida spp infection, that is the candidiasis incidence in 3rd trimester of pregnancy increases 3.7 times more than in the 1st and 2nd trimester of pregnancy. The risk of candidiasis in various gestational age was 15.625% in 1st trimester, 21.875% in 2nd trimester and 40.625% in 3rd trimester.

The study's results found that gestational age correlates with an increased risk of candida infection. The probability test for the 2nd trimester of pregnancy was found to be 1.51 times, or there was no significant increase in the frequency of the incidence of vulvovaginal candidiasis compared to the 1st trimester of pregnancy. However, when the probability test was carried out on 3rd trimester pregnant women, it was found that pregnant women at the 3rd trimester of pregnancy had 3.7 times the risk of being infected by *Candida spp*.

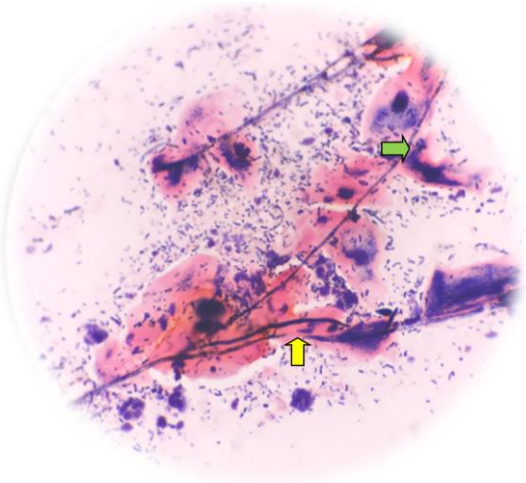


Figure 1. Yeast cell ( ) and pseudohyphae ( ) of *Candida spp.* appearance on microscopic examination with the Gram stain (400 x magnification).

The results of the study on samples whose gestational age was in the 1st trimester found that only a small proportion of five pregnant women (15.7%) had vulvovaginal candidiasis in 32 patients. This was in accordance with a study conducted by Fardiazar, et al who had conducted a study of vulvovaginal candidiasis in pregnant women, comparing recurrence rates of vulvovaginal candidiasis during the first, second, and third trimesters of pregnancy. They found that 90.7% of the patients were in the second and third trimesters of pregnancy. The study showed a significant difference of frequency between symptomatic recurrences that occurred during the three trimesters of pregnancy, with most occurring in the second and third trimesters.[11] During pregnancy, there was an increase in the levels of progesterone and estrogen hormones. Despite of inhibitory effect of progesterone on candida activity in neutrophils, estrogen reduces the ability of vaginal epithelial cells to inhibit candida growth. As many as 75% of women are generally at risk of being infected with this fungus without any symptoms or asymptomatic, which has no negative impact on the pregnancy itself.[12] Samples in the 2nd trimester of gestational age revealed that seven patients (21.88%) suffered from vulvovaginal candidiasis. This result was in accordance with the research by Zisova et al., who conducted a study concluding that increased gestational age, hyperestrogenemia, hormonal imbalance, and suppression of the mother's immune system all contribute to increased susceptibility to infections.[13] A study conducted in southern Nigeria found that pregnancy is a process that involves various hormonal changes in the body. After endometrial oxidation, estrogen and progesterone hormones will continue to increase gradually until the last week of pregnancy. The increase in estrogen levels begins at the 11th week of pregnancy and will continue to increase until the 24th week and still increase until the end of pregnancy.[14] The results of this study on patients in 3rd trimester of pregnancy found 13 patients (40.63%) with vulvovaginal candidiasis. These results were similar to those in the study by Brandao et al. on pregnant women in Brazil. They found that vulvovaginal candidiasis was the second most common cause of vaginitis after bacterial vaginosis.[15]

Ghaddar, et al. stated that estrogen is the most dominant reproductive hormone in supporting and maintaining *Candida spp.* infection. In vitro studies have shown that β-estradiol increases the growth of *Candida albicans* and directly stimulates dimorphic transmission from yeast to the hyphal form as well as increasing hyphae length.[16]

Gonzalves, et al. (2016) said that the candida species secrete hydrolytic enzymes that play an important role in tissue penetration, invasion, and damage to the host tissues. The enzymes most frequently involved in the pathogenesis and virulence of candida are aspartyl proteinase, phospholipase, lipase, and hemolysin. Aspartyl proteinase facilitates adhesion to host tissues, and its damage is associated with changes in the host immune response.[9] Several factors are associated with physiological changes, such as decreased cellular immunity, increased hormones, reduced vaginal pH, and increase the higher glycogen content in pregnancy. In fact, candida infection during pregnancy occurs due to high levels of placental estrogen, progesterone, and corticosteroids, which can decrease the vaginal defense mechanism to facilitate yeast growth.[17]

Pregnancy predisposes to primary and recurrent infections, and pregnant women have a two-fold increase in the frequency of vulvovaginal candidiasis compared to non-pregnant women. This is related to high levels of estrogen, glycogen stores, and other substrates.[18] Zhai, et al. found that the incidence of vulvovaginal candidiasis increases 100% during the 3rd trimester of pregnancy. The older the gestational age, the higher the risk of a pregnant woman to be infected with candida. High levels of progesterone have a suppressive effect on the cellular immune system, and, on the other hand, the promoter effect of gene expression affects the cellular synthesis of epithelial receptors that can bind candida.[19] The increase in estrogen facilitates yeast adherence to vaginal epithelial cells. In addition, it encourages hypha formation and elaboration of enzymes such as aspartyl proteinase and wasted phospholipase. The prevalence of vulvovaginal candidiasis increased by 36% in the third trimester of pregnancy.[20] Other factors that can increase the risk of vulvovaginal candidiasis in pregnancy, including diabetes mellitus and, in this study, poor hygiene can also act as confounding factor.[21]

Vulvovaginal candidiasis affects women globally, and therefore a better knowledge of the problem of candidiasis and colonization is needed, especially in pregnant women. Correct diagnosis, clinical symptom tracing, and risk factor screening should always be carried out in all women, both during pregnancy and women of reproductive age, to prevent labor complications such as premature rupture of membrane and low birth weight.[6,22] Vulvovaginal candidiasis is more susceptible to infecting women with high hormone levels, such as pregnant women, despite the fact that it does no harm to the fetus. However, if left untreated, the baby can be infected (oral thrush) during delivery and face serious health problems such as premature delivery.

Babies with oral thrush can cause the mother to be infected in the breastfeeding process, which causes candidiasis of the nipple.[23] Screening of risk factors is needed to prevent complications in both pregnant women and women of reproductive age for a meaningful psychological and sexual life.[24]

CONCLUSION

There is a tendency for increased frequency of vulvovaginal candidiasis infection with increased gestational age. Pregnant women, especially in the 3rd trimester of pregnancy, are more likely to have candida infection. Therefore, they should be examined and treated to control the infections.

DISCLOSURES

Acknowledgment

Thank you to the management and staff of the private midwifery practice Farida Hadjri Surabaya, Indonesia, who had permitted to conduct this research, and also to midwifery students in the Midwifery Program, Faculty of Medicine, Universitas Airlangga, who had given a lot of help during the research process.

Conflict of Interest

The authors declare there is no conflict of interest.

Funding Disclosure

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.

REFERENCES

1. Sardi JCO, Scorzoni L, Bernardi T, et al. Candida species: current epidemiology, pathogenicity, biofilm formation, natural antifungal products and new therapeutic options. J Med Microbiol. 2013;62(Pt 1):10-24. doi: 10.1099/jmm.0.045054-0. Epub 2012 Nov 22. PMID: 23180477.
2. Willems HME, Lowes DJ, Barker KS, et al. Comparative analysis of the capacity of the candida species to elicit vaginal immunopathology. Infect Immun. 2018;86(12):e00527-18. doi: 10.1128/IAI.00527-18. PMID: 30249743; PMCID: PMC6246903.
3. Aguin TJ, Sobel JD. Vulvovaginal candidiasis in pregnancy. Curr Infect Dis Rep. 2015;17(6):462. doi: 10.1007/s11908-015-0462-0. PMID: 25916994.
4. Sangaré I, Sirima C, Bamba S, et al. Prevalence of vulvovaginal candidiasis in pregnancy at three health centers in Burkina Faso. J Mycol Med. 2018;28(1):186-92. doi: 10.1016/j.mycmed.2017.08.006. Epub 2017 Sep 20. PMID: 28939305.
5. Blostein F, Levin-Sparenberg E, Wagner J, et al. Recurrent vulvovaginal candidiasis. Ann Epidemiol. 2017;27(9):575-82.e3. doi: 10.1016/j.annepidem.2017.08.010. Epub 2017 Aug 15. PMID: 28927765.
6. Kumar M, Saadaoui M, Al Khodor S. Infections and pregnancy: effects on maternal and child health. Front Cell Infect Microbiol. 2022;12:873253. doi: 10.3389/fcimb.2022.873253. PMID: 35755838; PMCID: PMC9217740.
7. Mtibaa L, Fakhfakh N, Kallel A, et al. Les candidoses vulvovaginales: étiologies, symptômes et facteurs de risque. Journal de Mycologie Medicale. 2017;27(2):153–8.
8. Venugopal D, Husain K, Mustafa SA, et al. Epidemiology, risk factors and antimicrobial profile of Vulvovaginal Candidiasis (VVC): A study among women in the central region of Saudi Arabia. J Mycol Med. 2021;31(2):101049. doi: 10.1016/j.mycmed.2020.101049. Epub 2020 Oct 15. PMID: 33153879.
9. Gonçalves B, Ferreira C, Alves CT, et al. Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. Crit Rev Microbiol. 2016;42(6):905-27. doi: 10.3109/1040841X.2015.1091805. Epub 2015 Dec 21. PMID: 26690853.
10. Pereira LC, Correia AF, da Silva ZDL, et al. Vulvovaginal candidiasis and current perspectives: new risk factors and laboratory diagnosis by using MALDI TOF for identifying species in primary infection and recurrence. Eur J Clin Microbiol Infect Dis. 2021;40(8):1681-93. doi: 10.1007/s10096-021-04199-1. Epub 2021 Mar 13. PMID: 33713006; PMCID: PMC8295079.
11. Fardiazar Z, Ronaci F, Torab R, et al. Vulvovaginitis candidiasis recurrence during pregnancy. Pak J Biol Sci. 2012;15(8):399-402. doi: 10.3923/pjbs.2012.399.402. PMID: 24199471.
12. Waikhom SD, Afeke I, Kwawu GS, et al. Prevalence of vulvovaginal candidiasis among pregnant women in the Ho municipality, Ghana: species identification and antifungal susceptibility of Candida isolates. BMC Pregnancy Childbirth.

2020;20(1):266. doi: 10.1186/s12884-020-02963-3. PMID: 32375724; PMCID: PMC7201979.
13. Zisova LG, Chokoeva AA, Amaliev GI, et al Vulvovaginal Candidiasis in Pregnant Women and its Importance for Candida Colonization of Newborns. Folia Med (Plovdiv). 2016;58(2):108-14. doi: 10.1515/folmed-2016-0018. PMID: 27552787.
14. Olowe OA, Makanjuola OB, Olowe R, et al. Prevalence of vulvovaginal candidiasis, tricho-moniasis and bacterial vaginosis among pregnant women receiving antenatal care in Southwestern Nigeria. Eur J Microbiol Immunol (Bp). 2014; 4(4):193-7. doi: 10.1556/EUJMI-D-14-00027. Epub 2014 Dec 16. PMID: 25544891; PMCID: PMC4271815.
15. Verwijs MC, Agaba SK, Darby AC, et al. Impact of oral metronidazole treatment on the vaginal microbiota and correlates of treatment failure. Am J Obstet Gynecol. 2020;222(2):157.e1-157.e13. doi: 10.1016/j.ajog.2019.08.008. Epub 2019 Aug 9. PMID: 31404542; PMCID: PMC6995998.
16. Ghaddar N, El Roz A, Ghssein G, et al. Emergence of vulvovaginal candidiasis among Lebanese pregnant women: Prevalence, risk factors, and species distribution. Infect Dis Obstet Gynecol. 2019;2019:5016810. doi: 10.1155/2019/5016810. PMID: 31467477; PMCID: PMC6699268.
17. Denning DW, Kneale M, Sobel JD, et al. Global burden of recurrent vulvovaginal candidiasis: a systematic review. Lancet Infect Dis. 2018;18 (11):e339-e347. doi: 10.1016/S1473-3099(18) 30103-8. Epub 2018 Aug 2. PMID: 30078662.
18. Brandão LDS, Boniek D, Resende Stoianoff MA, et al. Prevalence and antifungal susceptibility of Candida species among pregnant women attending a school maternity at Natal, Brazil. Lett Appl Microbiol. 2018;67(3):285-291. doi: 10.1111/lam. 13034. Epub 2018 Jul 12. PMID: 29908032.
19. Zhai Y, Liu J, Zhou L, et al. Detection of Candida species in pregnant Chinese women with a molecular beacon method. J Med Microbiol. 2018;67(6):783-789. doi: 10.1099/jmm.0.000740. PMID: 29676728; PMCID: PMC6096925.
20. Maldonado I, Cataldi S, Garbasz C, et al.; Red de Micología de la Ciudad Autónoma de Buenos Aires (RMCABA), Argentina; Red de Micología de la Ciudad Autónoma de Buenos Aires:. Identificación de levaduras del género Candida: los métodos convencionales frente a MALDI-TOF MS [Identification of Candida yeasts: Conventional methods and MALDI-TOF MS]. Rev Iberoam Micol. 2018;35(3):151-4. Spanish. doi: 10.1016/j.riam.2018.02.002. Epub 2018 Aug 3. PMID: 30078526.
21. Farr A, Effendy I, Frey Tirri B, et al. Guideline: Vulvovaginal candidosis (AWMF 015/072, level S2k). Mycoses. 2021;64(6):583–602. doi: 10.1111/ myc.13248.
22. Mucci MJ, Cuestas ML, Landanburu MF, et al. Prevalence of Candida albicans, Candida dubliniensis and Candida africana in pregnant women suffering from vulvovaginal candidiasis in Argentina. Rev Iberoam Micol. 2017;34(2):72-6. doi: 10.1016/j.riam.2016.09.001. Epub 2017 Apr 3. PMID: 28385421.
23. Nicholls S, MacCallum DM, Kaffarnik FA, et al. Activation of the heat shock transcription factor Hsf1 is essential for the full virulence of the fungal pathogen Candida albicans. Fungal Genet Biol. 2011;48(3):297-305. doi: 10.1016/j.fgb.2010.08. 010. Epub 2010 Sep 9. PMID: 20817114; PMCID: PMC3032048.
24. van Schalkwyk J, Yudin MH; Infectious Disease Committee. Vulvovaginitis: screening for and management of trichomoniasis, vulvovaginal candi-diasis, and bacterial vaginosis. J Obstet Gynaecol Can. 2015;37(3):266-74. doi: 10.1016/ S1701-2163(15)30316-9. PMID: 26001874.

ORIGINAL RESEARCH

Calcium serum concentration among pregnant women in a tertiary hospital and its satellite hospital in Medan, Indonesia

Muhammad Agung Khoiri*, Sarma N Lumbanraja, Duddy Aldiansyah, M. Fidel Ganis Siregar, Makmur Sitepu, M. Rhiza Tala
Department of Obstetric and Gynecology, North Sumatra University, Medan, Indonesia

ABSTRACT

Objectives: This study aimed to evaluate serum calcium concentration in pregnant women who made prenatal appointments to Obstetric and Gynecologic Outpatient Clinics at Adam Malik General Hospital, Medan, Indonesia, and its satellite hospitals.
Materials and Methods: This study was a descriptive study with a case series approach. The case series of the study included 35 pregnant women in their second or third trimester chosen by consecutive sampling method.
Results: The mean calcium serum level of pregnant women in the second and third trimester was 9.12±0.49 mg/dl and 8.97±0.26 mg/dl, respectively. The mean calcium level of pregnant women aged <20, 20-35, and >35 years old were 9.0±0.28 mg/dl, 9.07±0.44 mg/dl, and 8.96±0.06 mg/dl, respectively.
Conclusion: This study found that the mean calcium serum level in pregnant women who made prenatal appointments at Haji Adam Malik General Hospital, Medan, Indonesia, was normal.

Keywords: Calcium; pregnancy; second trimester; third trimester; maternal health

ABSTRAK

Tujuan: Mengetahui gambaran konsentrasi kalsium serum pada wanita hamil yang dirawat di Rumah Sakit Umum Pusat Haji Adam Malik, Medan, Indonesia, dan RS Jejaring.
Bahan dan Metode: Penelitian ini merupakan penelitian deskriptif observasional dengan pendekatan case series, dimana kasus serial dalam penelitian ini adalah 35 wanita hamil pada trimester dua dan tiga yang dipilih secara consecutive sampling.
Hasil: Dijumpai rerata kadar kalsium darah pada usia kehamilan trimester 2 adalah 9,12±0,49 mg/dl dan pada usia kehamilan trimester 3 adalah 8,97±0,26 mg/dl. Kadar kalsium rerata pada subjek penelitian usia<20 tahun, 20-35 tahun dan >35 tahun adalah 9,0±0,28 mg/dl, 9,07±0,44 mg/dl, dan 8,96±0,06 mg/dl, berturut.
Simpulan: Penelitian ini menemukan rerata kadar kalsium ibu hamil yang mengikuti kontrol kehamilan di poliklinik RSUP Haji Adam Malik Medan, Indonesia, adalah masih dalam rentang normal.

Kata kunci: Kalsium; kehamilan; trimester dua; trimester tiga; kesehatan ibu

***Correspondence:** Muhamad Agung Khoiri, Jl. Perjuangan Komp. Anthurium No. 18 Setia Budi, Medan, Indonesia. E-mail: muhammadagungkhoiri717@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.78-83
● Maj Obs Gin. 2022;30:78-83 ● Received 5 Jan 2022 ● Revised 10 Apr 2022 ● Accepted 22 Apr 2022 ● Published 1 Aug 2022

INTRODUCTION

In 2010, it was estimated that up to 287,000 women died during pregnancy and childbirth, with the majority of deaths attributed to maternal health issues. Gestational hypertension disease accounted for 2-8% of complications in pregnancy and attributed to low birth weight, preterm birth, and maternal mortality.[1] Pregnancy-related hypocalcaemia is still a common laboratory and clinical finding. Throughout pregnancy, a number of hormonal changes contribute to the relatively constant serum calcium levels. Despite the fact that several studies have found that ionized serum concentrations are rarely altered throughout pregnancy and lactation, if appropriate replenishment is not promoted, these concentrations are typically kept steady at the expense of the maternal skeletal storage. Balk et al. and Cormick et al. both conducted systematic reviews, and they both found that women in low- and middle-income countries are much more likely to have inadequate calcium intake and consequently low serum calcium concentrations.[2,3]

Meanwhile in Indonesia, pregnant women with low calcium level are still prominent. Ana Nurjannah's study in Palembang city from 2019 found that 66.7%; 40% and 41.7% of pregnant women in first, second and third trimester had hypocalcemia, respectively.[4] Other study conducted by Devi Kurniasari in Bandar Lampung showed that as many as 60% of pregnant women with preeclampsia had lower calcium level compared with 33% normal pregnant women.[5] Study in Makassar also found low calcium level in first and second trimester pregnant women as low as 7.79±0.44 and 7.64±0.36 mg/dL, respesctively.[6]

Pregnant women's average intake of vitamin D and calcium was 1.1 g and 433.3 mg, respectively, according to a study by Bardosono et al. involving 143 healthy first-trimester pregnant women living in Jakarta. This intake was 100 percent and 97.9 % below the recommended daily allowances for both nutrients.[7] Aji et al. and Sari et al. did additional research in North Sumatra and West Sumatra, and their findings revealed that more than 80% of participants had insufficient vitamin D intake, with an average intake of vitamin D ranging between 5.24 and 7.29 g/day.[8,9] According to a systematic review from three studies by Hartriyanti et al., pregnant women's average calcium consumption was between 45% and 80% below the estimated average requirement (EAR). Intakes of calcium averaged 536.23 mg, 614.41 mg, and 360 mg in these studies, respectively.[10]

In some studies, a relationship between hypocalcemia and high blood pressure has been discovered. Calcium intake has been found to be inversely related to the occurrence of gestational hypertension in some studies. Low calcium intake during pregnancy may stimulate parathyroid hormone secretion, resulting in an increase in intracellular calcium and, as a result, uterine smooth muscle contractibility. This chain of events could result in preterm birth, spontaneous abortion, or renin release from the kidney, which causes vasoconstriction and sodium and fluid retention. These physiological changes are capable of developing gestational hypertension and preeclampsia. According to studies, low serum calcium levels were found in women who already had preeclampsia, and calcium supplementation could reduce the risk of preeclampsia as well as maternal mortality and morbidity.[11]

Low calcium intake during pregnancy has been linked to a calcium metabolic disorder in the pregnant women, which may affect fetal development. Calcium supplementation in preeclampsia prevention was found to increase fetal birth weight and reduce the prevalence of neonatal intensive care, compared to the untreated group.[12]

Early detection of pregnant women's calcium levels can have an impact on the prevention of complications above. Based on the data on the description of calcium levels that has been done previously, we conducted a study aimed to evaluate maternal serum calcium level concentration among pregnant women in Obstetrics and Gynecology outpatient clinic in Haji Adam Malik General Hospital Medan and satellite hospitals in Medan. Haji Adam Malik General Hospital was chosen because of its status as tertiary health facility and main referring hospital in Sumatera Island that may represent pregnancy in variable conditions.

MATERIALS AND METHODS

Subjects and design of the study

This study was a descriptive study with a case series approach. Research was conducted in Obstetric and Gynecologic Outpatient Clinic of Haji Adam Malik General Hospital Medan, North Sumatra, Indonesia. The study population was healthy pregnant women who took antenatal care at hospital in their first or second trimester. The inclusion criteria are pregnant women who were in their first or second trimester and aged 18-40 years old. In contrast, pregnant women with thyroid and parathyroid disorder, impaired liver function, or renal disorder were excluded from this study. Samples were chosen by non-probability sampling with consecutive sampling techniques, which describes a process of conducting research including all the people

who meet the inclusion criteria and are conveniently available, as part of the sample. The researchers conduct research one after the other until they reach a required number of subjects. Sample was obtained by using descriptive categorical sample size formula which results in 35 minimal samples.

Serum calcium level examination

We assess the serum calcium level by using CPC Photometric method. As much as 3 mL of blood sample were placed in an Eppendorf tube and was centrifuged at 4000 rpm for 10 minutes. The serum was then homogenized by vortex and placed in the home temperature area (18-30ºC) for 1 minute. Lastly, the reading of the absorbance test and absorbance standard was done to reagencia blank in wavelength of 570 (578) nm.

Statistical analysis

Data collected were descriptively analyzed and presented in the distribution of frequency. Mean value and standard deviation were determined for numerical scale variables, e.g., serum calcium level.

Ethical clearance

The Ethical Committee Commission of Healthy Study in Medical Faculty of North Sumatra University/ Adam Malik General Hospital Medan related to health study practice has approved this study with Ethical Clearance Letter no. 646/KEP/USU/2020

RESULTS AND DISCUSSION

This study involved 35 pregnant women, dominated by women aged 20-35 years old (80%) and pregnant women in the second trimester (57.1%). The majority of the subjects were primigravida (54.3%) (Table 1).

Table 1. Study subjects' characteristics

	Subjects of Pregnant Women (n, %)
Age, n (%)	
< 20 years	2 (5.7)
20 – 35 years	28 (80)
> 35 years	5 (14.2)
Gestational Age, n (%)	
1st Trimester	20 (57.1)
2nd Trimester	15 (42.9)
Parity, n (%)	
Primigravida	19 (54.3)
Multigravida	16 (45.7)
Level of Education, n (%)	
Elementary School	2 (5.7)
Junior High School	3 (8.6)
Senior High School	25 (71.4)
Graduated	5 (14.3)

Mean calcium serum levels found in pregnant women in the second and third trimesters were 9.12±0.49 mg/dl and 8.97±0.26 mg/dl, respectively. Mean calcium serum level in subjects age < 20 years old, 20 -35 years old and > 35 years old were 9.0±0.28 mg/dl, 9.07±0.44 mg/dl, and 8.96±0.06 mg/dl, respectively. Analysis was done between pregnancy age and serum's calcium level with $p > 0.05$ ($P = 0.246$). Based on this analysis there was no significant relationship between pregnancy age and serum calcium level (Table 2).

Table 2. Mean serum calcium level based on pregnancy age

Trimester	Serum Calcium Level(mg/dl)				p value
	Mean	SD	Minimum	Maximum	
2nd Trimester (n=20)	9.12	0.49	7.60	9.90	.246
3rd Trimester (n=15)	8.97	0.26	8.50	9.40	

Table 3. Mean serum calcium level based on subject's age

Age	Serum Calcium Level (mg/dl)				p value
	Mean	SD	Minimum	Maximum	
<20 years old	9	0.28	8.80	9.20	
20-35 years old	9.07	0.44	7.60	9.90	.732
>35 years old	8.96	0.06	8.80	9.20	

Table 4. Mean serum calcium level based on parity

Parity	Serum Calcium Level (mg/dl)				p value
	Mean	SD	Minimum	Maximum	
Primigravida	9	0.58	7.60	9.90	.645
Multigravida	9.07	0.31	8.50	9.60	

Table 5. Mean serum calcium level based on education level

Education	Serum Calcium Level (mg/dl)			p value
	Mean	Minimum	Maximum	
Elementary	9.1	8.9	9.3	
Junior high	9.03	8.6	9.3	
Senior high	9.02	7.6	9.8	.488
Associate degree	9	8.8	9.2	
Bachelor degree	9.3	8.9	9.9	

Analysis of age and serum's calcium level from 35 women in this study shows no significant relationship with p > 0.05 (0.732). Mean calcium level found in under 20 years group, 20-35 years, and above 35 years are 9.00, 9.07, and 8.96, respectively (Table 3). Mean calcium found in primigravida is 9.00 and in multigravida is 9.07. Analysis of parity and serum's calcium level from 35 women in this study shows no significant relationship with p > 0.05 (0.645) (Table 4). Mean calcium found in pregnant women based on their education level are 9.1, 9.03, 9.02, 9, 9.3 for elementary education, junior high school, senior high school, associate degree, and bachelor degree, respectively. Analysis was done and there was no significant relationship between calcium serum level and education level in pregnant women with p > 0.05 (P = 0.488) (Table 5).

Nutritional status, maternal and neonatal health are important indicators of the burden of any disease. The most prevalent mineral in the body, calcium is crucial for many different biochemical processes, including bone formation, muscle contraction, and hormone and enzyme activity. In three different forms, ionic, protein-bound, and complexed, calcium in extracellular fluid maintains its physiologic equilibrium.[13] Hypocalcaemia in pregnancy remains a major health issue, particularly in the developing world where daily calcium intakes are suboptimal. This electrolyte imbalance can lead to severe maternofoetal and childhood consequences.[14]

In our study, the mean serum calcium level found among pregnant normocalcemia women was 9.12 mg/dL and 8.97 mg/dL for pregnant women in first and second trimester, respectively. This result was in line with the study of Aqbar et al.[15] who conducted a study involving 34 pregnant women in third trimester. This study found a normal calcium serum level average of 8.89 mg/dL. This result was also in line with Indonesian study performed by Setiarsih et al. which found that the mean levels of serum calcium were 8.94 mg/dL in the group of pregnant women and 9.74 mg/dL in the non-pregnant group. These values are within the normal range of 8.1-10.4 mg/dL. There was a significant difference in serum calcium levels between the pregnant and non-pregnant groups (P = 0.047) and the average value of serum calcium levels was lower in the pregnant group.[22] Our study also found that only one pregnant woman had low calcium level (7.81 mg/dL). While it is difficult to ascertain the risk factor for such cases, diet and exercise might be a contributing factor that cause the mother's low calcium level.

Furthermore, we discovered that mean serum calcium levels were higher in the second trimester than the third trimester, which was similar to Zapata et al.'s study in 2004.[16] When compared to younger pregnancy (10–12 weeks of gestation), almost all nearly term or older pregnancy (34–36 weeks of gestation) had lower serum calcium levels. This is believed to be the result of a twofold increase in intestinal calcium absorption as a maternal physiological adaptation to meet the fetal calcium requirement. Calcitriol levels can double during pregnancy, as previously stated, and this increase in calcitriol causes an increase in intestinal calcium absorption. However, an animal study found that the increase in intestinal calcium absorption occurred before the rise in free calcitriol levels, and that calcitriol and vitamin D receptors were not involved in the increase in intestinal calcium absorption during pregnancy. Other factors such as placental lactogen and prolactin were found to stimulate that increase in intestinal calcium absorption.[16]

In this study, maternal calcium level was found to be lowest in pregnant women older than 35 years old. According to Nordin (2018), healthy postmenopausal women accounted for 30% of the decrease in calcium

absorption until the age of 75. In addition, this late decrease was not associated with 25(OH)D or 1,25(OH)2D concentration. The reduced in gastrointestinal responses against 1,25(OH)2D also seemed to cause the decrease in calcium absorption in elder women.[17] Wulandari et al. conducted a cross-sectional study in 53 Indonesia pregnant women across couples of ethnicities and found that Madurese women with mean ages of 34.20±5.58 years old had the least calcium serum level of 7.7 mg/dL, compared to Chinese women with the mean age of 28.20 ±2.16 and had calcium serum level of 9.0 mg/dL (P = .000).

Ajong et al. found hypocalcemia predominated in pregnant women aged 21-25. However, it turns out that the percentage of hypocalcemia in pregnant women aged 31-49 years is also quite high (54.63%).[14] Our study also contradicted Katung et al., who stated that hypocalcemic pregnant women primarily found in the age range of 20 – 34 years old with the mean age of 26.6 years old.[18] It is well known that parathyroid hormone levels rise with age. This increase is estimated to reduce renal function, calcium absorption efficiency, and the 25-hidroxyvitamin D [25(OH)D] concentration that subsequently cause loss of bone mass in postmenopausal women. The level of 25(OH)D is the primary determinant of parathyroid serum level; it also causes the increase in calcium ion level, and causes the decrease in body weight. Studies found that changes in calcium ion level, body weight, and age would affect the parathyroid serum level only if the 25(OH)D serum level is lower than 80 nmol/liter.[17]

Low calcium serum levels could cause some pregnancy complications, including preeclampsia, lower birth weight, preterm labor, and neonatal death. Previous studies found that women with low-birth-weight fetuses had a lower mean serum calcium level. Calcium has been shown to reduce the contractility of uterine smooth muscle. A healthy calcium level during pregnancy may help to prevent preterm labor and low-birth-weight newborns.[19,20] An adequate maternal nutrition is associated with normal fetal development. Deficiency in maternal nutrition could deteriorate fetal brain development, leading to embryonic malformation and increased congenital defect incidence. Calcium is an essential micronutrient as the reduced maternal calcium reserve could affect maternal bone quality, reduce bone density, and increase bone resorption. Pregnancy in the third trimester was the most consequent trimester. Pregnant women in this state no longer produce calcium, so that calcium needs to be taken exogenously. Fetal nutrition during pregnancy solely depends on maternal nutrition so a good intake of calcium in this condition is crucial to prevent maternal calcium reserve consumption.[2]

CONCLUSION

This study found that the mean calcium serum level in pregnant women from Adam Malik General Hospital outpatient clinic involved in the study was normal. There was no significant relationship between serum calcium level with age (P = 0.732), parity (P = 0.645), education level (0.488), and pregnancy age (P = 0.246)

DISCLOSURES

Acknowledgment

The authors express gratitude to the Obstetrics and Gynecology Department of Adam Malik Medan General Hospital, North Sumatra University Teaching Hospital, and Sundari Medan Hospital. Authors also thank Sarma N Lumbanraja, Duddy Aldiansyah, Fidel Ganis Siregar, M. Rhiza Tala and Makmur Sitepu as our mentor and advisor in finishing this study.

Conflict of interest

The authors report no conflicts of interest in this work.

Funding Disclosure

This study does not receive any sponsorship from the other party.

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.

REFERENCES

1. World Health Organization. Guideline?: Calcium supplementation in pregnant women. World Heal Organ [Internet]. 2013;24. Available from: https://apps.who.int/iris/bitstream/handle/10665/85120/9789241505376_eng.pdf?sequence=1
2. Balk EM, Adam GP, Langberg VN, et al.;. Global dietary calcium intake among adults: a systematic review. Osteoporos Int. 2017;28(12):3315-24. doi: 10.1007/s00198-017-4230-x. Epub 2017 Oct 12. Erratum in: Osteoporos Int. 2018 Feb 26;: PMID: 29026938; PMCID: PMC5684325.
3. Cormick G, Betrán AP, Romero IB, et al. Global inequities in dietary calcium intake during pregnancy: a systematic review and meta-analysis. BJOG. 2019;126(4):444-56. doi: 10.1111/1471-

0528.15512. Epub 2018 Nov 27. PMID: 30347499; PMCID: PMC6518872.
4. Nurjannah A. Gambaran kadar kalsium darah pada ibu hamil di Rumah Sakit Islam Siti Khadijah Kota Palembang tahun 2019 [Blood calcium profile in pregnant women]. J Anal Kesehat. 2019;1–146.
5. Kurniasari D, Astriana, Yantina Y. Hubungan kadar kalsium dalam darah ibu hamil dengan kejadian pre eklamsi di RSUD H Abdul Moeloek Bandar Lampung [Blood calcium in pregnant women and preelampsia]. J Dunia Kesmas. 2017;6:97–103.
6. Marwidah. Pemberian suplemen kalsium pada ibu hamil trimester I dan II dalam pengaturan tekanan darah di Kabupaten Bulukumba [thesis on the internet]. Makassar, Indonesia; Universitas Hasanuddin; 2017.
7. Bardosono S. Maternal micronutrient deficiency during the first trimester among indonesian pregnant women living in Jakarta. eJournal Kedokt Indones. 2016;4(2):3–8. doi: 10.23886/ ejki.4.6281. 76-81.
8. Aji AS, Yerizel E, Desmawati, et al. The association between lifestyle and maternal vitamin D during pregnancy in West Sumatra, Indonesia. Asia Pac J Clin Nutr. 2018;27(6):1286-93. doi: 10.6133/apjcn.201811_27(6).0016. PMID: 30485928.
9. Keumala Sari D. Is micro evolution in tropical country women resulting low 25(OH)D level?: A cross sectional study in Indonesia. J Nutr Food Sci. 2014;04(01):1–7. doi: 10.4172/2155-9600.1000246
10. Hartriyanti Y, Suyoto PS, Muhammad HF, et al. Nutrient intake of pregnant women in Indonesia: a review. Malays J Nutr. 2012;18(1):113-24. PMID: 23713235.
11. Almaghamsi A, Almalki MH, Buhary BM. Hypocalcemia in pregnancy: A Clinical Review Update. Oman Med J. 2018;33(6):453-62. doi: 10.5001/omj.2018.85. PMID: 30410686; PMCID: PMC6206424.
12. Hofmeyr GJ, Lawrie TA, Atallah ÁN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018;10 (10):CD001059. doi: 10.1002/14651858. CD001059.pub5. PMID: 30277579; PMCID: PMC6517256.
13. Kumar A, Kaur S. Calcium: A Nutrient in Pregnancy. J Obstet Gynaecol India. 2017;67(5): 313-8. doi: 10.1007/s13224-017-1007-2. Epub 2017 May 22. PMID: 28867880; PMCID: PMC5561751.
14. Ajong AB, Kenfack B, Ali IM, et al. Prevalence and correlates of low serum calcium in late pregnancy: A cross sectional study in the Nkongsamba Regional Hospital; Littoral Region of Cameroon. PLoS One. 2019;14(11):e0224855. doi: 10.1371/journal.pone.0224855. PMID: 31697767; PMCID: PMC6837377.
15. Pontoh A, Tiho M, Purwanto D. Gambaran kadar kalsium total darah pada ibu hamil trimester III di Rumah Sakit Robert Wolter Mongisidi Manado. J Med dan Rehabil. 2018;1(2):1–4.
16. Vargas Zapata CL, Donangelo CM, Woodhouse LR, et al. Calcium homeostasis during pregnancy and lactation in Brazilian women with low calcium intakes: a longitudinal study. Am J Clin Nutr. 2004;80(2):417-22. doi: 10.1093/ajcn/80.2.417. PMID: 15277164.
17. Nordin BE, Need AG, Morris HA, et al. Effect of age on calcium absorption in postmenopausal women. Am J Clin Nutr. 2004;80(4):998-1002. doi: 10.1093/ajcn/80.4.998. PMID: 15447911.
18. Katung G, Akande T. The prevalence of hypocalcemia in pregnancy and peurperium in northwestern Nigeria. Trop J Obs Gynaecol. 2016;33(1):27–31.
19. Kant S, Haldar P, Gupta A, et al. Serum calcium level among pregnant women and its association with pre-eclampsia and delivery outcomes: A cross-sectional study from North India. Nepal J Epidemiol. 2019;9(4):795-803. doi: 10.3126/nje.v9i4.23150. PMID: 31970014; PMCID: PMC6964799.
20. Yang CY, Chiu HF, Chang CC, et al. Association of very low birth weight with calcium levels in drinking water. Environ Res. 2002;89(3):189-94. doi: 10.1006/enrs.2002.4369. PMID: 12176002.
21. Liu X, Wang X, Tian Y, et al. Reduced maternal calcium intake through nutrition and supplementation is associated with adverse conditions for both the women and their infants in a Chinese population. Medicine (Baltimore). 2017;96(18):e6609. doi: 10.1097/MD.0000000000006609. PMID: 28471956; PMCID: PMC5419902.
22. Setiarsih D, Wirjatmadi B, Adriani M. Bone density status and vitamin D and calcium concentrations in pregnant and non-pregnant women. Makara Journal of Health Research. 2016;20(3):63-8. doi: 10.7454/msk.v20i3.3540.

ORIGINAL RESEARCH

Clinical manifestations comparison in hospitalized pregnant and non-pregnant women with Covid-19 at Mataram University Hospital, Mataram, Indonesia

Putu Diah Ananda Putri Atmaja[1]*, Ario Danianto[2], Titi Pambudi Karuniawaty[3]
[1]Faculty of Medicine, Mataram University, West Nusa Tenggara, Indonesia, [2]Department of Obstetrics and Gynecology, Faculty of Medicine, Mataram University, West Nusa Tenggara, Indonesia. [3]Department of Pediatric, Faculty of Medicine, Mataram University, West Nusa Tenggara, Indonesia.

ABSTRACT

Objectives: To know a comparison of clinical manifestations in pregnant and non-pregnant Covid-19 patients who are hospitalized at Mataram University Hospital.
Materials and Methods: This study was a descriptive observational study with a cross-sectional approach, using secondary data in the form of medical records. This study uses a total sampling technique, sample selection based on affordable population, inclusion criteria, and exclusion criteria. The data was processed with SPSS 25th version and analyzed with a Chi-square analysis test.
Results: In this study, it was found that 145 women confirmed Covid-19 on RT-PCR, 89 of which were pregnant and 56 others weren't; 85.4% of the included pregnant women were in the 3rd trimester. Clinical manifestations in pregnant women are 73.0% asymptomatic while symptomatic in 60.7% of the non-pregnant women. In symptomatic pregnant women, most common clinical symptoms were nausea, vomiting, cough, and headache; while the most common clinical symptoms in non-pregnant women were cough, anosmia, and headache. Chi-square analysis test showed a significant relationship with P = 0.000 ($p < 0.05$) in clinical manifestation comparison.
Conclusion: There are differences in clinical manifestations in pregnant and non-pregnant women with Covid-19. The most common clinical manifestation in pregnant women was asymptomatic and in non-pregnant women the most common clinical manifestation was symptomatic.

Keywords: Covid-19; SARS-CoV-2; pregnancy; maternal health

ABSTRAK

Tujuan: Mengetahui perbandingan gejala klinis pada wanita hamil dan wanita tidak hamil dengan Covid-19 yang dirawat inap di RS Universitas Mataram.
Bahan dan Metode: Penelitian ini merupakan penelitian deskriptif observasional dengan pendekatan potong lintang, menggunakan data sekunder berupa rekam medis wanita hamil dan wanita tidak hamil yang terkonfirmasi positif Covid-19 dengan RT-PCR. Penelitian ini menggunakan teknik total sampling, pemilihan sampel dilakukan berdasarkan populasi terjangkau, kriteria inklusi, dan kriteria eksklusi. Data yang didapatkan diolah dengan SPSS versi 25 dan dianalisis dengan uji analisis Chi-square.
Hasil: Pada studi ini didapatkan 145 wanita konfirmasi Covid-19 dengan RT-PCR, dimana 89 merupakan wanita hamil dan 56 tidak hamil. Berdasarkan usia kehamilan pada kelompok wanita hamil 85.4% pada kehamilan trimester ke-3. Manifestasi klinis pada wanita hamil 73.0% asimptomatis dan pada wanita tidak hamil 60.7% simptomatis. Pada wanita hamil simptomatis gejala klinis yang paling banyak muncul adalah mual muntah, batuk, dan sakit kepala, dan pada wanita tidak hamil simptomatis gejala klinis yang paling banyak muncul adalah batuk, anosmia, dan sakit kepala. Pada analisis uji chi-square perbedaan manifestasi klinis pada wanita hamil dan tidak hamil dengan Covid-19 didapatkan P = 0.000 ($p < 0.05$) terdapat perbedaan bermakna pada manifestasi klinis.
Simpulan: Didapatkan perbedaan bermakna manifestasi klinis pada wanita hamil dan wanita tidak hamil dengan Covid-19. Sebagian besar manifestasi klinis pada wanita hamil dengan Covid-19 adalah asimptomatis dan pada wanita tidak hamil dengan Covid-19 adalah simptomatis.

Kata kunci: Covid-19; SARS-CoV-2; kehamilan; kesehatan ibu

***Correspondence:** Putu Diah Ananda Putri Atmaja, Faculty of Medicine, Mataram University, Jalan Pemuda No.37, Gomong, Selaparang, Mataram, NTB, Indonesia, Email: ptuatmaja@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.84-91
● Maj Obs Gin. 2022;30:84-91 ● Received 10 Feb 2022 ● Revised 14 Apr 2022 ● Accepted 22 Apr 2022 ● Published 1 Aug 2022

INTRODUCTION

Coronavirus Disease 2019 (Covid-19) is an acute respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Until October 2021 there have been more than 219 million positive cases worldwide and more than 4 million positive cases in Indonesia. SARS-CoV-2 can spread through various transmission.[1] These various transmissions promote SARS-CoV-2 virus to spread widely and very quickly, based on that the World Health Organization (WHO) established Covid-19 as a pandemic situation.[2-4] Based on clinical manifestations, Covid-19 infection can be divided into two, namely asymptomatic and symptomatic manifestations. In symptomatic manifestations there are respiratory symptoms and non-respiratory symptoms.[1]

Everyone can be infected with Covid-19, especially the vulnerable groups such as pregnant women. During pregnancy there are various physiological changes to support fetus growth and development.[3,5] Physiological change during pregnancy include response of the immune system from pro-inflammatory response in early pregnancy change to anti-inflammatory response in late trimester; this change can affect the immune system in response to viral infections.[3,5] Besides that, along with increasing gestational age and fetal weight, uterus can push diaphragm and reduce total lung capacity, so pregnant women are more susceptible to respiratory infection and respiratory failure.[3,5] In the coagulation system there is hypercoagulable condition, an increase in thrombin production and intravascular inflammation, an increased coagulation response associated with thromboembolic complications and the possibility of developing disseminated intravascular coagulation (DIC).[6]

Change in physiological function and immune system responses during pregnancy will affect body response to fight virus, this can affect clinical manifestations that appear in pregnant women with Covid-19. Most common symptoms in pregnant women are cough (59.7%) and fever (29.3%).[2] From a cohort study with 147 pregnant women with Covid-19, there were 8% with severe symptoms and 1% with critical symptoms.[1] In Indonesia, especially in West Nusa Tenggara, there has been no research on clinical manifestations of pregnant women with Covid-19. This study aims to determine the clinical manifestations of pregnant women with Covid-19, thus helping early detection and treatment of Covid-19 in pregnant women.

MATERIALS AND METHODS

This study was a descriptive observational study with a cross-sectional approach. Using secondary data in the form of medical records at Mataram University Hospital in May-December 2020. In this study there were 145 women with RT-PCR positive for Covid-19; 89 pregnant women and 56 non-pregnant women. The sample of this study was taken by total sampling technique of pregnant women with Covid-19 and non-pregnant women with Covid-19, this sample selection was based on affordable population, inclusion criteria, and exclusion criteria. Inclusion criteria are pregnant and non-pregnant women in productive age (15-49 years) with Covid-19 that are hospitalized in Mataram University Hospital and exclusion criteria are incomplete medical record, patients with comorbidities like asthma and hypertension. In clinical manifestations, asymptomatic conditions were defined for those who reported being in usual health with no signs or symptoms of Covid-19. The data were processed with SPSS 25th version.

RESULTS AND DISCUSSION

Age characteristic of women with Covid-19

From May-December 2020, there was a total of 145 women with RT-PCR positive for Covid-19, 89 of which were pregnant women. In the pregnant women group, women aged 26-35 years old dominate with 48 patients (53.9%), then 15-25 years old age with 23 patients (25.8%) and the least were 18 patients (20.2%) with the age of 36-45 years old. In non-pregnant group, participants were mostly aged 26-35 years with 27 patients (48.2%), then 15-25 years of age with 16 patients (28.6%), 12 patients (21.4%) in 36-35 years old, and the least was one patient (1.8%) with the age of >45 years (Table 1).

Characteristic of clinical manifestation in pregnant and non-pregnant women with Covid-19

There were 24 patients (27.0%) with symptomatic manifestations and 65 patients (73.0%) with asymptomatic manifestations in the pregnant women group. In the non-pregnant women group, there were 34 patients (60.7%) with symptomatic manifestations and 22 patients (39.3%) with asymptomatic manifestations (Table 2).

Table 1. Characteristic of age in pregnant and non-pregnant women with Covid-19

Age	Pregnant women n (%)	Non-pregnant women n (%)	Total n (%)
15-25 years	23 (25.8)	16 (28.6)	39 (26.9)
26-35 years	48 (53.9)	27 (48.2)	75 (51.7)
36-45 years	18 (20.2)	12 (21.4)	30 (20.7)
>45 years	0 (0.0)	1 (1.8)	1 (0.7)
Total	89 (100)	56 (100)	145 (100)

Table 2. Characteristic of clinical manifestations in pregnant and non-pregnant women with Covid-19

Clinical Manifestation	Pregnant women n (%)	Non-pregnant women n (%)	Total n (%)
Symptomatic	24 (27.0)	34 (60.7)	58 (40.0)
Asymptomatic	65 (73.0)	22 (39.3)	87 (60.0)
Total	89 (100)	56 (100)	145 (100)

Table 3. Characteristic of pregnant women with Covid-19

Characteristic	Symptomatic n (%)	Asymptomatic n (%)	Total n (%)
Age			
15-25 years	5 (20.8)	18 (27.7)	23 (25.8)
26-35 years	14 (58.3)	34 (52.3)	48 (53.9)
36-45 years	5 (20.8)	13 (20.2)	18 (20.2)
Gestational age			
1st trimester	3 (12.5)	3 (4.6)	6 (6.7)
2nd trimester	3 (12.5)	4 (6.2)	7 (7.9)
3rd trimester	18 (50)	58 (89.2)	76 (85.4)
Number of pregnancies			
Primigravida	10 (41.7)	18 (27.7)	28 (31.5)
Multigravida	14 (58.3)	47 (72.3)	61 (68.5)
Total	24 (100)	65 (100)	89 (100)

Based on age in pregnant women with Covid-19 group, there were five symptomatic patients (20.8%) and 18 asymptomatic patients (27.7%) in the 15-25 years old group, in the 26-35 years old group there were 14 symptomatic (58.3%) and 34 asymptomatic (52.3%), and there were five symptomatic (20.8%) and 13 asymptomatic (20.2%) in the 36-45 years old group. Based on gestational age, in the 1st trimester group there were three symptomatic (12.5%) and three asymptomatic (4.6%), in the 2nd trimester group there were three symptomatic (12.5%) and four asymptomatic (6.2%), while in the 3rd trimester group there were 10 symptomatic (41.7%) and 18 asymptomatic (27.7%). Based on gravida status, there were 10 symptomatic patients (41.7%) and 18 asymptomatic patients (27.7%) with primigravida, while in the multigravida group there were 14 symptomatic (58.3%) and 47 asymptomatic (72.3%) (Table 3).

Characteristic of clinical symptoms of pregnant and non-pregnant women with Covid-19

The most prevalent respiratory clinical symptoms in pregnant women were cough which was observed in eight patients (9.0%) and breathlessness in five patients (5.6%), while the most prevalent non-respiratory clinical symptoms was nausea and vomiting in 10 patients (11.2%), headache in seven patients (7.9%), and fatigue in five patients (5.6%). In non-pregnant women, the most prevalent respiratory clinical symptoms was cough which was observed in 18 patients (32.1%) and anosmia in 13 patients (23.2%), while the most prevalent non-respiratory clinical symptoms was headache in 13 patients (23.2%), nausea and vomiting in seven patients (12.5%), and fatigue in seven patients (12.5%) (Table 4).

Characteristic of clinical signs of pregnant and non-pregnant women with Covid-19

In the current study, clinical signs that were assessed are heart rate, respiratory rate, body temperature, and oxygen saturation. This study found that clinical signs in pregnant and non-pregnant women were mostly in normal range. In pregnant and non-pregnant women, the most prevalent observed heart rate was in the normal range in 82 (92.1%) and 52 (92.9%) patients, respectively. The most prevalent observed respiratory rate was in normal range in 70 (78.7%) pregnant women and in 45 (80.4%) non-pregnant women, while the most

prevalent observed body temperature was in normal range in 79 (88.8%) pregnant women and 51 (91.1%) non-pregnant women, and the most prevalent observed oxygen saturation was in normal range in 87 (97.8%) pregnant women and in 47 (83.9%) non-pregnant women (Table 5).

Chi-square analytic test comparison of clinical manifestation in pregnant and non-pregnant women with Covid-19

This study found that the most prevalent clinical manifestation in pregnant women was asymptomatic in 65 patients (74.7%) and was symptomatic in 34 non-pregnant women (58.6%) with p value 0.000 ($p<0.05$) which means there was a significant difference in clinical manifestations between pregnant and non-pregnant women with Covid-19 (Table 6).

Table 4. Clinical symptoms in pregnant and non-pregnant women with Covid-19

	Pregnant Women n (%)	Non-pregnant Women n (%)	Total n (%)
Respiratory clinical symptoms			
Cough	8 (9.0)	18 (32.1)	26 (17.9)
Breathless	5 (5.6)	10 (17.9)	15 (10.3)
Anosmia	1 (1.1)	13 (23.2)	14 (9.7)
Sore throat	2 (2.2)	4 (7.1)	6 (4.1)
Nasal congestion	2 (2.2)	4 (7.1)	6 (4.1)
Shortness of breath	0 (0)	0 (0)	0 (0)
Non-respiratory clinical symptoms			
Headache	7 (7.9)	13 (23.2)	20 (13.8)
Nausea vomiting	10 (11.2)	7 (12.5)	17 (11.7)
Fatigue	5 (5.6)	7 (12.5)	12 (8.3)
Fever	2 (2.2)	4 (7.1)	6 (4.1)
Diarrhea	1 (1.1)	3 (5.4)	4 (2.8)
Ageusia	1 (1.1)	2 (3.6)	3 (2.1)
Chest pain	2 (2.2)	0 (0)	2 (1.4)
Myalgia	0 (0)	1 (1.8)	1 (0.7)
Skin Rash	0 (0)	0 (0)	0 (0)
Conjunctivitis	0 (0)	0 (0)	0 (0)
Abdomen pain	0 (0)	0 (0)	0 (0)
Number of clinical symptoms			
1 symptom	9 (37.5)	10 (29.4)	19 (32.8)
2-3 symptoms	15 (62.5)	15 (44.1)	30 (51.7)
>3 symptoms	0 (0)	9 (26.5)	9 (15.5)
Total	24 (100)	34 (100)	58 (100)

Table 5. Clinical signs in pregnant and non-pregnant women with Covid-19

Clinical Signs	Pregnant Women n (%)	Non-pregnant Women n (%)	Total n (%)
Heart rate			
Tachycardia	7 (7.9)	2 (3.6)	9 (6.2)
Normal	82 (92.1)	52 (92.9)	134 (92.4)
Bradycardia	0 (0)	2 (3.6)	2 (1.4)
Respiratory rate			
Tachypnea	19 (21.3)	11 (19.6)	30 (20.7)
Normal	70 (78.7)	45 (80.4)	115 (79.3)
Body temperature			
Normal	79 (88.8)	51 (91.1)	130 (89.7)
Sub febrile	6 (6.7)	0 (0.0)	6 (4.1)
Fever	3 (3.4)	3 (5.4)	6 (4.1)
Hyperthermia	1 (1.1)	2 (3.6)	3 (2.1)
Oxygen saturation			
Normal	87 (97.8)	47 (83.9)	134 (92.4)
Low saturation	2 (2.2)	9 (16.1)	11 (7.6)
Total	89 (100)	56 (100)	145 (100)

Table 6. Result of Chi-square analytic test comparison of clinical manifestations

Clinical Manifestation	Pregnant Women n (%)	Non-pregnant Women n (%)	Total n (%)	P Value
Symptomatic	24 (41.4)	34 (58.6)	58 (100)	0.000*
Asymptomatic	65 (74.7)	22 (25.3)	87 (100)	
Total (%)	89 (61.4)	56 (38.6)	145 (100)	

Characteristic of age of women with Covid-19

The age of participants in this study was mostly in the range of 26-35 years, both in pregnant women with 48 patients (53.9%) and in non-pregnant women with 27 patients (48.2%). This was related to the fact that 26-35 years olds are said to be the beginning of the productive age which tends to have more activities and higher mobility. Hence, this group is more vulnerable to Covid-19.

Characteristic of clinical manifestation of pregnant and non-pregnant women with Covid-19

In this study, the most clinical manifestations in pregnant women were asymptomatic in 65 patients (73.0%) and in non-pregnant women was symptomatic in 34 patients (60.7%), with mostly 3rd trimester pregnant women with 18 patients (75%). Several studies also concluded that the most clinical manifestations in pregnant women are asymptomatic; this was thought to be related to immune system changes in pregnant women that caused a unique immune response in pregnant women with Covid-19.[7-9] Activation of bilateral immune system causes pregnant women to have a low risk to have severe symptoms of Covid-19. During pregnancy, there is a change in immune response from pro-inflammatory (Th-1 cells, Th-17 cells and proinflammatory cytokines) in early pregnancy to anti-inflammatory (Th-2 cells, T regulatory cells, and anti-inflammatory cytokines) in late pregnancy. Domination of anti-inflammatory cytokines (IL-10) and placenta hormone helps pregnant women escape a cytokine storm and microangiopathic thrombosis. On the other hand, domination of IL-10 has an antifibrotic effect in lung tissue by suppressing Th-1 and profibrotic effects of IL-4.[10] So, the clinical manifestations tend to be milder.

An observational study stated that pregnant women with Covid-19 tend to have asymptomatic clinical manifestations or mild symptoms.[11] This is associated with an increase in progesterone, estrogen, and allopregnanolone concentrations starting in 1st and 2nd trimester, then reaches its peak in the 3rd trimester. Increasing reproductive steroid hormone in pregnant women with Covid-19 plays a role in preventing disease severity and mortality.[11]

Changes in immune system, hormone system, and other physiological changes during pregnancy provide an advantage for pregnant women with Covid-19, especially in anti-inflammatory immune phase (2nd and 3rd trimester) which can protect pregnant women with Covid-19 from worsening symptoms or severe and critical symptoms. In addition, these changes cause the majority of pregnant women with Covid-19 to have asymptomatic clinical manifestations. On the other hand, although immune system change tends to be asymptomatic manifestation, asymptomatic people can cause the virus to spread more widely because the patient does not realize that she is carrying the virus and continues to carry out activities as usual, thus causing the spread of virus either as unaware as a silent spreader. However, in another study, it was found that the most clinical manifestation in pregnant women is symptomatic (67.4%).[12] It is different from the result in this study because there is no exclusion for pregnant women with comorbidity.

Characteristic of clinical symptoms of pregnant and non-pregnant women with Covid-19

In this study, the most common clinical symptoms in pregnant women with Covid-19 are nausea vomiting (11.2%), cough (9.0%), headache (7.9%), and breathless (5.6%). In a study published by Wiyati et al. (2021) the most common clinical symptoms in pregnant women are cough (26.7%), dyspnea (24.4%), and fever (13.3%).[7] In Allotey et al.'s systematic review the most common Covid-19 symptoms in pregnant women were cough (41%) and fever (40%).[5] In a prospective cohort study of pregnant women in USA it found the most prevalent first symptoms were cough (20%), sore throat (16%), myalgia (12%), and fever (12%).[13] Pregnant women with Covid-19 were less likely to have fever or myalgia than non-pregnant women in the same age.[5] Clinical symptoms of Covid-19 can be divided into two, respiratory symptoms and non-respiratory symptoms. The various clinical symptoms in patients with Covid-19 are related to expression of ACE2 receptors in various organs in the human body. Generally, the highest production of ACE2 is found in lungs, heart, ileum, kidneys, and the bladder.[14-20]

Clinical symptoms in Covid-19 are closely related to expression of ACE2 which is the site of attachment of SARS-CoV-2, high ACE2 expression in the respiratory tract increases the appearance of respiratory clinical symptoms. Non-respiratory symptoms are related to the presence of ACE2 expression outside the respiratory tract, which initiates the emergence of non-respiratory clinical symptoms.

Characteristic of clinical signs of pregnant and non-pregnant women with Covid-19

Characteristic of clinical signs in pregnant women and non-pregnant women with Covid-19 in this study were mostly in normal range; this is related to clinical manifestations in pregnant women as mostly asymptomatic and in non-pregnant women with Covid-19 as symptomatic with 2-3 clinical symptoms. In another systematic review which included over 64,000 pregnant women worldwide with Covid-19, only 10% attending or admitted to hospital for any reason and most symptomatic pregnant women with Covid-19 only experienced mild and moderate cold/flu-like symptoms.[5] So that does not provide significant change in clinical signs. In this study, clinical sign assessments were taken only on initial examination patients and not followed up, so that the existing data did not describe the overall clinical signs of pregnant and non-pregnant women with Covid-19 during treatment.

Chi-square analytic test comparison of clinical manifestation in pregnant and non-pregnant women with Covid-19

In this study, there were differences of clinical manifestations in pregnant and non-pregnant women with Covid-19. This can be seen in Table 6. In pregnant women, the most common clinical manifestation is asymptomatic (74.7%) while in non-pregnant women the most common clinical manifestation is symptomatic (58.6%). These different manifestations that appear are related to physiological change in pregnant women such as the immune system and hormonal change. In addition, most asymptomatic manifestations in pregnant women were in the 3rd trimester of pregnancy (85.4%) which provided an advantage due to changes in the immune system to anti-inflammatory and an increase in reproductive steroid hormones supporting the occurrence of asymptomatic clinical manifestations. The dominance of the sample of pregnant women with Covid-19 in the 3rd trimester of pregnancy is related to the screening policy set by the government where prior obstetrical treatment/action (delivery) screening is required.

Limitation

In this study, the data were taken cross-sectionally or only done once, so that the progression and course of the disease could not be observed. In addition, this study only assessed the clinical manifestation variables and did not include laboratory variables so that it could not assess the influence of these factors in the clinical manifestations of the disease.

Strength

This study is the first descriptive study in West Nusa Tenggara which discusses clinical manifestations of pregnant and non-pregnant women with Covid-19, so it can be used as a reference for other research on Covid-19 in pregnancy.

CONCLUSION

There are significant differences in clinical manifestations in pregnant and non-pregnant women with Covid-19. In pregnant women, the most clinical manifestations are asymptomatic, while in symptomatic the most common clinical symptoms are nausea, vomiting, cough, headache, shortness of breath, and weakness. In non-pregnant women with Covid-19, the most clinical manifestations are symptomatic with the most common clinical symptoms being cough, anosmia, headache, shortness of breath, nausea and vomiting, and weakness. Based on assessment of clinical signs both in pregnant and non-pregnant women with Covid-19 these were mostly in the normal range (heart rate 60-100x/minutes, respiration rate 12-20x/minutes, body temperature 36.5-37.2ºC, oxygen saturation 95-100%).

DISCLOSURES

Acknowledgment

The authors thank to Mataram University Hospital for support in collecting data and everyone who had contributed in this research.

Conflict of Interest

The authors declare there is no conflict of interest.

Funding Disclosure

This research has received no external funding.

Author Contribution

All authors have contributed to all process in this research, including preparation, data gathering and

analysis, drafting and approval for publication of this manuscript.

REFERENCES

1. World Health Organization (WHO). Transmisi SARS-CoV-2: Implikasi terhadap kewaspadaan pencegahan infeksi [SARS-CoV-2. Implication of infection prevention efforts]. WHO Guideline 2020. [internet] [Cited 2021 Jan 4]. Available from: https://www.who.int/docs/default-source/searo/indonesia/covid19/transmisi-sars-cov-2---implikasi-untuk-terhadap-kewaspadaan-pencegahan-infeksi---pernyataan-keilmuan.pdf?sfvrsn=1534d7df_4
2. Gao YJ, Ye L, Zhang JS, et al. Clinical features and outcomes of pregnant women with COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2020;20(1):564. doi: 10.1186/s12879-020-05274-2. PMID: 32746801; PMCID: PMC7396931.
3. Rohmah MK, Nurdianto AR. Corona Virus Disease 2019 (Covid-19) pada wanita hamil dan bayi: Sebuah tinjauan literatur. Medica Hospital Journal of Clinical Medicine. 2020;7(1): 329-36. doi: 10.36408/mhjcm.v7i1A.476.
4. Handayani RT, Setyorini C, Darmayanti AT, et al. Infeksi Covid-19 pada kehamilan dan persalinan. Jurnal Informasi Kesehatan Indonesia. 2020;6(1): 1-5. doi: 10.31290/jiki.v6i1.1503.
5. Allotey J, Stallings E, Bonet M, et al.; for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. BMJ. 2020;370:m3320. doi: 10.1136/bmj.m3320. Update in: BMJ. 2022 May 30;377:o1205. PMID: 32873575; PMCID: PMC7459193.
6. Ji HL, Zhao R, Matalon S, et al. Elevated plasmin(ogen) as a common risk factor for COVID-19 susceptibility. Physiol Rev. 2020;100(3):1065-75. doi: 10.1152/physrev.00013.2020. Epub 2020 Mar 27. PMID: 32216698; PMCID: PMC7191627.
7. Wiyati PS, Adawiyah R, Dewantiningrum J, Pramono BA. Maternal and perinatal outcomes with Covid-19: Lesson learned from the tertiary hospital. Bali Medical Journal. 2021;10(1):442-7. doi: 10.15562/bmj.v10i1.2229
8. Delahoy MJ, Whitaker M, O'Halloran A, et al. ; COVID-NET Surveillance Team. Characteristics and maternal and birth outcomes of hospitalized pregnant women with laboratory-confirmed COVID-19 - COVID-NET, 13 States, March 1-August 22, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(38):1347-54. doi: 10.15585/mmwr.mm6938e1. PMID: 32970655; PMCID: PMC7727497.
9. Wu X, Sun R, Chen J, et al. Radiological findings and clinical characteristics of pregnant women with COVID-19 pneumonia. Int J Gynaecol Obstet. 2020;150(1):58-63. doi: 10.1002/ijgo.13165. Epub 2020 Jun 3. Erratum in: Int J Gynaecol Obstet. 2021 Mar;152(3):465. PMID: 32270479; PMCID: PMC9087759.
10. Berhan Y. What immunological and hormonal protective factors lower the risk of COVID-19 related deaths in pregnant women? J Reprod Immunol. 2020;142:103180. doi: 10.1016/j.jri.2020.103180. Epub 2020 Jul 18. PMID: 32739645; PMCID: PMC7368414.
11. Pinna G. Sex and COVID-19: A protective role for reproductive steroids. Trends Endocrinol Metab. 2021;32(1):3-6. doi: 10.1016/j.tem.2020.11.004. Epub 2020 Nov 9. PMID: 33229187; PMCID: PMC7649655.
12. Breslin N, Baptiste C, Gyamfi-Bannerman C, et al. Coronavirus disease 2019 infection among asymptomatic and symptomatic pregnant women: two weeks of confirmed presentations to an affiliated pair of New York City hospitals. Am J Obstet Gynecol MFM. 2020;2(2):100118. doi: 10.1016/j.ajogmf.2020.100118. Epub 2020 Apr 9. PMID: 32292903; PMCID: PMC7144599.
13. Afshar Y, Gaw SL, Flaherman VJ, et al. ; Pregnancy CoRonavIrus Outcomes RegIsTrY (PRIORITY) Study. Clinical Presentation of Coronavirus Disease 2019 (COVID-19) in Pregnant and Recently Pregnant People. Obstet Gynecol. 2020;136(6):1117-25. doi: 10.1097/AOG.0000000000004178. PMID: 33027186; PMCID: PMC7673633.
14. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020;215:108427. doi: 10.1016/j.clim.2020.108427. Epub 2020 Apr 20. PMID: 32325252; PMCID: PMC7169933.
15. Cevik M, Kuppalli K, Kindrachuk J, et al. Virology, transmission, and pathogenesis of SARS-CoV-2. BMJ. 2020;371:m3862. doi: 10.1136/bmj.m3862. PMID: 33097561.
16. Ikawaty R. Dinamika interaksi reseptor ACE2 dan SARS-CoV-2 terhadap manifestasi klinis Covid-19. Jurnal Kesehatan dan Kedokteran. 2020;1(2):70-6. doi:10.24123/kesdok.V1i2.2869.
17. Beyerstedt S, Casaro EB, Rangel ÉB. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis. 2021;40(5):905-19. doi: 10.1007/s10096-020-04138-6. Epub 2021 Jan 3. PMID: 33389262; PMCID: PMC7778857.

18. Ejaz H, Alsrhani A, Zafar A, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020;13(12):1833-9. doi: 10.1016/j.jiph.2020.07.014. Epub 2020 Aug 4. PMID: 32788073; PMCID: PMC7402107.
19. Scialo F, Daniele A, Amato F, et al. ACE2: The major cell entry receptor for SARS-CoV-2. Lung. 2020;198(6):867-77. doi: 10.1007/s00408-020-00408-4. Epub 2020 Nov 10. PMID: 33170317; PMCID: PMC7653219.
20. Wang B, Kovalchuk A, Li D, et al. In search of preventive strategies: novel high-CBD Cannabis sativa extracts modulate ACE2 expression in COVID-19 gateway tissues. Aging (Albany NY). 2020;12(22):22425-44. doi: 10.18632/aging.202225. Epub 2020 Nov 22. PMID: 33221759; PMCID: PMC7746344.

ORIGINAL RESEARCH

Impact of E2 and FSH levels on the severity of Stress Urinary Incontinence (SUI) in menopausal women

Leny Suardi[1]*, Pribakti Budinurdjaja[1], Wiwit Agung Sri Nurcahyawati[2], Meitria Syahadatina Noor[3]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Lambung Mangkurat, Banjarmasin, Indonesia, [2]Department of Internal Medicine, Faculty of Medicine, University of Lambung Mangkurat, Banjarmasin, Indonesia, [3]Department of Reproductive Health and Public Health Nutrition, Faculty of Medicine, University of Lambung Mangkurat, Banjarmasin, Indonesia.

ABSTRACT

Objectives: This study aimed to analyze the relationship between E2 and FSH levels in menopausal women with the severity of Stress Urinary Incontinence (SUI) at Ulin Hospital, Banjarmasin, Indonesia.

Materials and Methods: This study used an analytic observational method with cross-sectional design in menopausal women diagnosed with Urinary Incontinence (UI) from October 2020 - March 2021. The independent variables were E2 and FSH levels. The dependent variable was the severity of SUI in menopausal women. The severity of SUI was determined by the Incontinence Severity Index (ISI) scoring. Data were analyzed by Spearman correlation.

Results: The subjects who met the criteria were 25 women. The results showed the prevalence rate of SUI was 5.8% with E2 and FSH levels of mild SUI (14.25 pg/mL and 49.70 mIU/mL), moderate (7.91 pg/mL and 54.13 mIU/mL), and severe (9.14 pg/mL) and 70.97 mIU/mL). The number of severity levels of mild SUI was 44%, moderate SUI was 48%, and severe SUI was 8%. Most patients with SUI aged >60 years, multipara, normal body mass index (BMI), duration of menopause <10 years, menarche <15 years, Intrauterine Device (IUD) contraception, and delivered with spontaneous vaginal delivery. There was no significant relationship between E2 levels and the severity of SUI with a p-value of 0.084 and a correlation coefficient of -0.353. There was no significant relationship between FSH level and severity of SUI with a p-value of 0.367 and a correlation coefficient of 0.189.

Conclusion: There was no significant relationship between E2 and FSH levels and the severity of SUI in menopausal women. It is necessary to do research on other factors that influence the high severity of SUI in menopausal women.

Keywords: E2; FSH; severity; SUI; menopause; maternal health

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk menganalisis hubungan kadar E2 dan FSH pada wanita menopause dengan tingkat keparahan Inkontinensia Urin Tipe Stres (IUS) di RSUD Ulin Banjarmasin, Indonesia.

Bahan dan Metode: Penelitian ini merupakan observasional analitik dengan pendekatan cross-sectional dengan populasi pada wanita menopause yang terdiagnosis Inkontinensia Urin (IU) periode bulan Oktober 2020 - Maret 2021. Variabel bebas adalah kadar E2 dan kadar FSH. Variabel tergantung adalah tingkat keparahan IUS pada wanita menopause. Tingkat keparahan IUS ditentukan dengan skoring Incontinence Severity Index (ISI). Data dianalisis dengan korelasi Spearman.

Hasil: Total yang memenuhi kriteria 25 subjek. Hasil penelitian menunjukkan angka prevalensi IUS sebanyak 5,8% dengan kadar rerata E2 dan FSH tingkat keparahan IUS ringan (14,25 pg/mL dan 49,70 mIU/mL), sedang (7,91 pg/mL dan 54,13 mIU/mL), berat (9,14 pg/mL dan 70,97 mIU/mL). Jumlah tingkat keparahan IUS ringan sebesar 44%, IUS sedang 48%, IUS berat 8%. IUS terbanyak pada usia >60 tahun, paritas multipara, Indeks Masa tubuh (IMT) normal, lama menopause <10 tahun, menarche <15 tahun, kontrasepsi IUD, metode persalinan spontan per vaginam. Tidak ada hubungan signifikan kadar E2 dengan tingkat keparahan IUS dengan p-value 0,084 dan koefisien korelasi sebesar -0,353. Hasil penelitian juga menunjukkan FSH tidak ada hubungan signifikan dengan tingkat keparahan IUS dengan p-value 0,367 dan koefisien korelasi sebesar 0,189.

Simpulan: Tidak terdapat hubungan signifikan antara kadar E2 dan FSH dengan tingkat keparahan IUS pada wanita menopause. Perlu dilakukan penelitian mengenai faktor-faktor lain yang mempengaruhi tingginya tingkat keparahan IUS pada wanita menopause.

Kata kunci: E2; FSH; tingkat keparahan; IUS; menopause; kesehatan ibu

***Correspondence:** Leny Suardi, Department of Obstetrics and Gynecology, Faculty of Medicine, University of Lambung Mangkurat, Banjarmasin, Indonesia. E-mail: suardi_leny@yahoo.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.92-100
● Maj Obs Gin. 2022;30:92-100 ● Received 15 Feb 2022 ● Revised 20 May 2022 ● Accepted 10 Jun 2022 ● Published 1 Aug 2022

INTRODUCTION

The increase in life expectancy has an impact on the number of menopausal women. Along within increasing age, health problems are also increasing, one of the organ problems related to menopause is urinary problems. Stress Urinary Incontinence accounts for about 56% of the major urinary problems in menopausal women.[1-3]

Stress urinary incontinence (SUI) is defined by the International Continence Society (ICS) as a condition characterized by the involuntary loss of urine as a result of increased intra-abdominal pressure due to exertion or sneezing or coughing. Symptoms include urination when coughing, straining, laughing, sneezing, running or other things that increase pressure in the abdominal cavity, hence it is related to quality of life.[4] In menopause (defined as the cessation of menstruation for 12 consecutive months), estrogen levels decrease and FSH (Follicle Stimulating Hormone) levels increase significantly, resulting in hormonal fluctuations and physiological changes in the genitalia. The decrease in estrogen that occurs due to menopause causes thinning of the epithelium, weakened tissue and decreased blood flow and elasticity of the vaginal walls.[5] Barbara et al. (2017) reported that women with SUI had significantly lower E2 levels than the control group, and also reported a positive association between hypermobility of bladder neck with SUI.[6]

Symptoms of urine leakage experienced by patients due to changes in urethral closing pressure affect the severity of incontinence, some are mild, moderate and severe, so the symptoms suffered by each patient vary. One way to measure the severity of IUS is by using the Incontinence Severity Index (ISI). Murphy et al. (2000) found the validity of the ISI associated with the Urogenital Distress Inventory (UDI-6) to determine the severity of IU.[7,8] Assessment of the severity of IUS is important when it is associated with E2 and FSH levels in menopausal women for diagnostic and therapeutic purposes.

EPIC study conducted in 2008 globally found that around 348 million people in the world had experienced IU, showing an increase of 10.8% to 286 million in 2013, and is estimated to increase by 21.6% to 423 million in 2013. In 2018, the global prevalence of IU is anticipated to increase from 8.2% in 2008 to 8.5%. The last epidemiological study in Indonesia was published in 2014 and involved six teaching hospitals, namely: Jakarta, Bandung, Semarang, Surabaya, Makassar, and Medan. From a total of 2,765 respondents who met the inclusion criteria, the total prevalence of IU was 13%, increasing with age.[7] Many are too shy to discuss this condition with a healthcare provider and some believe it is a normal part of aging that they have to deal with. The result can be isolation and limited social activities and interactions. In fact, IUS is a health problem at the age of menopause that can be resolved. Prolonged IUS if not treated immediately will affect a person's quality of life and can cause life problems both in terms of medical, social, economic and psychological. A survey conducted at the Geriatric Polyclinic of Cipto Mangunkusumo Hospital, Jakarta, in 2006, of all patients who experienced IU, the pressure type occurred in 17.3% of patients.[9,10]

Sandvik et al. (2000) also reported that the prevalence of IU increases with age, and half of IU is mostly in the stress type with a prevalence of 15% aged 45-59 and an increase of 33% aged 60.[7] Currently in Banjarmasin there are no data on IUS or studies that measure E2 and FSH levels were associated with the severity of IUS. On this basis, researchers are interested in examining whether there is a relationship between E2 and FSH levels in menopausal women with the severity of IUS at Ulin Hospital Banjarmasin.

MATERIALS AND METHODS

The research design used was analytic observational with a cross-sectional approach. The study was conducted at the Geriatrics Polyclinic and Gynecological Polyclinic of Ulin Hospital Banjarmasin from October 2020 to March 2021 with the target population being all menopausal women diagnosed with IU. All target populations were interviewed using the QUID questionnaire followed by selection. Inclusion criteria were menopausal women aged more than 45 years, IUS was established by QUID, did not suffer from other gynecological diseases, except patients with POP grade < 2, not diagnosed with DM as evidenced by blood sugar examination fasting and while peripheral, there was no diagnosis of UTI from the urinalysis examination and the patient was willing to be the subject of the study in writing. Exclusion criteria were a history of hysterectomy surgery, oophorectomy, BMI > 30 (obese) with measurements of height and weight, neurological disease, chronic cough, having disease, abnormality or tumor in the pelvic area, having a history of undergoing radiotherapy, estrogen hormonal therapy, smoking, and alcoholic. Respondents who met the inclusion and exclusion criteria were continued with the examination of blood E2 and FSH levels as well as filling in the ISI scoring to determine the severity of IUS. All members of the population who met the inclusion and exclusion criteria were taken as research subjects. The independent variables in this study were blood E2 and FSH levels with the dependent variable

being the severity of IUS./ After classifying the severity, the researchers looked for the relationship between E2 levels and blood FSH levels with the severity of IUS in postmenopausal women, processed by the SPSS program and analyzed by Spearman's test with a 95% Confidence Interval; it is said to be significant if the p value < 0.05 then it is said to be related, whereas if the p value > 0.05 it is said to be unrelated. This study met the ethical clearance of the ethics commission of Ulin Hospital Banjarmasin with number 113/IX-Reg Riset/RSUDU/20.

RESULTS AND DISCUSSION

The total number of menopausal women who came to the Gynecology Outpatient Clinic and Geriatric Outpatient Clinic was 527. Of these 527 patients, the incidence of IU was 10.6% (56 per 527) and SUIwas 5.8% (31 per 527). Of the 31 patients, five patients with UTI and one patient with DM were found, so in this study only 25 participants met the inclusion and exclusion criteria. The prevalence of SUI in this study is lower than the study in India conducted by Aathira et al. using QUID where the prevalence of IU was 26.47%, and IUS was 13.9%.[9] A survey conducted at the Geriatric Outpatient Clinic of Cipto Mangunkusumo Hospital, Jakarta in in 2006 reported 17.3% of all patients experiencing SUI.[10] In China in 2009, the prevalence rate of IUS was 18.9%.[11] The latest research in India in 2018 from 418 cases, found 77 cases (18.4%) having SUI.[12]

The prevalence rate of SUI in this study was lower because IU was considered a taboo and embarrassing thing to talk about and to tell doctors, so it is often not reported by patients or their families. Because there is an assumption that the problem is a shameful thing, so there is no good record made. Vito et al. (2013) evaluated the impact of IU including depression, anxiety, shame and withdrawal. This impact makes patients reluctant to report to their families or to go to the doctor.[13] The low prevalence rate in this study was also due to the time, the research was conducted during the Covid-19 pandemic, especially Banjarmasin city was included in the red zone areal therefore, the number of patients visited to the hospital was decreased. Besides the age factor makes patients not dare to visit the hospital.[14]

Menopausal women who experienced SUI in this study were mostly aged > 60 years compared to those aged <60 years (Table 1). This result is the same as the study at India in 2018 by Gita et al. which reported an increase in the number of SUI at age > 60 by 83.3% and age 40-60 by 51.81%.[12] IGPSuka Aryana et al. in the 2018 Geriatric Opinion also reported that SUI was 22% suffered by women aged between45-64 years.[15] In general, women of menopausal age will experience hormonal, physical and psychological changes. One of the physical changes in the menopausal period is urogenital changes in the form of atrophy in the genitals and urinary tract, resulting in SUI.[3]

Parity is one of the risks of SUI. The results of this study showed that the highest number of SUI was in the group of menopausal women with multiparity, namely 88.0%. The results of this study are supported by research by Gabriela et al. (2019) who reported that those who had never given birth had a 1 in 10 chance, while those who had given birth had an increased SUI probability of 1 in 3 deliveries. According to research by Fred et al. (2013) vaginal delivery can result in injury to the structures in the pelvic floor. These pathophysiological changes in the muscle structure and fascia of the pelvic floor result in a pelvic support defect and pelvic floor dysfunction.[16]

In addition to labor factors, obesity is also a risk factor for SUI. A systematic review by Bray (2015) said there was strong association between overweight and SUI. When a person gains weight, the size of fat cells will increase and then the number will increase. The increased BMI will be followed by an increase in intra-abdominal pressure which is higher so that it will suppress the pelvic floor thereby reducing the ability to control the urethra and bladder.[17] In this study, respondents who had a normal BMI had a small risk factor for SUI.

In this study (Table 1), there was one respondent with severe SUI in multipara and one respondent with nullipara. In the study of Gabriela et al, it is said that the level of SUI is influenced by parity. This is in contrast to the Norwegian EPINCONT study in 2001 which said the effect of parity was dependent on age, the severity of clinical SUI was not significantly associated with parity.[18] It is known that the decrease in estrogen secretion from the ovaries that occurs in menopausal women causes important urogenital changes. In this study, it was reported that mostly the respondents who experienced SUI were respondents with menopause > 10 years. These results are the same as the results of a study by Fidel (2016) which reported that the length of menopause was strongly negatively correlated with serum E2 levels with a value of r = -0.880, which indicates that the longer menopause will lower the E2 levels.[19]

Table 1 Characteristics of respondents to the severity of SUI

Characteristics	Total (%)	Light n (%)	Currently n (%)	Heavy n (%)
Age (Years)				
<60	10(40)	6 (60.0)	4(40.0)	0(0.0)
≥60	15 (60)	5 (33.3)	8(53.3)	2 (13.3)
Parity				
Pimipara	1(4.0)	1 (100.0)	0 (0.0)	0 (0.0)
Multipara	22 (88.0)	10 (45.5)	11 (50.0)	1 (4.5)
Grandemultipara	1 (4.0)	0 (0.0)	1 (100)	0 (0.0)
Nullipara	1 (4.0)	0 (0)	0 (0)	1 (100)
Body Mass Index				
18.5 - 24.9 (Normal)	14 (56.0)	7 (50.0)	5 (35.7)	2 (14.3)
25.0-29.9 (Overweight)	11 (44.0)	4 (36.4)	7 (63.6)	0(0.0)
Duration of menopause (Year)				
<10	13 (52.0)	8 (61.5)	5 (38.5)	0 (0.0)
≥10	12 (48)	3 (25.0)	7 (58.3)	2 (16.7)
Menarche (Year)				
<15	23 (92.0)	9 (39.1)	12 (52.2)	2 (8.7)
≥15	2 (8.0)	2 (100))	0 (0.0)	0 (0.0)
Contraception				
Pill	6 (24.0)	1 (16.7)	5 (83.3)	0(0.0)
Inject 3 months	4 (16.0)	1 (25.0)	3 (75.0)	0(0.0)
IUD	12 (48.0)	7 (58.3)	4(33.3)	1 (8.3)
No family planning	2 (8.0)	1 (50.0)	0 (0.0)	1(50.0)
MOW	1 (4.0)	1 (100)	0(0.0)	0(0.0)
Delivery Method				
Spontaneous-vaginal	20(80.0)	8 (40.0)	11 (55.0)	1 (5.0)
Caesarean section	3 (12.0)	2 (66.7)	1 (33.3)	0 (0)
Spontaneous and caesarean section	1 (4.0)	1 (100)	0 (0)	0 (0)
Nullipara	1 (4.0)	0 (0.0)	0 (0.0)	1 (100)
Educational background				
Primary school	2 (8.0)	0 (0.0)	2 (10.00)	0 (0.0)
Junior High School	3(12.0)	1 (33.3)	2(66.7)	0 (0.0)
Senior High School	6 (24.0)	2 (33.3)	2 (33.3)	2 (33.3)
Associate degree	6 (24.0)	4 (66.7)	2 (33.3)	0 (0)
Bachelor degree	8 (32.0)	4 (50.0)	4(50.0)	0 (0)
Employment history				
Non-Housewife	10(40.0)	5 (50.0)	5 (50.0)	0 (0.0)
Housewife	15 (60.0)	6 (40.0)	7(46.7)	2 (13.3)
Ethnic group				
Banjar	17(68.0)	6 (35.3)	10 (58.8)	1 (5.9)
Java	6 (24.0)	4 (66.7)	2 (33.3)	0 (0.0)
Dayak	1 (4.0)	0 (0.0)	0 (0.0)	1 (100)
Batak	1 (4.0)	1 (100)	0 (0.0)	0 (0.0)
Total	25 (100)	11 (44.0)	12(48.0)	2 (8.0)

Note: Primipara (female who gave birth to a baby weighing more than 500 grams or a gestational age of 20 weeks total 1 time), Multipara (amount 2-4), grande multipara (amount >4), Nullipara (never gave birth), housewife who only takes care of various domestic work, not working in the office.

Bjelland et al. (2018) reported that the sooner the age of menarche, the slower the age of menopause, and vice versa, the slower the age of menarche, the sooner the menopause. From the research, it can be seen that almost all of them experienced menarche at age 15 years. This is influenced by several factors, one of which is nutrition. Someone who has good nutrition will experience menarche more quickly because nutrition affects the formation of body fat which will indirectly metabolize fat by several hormones, namely the hormone estrogen. In this study, the younger the age of menarche, the longer the menopause.[20]

In this study, spontaneous vaginal delivery had a higher severity than delivery by cesarean section. This is similar to research conducted by Gyhagenetal (2013). Severity of moderate to severe SUI was more common after vaginal delivery (21.3%) compared to cesarean section (13.5%) with 95% CI (1.40–2.03).[21]

Based on the distribution of SUI severity, it was found that the severity level of 8.0% occurred at age > 60 years, mild and moderate levels occurred at the age <60 years (44.0%, 48.0%) (Table 1). This result is similar to the Hannestad study which reported that the higher the age of the respondent, the higher the severity of SUI. In women who had SUI under 45 years, 57% had mild

SUI, 31% moderate SUI, and 12% severe SUI while for women between 45 and 59 years (46%, 33%, 21%). In the age group 60 years, 24% mild SUI and 31% moderate SUI, and 44% severe SUI.[7]

In the results of this study (Table 2) the mean level of E2 showed lower result in the moderate SUI than in the severe SUI. The E2 level should be lower in the severe SUI than in the moderate level, by analysis the lower the value of the E2 level indicates the more severe the severity of SUI. The discrepancy in the value of this level was due to the small sample population of 25 respondents so that only two respondents were found with severe SUI severity. To know the value of the lowest E2 level read by our tool is only limited to a value of <9; however, the overall value of E2 levels in this study is in accordance with the menopause criteria, namely E2 <30 pg/ml. The low level of E2 in SUI was supported by Areti et al.'s (2017) study that women with SUI had significantly lower serum E2 levels compared to the control group (17.30 + 8.16 vs 24.22 + 8.99, P < 0.001).[22] This study is also supported by research by Bai et al. (2004) who examined the estrogen receptor in SUI women; the results obtained lower estrogen levels in SUI women compared to controls.[23]

The mean value of FSH levels in the results of this study (Table 2) showed a value of 70.97 mIU/ml in severe SUI, moderate SUI 54.13 mIU/ml and mild SUI 49.70 mIU/ml. This is consistent with the theory that menopausal women have FSH levels > 40 mIU/ml. Analysis of this data shows that the higher the FSH value, the more severe the severity of SUI. As in the study of Iris et al. who conducted a study of FSH levels in post-oovorectomy dogs, the plasma FSH-concentration greatly determines the occurrence of IU. Changes in the anatomy of the ovary due to the aging process that causes sclerosis and a reduced number of primordial follicles, as well as a decreased in the activity of steroid hormone synthesis. The decline in estrogen levels will mark the beginning of the climacteric and continue to decline during menopause, reaching its lowest level during the menopausal period. This causes negative feedback on the hypothalamus, which in turn causes an increase in gonadotropin production, resulting in hypergonadotropin-hypo-gonadism conditions.[3]

Based on Table 3 in this study, the highest mean E2 levels were at age > 60 years and the lowest was at age <60 years. The results of this study are in contrast to the research of Fidel et al. in 2016 who stated that age, parity and duration of menopause were strongly negatively correlated with E2 levels.[24] Likewise, Randolph et al.'s (2004) study reported that E2 levels decreased significantly with age, with a sharper decline at higher age. Similarly, FSH levels increase significantly with age.[25]

In this study (Table 3) menopause duration >10 years had a higher average E2 level compared to menopause duration <10 years, while FSH levels were higher in menopause < 10 years compared to menopause >10 years (Table 3) This study result is in contrast to the study by Fidel et al. (2016) who reported that the duration of menopause was strongly negatively correlated with serum E2 levels, with an r value of -0.880, which indicates that the longer menopause the lower the E2 levels.[19]

Table 2. Mean levels of E2, FSH with severity of SUI

No	SUI Severity	n (%)	Average E2 (pg/mL)	Standard Deviation	Mean FSH (mIU/mL)	Standard Deviation
1	Mild	11(44)	14.25	5.78	49.70	17.61
2	Moderate	12 (48)	7.91	9.64	54.13	19.53
3	Severe	2 (8)	9.14	12.92	70.97	16.96

Table 3. Mean levels of E2 and FSH with age

Characteristics	n (%)	E2 (pg/mL)		FSH (mIU/mL)	
		mean	Standard Deviation	mean	Standard Deviation
Age (Years)					
< 60	10 (40)	10.17	9.05	55.92	21.59
≥ 60	15 (60)	11.21	8.52	51.93	17.04
Duration of menopause (Year)					
< 10	13 (52.0)	11.47	7.32	59.15	19.08
≥10	12(48.0)	13.08	8.12	47.44	16.88

Table 4. The results of the analysis of E2, FSH levels with the severity of SUI

Spearman's Correlation	*P values*	Correlation coefficient
E2 levels with SUI severity	0.084	-0.353
FSH levels with severity of SUI	0.367	0.189

In this study (Table 3), the highest mean E2 levels were found at age > 60 years and the lowest at age <60 years. The results of this study contradict the research of Fidel et al. that said that parity age and duration of menopause had a strong negative correlation with E2 levels.[24] Likewise, a study by Randolph et al. (2004) reported that E2 levels decreased significantly with age, with a sharper decline at higher age. Similarly, FSH levels increase significantly with age.[25]

In this study (Table 3) menopausal duration > 10 years had a higher average E2 level compared to menopause duration < 10 years, while FSH levels were higher in menopause < 10 years compared to menopause > 10 years (Table 3). This study results contrast with research by Fidel et al. (2016) which reported that the length of menopauseduration was strongly negatively correlated with serum E2 levels, with a value of r = -0.880, which indicates that the longer menopause duration the lower the E2 level.[19]

Based on Table 4, the significance value or Sig (2-tailed) was 0.084, meaning that there was no significant relationship between E2 levels and the severity of SUI (p > 0.05). The results of this study are supported by research by Waetjen et al. (2011) who found that changes in endogenous E2 levels from year to year had no effect on the development or worsening of IU in women undergoing the menopausal transition. It is reported that the distribution and density of estrogen receptors can vary in different tissues depending on estrogen exposure and menopausal status. Genotypic variations in the estrogen receptor and estrogen metabolism may lead to different effects of estrogen on IU.[26] The results of this analysis contradict the study by Khanjani (2017) that the decrease of estrogen causes atrophy of the urogenital mucosa, lining of the urethra and bladder so that it can affect the severity of IU.[2] This study is also in contrast to Gopal et al.'s (2008) which reported a sharp decrease in E2 levels over time had significantly lower IU scores. It was reported that women between the ages of 45 and 49 years had significantly higher IU scores than women older than 55 years.[27]

The relationship between the variable levels of E2 and the severity of SUI in this study, obtained a correlation coefficient of -0.353, meaning that the level of strength of the relationship between the variables of severity and levels of E2 (weak relationship).

The direction (type) of the relationship between the E2 level variable and the severity of SUI with the correlation coefficient number in the above results is negative, namely -0.353 so that the strength of the relationship between the two variables is not unidirectional (type of relationship is not unidirectional). Thus, it can be interpreted that the lower the level of E2, the severity of SUI also increases.

Based on the results of the significant relationship between FSH levels and the severity of SUI (Table 4), it is known that the significance value or Sig (2-tailed) of 0.367 means that there is no significant relationship between the FSH level variable and the severity of SUI. The results of this study are similar to those of Elaine et al. who reported that FSH levels changed significantly during the menopausal transition, not differing between those with IU and those without IU.[26]

The relationship between the FSH level variable and the severity of SUI in this study obtained a correlation coefficient of 0.189, meaning that the level of strength of the correlation between the severity variable and FSH levels (very weak relationship).

The direction (type) of the relationship between the FSH level variable and the severity of SUI with the correlation coefficient number in the above results is positive, namely 0.189 so that the strength of the relationship between the two variables is unidirectional (type of unidirectional relationship). Thus, it can be interpreted that the higher the level of FSH, the severity of SUI also increases.

High FSH at menopause due to the gradual loss of ovarian function will reduce its ability to respond to stimulation by pituitary hormones to produce steroid hormones. The pituitary gland will stimulate the ovaries to secrete FSH so that FSH levels will increase due to the loss of the negative feedback mechanism of ovarian steroids and inhibit the gonadotropin release.[24]

In this study, E2 levels and FSH levels did not completely cause the severity of SUI, but were also influenced by parity factors and delivery methods. In a

study conducted by Rami et al. (2020) it was reported that older women, obesity, a history of gynecological surgery, and a history of vaginal delivery and parity had major correlations with the occurrence of SUI.[6,28]

According to research by Jianping et al. (2021) oxidative stress causes apoptosis in granulosis cells from follicles in the ovaries. Apoptosis will cause follicles to become atresia, degenerative and decrease in number. Disorders of folliculogenesis which is described by the small number of follicles and the small diameter of the follicles will interfere with steroidogenesis which results in the formation of sex steroid hormones being disrupted. Low estrogen levels will form fewer FSH receptors in the follicle so that it cannot form a dominant follicle, thus folliculogenesis will also be inhibited. Oxidative stress in the initiation of apoptosis in granulosa cells of primordial follicles and growing follicles can be caused by various stimuli, such as alcohol, radiation and smoking, malnutrition, obesity and overactivity.[29]

The advantage of this study is that there are still not many studies that have raised the topic of the relationship between E2 levels and FSH levels with the severity of SUI using the ISI scoring system in menopausal women. Researchers can also find out the prevalence of SUI in menopausal women at Ulin Hospital Banjarmasin and determine the relationship between E2 and FSH levels with the severity of SUI in menopausal women. The limitation of this study is that the E2 level measurement instrument cannot read E2 levels at levels below 9 (pg/mL) so E2 levels <9 pg/mL, cannot be read on laboratory examination equipment at Ulin Hospital Banjarmasin.

CONCLUSION

There was no significant relationship between E2 and FSH levels with the severity of SUI in menopausal women. It is necessary to do research on other factors that influence the high severity of SUI in menopausal women.

DISCLOSURES

Acknowledgment

The author would like to thank Ulin Hospital Banjarmasin for granting research permission with the contract number 408/LPPM/STIKes-MCB/IX/2020, then to the three supervisors, Dr. dr Pribakti B, SpOG, Subsp. Urogin RE, dr. Wiwit Agung S,N, Sp.PD, Subsp. Ger, and Dr. dr. Meitria S, N, M. Kes for contribution in carrying out this research. The author also thanks all teaching staff of the Obstetrics and Gynecology Study Program, Faculty of Medicine, University of Lambung Mangkurat, Banjarmasin, PASOGIN Faculty of Medicine, University of Lambung Mangkurat, dr. Fithri Nadya, Mawarti, S.ST for the time and energy given during the research.

Conflict of Interest

All authors have no conflict of interest.

Funding Disclosure

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.

REFERENCES

1. Whiteley J, DiBonaventura Md, Wagner JS, Alvir J, Shah S. The impact of menopausal symptoms on quality of life, productivity, and economic outcomes. J Womens Health (Larchmt). 2013;22 (11):983-90. doi: 10.1089/jwh.2012.3719. Epub 2013 Oct 1. PMID: 24083674; PMCID: PMC3820128.
2. Khanjani S. Effect of conjugated estrogen in stress urinary incontinence in women with menopause. International Journal of Clinical Medicine. 2017:8(6):375-85. doi: 10.4236/ijcm.2017.86035
3. Pribakti B. Menopause and stress urinary incontinence. Urogynecology and pelvic reconstruction surgery. PT. Kalimantan Wangi Grafika; 2019. p. 39-46
4. Sountoulidis P. Stress Urinary Incontinence [internet]. Committees Stress Urinary Incontinence. ICS; 2018. Available from: https://www.ics.org/committees/standardisation/terminologydiscussions/sui
5. Ali B. Menopause and andropause. Jakarta: Sarwono Prawirohardjo Bina Pustaka Foundation; 2003. p. 1-138
6. Bodner-Adler B, Bodner K, Kimberger O, et al. Role of serum steroid hormones in women with stress urinary incontinence: a case-control study. BJU Int. 2017;120(3):416-21. doi: 10.1111/bju.13902. Epub 2017 May 29. PMID: 28556379.
7. Hannestad YS, Rortveit G, Sandvik H, et al; Norwegian EPINCONT study. Epidemiology of

Incontinence in the County of Nord-Trøndelag. A community-based epidemiological survey of female urinary incontinence: the Norwegian EPINCONT study. Epidemiology of Incontinence in the County of Nord-Trøndelag. J Clin Epidemiol. 2000 Nov;53(11):1150-7. doi: 10.1016/s0895-4356(00)00232-8. PMID: 11106889.
8. Murphy M, Culligan PJ, Arce CM, et al. Construct validity of the incontinence severity index. Neurourol Urodyn. 2006;25(5):418-23. doi: 10.1002/nau.20246. PMID: 16652379.
9. Ajith AK, Rekha A, Duttagupta S, et al. Prevalence and factors of urinary incontinence among postmenopausal women attending the obstetrics and gynecology outpatient service in a tertiary health care center in Kochi, Kerala. Indian J Community Med. 2019;44(Suppl 1):S30-S33. doi: 10.4103/ijcm.IJCM_29_19. PMID: 31728086; PMCID: PMC6824164.
10. Rahardjo HE. Urinary incontinence in the elderly. Guidelines for the management of urinary incontinence in adults. Jakarta: Indonesian Continence Association (PERKINA); 2012. p. 74-90
11. Zhu L, Lang J, Liu C, et al. The epidemiological study of women with urinary incontinence and risk factors for stress urinary incontinence in China. Menopause. 2009;16(4):831-6. doi: 10.1097/gme.0b013e3181967b5d. PMID: 19240656.
12. Guin G, Choudhary A, Dadhich R. Prevalence of stress urinary incontinence and its associated risk factors amongst females attending tertiary referral centre. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2018;7(6):2115-20. doi: 10.18203/2320-1770.ijrcog20181978
13. Leanza V, Passanisi A, Leanza G. Urinary incontinence: Quality of life and psychological aspects. Urogynaecologia International Journal. 2013;27(1). doi: 10.4081/uij.2013.e3
14. Rhatomy S, Prasetyo TE. Impact of COVID-19 on primary care visits: Lessons learned from the early pandemic period. Journal of Community Empowerment for Health. 2020;3(2): 102-7. doi: 10.22146/jcoemph.57918
15. Aryana S, Astika N, Kuswardhani T. Geriatric opinion. Bali Branch of the Indonesian Medical Gorontology Association. 2018
16. Kirss F, Lang K, Toompere K, et al. Prevalence and risk factors of urinary incontinence among Estonian postmenopausal women. Springerplus. 2013;2:524. doi: 10.1186/2193-1801-2-524. PMID: 24171152; PMCID: PMC3806982.
17. Bray R, Digesu G. Editorial: The Relationship between obesity and urinary incontinence and its causes. Crit Care Obst & Gyne. 2015;1:1. doi: 10.21767/2471-9803.100002
18. Rortveit G, Hannestad YS, Daltveit AK, et al. Age- and type-dependent effects of parity on urinary incontinence: the Norwegian EPINCONT study. Obstet Gynecol. 2001;98(6):1004-10. doi: 10.1016/s0029-7844(01)01566-6. PMID: 11755545.
19. Siregar FG. Estradiol serum levels in menopausal women with and without vasomotor syndrome in Medan. ASPIRE Conference Proceedings. The 6th Congress of the Asia Pacific Initiative on Reproduction (ASPIRE 2016). 2016:4;89-98.
20. Bjelland EK, Hofvind S, Byberg L, et al. The relation of age at menarche with age at natural menopause: a population study of 336 788 women in Norway. Hum Reprod. 2018;33(6):1149-57. doi: 10.1093/humrep/dey078. PMID: 29635353; PMCID: PMC5972645.
21. Gyhagen M, Bullarbo M, Nielsen TF, et al. A comparison of the long-term consequences of vaginal delivery versus caesarean section on the prevalence, severity and bothersomeness of urinary incontinence subtypes: a national cohort study in primiparous women. BJOG. 2013;120(12):1548-55. doi: 10.1111/1471-0528.12367. Epub 2013 Jun 21. PMID: 23786421.
22. Augoulea A, Sioutis D, Rizos D, et al. Stress urinary incontinence and endogenous sex steroids in postmenopausal women. Neurourol Urodyn. 2017;36(1):121-125. doi: 10.1002/nau.22885. Epub 2015 Sep 18. PMID: 26380958.
23. Bai SW, Jung YW, Kwon HS, et al. The role of estrogen receptor, progesterone receptor and p53 in development of stress urinary incontinence. Yonsei Med J. 2004;45(5):885-90. doi: 10.3349/ymj.2004.45.5.885. PMID: 15515200.
24. Reichler IM, Hung E, Jöchle W, et al. FSH and LH plasma levels in bitches with differences in risk for urinary incontinence. Theriogenology. 2005;63(8):2164-80. doi: 10.1016/j.theriogenology.2004.09.047. PMID: 15826681.
25. Randolph JF Jr, Sowers M, Bondarenko IV, et al. Change in estradiol and follicle-stimulating hormone across the early menopausal transition: effects of ethnicity and age. J Clin Endocrinol Metab. 2004;89(4):1555-61. doi: 10.1210/jc.2003-031183. PMID: 15070912.
26. Waetjen LE, Johnson WO, Xing G, et al.; Study of Women's Health Across the Nation. Serum estradiol levels are not associated with urinary incontinence in midlife women transitioning through menopause. Menopause. 2011;18(12):1283-90. doi: 10.1097/gme.0b013e31821f5d25. PMID: 21785372; PMCID: PMC3308014.
27. Gopal M, Sammel MD, Arya LA, et al. Association of change in estradiol to lower urinary tract

symptoms during the menopausal transition. Obstet Gynecol. 2008;112(5):1045-52. doi: 10.1097/AOG.0b013e31818b4cad. PMID: 18978104; PMCID: PMC2813704.

28. AlAzab R, Alomari RA, Khader YS, et al. Stress urinary incontinence among Jordanian women living in rural areas: Prevalence, associated factors and self-management behaviours. Arab J Urol. 2021;19(4):469-72. doi: 10.1080/2090598X.2021.1926751. PMID: 34881064; PMCID: PMC8648036.
29. Wang J, Jia R, Gong H, et al. The effect of oxidative stress on the chicken ovary: Involvement of microbiota and melatonin interventions. Antioxidants (Basel). 2021;10(9): 1422. doi: 10.3390/antiox10091422. PMID: 34573 054; PMCID: PMC8472688.

SYSTEMATIC REVIEW

Updated study of peripartum cardiomyopathy and preeclampsia

I Gusti Ngurah Agung Trisnu Kamajaya*, Made Bagus Dwi Aryana
Mangusada Regional General Hospital, Badung, Bali, Indonesia

ABSTRACT

Objectives: This paper aims to review the literature related to peripartum cardiomyopathy (PPCM) and preeclampsia (PE) in order to know their frequency and relationship and the current knowledge on their pathophysiology and management.
Materials and Methods: The articles reviewed in this study were primary clinical studies published around 2016 and 2021, retrieved using Google Scholar and PUBMED databases. After several evaluations, 14-full-text studies written in English were examined.
Results: Overall prevalence of PE in PPCM cases varied, about 9.9% - 44% in the individual studies. The lactation hormone prolactin and placental-derived anti-angiogenic factor soluble Fms-like tyrosine kinase 1 (sFlt-1), which had been known to be able to cause cardiac dysfunction, were elevated in both PE and PPCM. This partly explained the pathophysiology that the incidence of concurrent PE in women diagnosed with PPCM was four times more than that in the general population.
Conclusion: Epidemiologic studies showed significant overlap between PE and PPCM patients. However, there were not enough good quality data to fully draw conclusions about the relationship between PE and PPCM, whether PE as the independent risk factor of PPCM or an early predictor of PPCM development.

Keywords: cardiomyopathy; peripartum; preeclampsia; pregnancy; cardiovascular disease

ABSTRAK

Tujuan: Tujuan dari tulisan ini adalah untuk meninjau literatur peripartum kardiomiopati (PPCM) dan preeklamsia (PE), untuk menentukan frekuensi dan hubungan antara PPCM dan PE, serta pengetahuan terkini tentang patofisiologi dan manajemennya.
Bahan dan Metode: Artikel yang diulas dalam penelitian ini adalah studi klinis primer yang diterbitkan sekitar tahun 2016 dan 2021, diambil dari database Google Scholar dan PUBMED. Setelah beberapa evaluasi, 14 studi teks lengkap yang ditulis dalam bahasa Inggris diperiksa.
Hasil: Prevalensi PE secara keseluruhan pada kasus PPCM bervariasi, sekitar 9,9% - 44% pada setiap studi. Hormon laktasi prolaktin dan faktor anti-angiogenik yang diturunkan dari plasenta larut Fms-like tyrosine kinase1 (sFlt-1), yang telah terbukti dapat menyebabkan disfungsi jantung, meningkat pada PE dan PPCM, hal ini menjelaskan sebagian patofisiologi kejadian PE pada wanita yang didiagnosis dengan PPCM empat kali lebih banyak dari populasi umum.
Simpulan: Studi epidemiologi menunjukkan tumpang tindih yang signifikan antara pasien PE dan PPCM. Namun, tidak cukup data berkualitas baik untuk sepenuhnya menarik kesimpulan tentang hubungan PE dan PPCM, apakah PE sebagai faktor risiko independen PPCM atau sebagai prediktor awal perkembangan PPCM.

Kata kunci: kardiomiopati; peripartum; preeklamsia; kehamilan; penyakit jantung

***Correspondence:** I Gusti Ngurah Agung Trisnu Kamajaya, Made Aryana, Mangusada Regional General Hospital, Badung, Bali, Indonesia. E-mail: trisnukamajaya@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V30I22022.101-107
● Maj Obs Gin. 2022;30:101-107 ● Received 17 Mar 2022 ● Revised 10 May 2022 ● Accepted 10 Jun 2022 ● Published 1 Aug 2022

INTRODUCTION

Cardiovascular disease (CVD) is one of the causes of maternal and fetal death causes in pregnancy. The smaller part of pregnancy-specific CVD is peripartum cardiomyopathy (PPCM), a rare but serious heart disease.[1] PPCM can be defined as new-onset heart failure that occurred during pregnancy and through several months following delivery, with no previous history of heart disease and abnormality.[2,3]

PPCM is a global disease with epidemiology that varies geographically. The incidence of PPCM in the United States was around 1:1000 to 1:4000 live births, in Japan about 1:20,000 live births, in South Africa at a ratio of 1:1000, meanwhile in Haiti and Nigeria, as the "hot spots", it occurred up to 1% of all pregnancies.[1,2,4] PPCM related to death, the need for a left ventricular assist device, the need for a transplant, and the continued decrease in ejection fraction. The five-year mortality rate among PPCM women in developing countries is approximately 25%, with the infant mortality rate around 50-75%. PPCM accounts for 5% of U.S. women's heart transplants, but in most parts of the world, this is not the available treatment option.[5-7]

The exact etiology of PPCM is still unknown. Hypothetically, the etiology that has been proposed are autoimmunity, viral myocarditis, selenium deficiency, fetal microchimerism that leads to autoimmune response, and genetic factors.[1,7] Recent studies have shown that PPCM is a kind of vascular disease triggered by potent anti-angiogenic agents secreted from the placenta and pituitary gland in the late phase of pregnancy. In this case, the frequent association between PPCM and preeclampsia (PE) is a particular concern because PE can also be caused by the excessive placenta secretion of those anti-vascular factors.[7] Meanwhile, not all women with PE will continue to develop superimposed PPCM. It is not clear whether PE is an early marker for women with high-risk characteristics of future cardiovascular disease or the independent risk factor for future PPCM. Factors that predispose women to PE, such as obesity, metabolic abnormalities, insulin resistance, and endothelial dysfunction, are also found in the risk profile for CVD.[1,7]

The aims of this paper were to review the literature on PE and PPCM, and to determine their frequency of association. This study also aimed to review the current knowledge of its pathophysiology and management.

MATERIALS AND METHODS

The literature included was searched from Google Scholar and PUBMED databases using keyword combinations (MeSH term and free text), including ("PPCM" OR "peripartum cardiomyopathy") AND ("preeclampsia" OR "preeclampsia"). This review included clinical studies that evaluated both peripartum cardiomyopathy and preeclampsia, such as observational studies (cohort, case-control) and case report studies. The articles reviewed were novel studies that were published around 2016-2021. Non-English publications and secondary studies (literature review, systematic review) were excluded. A total of 4,699 publications were obtained from two databases. After several evaluations, 14 studies were examined in this review, showed in Figure 1.

RESULTS AND DISCUSSION

The included studies' information are listed in Table 1. Overall, almost 3 million subjects were included.[1-15] Sample size of the cohort study varied from 21 to 1,088,063 women, with 1 - 35 years study period, and the majority of women were nulliparous. The women's mean age of PPCM patients was around the third decade of life. The overall prevalence of PE in PPCM case varied in the individual studies, which was around 9.9 - 44%.[1-11] The case reports study presents PPCM with PE comorbid case from 22-41 year-old women with the most common symptoms of dyspnea and edema. PPCM was diagnosed in the antepartum, intrapartum, and postpartum periods. Most cases showed rapid changes in the patient's hemodynamic and dramatic improvement from the need for intensive care to sudden cardiac arrest, the return of spontaneous circulation, progressively improved general condition, and gradually increased LVEF after diuretic, anti-prolactin, and other cardiac medicine administration.[12-15]

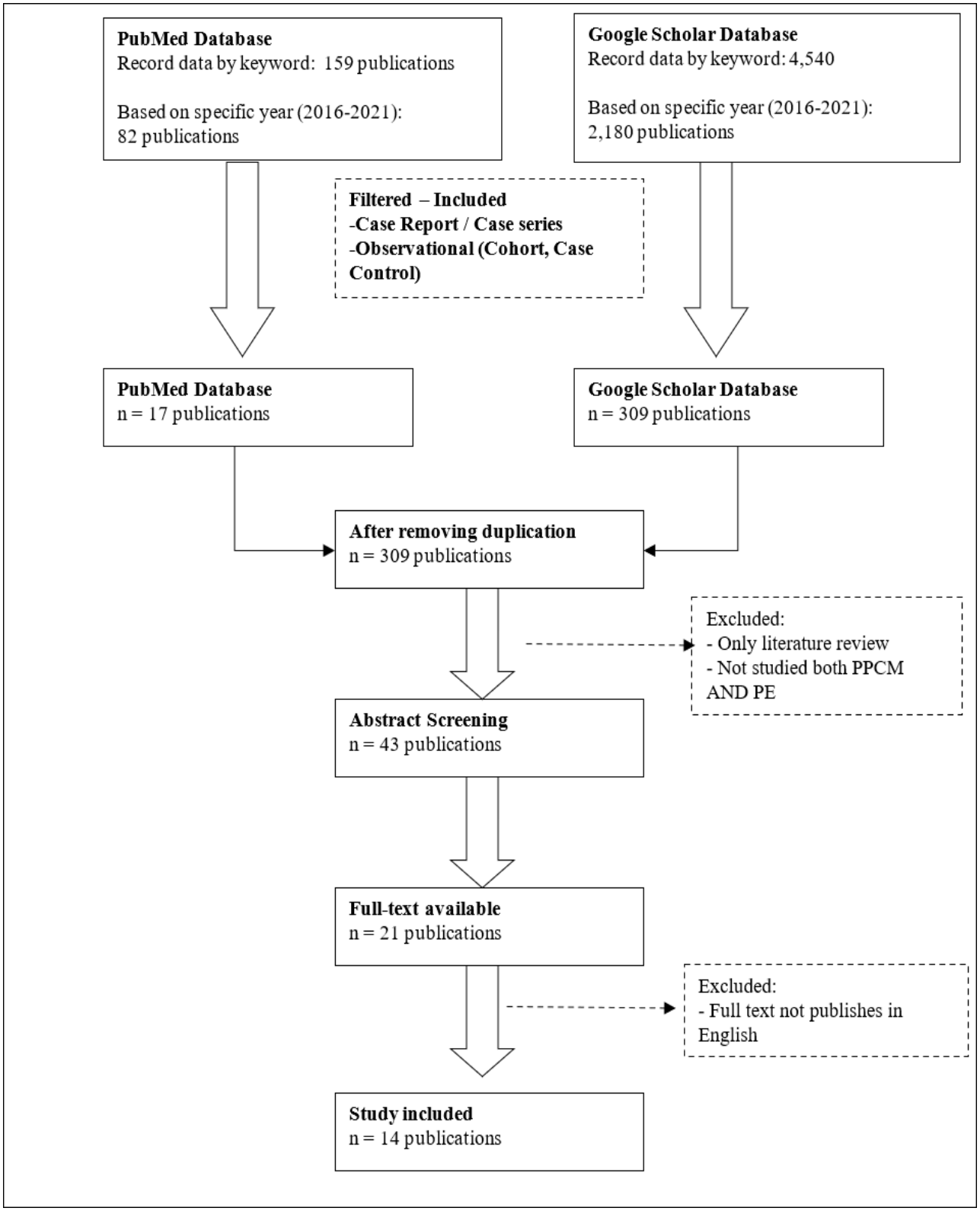


Figure 1. Flowchart of included studies

It has been known that PE and PPCM share in risk factors and characteristics. The prevalence of both diseases is increased in women with a history of diabetes, obesity, multiple pregnancies, and extreme childbearing age.[2-10] The overlap of risk factors between those two diseases indicates that there may be a pathophysiological relationship. Compared with age-matched PPCM in pregnant women without PE, patients with PE have a greater degree of diastolic dysfunction and decreased overall LV tone.[3] There are two main theories about cardiac function alteration or change in PE. The first theory is about the increase of cardiac output (CO) that happens with slightly increased systemic vascular resistance (SVR). The other hypothesis is the theory that the low CO content is accompanied by increased SVR. Literature found that the elevation of the lactation hormone prolactin and placental-derived anti-angiogenic factor soluble Fms-like tyrosine kinase 1 (sFlt-1) were found in both PPCM and PE. It was shown that sFlt-1 could cause cardiac dysfunction.[6,14] Gammill et al. (2018) reported that women with PE are more likely to carry protein-altering mutations in genes related to cardiomyopathy as seen in PPCM. About 55% of the mutations happened in the TTN gene to encode cardiac troponin C and troponin.[5] These may at least partly explain the pathophysiology that the incidence of concurrent PE in a patient diagnosed with PPCM is more than four times higher than that of the general population. It also indicates that genetic variations likely cause geographical differences of the incidence around the world. MicroRNAs (miRNAs) are a class of small noncoding RNAs of ~22 nt in length, which are involved in the regulation of gene expression at the posttranscriptional level by degrading their target mRNAs and/or inhibiting their translation. Numerous biological processes, including cell division, proliferation, apoptosis, and the preservation of normal cellular physiology, are regulated by miRNAs. The heart in embryonic, postnatal, and adult stages all expresses many miRNAs. Heart development disruption, aberrant cardiac cell differentiation, or genetic loss of miRNAs are all linked to cardiac dysfunction.[16,17]

Careful assessment of the risk factors in pregnant women could help prevent PPCM.[18] Reducing the risk for relapse of heart failure in a subject with PPCM with or without a subsequent pregnancy is promoted if there is a more rapid return to LVEF 55% after initial diagnosis, especially if that occurs by 1-year postpartum.[19] Delayed time to diagnosis is associated with lower rates of LV recovery.[20] The diagnosis of PPCM in some studies months following delivery showed that the pre-existing heart disease had been ruled out; no other known etiology for heart failure; and the echocardiography examination showed mode fractional shortening of < 30% or LVEF < 45% or both, and an end-diastolic dimension of > 2.7 cm/m^2. In clinical practice, there are no specific biomarkers that have been used for PPCM. Its presentations are generally similar to common sign and symptoms that appear in heart failure patients, which indicates volume overload and systemic hypoperfusion.[2,11-15]

The management of the new onset of acute heart failure in PPCM is the same as any other cause of acute heart failure. Oxygen treatment is administered carefully in hypoxic patients (SpO_2 < 90%), as overtreatment in non-hypoxic women will lead to vasoconstriction, which can reduce cardiac output. Diuretics are used in the case of fluid retention and pulmonary congestion. Treatment with an inotropic regimen is considered in severe cases of low cardiac output and hypoperfusion. The administration of low molecular weight heparin as the prophylactic anticoagulation is indicated in cases of LVEF < 35% as PPCM may increase risk for thromboembolism. Nitroglycerine as a vasodilator agent is recommended to reduce preload-afterload and increase SV in cases of systolic blood pressure > 110 mmHg. In managing cardiogenic shock, the extracorporeal membrane oxygenation or left ventricular assist device are indicated as a bridge to recovery. The use of bromocriptine in the treatment of cardiomyopathy was reported effective. It works by inhibiting pituitary prolactin secretion. Excessive prolactin secretion is hypothesized to increase levels of the 16 kDa anti-angiogenic prolactin fragment, which has a key role in the pathological mediator of PPCM through impaired myocardial micro vascularization.[11-15] PE as comorbid PPCM is treated as common PE management, including the management in BP control and MgSO4 therapy.[2] Almost all studies reported that the majority of the patients experienced gradual recovery of LV systolic function.[1-15] Lindley et al. reported a higher mortality risk among women with concomitant PE and PPCM than those with PPCM without PE.[6]

Table 1. Information of included studies evaluating peripartum cardiomyopathy and preeclampsia

Authors, Year	Type of Study Number of sample/ Region (Period)/ Age	Result and Reported Data
Malhamé et al., 2019[1]	Cohort n = 1,024,035 pregnancies U.S.A (2011 – 2014) 15–55 years (31.8 ± 6.8)	-64,503 (6.3%) had PE -874 had PPCM (283 with PE; 591 without PE) -Cumulative incidence of PPCM was 1:1172 deliveries -Cumulative incidence of PPCM among PE was 1:228 deliveries - Women with PE-PPCM had a higher risk of major adverse cardiovascular events (MACE) than women PPCM without PE (adjusted RR 1.29, 95% CI [1.06, 1.57])
Ersbøll et al., 2016[2]	Cohort n = 619 084 deliveries Denmark (2005-2014) ≥18 years (31.7 ± 6.3)	-61 women (1:10,149 deliveries) meet EORP PPCM registry's criteria. -33 / 61 PPCM patients have hypertensive disorder of pregnancy -Mean duration from delivery to diagnosis: 25±44 days -Majority recovered LVEF within one year
Ersbøll, et al., 2018[3]	Cohort n = 84 women Denmark (2005-2014) ≥18 years (30.7 ± 6.0)	-3 groups age-matched: PPCM, severe PE, uncomplicated pregnancy - In 91 months median time follow-up, 85% PPCM group have no heartfailure symptoms - PPCM group's mean LVEF was normal (62%), but significantly (P< 0.0001) lower than uncomplicated pregnancies group (67%) andPE group (69%)
Krishnamoorthyet al., 2016[4]	Cohort n = 4859 USA (2009-2010) 15–60 years (30.3±0.2)	-Prevalence of PPCM was 0.04% (1:2367) -78% diagnose at postpartum, 18% in peripartum, 4% antepartum -PE found in 9.9% PPCM patient -PPCM was more common in African-Americans (43.9%)
Lindley et al., 2017[6]	Cohort n = 39 patient PPCM Barnes (2004-2014) 27.4±7.4 years	-44% women (17/39) with PPCM had PE -During one-year follow up, patients with PE had worse event-freesurvival (4/15 with vs. 1/17 without PE, p= 0.16)
Behrens et al., 2019[8]	Cohort n = 1,088,063 women / 2,078,822 pregnancies Denmark (1978-2012)	-39/126 (30%) PPCM women had gestational hypertension -Risks of PPCM were significantly higher in women with gestational hypertension than in women with normotensive pregnancies

PE=preeclampsia ; PPCM=peripartum cardiomyopathy; SC= sectio-caesarian; LVEF=left ventricular ejection fraction

CONCLUSION

Epidemiologic studies show significant overlap between PE and PPCM patients. However, there are not enough data of good quality to fully draw conclusions about the relationship between PE and PPCM, whether PE is the independent risk factor of PPCM or an early predictor of PPCM development. The diagnosis by exclusion and high index of suspension is the key to identifying this rapidly progressing condition. Early diagnosis and close monitoring of the patients would improve the patient's outcome. Most cases showed gradually improved general condition after diuretic, anti-prolactin, and other cardiac medicine administration after PPCM was diagnosed. A fresh perspective into the role of genetics, molecular pathogenesis, and clinical studies has yielded potential disease-specific therapies for PPCM and PE, but many questions remain unanswered.

DISCLOSURES

Acknowledgment

The author thanks dr. Made Aryana for helping and supporting in the making of this paper.

Conflict of Interest

The authors declare there is no conflict of interest.

Funding Disclosure

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.

REFERENCES

1. Malhamé I, Dayan N, Moura CS, et al. Peripartum cardiomyopathy with co-incident preeclampsia: A cohort study of clinical risk factors and outcomes among commercially insured women. Pregnancy Hypertens. 2019;17:82-8. doi: 10.1016/j.preghy.2019.05.014. Epub 2019 May 9. PMID: 31487662.
2. Ersbøll AS, Damm P, Gustafsson F, et al. Peripartum cardiomyopathy: a systematic literature review. Acta Obstet Gynecol Scand. 2016;95(11):1205-19. doi: 10.1111/aogs.13005. PMID: 27545093.
3. Ersbøll AS, Bojer AS, Hauge MG, et al. Long-term cardiac function after peripartum cardiomyopathy and preeclampsia: A Danish nationwide, clinical follow-up study using maximal exercise testing and cardiac magnetic resonance imaging. J Am Heart Assoc. 2018;7(20):e008991. doi: 10.1161/JAHA.118.008991. PMID: 30371259; PMCID: PMC6474952.
4. Krishnamoorthy P, Garg J, Palaniswamy C, et al. Epidemiology and outcomes of peripartum cardiomyopathy in the United States: findings from the Nationwide Inpatient Sample. J Cardiovasc Med (Hagerstown). 2016;17(10):756-61. doi: 10.2459/JCM.0000000000000222. PMID: 25943626.
5. Gammill HS, Chettier R, Brewer A, et al. Cardiomyopathy and preeclampsia: shared genetics? Circulation. 2018;138(21):2359-66. doi: 10.1161/CIRCULATIONAHA.117.031527
6. Lindley KJ, Conner SN, Cahill AG, et al. Impact of preeclampsia on clinical and functional outcomes in women with peripartum cardiomyopathy. Circ Heart Fail. 2017;10(6):e003797. doi: 10.1161/CIRCHEARTFAILURE.116.003797. PMID: 28572214; PMCID: PMC5520674.
7. Bello N, Rendon ISH, Arany Z. The relationship between preeclampsia and peripartum cardiomyopathy: a systematic review and meta-analysis. J Am Coll Cardiol. 2013;62(18):1715-23. doi: 10.1016/j.jacc.2013.08.717. Epub 2013 Sep 4. PMID: 24013055; PMCID: PMC3931606.
8. Behrens I, Basit S, Lykke JA, et al. Hypertensive disorders of pregnancy and peripartum cardiomyopathy: A nationwide cohort study. PLoS One. 2019;14(2):e0211857. doi: 10.1371/journal.pone.0211857. PMID: 30785920; PMCID: PMC6382119.
9. Chaitra S, Kumar S, Malapure P, et al. Peripartum cardiomyopathy: A 5-year retrospective study in a tertiary care center, India. Int J Clin Obstet Gynaecol 2019;3(2):206-9. DOI: 10.33545/gynae.2019.v3.i2d.35
10. Isogai T, Matsui H, Tanaka H, et al. In-hospital management and outcomes in patients with peripartum cardiomyopathy: a descriptive study using a national inpatient database in Japan. Heart Vessels. 2017;32(8):944-51. doi: 10.1007/s00380-017-0958-7. Epub 2017 Feb 23. PMID: 28233090.
11. Karaye KM, Ishaq NA, Sa'idu H, et al; PEACE Registry Investigators. Incidence, clinical characteristics, and risk factors of peripartum cardiomyopathy in Nigeria: results from the PEACE Registry. ESC Heart Fail. 2020;7(1):235-43. doi: 10.1002/ehf2.12562. Epub 2020 Jan 28. PMID: 31990449; PMCID: PMC7083508.
12. Hoy M, Flavin K, Prasad V. A complex obstetric case. J Intensive Care Soc. 2017;18(3):239-43. doi: 10.1177/1751143717700910. Epub 2017 Apr 3. PMID: 29118838; PMCID: PMC5665137.
13. Hakata S, Umegaki T, Soeda T, et al. Bromocriptine use for sudden peripartum cardiomyopathy in a patient with preeclampsia: a case report. JA Clin Rep. 2019;5(1):38. doi: 10.1186/s40981-019-0256-8. PMID: 32026046; PMCID: PMC6966983.
14. Sethi D, Kumar N. Peripartum cardiomyopathy with preeclampsia in a parturient: A case report with literature review. Turk J Emerg Med. 2020;20(4):202-5. doi: 10.4103/2452-2473.297467. PMID: 33089031; PMCID: PMC7549512.
15. Chou MH, Huang HH, Lai YJ, et al. Cardiac arrest during emergency cesarean section for severe preeclampsia and peripartum cardiomyopathy. Taiwan J Obstet Gynecol. 2016;55(1):125-7. doi: 10.1016/ j.tjog.2015.12.010. PMID: 26927264.
16. Espinoza-Lewis RA, Wang DZ. MicroRNAs in heart development. Curr Top Dev Biol. 2012;100:

279-317. doi: 10.1016/B978-0-12-387786-4.00009-9. PMID: 22449848; PMCID: PMC4888772.
17. Pang JKS, Phua QH, Soh BS. Applications of miRNAs in cardiac development, disease progression and regeneration. Stem Cell Res Ther. 2019;10(1):336. doi: 10.1186/s13287-019-1451-2. PMID: 31752983; PMCID: PMC6868784.
18. Scardovi AB, De Maria R. Peripartum cardiomyopathy: Challenges and solutions. 2017; 8: 31-40. doi: 10.2147/RRCC.S103577
19. Fett JD. Promoting full recovery and improved relapse-free prognosis in the diagnosis and treatment of peripartum cardiomyopathy. J Am Coll Cardiol. 2020;76(20):2365-7. doi: 10.1016/j.jacc.2020.09.599. PMID: 33183510.
20. Lewey J, Levine LD, Elovitz MA, et al. Importance of Early Diagnosis in Peripartum Cardiomyopathy. Hypertension. 2020;75(1):91-7. doi: 10.1161/HYPERTENSIONAHA.119.13291. Epub 2019 Nov 11. PMID: 31707840; PMCID: PMC6906246.

MAJALAH OBSTETRI & GINEKOLOGI
Journal of Obstetrics & Gynecology Science

SUBSCRIPTION FORM

To subscribe to the journal and/or to purchase individual issue of the journal, please complete this form and send the completed form to e-mail address: mog@journal.unair.ac.id.

Name : .....
Institution : .....
: .....
Address : .....
: .....
Phone : ..... E-mail : .....

I intend to :

☐ subscribe to the journal for ..... publication year(s) starting from publication year of ..... to ..... with payment* in the following currency :
- ☐ IDR 300,000 per publication year
- ☐ USD 30 per publication year

☐ Purchase individual issue of the journal. Please specify the edition/year of the journal and the quantity of the issue(s) :

No.	Edition no.	Year	Quantity

No.	Edition no.	Year	Quantity

with payment* in the following currency :
- ☐ IDR 100,000 per issue
- ☐ USD 10 per issue

*the mentioned prices have not included the delivery fee

The ordered journal(s) will be delivered to :

Name : .....
Institution : .....
: .....
Address : .....
: .....
Phone : ..... E-mail : .....

On the payment method and other related costs, kindly contact Ms. Priska Dwi Wahyurini, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Hospital, Jalan Prof dr. Moestopo 6-8, Surabaya 60286, Indonesia. Phone: +6281227593208. E-mail: mog@journal.unair.ac.id

Date of order (DD/Month/YYYY) : .....

Signature : .....


0854 0386
9 772598 101001