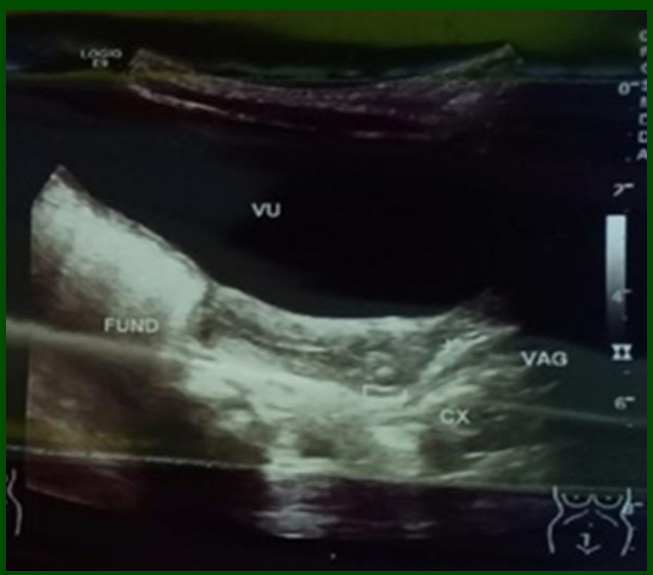
DOAJ DIRECTORY OF OPEN ACCESS JOURNALS

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE
Vol. 30 No. 3 December 2022



USG of the cervix of a patient with organic Central Precocious Puberty (CPP)

Original Research

- The coping process and acceptance among women with cervical cancer
- Cobas® 4800 HPV test is accurate for detecting high risk Human Papillomavirus from urine samples at dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia
- Maternal and neonatal outcomes in delivery with diagnosis of antepartum hemorrhage due to placenta previa at a tertiary hospital in Surabaya, Indonesia
- Serological description of neonatal umbilical cord blood from pregnant women confirmed with positive COVID-19 by RT-PCR at Rumah Sakit Umum Pusat H. Adam Malik, Medan, Indonesia

Case Reports

- Comprehensive management of pregnant woman with Sjögren's syndrome
- Psychological aspects of precocious puberty child during the COVID-19 pandemic

Review Article

- The role of antihypertensive drugs in patients with preeclampsia and how to prevent it

Systematic Review

- The role of adequate vitamin D levels in the menstrual cycle of reproductive-age women

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. 3 December 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. 3 December 2022

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

CONTENT

ORIGINAL RESEARCH :

1. The coping process and acceptance among women with cervical cancer
   Ummu Kulsum, Dwi Izzati, Eighty Mardiyan Kurniawati, Sulistiawati ..... 108 – 115

2. Cobas® 4800 HPV test is accurate for detecting high risk Human Papillomavirus from urine samples at dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia
   Indiarto Wityawan, Andrijono, Aria Kekalih ..... 116 – 121

3. Maternal and neonatal outcomes in delivery with diagnosis of antepartum hemorrhage due to placenta previa at a tertiary hospital in Surabaya, Indonesia
   Sarah Nia Amru, Indra Yuliati, Philia Setiawan ..... 122 – 127

4. Serological description of neonatal umbilical cord blood from pregnant women confirmed with positive COVID-19 by RT-PCR at Rumah Sakit Umum Pusat H. Adam Malik, Medan, Indonesia
   Benjamin Sihite, Makmur Sitepu, Khairani Sukatendel, Sarma Nursani Lumbanraja, Iman Helmi Effendi, Rizki Yaznil , Edy Ardiansyah ..... 128 – 133

CASE REPORTS :

5. Comprehensive management of pregnant woman with Sjögren's syndrome
   Giovanny Azalia Gunawan, Adinda Ayu Dyah Rahadina, Budi Prasetyo ..... 134 – 138

6. Psychological aspects of precocious puberty child during the COVID-19 pandemic
   Nurul Ima Suciwiyati, Nur Rochmah, Muhammad Faizi, Fadhil Abiyyu ..... 139 – 145

REVIEW ARTICLE :

7. The role of antihypertensive drugs in patients with preeclampsia and how to prevent it .....
   I Gde Sastra Winata, I Wayan Agus Surya Pradnyana, Maria Septiana Parmonang Aroean 146 – 153

SYSTEMATIC REVIEW :

8. The role of adequate vitamin D levels in the menstrual cycle of reproductive-age women
   Ahila Meliana, Hana Salsabila, Bendix Samarta Witarto, Manik Retno Wahyunitisari ..... 154 – 160

Cover :
USG of the cervix of a patient with organic Central Precocious Puberty (CPP)

This edition page 140

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 coping process and acceptance among women with cervical cancer

Ummu Kulsum[1], Dwi Izzati[1]*, Eighty Mardiyan Kurniawati[2], Sulistiawati[3]
[1]School of Midwifery, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
[3]Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Article Info
Received Mar 18, 2022
Revised Jul 17, 2022
Accepted Aug 20, 2022
Published 1 Dec, 2022

Corresponding author:
Dwi Izzati
dwi_izzati@fk.unair.ac.id

Keywords:
Coping process
Acceptance
Cervical cancer

ABSTRACT

Objective: To explore how the process of coping among women with cervical cancer.

Materials and Methods: This study used a qualitative method with phenomenological design. Data were obtained through in-depth interviews. The sampling technique used was purposive sampling. Seven participants were selected according to the inclusion and exclusion criteria. Data analysis techniques used were transcribing verbatim data, data coding, categorizing, developing thematic contexts, and interpreting data.

Results: The results of this study revealed that social support, hobbies, and spirituality helped women to cope with their illnesses. The results of this study have implications for health care providers to provide holistic care to women with cervical cancer.

Conclusion: The process of coping and acceptance of the condition was different among women with cervical cancer, which was influenced by social support, hobbies, and spirituality.

Cite this as: Kulsum, U., Izzati, D., Kurniawati, E.M. & Sulistiawati (2022). The coping process and acceptance among women with cervical cancer. Majalah Obstetri & Ginekologi, 30(3), 108-115. https://doi.org/10.20473/mog.V30I32022.108-115.

INTRODUCTION

Cervical cancer is the second most common cancer in women aged 15 to 44 years.[1] In Indonesia, more than 50% of cervical cancer cases resulted in death.[2] Cancer mortality is estimated to increase due to the tendency for patients to seek treatment at an advanced stage when treatment can no longer provide maximum results.[3] At Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, the number of new cervical cancer cases is larger than other gynecologic cancers.[4]

Gynecologic cancer presents challenges associated with difficult treatment, adverse side effects, and poor prognosis.[5] In addition, diagnosis and treatment of cervical cancer present psychological challenges.[6] Cancer-related stress may arise within multiple dimensions. They include physical, psychosocial, spiritual, existential,[7] and economic dimensions.[8] In early diagnosis, rejection from the patient often occurs.[9] The side effects of the treatment in the form of surgery, radiotherapy, or chemotherapy, usually result in health problems and psychologically lead to rejection.[10] At an advanced stage, often there is death concern as well as relationship changes with family or spouse that may cause stress and increase tension.[7] Naturally, various efforts will be taken by individuals to get through these stressful situations. The coping process is intended to make the body adapt efficiently to stressful experiences.[11] The coping process in cervical cancer

patients starts from the onset of abnormal symptoms, followed by diagnosis and treatment, and then subsequent acceptance of the condition.[12]

Research shows that the major focus of medical cancer is on the treatment with the indicators of success are only seen from the patient's recovery, survival expectations, and complications, while the psychosocial effects of treatment such as spiritual needs tend to be neglected.[13,14] However, cancer survivors are looking for a holistic approach that sees them as individuals with unique attributes.[15] Therefore, the exploration of how women cope with cervical cancer is prominent to study. The purpose of this study was to explore the coping process of women with cervical cancer to the acceptance of the condition.

MATERIALS AND METHODS

This qualitative study applied a phenomenological design to explore the coping process of women suffering from cervical cancer in Dr. Soetomo General Academic Hospital, Surabaya. Data were obtained through in-depth interviews. The sampling technique used was purposive sampling. Seven participants were selected based on the inclusion and exclusion criteria. The inclusion criteria were: a) cervical cancer patients who were undergoing treatment at Dr. Soetomo Hospital (outpatient and inpatient), b) cervical cancer patients who were generally in good medical condition, and c) willing to be a participant in the study. Meanwhile, the exclusion criteria were cervical cancer patients with communication problems, either due to decreased physical condition or language barriers. The data analysis techniques used were transcribing verbatim data, coding, categorizing, developing thematic contexts, and interpreting data.

RESULTS AND DISCUSSION

Participants' characteristics

The participants' age ranged from 34 to 52 years old. There were four participants with the elementary school as their latest education levels. There was each one participant with the latest education level of junior high school, senior high school, and Bachelor's degree. Their occupations vary such as housewife, trader, farmer, entrepreneur, and two participants worked as private employees. Six participants were married and one participant was divorced. All of them used BPJS. Three participants were diagnosed with stage IIB cervical cancer and the other four were diagnosed with stage IIIB cervical cancer. The length of time since the participants were first diagnosed with cervical cancer varied from 3 months to more than 1 year (Table 1).

Table 1. Overview of the participants of the study

Code	Age (years)	Education Level	Occupation	Marital Status	Health Insurance	Diagnosis	Cervical Cancer Diagnosis
P1	47	Elementary School	Housewife	Married	BPJS	Stage IIB Cervical Cancer Chemotherapy I	3 months
P2	35	Elementary School	Trader	Married	BPJS	Stage IIB Cervical Cancer Post Chemotherapy + Post ER 35 times	More than 1 year
P3	50	Elementary School	Farmer	Married	BPJS	Stage IIIB Cervical Cancer Pro Chemotherapy II	4 months
P4	34	Elementary School	Farmer	Widowed	BPJS	Stage IIB Cervical Cancer + Active Fluxus + Anemia + Pro Cito ER	3 months
P5	49	Junior High School	Employee	Married	BPJS	Stage IIIB Cervical Cancer + Pro Chemotherapy I + Pro ER	More than 1 year
P6	44	Senior High School	Employee	Married	BPJS	Stage IIIB Cervical Cancer + Anemia + Pro Chemotherapy I + Pro ER	3 months
P7	52	Bachelor's Degree	Entrepreneur	Married	BPJS	Stage IIIB Cervical Cancer + Pro Chemotherapy IV + Pro ER	6 months

Feelings during the early phase of being diagnosed with cervical cancer

It was found that the participants' feelings when initially diagnosed with cervical cancer were a shock, sadness, fear, and denial. Direct observation during the interview exposed different expressions shown by the seven participants. Participants P2, P3, and P6 were calmer and more relaxed in showing their feelings.

> *"I was very sad. Why should this be? I've never been sick before." (P2)*

Meanwhile, participants P1, P4, P5, and P7 showed a more emotional expression (crying).

> *"I was so shocked … how come I suddenly got this illness. I have never been ill. I kept getting shocked (she started crying); I did not have a calm mind at home. I was sad…" (P1)*

Social support

In this study, it was revealed that participants got social support from family, healthcare providers, peer groups, and their co-workers.

Family support

All participants obtained support from their families. The support was in the form of emotional support, mentoring, attention, and assistance such as basic needs (food, mobilization), and financial support.

> *"We want to be cured; money can be sought." (P1, P2, P3, P4)*
> *"I went here with my husband" (P3, P5, P7).*
> *"I am cheered up. ``All people, my family said 'you should have the chemotherapy, you must be healed'. Everyone asked me to do it (the chemotherapy). My mother-in-law said' you should have chemotherapy…' 'You are not the only one that suffers from it. Please cheer up'. My family has been getting more attention since I was sick. Before going to work, they fed me since usually I didn't have an appetite" (P5)*

One participant thought that she had a lack of support from her husband. She said:

> *"(My husband was) Impatient, I was peeved. It was not my illness that pissed me off, it was my husband" (P6)*

However, P6 got support from her big family, such as sisters, brothers, and parents-in-law.

> *"My parents-in-law helped me. My children and their grandparents (parents-in-law). I do not cook often, my mother cooked for us. My sister stay with me here" (P6)*

Family factors motivated participants to fight the disease as expressed by participants P2, P4, P5, and P6. Their children were their best motivation for treatment.

> *"My children are still young. I need to recover to be able to work again…" (P4).*
> *"I pity my children and my children-in-law. They worked and drove for me. I pity them if my treatment got canceled" (P5)*
> *"Family. And God." (P6)*

Support from healthcare providers

Five participants said that health workers provided emotional support, information about treatment, and assistance. Emotional support and information about the treatment were perceived by participants P1, P2, P5, and P6.

> *"The health workers (in the gynecology room) took me out for a walk and gave me pieces of advice. They advised me to be patient … the doctors also gave me advice." (P1)*

Participant P5, who had postponed the chemotherapy about a year ago due to ignorance of the therapeutic procedure, at the time of this study, was prepared thanks to family support and information from health workers.

> *"The doctor said 'cheer up' do not be afraid, do not listen to what people said … the staff said I should take meal regularly" (P5)*

The assistance given by the health care providers is reflected from the statement of participant P7.

> *"…The first time I registered, I got help, 'please write here, and write the data'; the workers took me to the locket, to POSA (one-stop oncology poly). They were really helpful" (P7)*

Support from peer group

Support from other cervical cancer patients was very helpful for participants in coping with their illness as reflected from the statement of P1, P2, P3, and P5.

> *"After I arrived here at the foundation, there were a lot of friends (cervical cancer patients). At the foundation, I was more relaxed. Many of them were in worse condition than me. I thank God." (P1)*
> *"They support me, 'Do not be afraid. We can. There were friends being in chemotherapy, surgery. They said I should not fear chemotherapy, it is ok" (P3, P5).*
> *"There was a group (WhatsApp group). A place we can share. Up until now. I am happy … to communicate with them. They give me hope. If we are together I was not anxious. (P2)*

However, referring to participant P2, in the WhatsApp group of cancer survivors she was in, there were some friends who chose to leave the group when they heard the sad news about one of their group members' deaths. The sad news scared the survivor.

> *"There was a member who left the group (WhatsApp group). I asked, 'why did you leave?'. "She said she was scared. My best friends were all dead'. "(P2)*

Social support from the workplace

Participants also got support from their workplace. This is as expressed by participants P5 and P6. They are private employees.

> *"My boss went to my house, his niece, too. '(if you want) continue working, do not force yourself, if you are tired just sit down, many of your friends will help'. However, in the end, I stopped working, it was difficult" (P5 cried). (P5)*
> *"The HRD (staff) summoned me. There was a special policy. Since I need to have the chemotherapy, they would not make it difficult for me" (P6)*

Hobbies

Some participants said that doing activities they like (hobbies) helps overcome negative feelings and helps them cope with their pain. This was revealed by the participants P5 and P7.

> *"… I want a radio so I would not think about it (the illness). Sometimes, I was sad. I bought a radio. I asked my husband to buy the radio, to avoid confusion or boredom. To forget it, then I fell asleep" (P5)*
> *"I went for a morning walk in front of my house. If I wanted, I cooked, made cookies, saw plants to avoid boredom. I feel happy whenever I see plants"(P7)*

Spiritual

Most of the participants said that spirituality helps participants in coping with their illness, as stated by participants P1, P2, P3, P4, P6, and P7.

> *"After sholat (praying), I feel relaxed" (P7)*

However, each patient has different interpretations of cervical cancer. Participants P1 and P2 believed that the cervical cancer was the test for them (P1, P2).

> *"I have to face it; this is a test for me. I should accept this. I should be sincere. I should be courageous. This is the sign of God's love to us" (P1)*

Participants P1, P3, and P6 felt that the pain was a chance to get closer to God.

> *"It is the time for us to surrender, to be better. Illness can change people" (P6).*

Meanwhile, participants P5 expressed anger and neglect she felt towards God.

> *"There was once I thought, 'how come I was given a disease like that'. My child said, ``What can we do? It is His decision." (P5)*

Acceptance

The stages of cervical cancer acceptance are different for each participant. Participants P1, P2, P3, P4, P6, and P7 said they immediately accepted their condition and immediately sought medical treatment after being diagnosed with cervical cancer.

> *"Slowly but surely I became courageous. After coming to the foundation, I felt relieved, I was not afraid to get treatment. I should get treatment. There was no fear, no sadness. There was a bit of sadness, but it disappeared. I did not really remember" (P1)*

Different experiences applied to participant P5 that she took longer to accept the condition. This participant had been diagnosed with cervical cancer about one year ago but was undergoing medical treatment when the study was conducted.

"I was ready not long ago; I did not want to get treatment before". (P5)

In this study, participants got support from family, healthcare providers, peer groups, and the workplace. Participants got major support from their families. Based on the Family Caregiver Alliance in Wood et al. (2015),[16] families are the main caregivers, which takes up to 83% of all caregivers, who care for family members who got the illness, either physically or mentally. Family support is crucially needed by cervical cancer patients after cancer diagnosis and treatment. This support is either directly or indirectly. Direct care is carried out directly to patients, such as symptom management, emotional support, administering medication, and assistance for basic needs such as mobility, eating, and bathing. Indirect care such as medication, transportation, replacing patient duties, coordination, and control schedules, as well as helping with medical and financial bills.[17] Family support can be obtained from parents, spouses, siblings, or from other family members outside the nuclear family. Family support enables the family to function properly with full capabilities and resources to improve the adaptation and health of family members.[18] In this study, all participants received support from their family members. Although P6 felt that she did not get enough support from her husband, she received support from his parents and siblings. Participant P6 said that her husband showed more emotional responses than she did, such as fear, confusion, and crying. The patient and the family can experience denial or rejection. This is in accordance with a study by Wood et al.[16] that in addition to causing stress to patients, the diagnosis of cancer also causes stress for the family. A study by Kusumaningrum et al.[19] also yielded similar results that the diagnosis of cervical cancer has become a huge burden for both the patient and the family. Family members and the patients both struggle to fight cancer.[20]

Family factors, especially children, became the main motivation for most of the participants to face their illness, as conveyed by participants P2, P4, P5, and P6. This is in line with a study by Deshmukh et al. that close family members, especially children or mothers, are key motivators for patients to complete treatment.[21]

There were five participants who said that they received support from healthcare providers. The support was in the form of emotional support, information about treatment, and assistance. Every cancer patient or family has various desired information regarding the disease. Information about medical diagnosis and management is expected in the early stages of diagnosis of cancer.[22] Support from health professionals in the form of counseling and motivation is important for patients to comply with and complete treatment.[21]

The peer group was one of the supporters of cervical cancer patients. Four participants got support from peer groups and two participants got support from the workplace. Humans are social beings. We definitely need interaction to achieve social adjustment. Social interaction is the relationship between individuals.[23] Participant P2 had a WhatsApp group consisting of fellow cervical cancer survivors. Through this media, survivors exchange experiences about the side effects of therapy, how to treat side effects, encourage each other, exchange information about control schedules and administrative processes. Meeting people who have had the same disease and have had similar experiences will be of great benefit and help to the patient.[24] Participants P1, P3 and P5 said meeting a group of fellow cancer survivors made them courageous to start treatment and helped them to cope with fears of the therapy. This is in line with a study by Weis,[25] that peer groups can help patients overcome the fear of the unknown and the fear of death by getting to know each other and sharing their experiences. However, not all survivors felt this way, based on the experience of participant P2, some cervical cancer survivors chose to leave the group because they were more stressed. Information about the sad news experienced by one cancer survivor scared the patients. As social beings, there is a reciprocal relationship that can influence individuals,[23] just as bad news also negatively affects the patient's psychological condition.

Thus, positive information and support from the cancer survivor community are essential for the patient's emotional and social well-being for enhancing short-term and long-term recovery.[26] Whereas bad news can cause additional stress for the patient.

Support from the workplace was described by participants P5 and P6 who worked as private employees. Cervical cancer patients encountered lost productive days due to the long duration of hospitalization.[27] Hence, the support from the workplace is very helpful to cope with their illness. According to Deshmukh et al.[21], apart from family support and nutritional support, workplace support is one of the patient's motivations to complete treatment, especially if the patient is the breadwinner (Figure 1). Some patients with long duration of treatment struggle with financial issues and need support to fulfill daily expenses.

The findings in this study confirmed the study conducted by Deshmukh et al.[21] that in a long duration of treatment, patients need support from family members, peer groups, health care providers, and the workplace.

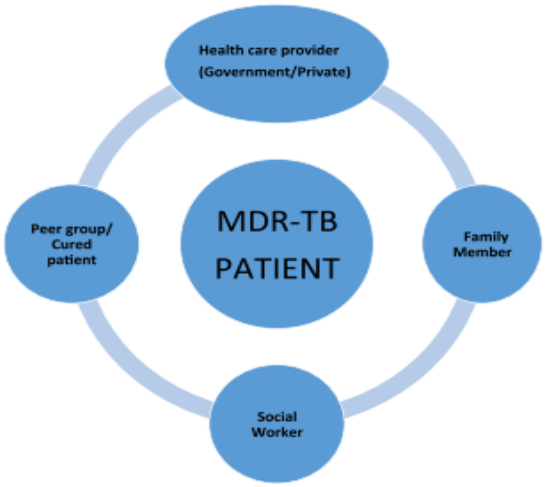


Figure 1. Patient's support group (Deshmukh, et al., 2018)

In addition to social support, some participants said that doing activities they like (hobbies) can overcome negative feelings and help them cope with their pain as described by participants P5 and P7.

Rasmun wrote that to overcome psychological problems, individuals can use short-term and long-term coping methods. One of the short-term coping methods is to switch to other activities in order to forget the problems, such as doing hobbies/activities that one likes,[28] be it indoors or outdoors, whether with physical activity or not, which can be entertaining, provide satisfaction, and induce relaxation.[29] Referring to Fujiwara et al.[30] individuals who like sports and cultural activities will benefit physically and mentally. It can minimize depression and improve physical health.

The phases of cervical cancer acceptance are different for each patient and require different times. Most of the participants said they quickly accepted their condition and faced the disease constructively by directly seeking treatment at a referral hospital (Dr. Soetomo General Academic Hospital). Acceptance is the basis for everyone to accept the reality of life, all good or bad experiences. Kralik et al. (2010) stated that the way a person views himself and his illness affects a person in adjusting to the self-care that must be carried out.[31] In addition, other factors that can affect the adjustment and acceptance of cervical cancer that exacerbate psychological conditions are poor prognosis, difficult living conditions, social situations, young age, and trauma.[10] Anxiety in patients is also influenced by educational factors[32] as participants with higher education tend to be more concerned and look for more information. They have more awareness regarding their cancer. Participants have more awareness and understanding regarding cancer they suffer from and the risk to their bodies. Nevertheless, this is what causes anxiety in highly educated participants to increase. Munkres et al., as cited in Bowman et al.,[20] found that one of the conditions that worse stress on cancer is a low-socioeconomic status and the number of symptoms related to the disease. Participant P5 said that she had a financial problem as her physical condition forced her to stop working and at the same time, her house rent had to be paid. Anger and feeling neglected are some of the factors that caused P5 to be more emotional and dramatic when diagnosed with cervical cancer. The spiritual factors also affect acceptance of cervical cancer. Spiritual activity has been associated with lower stress levels, reduced anger and anxiety, and social isolation as well as better adjustment to their condition.[24,33]

CONCLUSION

A cervical cancer diagnosis is considered a tragedy that creates a stressful situation for a woman, not only due to the physical constraint but also because of psychosocial, economic, spiritual, and existential challenges. To be able to overcome this, women need support from family, peer groups, health care providers, and the workplace. In addition, in order to overcome negative feelings, women should have hobbies and get closer to God. The findings in this study are expected to be a reference for qualitative studies for health care providers to provide holistic care for women with cervical cancer.

DISCLOSURES

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

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. WHO. Cancer Country Profiles: Indonesia [Internet]. Cancer Country Profiles. 2014 [cited 2020 Feb 27]. p. 22–3. Available from: https://www.who.int/publications/m/item/cancer-idn-2020
2. ICO/IARC. Indonesia: Human Papillomavirus and Related Cancers, Fact Sheet 2018 I. Key data on HPV and HPV-related cancers. 2018;6–7.
3. WHO. Cervical cancer [Internet]. 2018 [cited 2020 Feb 27]. Available from: https://www.who.int/health-topics/cervical-cancer#tab=tab_1
4. RSUD Dr. Soetomo. Rekapitulasi data pasien baru POSA tahun 2019 [Data collection of new patients in Oncology Clinic]. Surabaya: RSUD Dr. Soetomo; 2019.
5. Myers Virtue S, Manne SL, Darabos K, et al. Emotion episodes during psychotherapy sessions among women newly diagnosed with gynecological cancers. Psychooncology. 2015;24(9):1189-96. doi: 10.1002/pon.3737. Epub 2014 Dec 17. PMID: 25521772; PMCID: PMC4470875.
6. Khalil J, Bellefqih S, Sahli N, et al. Impact of cervical cancer on quality of life: beyond the short term (Results from a single institution): Quality of life in long-term cervical cancer survivors: results from a single institution. Gynecol Oncol Res Pract. 2015;2:7. doi: 10.1186/s40661-015-0011-4. PMID: 27231567; PMCID: PMC4880873.
7. De Faye BJ, Wilson KG, Chater S, et al. Stress and coping with advanced cancer. Palliat Support Care. 2006;4(3):239-49. doi: 10.1017/s1478951506060317. PMID: 17066965.
8. Suhardin S, Kusnanto K, Krisnana I. Acceptance and Commitment Therapy (ACT) meningkatkan kualitas hidup pasien kanker [Acceptance and Commitment Therapy (ACT) improves cancer patients' quality of live]. Jurnal Ners. 2016: 11(1);118–27. doi:10.20473/jn. v11i1.1341
9. Susanti E. Gambaran penerimaan pasien awal terdiagnosa kanker serviks di poli onkologi satu atap (POSA), RSUD Dr. Soetomo Surabaya [Profile of admission with early diagnosis of cervical cancer at Oncology Clinic]. Surabaya: Universitas Airlangga; 2017.
10. Czerw AI, Religioni U, Deptała A, et al. Pain, acceptance of illness, adjustment to life with cancer and coping strategies in prostate cancer patients. Arch Med Sci. 2017;13(6):1459-1466. doi: 10.5114/aoms.2016.58458. Epub 2016 Mar 8. PMID: 29181078; PMCID: PMC5701675.
11. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. Dialogues Clin Neurosci. 2006;8(4):367-81. doi: 10.31887/DCNS.2006.8.4/bmcewen. PMID: 17290796; PMCID: PMC3181832.
12. Chen PY, Chang HC. The coping process of patients with cancer. Eur J Oncol Nurs. 2012;16(1):10-6. doi: 10.1016/j.ejon.2011.01.002. Epub 2011 Mar 3. PMID: 21376664.
13. Baldacchino D. Spiritual care education of health care professionals. Religions. 2015;6(2):594–613. doi: 10.3390/rel6020594.
14. Jefford M, Rowland J, Grunfeld E, et al. Implementing improved post-treatment care for cancer survivors in England, with reflections from Australia, Canada and the USA. Br J Cancer. 2013;108(1):14-20. doi: 10.1038/bjc.2012.554. Epub 2012 Dec 20. PMID: 23257892; PMCID: PMC3553535.
15. Olesen ML, Hansson H, Ottesen B, et al. The psychosocial needs of gynaecological cancer survivors: A framework for the development of a complex intervention. Eur J Oncol Nurs. 2015;19(4):349-58. doi: 10.1016/j.ejon.2015.01.007. Epub 2015 Feb 16. PMID: 25697547.
16. Wood AW, Gonzalez J, Barden SM. Mindful caring: using mindfulness-based cognitive therapy with caregivers of cancer survivors. J Psychosoc Oncol. 2015;33(1):66-84. doi: 10.1080/07347332.2014.977418. PMID: 25397963.
17. Given BA, Given CW, Kozachik S. Family support in advanced cancer. CA Cancer J Clin. 2001;51(4):213-31. doi: 10.3322/canjclin.51.4.213. PMID: 11577488.
18. Friedman M., et al. Buku ajar keperawatan keluarga. Riset, teori dan praktik V [Textbook on family nursing. Research, theory, and practice V]. Tiar E, editor. Jakarta: ECG; 2010.
19. Kusumaningrum T, Pradanie R, Yunitasari E, et al. Peran keluarga dan kualitas hidup pasien kanker serviks [Family role and the quality of life of cervical cancer patients]. Jurnal Ners. 2016; 11(1):112–7. doi: 10.20473/jn.v11i1.1920.
20. Bowman KF, Deimling GT, Smerglia V, et al. Appraisal of the cancer experience by older long-term survivors. Psychooncology. 2003;12(3):226-38. doi: 10.1002/pon.630. PMID: 12673807.
21. Deshmukh RD, Dhande DJ, Sachdeva KS, et al. Social support a key factor for adherence to multidrug-resistant tuberculosis treatment. Indian J Tuberc. 2018;65(1):41-47. doi: 10.1016/j.ijtb.2017.05.003. Epub 2017 Jun 2. PMID: 29332647.
22. Adams E, Boulton M, Watson E. The information needs of partners and family members of cancer patients: a systematic literature review. Patient Educ Couns. 2009;77(2):179-86. doi: 10.1016/

j.pec.2009.03.027. Epub 2009 Apr 29. PMID: 19406609.
23. Walgito B. Psikologi social [Social psychology]. Yogyakarta: Andi Offset; 2001.
24. Jafari N, Farajzadegan Z, Zamani A, et al. Spiritual therapy to improve the spiritual well-being of Iranian women with breast cancer: a randomized controlled trial. Evid Based Complement Alternat Med. 2013;2013:353262. doi: 10.1155/2013/353262. Epub 2013 Aug 18. PMID: 24023572; PMCID: PMC3759260.
25. Weis J. Support groups for cancer patients. Support Care Cancer. 2003;11(12):763-8. doi: 10.1007/s00520-003-0536-7. Epub 2003 Oct 15. PMID: 14564493.
26. Burnette CE, Roh S, Liddell J, et al. American indian women cancer survivor's needs and preferences: Community support for cancer experiences. J Cancer Educ. 2019;34(3):592-599. doi: 10.1007/s13187-018-1346-4. PMID: 29546486; PMCID: PMC6139076.
27. Novaes HM, Itria A, Silva GA, et al. Annual national direct and indirect cost estimates of the prevention and treatment of cervical cancer in Brazil. Clinics (Sao Paulo). 2015;70(4):289-95. doi: 10.6061/clinics/2015(04)12. PMID: 26017797; PMCID: PMC4418354.
28. Rasmun. Stres, koping dan adaptasi [Stress, coping, and adaptation]. Jakarta: Sagung Seto; 2009.
29. Nurhariyadi D. Preferensi ruang hobi. Temu Ilmiah IPLBI [Hobby space preference IPLBI Scientific Meeting]. 2016;135–40.
30. Fujiwara D, Kurdna L, Cornwll Tet al. Further analysis to value the health and educational benefits of sport and culture [Internet]. 2015. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/446273/Health_and_educational_benefits_of_sport_and_culture.pdf
31. Kralik D, Price K, Telford K. The meaning of self-care for people with chronic illness. J Nurs Health Chronic Illn. 2010;2(3):197–204. doi: 10.1111/j.1752-9824.2010.01056.x
32. Fauziah RN. Kecemasan pada penderita kanker [Anxiety in cancer patients] [Internet]. eprints.ums.ac.id. Universitas Muhammadiyah Surakarta; 2016. Available from: http://eprints.ums.ac.id/43931/12/NASKAH PUBLIKASI.pdf
33. Zwingmann C, Wirtz M, Müller C, et al. Positive and negative religious coping in German breast cancer patients. J Behav Med. 2006;29(6):533-47. doi: 10.1007/s10865-006-9074-3. Epub 2006 Sep 2. PMID: 16951991.

ORIGINAL RESEARCH

Cobas® 4800 HPV test is accurate for detecting high risk Human Papillomavirus from urine samples at dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia

Indiarto Wityawan[1], Andrijono[1], Aria Kekalih[2]
[1]Department Obstetrics & Gynecology, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[2]Department of Community Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.

Article Info
Received Aug 3, 2022
Revised Oct 17, 2022
Accepted Nov 15, 2022
Published Dec 1, 2022

Corresponding author:
Indiarto Wityawan
indiartospog@gmail.com

Keywords:
Papillomavirus
Urine
4800 Cobas®
Genotyping
Maternal health

ABSTRACT

Objective: To find the accuracy, sensitivity, specificity, as well as predicted values, both positive and negative, of urine samples using Cobas® 4800 in detecting high risk Human Papillomavirus.

Materials and Methods: This study was a cross-sectional study with a total of 72 samples taken from medical records of hrHPV DNA examination with Cobas® 4800 in 2017-2020. Study subjects were called for re-examination of urine samples and cervical samples using Cobas® 4800. Samples with positive hrHPV DNA in the cervix, urine, or both were examined for cervical fluid-based cytology (LBC). Data were analyzed using Chi-square.

Results: Overall, 84.72% agreement was detected through specimens of urine and cervical mucus tested of hrHPV DNA with Cobas® 4800. In all samples, a significant rate of concordance detection of hrHPV DNA with Cobas® 4800 was reported (κa = 0.62; 95% IC: 39-84). In this population, in determining the presence of hrHPV DNA in cervical and urine specimens, it was found that the sensitivity, specificity, positive predictive value and negative predictive value were respectively 87.5% (95% IC: 64–97%), 84% (95% IC: 72–91%), 60.9% (95% IC: 40.8–77.8%), and 96 % (95% IC: 86.3–98.9%).

Conclusion: The presence of hrHPV infection in the cervix can be determined by detecting hrHPV DNA in the urine. According to these findings, urine samples subjected to the Cobas® 4800 HPV test may be helpful for the clinical treatment of HPV infection.

Cite this as: Wityawan, I., Andrijono, & Kekalih, A. (2022). Cobas® 4800 HPV test is accurate for detecting high risk Human Papillomavirus from urine samples at dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia. Majalah Obstetri & Ginekologi, 30(3), 116-121. https://doi.org/10.20473/mog.V30I32022.116-121

INTRODUCTION

Cervical cancer has the highest prevalence and it is the fourth leading cause of death from all cancers. Human papillomavirus (hrHPV) is a virus that poses a high risk of infection, considered the main etiology of cervical cancer.[1] According to WHO, one of the global goals is to provide a technique for expediting the eradication cervical carcinoma, which has become a concern of global health-related services. It is intended that 70% of women be screened at the age of 35 and then again at the age of 45 by 2030.[2-5] The hrHPV DNA test has to be the most sensitive screening procedure for CIN 2+ with sensitively value of 98.3% and a specificity values of 85.3-86.2%.[6]

According to Indonesia's 2018 health profile data, women who have screened for cervical cancer with acetate visual inspection were 7.34%.[4,5] However, this low achievement was because the screening methods needed pelvic examination, which is invasive, painful for the patients, time-consuming for healthcare profes-

sionals, and difficult to do in settings with limited resources. Therefore, the development of non-invasive self-sample collection techniques might potentially have the benefit of raising the acceptability of the screening processes. Cytology-based screening is being replaced by primary screening or co-testing based on the human papillomavirus (HPV). For this, the use of urine, which is simple to collect, would be beneficial. Furthermore, molecular techniques to identify DNA in urine samples are already regularly used to diagnose prevalent sexually transmitted diseases, including *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.[7]

HPV does not have a preference for the urinary system, in contrast to its preference for the cervix and other anogenital anatomical regions.[8-11] Therefore, the presence of HPV in urine is very certainly due to secondary cervix exfoliation or other anogenital lesions. The purpose of this study was to assess urine testing for high risk HPV in a group with a high prevalence of the disease. The clinical effectiveness of self urine-based sampling was also assessed in comparison to cervical sampling, and the results were compared to the presence of cervical disease as determined by histology. The Cobas® 4800 HPV test, an FDA-approved real-time PCR assay created for the simultaneous genotyping of HPV-16 and HPV-18 and the detection of high-risk HPV (HR-HPV), was utilized for this purpose.[12,13]

MATERIALS AND METHODS

This study used a cross-sectional design of a diagnostic test to compare urine hrHPV DNA to cervical hrHPV DNA preparations, which was the gold standard that carried out at the Kencana Women Health Cluster from January to December 2020, at dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Patients aged 30-60 years were enrolled on this study. Pregnant women and those who had given birth within the past three months of the examination date were excluded. The patients were recalled for cervical and urine hrHPV DNA examinations on the same day and a cytology examination with liquid-based cytology (LBC) was performed if the results of the hrHPV examination were positive, either in cervical swabs, urine, or both.

Cervical samples were taken using a cervical brush by the doctors and deposited in five days in a real-time polymerase chain Cell Cobas® medium bottle (Roche Diagnostic). Cervical specimens taken for PCR cell collection at Cobas® media are stable for up to 6 months at 2–30º C for use with the Cobas® 4800 test for HPV testing.[5] In sterile containers, we collected urine specimens identically dated as the pelvic examination and delivered to a laboratory for further processing within five days. A minimum of each urine sample was diluted to a volume of 20 milliliters, and centrifuged for 10 minutes at 4000 x g. The solid pellet was resuspended in water following centrifugation of five milliliters supernatant into a vial of PCR collect media. The Cobas® 4800 test was used to process urine samples, despite the fact that it had not been verified for use for this type of specimen.[12,13]

In a single system, the Cobas® 4800 system combines completely real-time PCR technique, enabling automated sample preparation. In addition to hrHPV genotypes, the test identified globin gene of human cells. In a single tube, amplification and detection of polymerase chain reaction took place, with probes containing four separate dyes that act as reporters tracking the multiplex reaction's distinct targets. There were four different dyes: Reporter dye 1 observing the hrHPV pool containing 12 human papillomavirus (HPV) targets (HPV-31, -33; -35; 39; 45; 51), while 2 and 3 dyes observing two forms of HPV, the type16 and type 18. Dye 4 examined the b-globin protein to determine the adequacy of the cells, their extraction, and amplification. The examination was conducted according to the producer's recommendations for the extraction of DNA with Cobas® X 480 and real-time PCR with the Cobas® Z 480.[11,12]

Sensitivity, PPV (positive predictive value), specificity, NPV (negative predictive value) are the terms used to describe the prediction accuracy of hrHPV detection in urine speciments, which is measured as percentages with confidence intervals of 95% in comparison to cervical sample detection (gold standard) (95% CI). The Kappa statistic (Cohen's Kappa) was utilized to ascertain if test concordance was poor (κ=0), slight ($0.01<\kappa<0.20$), fair ($0.21<\kappa<0.40$), moderate ($0.41<\kappa<0.60$), substantial ($0.61<\kappa<0.80$), nearly perfect ($0.81<\kappa<1$), or perfect (κ=1). Differences between paired proportions were calculated using the McNemar's test. $P<0.05$ was utilized as the significance level.[14]

RESULTS AND DISCUSSION

The b-globin gene was detected in every 72 cervix and urinary specimens used in this study. Preliminary data from 2017-2020 tests showed that 42 women had previously tested positive for hrHPV DNA, while 30 women had previously tested negative. A prevalence of 34.7% was found in 25 women who had positive test results of hrHPV using a minimum one of the two specimens examined. In urine samples, the prevalence of carcinogenic type hrHPV was 31.9%, while in cervical samples, it was 22.2% (Table 1).

Table 1. Concordance and agreement in detecting cervical and urine samples for HPV DNA analysis.

		Cervical Samples		% Agreement	κ^a (95% IC)
		Positive	Negative		
Urine samples	Positive	14	9	84.72%	0.62 (39-84)
	Negative	2	47		

a: Cohen's Kappa

There was an overall concordance of 84.72% between hrHPV identification in urine and cervical secretions specimens. The identification of hrHPV DNA in both samples had a high concordance rate (κ= 0.62; 95 % IC: 39–84). For both types of samples, there were 11 disparities in the results. In two of them, hrHPV was detected in the cervix but not in the urine. However, nine positive samples were obtained for hrHPV in the urine but negative in the cervix. Overall, for detecting hrHPV DNA extracted from urine compared to cervical samples, sensitivity, PPV (positive predictive value), specificity, and NPV (negative predictive value) were 87.5% (95% IC: 64–96), 83.9% (95 % IC: 72–91), 95.9% (95 % IC: 86–99), and 60.9% (95% IC: 41–78), respectively. For the pool of HR-genotypes, the prevalence of hrHPV samples of urine was higher compared to cervical samples (without HPV16 and HPV 18).

Table 2 compares the sensitivity, PPV (positive predictive value), specificity and NPV (negative predictive value) of particular PCR analysis (HPV type 16, HPV type 18, and another hrHPV) comparing those found in urine specimens to those found in cervical specimens. The sensitivity of any hrHPVgenome was 84.62% (95% IC = 58–96), and the Cohen's Kappa was moderate.

Twenty-five women received cytological results, with 17 (68%) being negative for intraepithelial lesions, 5 (20%) having LSIL (Low Grade Squamous Intraepithelial Lesions), 2 (8%) having ASCH (Atypical Squamous Cells, could not exclude HSIL), and 1 (4%) having ASCUS (Atypical Squamous Cells of Uncertain Significance) (Table 3). To find out the factors that influence the results of the urine DNA hrHPV examination, a relationship test was carried out between the factors that might affect the examination results (age, education, and parity) with the suitability of the urine DNA hrHPV results to the cervix as shown in Table 4.

Table 2. Specific genotyping sensitivity, specificity, NPV, and PPVurinalysis specimens (IC 95%).

	HPV type 16	HPV type 18	12 HR-HPV[a]
Sensitivity (95 IC%)	-	100% (21.100)	84.62% (58.96)
Spesifisity (95 IC%)	-	100% (95.100)	84.75% (73.92)
PPV[b] (95 IC%)	-	100% (21.100)	55% (34.74)
NPV[c] (95 IC%)	-	100% (95.100)	96% (87.99)
κ (95 IC%)	-	1 (77-123)	0.57 (35.79)

a hrHPV other than type 16 and type 18
b Predictive values that are positive.
c Predictive values that are negative.

Table 3. hrHPV infection prevalence cervical and urinary examinations sample method compared to cytology results

Cytology	*n*	12 hrHPV		HPV 16		HPV 18	
		Cervical	Urine	Cervical	Urine	Cervical	Urine
Negative[a]	17 (68%)	7/13 (54%)	14/20 (54%)	0/0	0/0	0/1	0/1
ASCUS[b]	1 (4%)	1/13 (8%)	1/20 (5%)	0/0	0/0	0/1	0/1
LSIL[c]	5 (20%)	3/13 (23%)	3/20 (15%)	0/0	0/0	1/1	1/1
ASCH[d]	2 (8%)	2/13 (15%)	2/20 (10%)	0/0	0/0	0/1	0/1
Total	25	13	20	0	0	1	1

Table 4. Age, level of education, parity, and concordance between urine and cervical samples

	Concordance		Total	P
	Yes	No		
Age				
≤40 yo	40 (86.9%)	6 (13.1%)	46 (63.9%)	0.353
>40 yo	21 (80.8%)	5 (19.2%)	26 (36.1%)	
Level of education				
Basic (< high school)	6 (66.7%)	3 (33.3%)	9 (12.5%)	0.134
> high school	55 (87.3%)	8 (12.7%)	63 (87.5%)	
Parity				
Nulli/Primiparous	54 (83.1%)	11 (16.9%)	65 (90.3%)	0.296
Multiparous	7 (100%)	0 (0%)	7 (9.7%)	

Some data suggest that using self-collected urine, rather than cervical samples, as an option for HPV testing could be beneficial. First, HPV genotypes urinalysis and cervix lesions tissue specimens are agreed significantly. Urine contaminated with exfoliated cervical cells infected with HPV is known to rise as the severity of cervical lesions increases. Thus, HPV presence in urine, that resembles an HPV infection in the cervix, requires constant monitoring.[15]

Urine sample for the diagnosis of oncogenic HPV has been studied in several research. Because various factors, such as the urine sample technique, conditions of storing, centrifuging, and extracting DNA, and HPV DNA test, might adversely influence HPV DNA detection, HPV DNA testing in the urine has a variety of limits applicable to this purpose.[15]

We examined 72 matched cervix and urine specimens from women who have been referred to gynecology unit by community physicians for examination due to abnormal results of Pap smear or VIA screening outcomes. Due to the fact that the research was done on a selected sample a group of women previously possessed an abnormality VIA or pap smear test, HPV infection was quite prevalent (>50%), as expected. Urine had a higher prevalence (31.9%) than cervical specimens (22.2%). The presence of hrHPV-DNA from epithelial tissues of the urethra and vulva, which are similarly vulnerable to hrHPV infection, could be one explanation. In 11 samples, there was a discrepancy, with two samples having positive hrHPV in the cervix but negative in urine sample and nine specimens having positive hrHPV in the urine but negative in the cervix. These 11 samples had normal cervical cytology examinations using liquid-based cytology (LBC). Some explanations on this may be the possibility of a faster regression in the cervix than in the urine. Another possibility is that there was previous sexual contact so that hrHPV transmission occurred, while the cervix had no infection process yet. In this group, the possibility of primary hrHPV infection originating from the urinary tract required further investigation. Some literature mentions the possibility of hrHPV infection as a cause of urinary tract cancer. The most common is the bladder cancer (transitional cell cancer) of 22%.[9-11]

We discovered a significant concordance rate of HR-HPV DNA detection and an overall agreement of 84.72%. (κ=0.62; 95% IC: 0.39–0.84). The sensitivity was 87.5% and the specificity was 83.9%. According to Pathak et al., HPV infection detection in urine had a pooling sensitivity of 87% and specificity of 94%, while hrHPV had a 77% sensitivity, 88% specificity in a meta-analysis and systematic review on precision of urine HPV testing for cervical HPV infection.[16] The HPV types 16 and 18 detection through urine exhibited a combined sensitivity and specificity of 73% and 98%, respectively.[16] When urine samples were obtained as first voiding instead of random or midstream urine samples, meta-regression revealed a 22-fold increase in overall accuracy.[16]

The sensitivity of first voiding urine is significantly higher than random or intermediate urine samples, resulting in a considerable difference in accuracy. The results of this study were better than those of Oliveira et al. (sensitivity of 50.0% with a Kappa value of 0.55), of Tranberg et al. with sensitivity of 63.9% with a Kappa value of 0.66), and of Sahasrabuddhe et al. with sensitivity of 51.6% with a Kappa value of 0.55 with CLART assay (κ=0.55).[17,18]

These findings were in contrast with those of Bernal et al. (sensitivity 88%, Kappa value 0.76), of Ostensson et al. (with Abbot RealTime sensitivity 33-100%, Kappa ranged from 0.36 to 0.85), and of Ornskov et al. with Abbot RealTime sensitivity 33-100%, Kappa ranged from 0.66 to 0.77).[19,20] The sensitivity of 12 hrHPV other than HPV types 16 and 18 was calculated to be 84.62%. Because there were no samples with a single infection with HPV type 16 and just one specimen having only one infection of HPV type 18, it was not done for HPV types 16 and 18. Using bivariate analysis

on the variables in the research subjects, the researchers looked for factors that could influence the outcome of a urine hrHPV DNA examination. The investigation found no research variables in terms of age, education level, or parity that were connected to the outcomes of the HPV DNA urine screening. With respect to alternative HPV detection and/or genotyping assays, we chose the Cobas® 4800 HPV test for our investigation. This real-time PCR-based assay test offers a number of benefits. First of all, the test simultaneously gives partial HPV genotyping for HPV-16 and HPV-18, in addition to reporting the existence of HR HPV genotypes. Second, since the test has been modified for primary specimens, it is highly automated and simple to use. Finally, the findings will be available around 4 hours after receiving the materials.

CONCLUSION

The findings of this research encourage the use of urine in conjunction with Cobas® 4800 HPV testing among women who have severe cervical lesions. Validation should be performed before using urine/Cobas® 4800 as a diagnostic test. More research is needed to show their equal performance in a group undergoing initial screening. If the findings are validated, urine collection may be used within populations with limited availability of healthcare providers or where, for example, pelvic examination is not practical. Additionally, when molecular methods are used in conjunction with initial tests for primary cervical cancer screening, urine samples may be used as a suitable substitute for cervical specimens. Besides for vaccination trials, disease surveillance, and epidemiological investigations, urine can also be utilized to evaluate HPV prevalence.[21-23]

DISCLOSURES

Acknowledgment

Authors like to express their appreciation to all patients who consented to take part for this research. The authors appreciate our parents and relatives for their intellectual and psychological assistance.

Conflict of interest

This study's authors claim no conflicts of interest.

Funding

This research has received no external funding.

Author contribution

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

REFERENCES

1. de Sanjosé S, Brotons M, Pavón MA. The natural history of human papillomavirus infection. Best Pract Res Clin Obstet Gynaecol. 2018;47:2-13. doi: 10.1016/j.bpobgyn.2017.08.015. Epub 2017 Sep 6. PMID: 28964706.
2. Global strategy to accelerate the elimination of cervical cancer as a public health problem [Internet]. World Health Organization 2020. Available from: https://www.who.int/publications/i/item/9789240014107
3. 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.
4. Kementerian Kesehatan Republik Indonesia. Komite Penanggulangan Kanker Nasional. Panduan penatalaksanaan kanker serviks [Guidelines for cervical cancer management]. Jakarta; 2018.
5. Kementrian Kesehatan Republik Indonesia. Profil kesehatan Indonesia 2018. Gambar 6.66. Persentase pemeriksaan deteksi dini kanker leher rahim dan payudara pada perempuan usia 30-50 tahun menurut provinsi s/d tahun 2018 [Percentage of early detection of cervical and breast cancer in women aged 30-50 by province to 2018]. Jakarta; 2018. p. 250.
6. Melnikow J, Henderson JT, Burda BU, et al. Screening for cervical cancer with high-risk human papillomavirus testing: A systematic evidence review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Aug. Report No.: 17-05231-EF-1. PMID: 30256575.
7. Bernal S, Palomares JC, Artura A, et al. Comparison of urine and cervical samples for detecting human papillomavirus (HPV) with the Cobas 4800 HPV test. J Clin Virol. 2014;61(4):548-52. doi: 10.1016/j.jcv.2014.10.001. Epub 2014 Oct 12. PMID: 25453566.
8. Senkomago V, Henley SJ, Thomas CC, et al. Human papillomavirus-attributable cancers - United States, 2012-2016. MMWR Morb Mortal Wkly Rep. 2019;68(33):724-28. doi: 10.15585/

mmwr.mm6833a3. PMID: 31437140; PMCID: PMC6705893.
9. Li N, Yang L, Zhang Y, et al. Human papillomavirus infection and bladder cancer risk: a meta-analysis. J Infect Dis. 2011;204(2):217-23. doi: 10.1093/infdis/jir248. PMID: 21673031; PMCID: PMC3114469.
10. Abdollahzadeh P, Madani SH, Khazaei S, et al. Association between human papillomavirus and transitional cell carcinoma of the bladder. Urol J. 2017;14(6):5047-50. doi: 10.22037/uj.v14i6.3748. PMID: 29101759.
11. Cai T, Di Vico T, Durante J, et al. Human papilloma virus and genitourinary cancers: a narrative review. Minerva Urol Nefrol. 2018;70(6): 579-587. doi: 10.23736/S0393-2249.18.03141-7. Epub 2018 Aug 29. PMID: 30160386.
12. Roche Molecular Systems I. Cobas® PCR Urine Sample Kit. 2013 [Internet]. Available from: http://ekstern.infonet.regionsyddanmark.dk/Files/Formularer/Upload/2013/09/cobas® PCR Urine Sample Kit (05170621001-01 Doc Rev 6 0).pdf
13. Roche. Cobas®. Short guide for cervical sample collection using the Rovers. 2015 [Internet]. Availabe from: htttp://chumontreal.com/laboratoires/images/stories/documents/nouvelles/Short_guide_prelevement_col_avec_Rovers_Cervex_Brush_anglais_20 15-02-27.pdf
14. Dahlan, MS. Penelitian diagnostik. Dasar-dasar teoritis dan aplikasi dengan program SPSS dan stata. [Diagnostic research, Theory and application with SPSS ans stata]. Seri Evidence Based Medicine 5. Jakarta: Salemba Medika; 2009.
15. Chatzistamatiou K, Vrekoussis T, Tsertanidou A, et al. Acceptability of Self-Sampling for Human Papillomavirus-Based Cervical Cancer Screening. J Womens Health (Larchmt). 2020;29(11):1447-56. doi: 10.1089/jwh.2019.8258. Epub 2020 Jul 30. PMID: 32757997.
16. Pathak N, Dodds J, Zamora J, et al. Accuracy of urinary human papillomavirus testing for presence of cervical HPV: systematic review and meta-analysis. BMJ. 2014;349:g5264. doi: 10.1136/bmj.g5264. PMID: 25232064; PMCID: PMC4166201.
17. Oliveira CM, Musselwhite LW, de Paula Pantano N, et al Detection of HPV E6 oncoprotein from urine via a novel immunochromatographic assay. PLoS One. 2020;15(4):e0232105. doi: 10.1371/journal.pone.0232105. PMID: 32320451; PMCID: PMC7176116.
18. Tranberg M, Jensen JS, Bech BH, et al. Urine collection in cervical cancer screening - analytical comparison of two HPV DNA assays. BMC Infect Dis. 2020;20(1):926. doi: 10.1186/s12879-020-05663-7. PMID: 33276740; PMCID: PMC7716507.
19. Daponte A, Michail G, Daponte AI, et al. Urine HPV in the Context of Genital and Cervical Cancer Screening-An Update of Current Literature. Cancers (Basel). 2021;13(7):1640. doi: 10.3390/cancers13071640. PMID: 33915878; PMCID: PMC8036396.
20. Ørnskov D, Jochumsen K, Steiner PH, et al. Clinical performance and acceptability of self-collected vaginal and urine samples compared with clinician-taken cervical samples for HPV testing among women referred for colposcopy. A cross-sectional study. BMJ Open. 2021;11(3):e041512. doi: 10.1136/bmjopen-2020-041512. PMID: 33674367; PMCID: PMC7939007.
21. Lee EH, Um TH, Chi HS, et al. Prevalence and distribution of human papillomavirus infection in Korean women as determined by restriction fragment mass polymorphism assay. J Korean Med Sci. 2012;27(9):1091-7. doi: 10.3346/jkms.2012.27.9.1091. Epub 2012 Aug 22. PMID: 22969258; PMCID: PMC3429829.
22. Zhou HL, Zhang W, Zhang CJ, et al. Prevalence and distribution of human papillomavirus genotypes in Chinese women between 1991 and 2016: A systematic review. J Infect. 2018;76(6): 522-8. doi: 10.1016/j.jinf.2018.02.008. Epub 2018 Mar 1. PMID: 29477803.
23. Gultekin M, Dundar S, Keskinkilic B, et al. How to triage HPV positive cases: Results of four million females. Gynecol Oncol. 2020;158(1):105-11. doi: 10.1016/j.ygyno.2020.04.698. Epub 2020 Apr 30. PMID: 32362567.

ORIGINAL RESEARCH

Maternal and neonatal outcomes in delivery with diagnosis of antepartum hemorrhage due to placenta previa at a tertiary hospital in Surabaya, Indonesia

Sarah Nia Amru[1], Indra Yuliati[2]*, Philia Setiawan[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 Anesthesiology and Reanimation, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Article Info
Received Dec 9, 2021
Revised May 19, 2022
Accepted Jun 20, 2022
Published Dec 1, 2022

Corresponding author:
Indra Yuliati
indra.yuliati@fk.unair.ac.id

Keywords:
Antepartum hemorrhage
Placenta previa
Maternal outcomes
Neonatal outcomes
Maternal health

ABSTRACT

Objective: To identify maternal and neonatal outcomes in delivery with diagnosis of antepartum hemorrhage (APH) due to placenta previa.
Materials and Methods: This was a descriptive retrospective study with cross-sectional design. Samples were taken using medical records with convenience sampling technique. Deliveries with history of APH due to placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, on January 1 until December 31, 2019, were included.
Results: In our study, 36 mothers were included. Maternal characteristics included age of 20–35 years in 72.2%, overweight in 50%, referral visits in 69.4%, from out of town (66.7%), bleeding onset at 3rd trimester (97.2%), primigravida (8.3%), nulliparity (13.9%), 69.4% with history of C-section, and 83.3% no hospital readmissions. Maternal outcomes included 100% mothers diagnosed with complete placenta previa and performed C-section. The mothers were mostly (69.4%) diagnosed with placenta accreta spectrum (PAS). There were 36.1% hysterectomy, 33.3% postpartum hemorrhage, 50% blood transfusions, and zero maternal mortality. Neonatal outcomes included prematurity in 80%, low birth weight (LBW) in 51.5%, while 77.1% and 85.7% of newborns had no asphyxia at 1 and 5 minutes, consecutively.
Conclusion: All mothers experienced complete placenta previa, and underwent C-section with most of the mothers were diagnosed with PAS. Less than half of them needed hysterectomy intervention because other patients with focal type PAS were planned for conservative surgery. Moreover, they mostly did not have postpartum hemorrhage with half of them needed blood transfusion. There was zero maternal mortality, with most newborns experienced prematurity, LBW but no significant asphyxia.

Cite this as: Amru, S.N., Yuliati, I., & Setiawan, P. (2022). Maternal and neonatal outcomes in delivery with diagnosis of antepartum hemorrhage due to placenta previa at a tertiary hospital in Surabaya, Indonesia. Majalah Obstetri & Ginekologi, 30(3), 122-127. https://doi.org/10.20473/mog.V30I32022.122-127.

INTRODUCTION

Bleeding during pregnancy is still the leading cause of maternal death worldwide.[1] The bleeding includes Postpartum Hemorrhage (PPH) and Antepartum Hemorrhage (APH). PPH is defined as bleeding ≥ 500 ml in vaginal delivery and ≥ 1000 ml in C-section delivery.[1-3] APH is defined as bleeding from and/or into the genital tract that occurs from 24 weeks of gestation until before the birth of the baby.[1,4,5] Placenta previa, as one of the main cause of APH, is defined as an abnormally implanted placenta in the lower uterine segment that either partially or completely covers the internal os.[6,7]

Furthermore, pregnancies with APH due to placenta previa have been associated with many adverse maternal and neonatal outcomes. Complications of

placenta previa occur in 0.52% of pregnancies in the world with the highest incidence found in Asia with a prevalence of 1.22%.[8] The incidence of placenta previa in Dr. Soetomo General Academic Hospital, Surabaya, based on a study conducted by Aulidiah.[9] in 2014-2015 were 83 of 2,176 (3.81%) deliveries.

This study was in line with the National Mid-Term Development Plan for the period of 2020-2024, which one of the indicators of success is the decrease of the maternal mortality rate (MMR) and infant mortality rate (IMR) in Indonesia which is currently still far from the target.[5] In Surabaya, studies related to maternal and neonatal outcomes in delivery with history of APH due to placenta previa were still limited. Identifying the adverse maternal and neonatal outcomes would be beneficial for more effective prevention and management by medical personnel in the future. Therefore, this study aimed to identify maternal and neonatal outcomes in delivery with history of APH due to placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

This study was a descriptive retrospective study with cross-sectional design. Samples were taken using medical records with convenience sampling technique. The samples of this study were deliveries with history of APH due to placenta previa at Dr. Soetomo General Hospital on January 1 – December 31, 2019. Inclusion criteria consisted of mothers with gestational age of $\geq$ 24 weeks and had complete medical records. Data collected included sociodemographic characteristics; obstetric characteristics; maternal outcomes including placenta accreta spectrum (PAS), C-section delivery, hysterectomy, blood transfusion, postpartum hemorrhage, and maternal mortality; neonatal outcomes including preterm birth, birth weight, and asphyxia. The data in this study were analyzed using SPSS version 23. This study has obtained ethical approval from Dr. Soetomo General Hospital Surabaya in 2020 with the number of ethical clearance 0188/LOE/301.4.2/XI/2020.

xxx

RESULTS AND DISCUSSION

Total deliveries at Dr. Soetomo General Hospital Surabaya in 2019 was 1,358, and 133 of them had placenta previa (9.79%). In 133 deliveries with placenta previa, the researchers obtained 64 data with only 36 data met the inclusion criteria. There were 35 mothers with single pregnancies and one mother with multiple pregnancies (gemelli). Thus, the number of babies born was 37, but two babies experienced IUFD (Intrauterine Fetal Death), so the number of live births included in this study was 35.

Sociodemographic characteristics of mothers with placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Table 1. Distribution of sociodemographic characteristics of mothers with placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2019.

Sociodemographic characteristics	(n=36)	(%)
Age		
20 – 35 years old	26	72.2
>35 years old	10	27.8
Body Mass Index (BMI) (kg/m^2)		
18.5 – 24.9 (ideal)	9	25
25 – 29.9 (overweight)	18	50
≥30 (obese)	9	25
Visit		
Self-reffered	11	30.6
Referral	25	69.4
Regional Origin		
Surabaya	12	33.3
Outside Surabaya	24	66.7

Mothers with APH due to placenta previa were mostly diagnosed at the age of 20-35 years (72.2%), with most BMI were considered overweight (50%). The majority of subjects visited Dr. Soetomo General Hospital by referral (69.4%), with most of the subjects' regional origin were from outside of Surabaya (66.7%).

Obstetric characteristics of mothers with placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Maternal obstetric characteristics mostly came with bleeding at the 3rd trimester (97.2%) with the lowest gestational age were at 26/27 weeks and the highest were at 37/38 weeks. There were 8.3% primigravida while the rest were multigravida and 13.9% nulliparity, and the rest are mostly multiparity. Most mothers had history of C-section delivery (69.4%), had no history of abortion (61.1%) and had no history of hospital readmissions at Dr. Soetomo General Hospital Surabaya (83.3%).

Maternal and neonatal outcomes of mothers with placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

In our study, it was found that all pregnant women had complete placenta previa. The results of this study were

in line with previous studies where the most common type of placenta previa was complete placenta previa, with the prevalence of 76.6% and 78.5%.[10,11] All pregnant women in our study underwent C-section delivery due to complete placenta previa that covered the internal os, making the baby unable to be delivered vaginally.

Tabel 2. Distribution of obstetric characteristics of mothers with placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2019

Obstetric characteristics	(n=36)	(%)
Gestational age at onset of bleeding		
T2 (14 – 27 weeks)	1	2.8
T3 (28 – 41 weeks)	35	97.2
Gravida		
GI	3	8.3
GII	8	22.2
G≥III	25	69.4
Parity		
P0	5	13.9
P1	15	41.7
P2	12	33.3
P≥3	4	11.1
Abortion		
A0	22	61.1
A1	8	22.2
A2	6	16.7
History of C-section Delivery		
No	11	30.6
1x	17	47.2
2x	8	22.2
History of hospital readmissions at Dr. Soetomo General Hospital Surabaya		
No	30	83.3
2x	5	13.9
3x	1	2.8

Placenta accreta spectrum (PAS) also known as abnormal placentation, is when trophoblasts invade the myometrium layer. PAS must be suspected in all mothers with placenta previa because it represents most placenta previa cases, especially in mothers with a history of C-section delivery.[11] In our study, 69.4% of mothers experiencing PAS with the highest proportion was placenta accreta type (33.3%). A study conducted by Sekiguchi et al.[12] reported that PAS was more common in complete placenta previa compared to other types, which is in line with the results of this study where all respondents experienced complete placenta previa.

However, the remaining mothers (69.4%) did not undergo hysterectomy. It could be because some of them were planned for conservative surgery instead of hysterectomy, particularly in mothers with focal type PAS where the uterine infiltration was less than 50%.[15]

Table 3. Distribution of maternal outcomes of mothers with placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2019.

Maternal Outcomes	(n=36)	(%)
Complete Placenta Previa	36	100
Placenta Accreta Spectrum (PAS)		
No PAS	11	30.6
PAS:		
Placenta Accreta	12	33.3
Placenta Increta	9	25
Placenta Percreta	4	11.1
C-section Delivery	36	100
Hysterectomy		
Yes	13	36.1
No	23	63.9
Blood Transfusion		
Yes	18	50
No	18	50
Postpartum Hemorrhage (PPH)		
Yes (≥1000 mL)	12	33.3
No (<1000 mL)	24	66.7
Haemoglobin (Hb)		
Hb Pre-Op (g/dL)		
<11	21	58.3
≥11	15	41.7
Hb Post-Op (g/dL)		
<11	21	58.3
≥11	15	41.7
Maternal Mortality	0	0

Table 4. Distribution of neonatal outcomes of mothers with placenta previa at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2019.

Neonatal Outcomes	(n=35)	(%)
Preterm Birth		
Yes	28	80
No	7	20
Gestational Age at Birth		
Very Preterm (28 - <32 weeks)	2	5.7
Moderate to late Preterm (32 - <37 weeks)	26	74.3
Aterm (≥37 weeks)	7	20
Birth Weight		
VLBW* (<1.500 g)	1	2.9
LBW** (<2.500 g)	17	48.6
Normal (≥2.500 g)	17	48.6
Asphyxia		
Apgar Score at 1 minute		
a. Asphyxia (<7)	8	22.9
b. Not Asphyxia (≥7)	27	77.1
Apgar Score at 5 minute		
a. Asphyxia (<7)	5	14.3
b. Not Asphyxia (≥7)	30	85.7

*VLBW = Very Low Birth Weight
**LBW = Low Birth Weight

The outcome of blood transfusion showed that half of the mothers needed blood transfusions while the others did not with a ratio of 1:1. In mothers who received blood transfusions, the type of transfusion with the highest proportion was PRC with the percentage of 77.8%, followed by WB with the percentage of 27.8%. It was also observed that Hb levels before surgery and after surgery obtained the same distribution. Most of the mothers had anemia before surgery and after surgery (postpartum anemia) with Hb cut-off of <11 g/dL.[16] However, in our study, the timing of blood transfusion was not recorded.

The proportion of mothers who experienced PPH (33.3%) was lower than mothers who did not experience PPH (66.7%). This result was in line with our study, where only less than half of the mothers needed the intervention of hysterectomy, with half of them needed a blood transfusion. Maternal mortality can be caused by various factors, such as delays in healthcare access and poor health services. No maternal mortality was found in our study. It showed that the management of referral systems and bleeding in respondents had been well resolved.

Neonatal outcomes were primarily delivered preterm (80%). Most deliveries occurred at 36/37 weeks' gestation. Most newborns who experienced prematurity were in the moderate to late preterm category (74.3%), between 32 - <37 weeks. Complete placenta previa is more often associated with the risk of prematurity due to a higher risk of massive obstetric bleeding in complete placenta previa.[12,17]

The outcome of infants' birth weight was <2500 g (51.5%), which was reclassified into low birth weight and very low birth weight was slightly higher than the outcome of normal birth weight (48.6%). Infants with birth weight <2.500g were mostly delivered at 32 - <37 weeks' gestation (moderate to late preterm). This could be related to the bleeding of placenta previa that lead to inadequate oxygen supply to the fetus, which then resulted in fetal hypoxia, intrauterine growth retard-ation, prematurity, and low birth weight.[2,18,19]

The newborns' asphyxia was assessed based on the Apgar score as an initial assessment measured at 1 and 5 minutes. In our study, most newborns did not experience asphyxia at 1 and 5 minutes based on Apgar score measurement $\geq$ 7 (77.1%; 85.7%). Placenta previa was reported as a maternal risk factor for asphyxia but did not significantly affected asphyxia in newborns.[20]

Our study had several limitations, including the usage of secondary data in the form of medical records, a lot of subjects must be excluded due to their incompleteness of data. This study also did not include other risk factors such as a previous history of placenta previa, infertility therapy, number of antenatal care (ANC), the location of placenta previa, cervical length, and placental thickness; and the timing of blood transfusion were not recorded due to limited data.

CONCLUSION

In conclusion, maternal outcomes showed that all mothers experienced complete placenta previa and underwent C-section delivery with most were diagnosed with placenta accreta spectrum (PAS). Less than half of them needed hysterectomy intervention because the other patients were planned for conservative surgery, particularly in patients with focal type PAS. Moreover, they mostly did not have postpartum hemorrhage with half of them needed blood transfusion. There was zero maternal mortality. Neonatal outcomes showed that most of their newborns experienced prematurity and low birth weight but no significant asphyxia. Future studies need to consider other risk factors of placenta previa, and prospective studies are still needed to obtain more objective and accurate results.

DISCLOSURES

Acknowledgment

We would like to express our gratitude to Dr. Soetomo General Academic Hospital Surabaya and Faculty of Medicine, Universitas Airlangga who have facilitated this study. We would also like to thank all the staffs of the Medical Record Center and Installation of Technology, Communication and Information (ITKI) of Dr. Soetomo General Academic Hospital Surabaya who have helped in obtaining the medical records.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors received no financial support for this work.

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. Fan D, Wu S, Liu L, et al. Prevalence of antepartum hemorrhage in women with placenta previa: a systematic review and meta-analysis. Sci Rep. 2017;7:40320. doi: 10.1038/srep40320. PMID: 28067303; PMCID: PMC5220286.
2. Senkoro EE, Mwanamsangu AH, Chuwa FS, et al. Frequency, risk factors, and adverse fetomaternal outcomes of placenta previa in Northern Tanzania. J Pregnancy. 2017;2017:5936309. doi: 10.1155/2017/5936309. Epub 2017 Feb 21. PMID: 28321338; PMCID: PMC5339534.
3. Wormer KC, Jamil RT, Bryant SB. Acute postpartum hemorrhage. 2022 May 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 29763164.
4. UNICEF. Maternal mortality [Internet]. 2019 [cited 2021 Sep 12]. Available from: https://data.unicef.org/topic/maternal-health/maternal-mortality/
5. SDKI. Laporan Survei Demografi dan Kesehatan Indonesia [Indonesia Demogrpahic and Health Survey Reports] [Internet]. 2017 [cited 2020 Apr 4]. Available from: https://www.bps.go.id/statictable/2020/10/21/2111/laporan-survei-demografi-dan-kesehatan-indonesia.html
6. Jauniaux E, Alfirevic Z, Bhide AG, et al.; Royal College of Obstetricians and Gynaecologists. Placenta praevia and placenta accreta: diagnosis and management: Green-top Guideline No. 27a. BJOG. 2019;126(1):e1-e48. doi: 10.1111/1471-0528.15306. Epub 2018 Sep 27. PMID: 30260097.
7. Reddy UM, Abuhamad AZ, Levine D, et al.; Fetal Imaging Workshop Invited Participants. Fetal imaging: executive summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop. J Ultrasound Med. 2014;33(5):745-57. doi: 10.7863/ultra.33.5.745. PMID: 24764329.
8. Cresswell JA, Ronsmans C, Calvert C, et al. Prevalence of placenta praevia by world region: a systematic review and meta-analysis. Trop Med Int Health. 2013;18(6):712-24. doi: 10.1111/tmi.12100. Epub 2013 Apr 1. PMID: 23551357.
9. Aulidiah AE. Hubungan antara paritas ibu dengan kejadian plasenta previa di RSUD Dr.Soetomo tahun 2014-2015 [Correlation between maternal parity and placenta previa incidence in Dr Soetomo Hospital, 2014-2015] [undergraduate thesis] Surabaya: Universitas Airlangga; 2017.
10. Long SY, Yang Q, Chi R, et al. Maternal and neonatal outcomes resulting from antepartum hemorrhage in women with placenta previa and its associated risk factors: A single-center retrospective study. Ther Clin Risk Manag. 2021;17:31-38. doi: 10.2147/TCRM.S288461. PMID: 33469297; PMCID: PMC7811482.
11. Jatiningrum T, Wiyati PS, Wijayahadi N. Luaran Maternal Dan Perinatal Pada Persalinan Dengan Perdarahan Antepartum Akibat Kelainan Lokasi Implantasi Plasenta Di RSUP Dr. Kariadi Semarang Tahun 2013-2014 [Maternal and perinatal outcome in delivert with antepartum bleeding due to abnormal placenta implantation site in Dr Kariadi Hospital, Semarang, in 2013-2014. Jurnal Kedokteran Diponegoro. 2015;4(4):1542-51.
12. Sekiguchi A, Nakai A, Kawabata I, et al. Type and location of placenta previa affect preterm delivery risk related to antepartum hemorrhage. Int J Med Sci. 2013;10(12):1683-8. doi: 10.7150/ijms.6416. PMID: 24151440; PMCID: PMC3804794.
13. Arisani G, Hatini EE, Noordiati. Analisis hubungan plasenta previa terhadap luaran maternal dan perinatal di Rumah Sakit Umum Daerah dan Kota Palangka Raya [Analysis of correlation between placenta previa and maternal and perinatal outcomes in Regional Hospital, Palangka Raya]. J Kebidanan Indones. 8(2):12–25. doi: 10.36419/jkebin.v8i2.12.
14. Daglar K, Tokmak A, Kirbas A, et al. Risk factors for hysterectomy among patients with placenta previa totalis. Proc Obstet Gynecol 2016;6(2):1–10. doi: 10.17077/2154-4751.1319.
15. Akbar MIA, Aryananda R. Tekhnik operasi konservatif pada invasi plasenta abnormal (Abnormally Invasive Placenta/AIP) [Conservative surgical technique in AIP]. Conference: Workshop Kegawatdaruratan Obstetri - PIT Fetomaternal, March 2019.
16. Mremi A, Rwenyagila D, Mlay J. Prevalence of post-partum anemia and associated factors among women attending public primary health care facilities: An institutional based cross-sectional study. PLoS One. 2022;17(2):e0263501. doi: 10.1371/journal.pone.0263501. PMID: 35113955; PMCID: PMC8812965.
17. World Health Organization (WHO). Preterm Birth [Internet]. 2018 [cited 2020 Mar 27]. Available from: https://www.who.int/news-room/fact-sheets/detail/preterm-birth
18. Jing L, Wei G, Mengfan S, et al. Effect of site of placentation on pregnancy outcomes in patients with placenta previa. PLoS One. 2018;13(7):e0200252. doi: 10.1371/journal.pone.0200252. PMID: 30016336; PMCID: PMC6049903.

19. Varouxaki N, Gnanasambanthan S, Datta S, et al. Antepartum haemorrhage. Obstet Gynaecol Reprod Med 2018;28(8):237–42. doi: 10.1016/j.ogrm.2018.07.001.

20. Aslam HM, Saleem S, Afzal R, et al. Risk factors of birth asphyxia. Ital J Pediatr. 2014;40:94. doi: 10.1186/s13052-014-0094-2. PMID: 25526846; PMCID: PMC4300075.

ORIGINAL RESEARCH

Serological description of neonatal umbilical cord blood from pregnant women confirmed with positive COVID-19 by RT-PCR at Rumah Sakit Umum Pusat H. Adam Malik, Medan, Indonesia

Benjamin Sihite, Makmur Sitepu, Khairani Sukatendel, Sarma Nursani Lumbanraja, Iman Helmi Effendi, Rizki Yaznil, Edy Ardiansyah
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Rumah Sakit Umum Pusat H. Adam Malik, Medan, Indonesia

Article Info
Received Sep 3, 2022
Revised Oct 25, 2022
Accepted Nov 1, 2022
Published Dec 1, 2022

Corresponding author:
Benjamin Sihite
benjaminsihite718@gmail.com

Keywords:
COVID-19
RT-PCR
Vertical transmission
Neonatal umbilical serology
IgG
IgM

ABSTRACT

Objective: To evaluate the serological description of the neonatal umbilical cord in COVID-19 mothers confirmed by RT-PCR at Rumah Sakit Umum Pusat (RSUP) H. Adam Malik Medan in January-June 2021.

Materials and Methods: This study was an observational study with a case series approach where the cases were mothers infected with SARS CoV-2 confirmed by RT-PCR. The study was conducted at Universitas Sumatera Utara (USU) Hospital Laboratory and RSUP H. Adam Malik for 6 months, from January 2021 to June 2021. The data collected were analyzed using descriptive statistics. If the data were normally distributed, they were presented as mean ± SD; otherwise, they were presented as median (min-max) for each variable. The Statistical Package for Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis.

Results: Neonatal umbilical cord serology results (IgM and IgG) were predominantly non-reactive, where IgM was non-reactive in 43 neonates (97.7%) and IgG was non-reactive in 37 neonates (84.1%). In mothers without COVID-19 symptoms, neonate umbilical cord serology results were dominated by non-reactive IgM (88.6%) and IgG (79.5%). In mothers who recovered from COVID-19, neonate umbilical cord serology results were also dominated by non-reactive IgM (95.5%) and IgG (81.8%).

Conclusion: The neonatal umbilical cord serology results from the mother confirmed with positive COVID-19 were nonreactive IgG and IgM in the majority of 35 (79%) samples, reactive IgG in 7 (15.9%), and reactive IgM in 1 (2%) sample.

Cite this as : Sihite, B., Sitepu, M., Sukatendel, K., et al. (2022). Serological description of neonatal umbilical cord blood from pregnant woman confirmed with positive COVID-19 by RT-PCR at Rumah Sakit Umum Pusat H. Adam Malik, Medan, Indonesia. Majalah Obstetri & Ginekologi, 30(3), 128-133. https://doi.org/10.20473/mog.V30I32022.128-133.

INTRODUCTION

Current COVID-19 pandemic raises concern about its effect on pregnancy. Reports of neonatal COVID-19 infection immediately after delivery indicate either transplacental migration or horizontal transmission by direct surface contact during delivery[1] or during breastfeeding with virus migration.[1-2]

The placenta is a physical and immunological defense against fetal infection. Maternal natural killer (NK) cells, decidual macrophages, and T cells inhabit the placenta decidua. Immune cells in the decidua are

essential for placenta remodeling and implantation. Their absence is linked to miscarriage and other negative pregnancy outcomes.[3] When the maternal-fetal interface barrier fails, pathogens cleave the maternal innate immune system and placental trophoblast defenses of the fetus by mechanisms that are not fully elucidated.[4]

Several studies have found infected newborns by testing viruses in samples of placenta, amniotic fluid, umbilical cord blood, and neonate throat swabs.[5] Other publications indicate the possibility of vertical transmission due to the presence of IgM in certain neonates from mothers infected with SARS-CoV-2.[6] Several studies have shown three cases of neonates with positive anti-SARS-CoV-2 IgM and IgG serology at birth from SARS-CoV-2-infected mothers. While maternal IgG antibodies cross the placenta, IgM comes from the fetus, thus suggesting SARS-CoV-2 virus exposure in the uterus. The sensitivity and specificity of IgM detection would be 88.2%/96.2% and 70.2%/99%, which is much higher than observed for other viral infections.[7]

Transfer of maternal IgG to the placenta is an important mechanism for fetal protection when fetal humoral immune response is insufficient. Given that IgM is not normally transferred from mother to fetus due to its larger macromolecular structure under normal conditions, some studies have speculated that neonates may have been infected with SARS-CoV-2 in utero from mothers with COVID-19.[8]

In North Sumatra, Indonesia, the Central General Hospital (*Rumah Sakit Umum Pusat*/RSUP) H. Adam Malik Medan is one of the referral hospitals for COVID-19 cases from other hospitals in North Sumatra. According to provisional data, at RSUP H. Adam Malik Medan, North Sumatra, from July-November 2020, it received around 34 pregnant patients with suspected or confirmed COVID-19, with confirmed cases ranging from 7–15 patients per month. The authors were interested in evaluating serological description of neonates' umbilical cord blood from mothers with confirmed COVID-19 by RT-PCR examination for evaluation of mother/infant immune reaction and to clarify potential COVID-19 vertical transmission from mother to child.

MATERIALS AND METHODS

This study was an observational study with a case series approach where the case comprised of mothers infected with SARS CoV-2 confirmed by RT-PCR. The study was conducted at RS Universitas Sumatera Utara (USU) Laboratory and RSUP H. Adam Malik for 6 months from January to June 2021. The samples were pregnant women who came to RSUP H. Adam Malik and RS USU who met inclusion criteria, namely women in 3rd trimester pregnancy and positive COVID-19 confirmed by RT-PCR, while defective blood or serum preparations were excluded from the study. Sampling was done by non-probability sampling, ie. by the consecutive sampling technique.

Tools needed in this research were PPE (Personal Protection Equipment), frozen tube (red cap tube), 3 cc syringe, centrifuge, timer, aliquot, aliquot storage box, refrigerator freezer, YHLO brand rapid test, buffer, stopwatch (timer), and 10-20 mcl micro pipette. The research material was derived from umbilical cord blood/serum of mothers who were confirmed positive with RT-PCR.

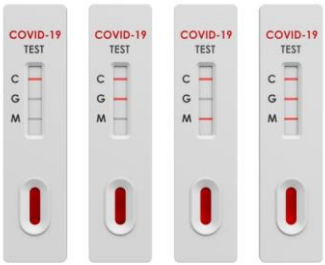


Figure 1. YHLO Antibody

Notes:
1. Negative result: if only C line appears, and G and M lines do not exist.
2. Positive results: if there is a C line and an M or G line, it indicates presence of antibodies to SARS CoV-2 virus.
3. Invalid: if there is no C line, the result is invalid even though there is a G or M line.

Statistical analysis

The data were analyzed descriptively to determine the frequency distribution of the research subjects based on the characteristics of the research sample. The data are displayed in a frequency distribution table with percentage values for each variable. Prior to analysis, a normality test was carried out first with the Kolmogorov-Smirnov test. If the data were normally distributed, they were presented as mean ± SD; otherwise, they were presented as Median (Min-Max) for each variable. The Statistical Package for Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis.

RESULTS AND DISCUSSION

The characteristics of the research subjects are presented in Table 1.

Table 1. Characteristics of research subjects

Characteristics	n = 44
1. Maternal characteristics	
Age, years old (Mean±SD)	28.91±5.810
Parity, n(%)	
Primiparous	14 (31.8)
Secundiparous	11 (25.0)
Multiparous	19 (43.2)
Swab PCR, n(%)	
Positive	44 (100.0)
Symptomatic	5 (11.4)
Asymptomatic	39 (88.6)
Negative	0 (0.0)
Hemoglobin, gr/dl (Mean±SD)	11.33 ± 1.86
Hematocrit, % (Mean ±SD)	33.02 ± 5.16
Leukocytes, sel/mm^3 (Mean ±SD)	11.725.45 ± 4612.52
Platelets, sel/mm^3 (Mean ±SD)	262.318.18 ± 92.950.79
NeutrofiltLymfosit Ratio (NLR)	6.09 ± 1.36
Chest X-ray image, n(%)	
Bronchopneumonia	26 (59.1)
Right pleural effusion	1 (2.3)
Cor and pulmo normal	17 (38.6)
Treatment duration, days	7.63 ± 2.68
Maternal outcome, n(%)	
Cured	42 (95.5)
Death	2 (4.5)
2.Neonates characteristics	
IgM immunoserology	
Reactive	1 (2.3)
Non-Reactive	43 (97.7)
IgG immunoserology	
Reactive	7 (15.9)
Non-Reactive	37 (84.1)
IgM & IgG immunoserology	
Reactive	1 (2.3)
Non-Reactive	43 (97.7)
Swab PCR, n(%)	
Positive	0 (0.0)
Negative	44 (100.0)

Based on mothers' characteristics, the mean age of research subjects was 28.91 years. The majority were multigravida, as many as 19 subjects (43.2%). All study subjects were pregnant women with positive COVID-19 confirmed by RT-PCR swab in as many as 44 patients (100%). Five patients (11.4%) were symptomatic, and 39 patients (88.6%) were asymptomatic. Based on subject outcome, as many as two subjects (4.5%) died, and 42 other subjects (95.5%) were declared cured.

Neonates characteristics based on immunoserological examination of IgM and IgG antibodies found one subject (2.3%) was IgM reactive, seven subjects (15.9%) were IgG reactive, and one subject (2.3%) was reactive to both IgM and IgG. IgG. However, on RT-PCR swab examination of neonates, all were negative for COVID-19.

Immunoserology results of neonates from pregnant women with positive COVID-19 confirmed by RT-PCR

Based on clinical manifestations of COVID-19 positive pregnant women as confirmed by RT-PCR, neonates IgM antibodies were found in one baby (2.3%). Of COVID-19 positive pregnant women as confirmed by RT-PCR with symptoms, neonates IgG antibodies were found in three babies (6.8%). Based on the condition of COVID-19 positive pregnant women as confirmed by RT-PCR who were died, neonates IgM antibodies were found in one baby (2.3%) and neonates IgG antibodies were also found in one baby (2.3%).

Table 2. IgM and IgG immunoserology result of neonates from pregnant women with positive COVID-19 confirmed by RT-PCR based on clinical manifestations.

		Neonates immunoserology IgM (N=44)		Neonates immunoserology IgG (N=44)		Total
		Reactive (%)	Non Reactive (%)	Reactive (%)	Non Reactive (%)	
Clinical Manifestations	Symptomatic	1 (2.3)	4 (9.1)	3 (6.8)	2 (4.5)	5 (11.4)
	Asymptomatic	0 (0.0)	39 (88.6)	4 (9.1)	35 (79.5)	39 (88.6)
Maternal Outcome	Cured	0 (0.0)	42 (95.5)	6 (13.6)	36 (81.8)	42 (95.5)
	Death	1 (2.3)	1 (2.3)	1 (2.3)	1 (2.3)	2 (4.5)
Total		1 (2.3)	43 (97.7)	7 (15.9)	37 (84.1)	44 (100)

Table 3. Immunoserological test result of neonates from pregnant women with positive COVID-19 confirmed by RT-PCR against neonates PCR swab examination results.

Immunoserological test result		Neonates PCR Swabs (N=44)		Total
		Positive (%)	Negative (%)	
IgM	Positive	0 (0.0)	1 (2.3)	1 (2.3)
	Negative	0 (0.0)	43 (97.7)	43 (97.7)
IgG	Positive	0 (0.0)	7 (15.9)	7 (15.9)
	Negative	0 (0.0)	37 (84.1)	37 (84.1)
IgG & IgM	Positive	0 (0.0)	1 (2.3)	1 (2.3)
	Negative	0 (0.0)	43 (97.7)	43 (97.7)
Total		0 (0.0)	44 (100.0)	44 (100.0)

From neonates of pregnant women positive for COVID-19 as confirmed by RT-PCR who underwent immuno-serological examination, one baby (2.3%) had reactive IgM, seven (15.9%) had reactive IgG, and another baby (2.3%) had reactive IgM and IgG, but all tested negative for COVID-19 on RT-PCR swab examination.

Of pregnant women with positive COVID-19 confirmed by RT-PCR in this study, neonates' IgM antibodies were found in one baby (2.3%). Of pregnant women with positive COVID-19 confirmed by RT-PCR with symptoms, neonates IgG antibodies were found in three babies (6.8%). Based on the condition of women with positive COVID-19 confirmed by RT-PCR who died, neonates IgM antibodies were found in one baby (2.3%). From pregnant women with positive COVID-19 confirmed by RT-PCR who died, neonates with IgG antibodies were found in one baby (2.3%).

Zeng et al. examined six infants born to six women with confirmed COVID-19 and discovered that they all had higher IgG and IgM antibodies (10 AU/mL) than normal levels, with IgG levels of 125.5 AU/mL and IgM levels of 39.6 AU/mL. IgG is passively transferred across the placenta from mother to fetus, beginning at the end of the second trimester and reaching high levels at birth. However, the detected IgM is usually not transferred from mother to fetus due to its larger macromolecular structure.[9] ACE2 expression is seen in many tissues directly associated with developing pregnancy, whereas a recent single-cell RNA sequencing analysis showed ACE2 expression in maternal-fetal stromal, perivascular, placental, and decidua cells. Kotlyar et al. hypothesized the possibility of in utero transmission because IgM cannot cross the placenta.[10]

A recent journal reviews also stated that IgG or IgM was detected in 90% of infants with negative PCR swabs from mothers with confirmed COVID-19 (10/11; 95% CI: 73.9%–107.9%). For IgG and IgM, the mean antibody levels detected were 75.49 AU/ml (range, 7.25-140.32 AU/ml) and 3.79 AU/ml (range, 0.16-45.83 AU/ml), respectively (p = 0.0041). A total of 19 studies were reported in China and the other countries. China reported 4.2% of infants contracted COVID-19 vertically from their mothers, while outside China it was 10.5%. The method of delivery by cesarean section was found in 10% of positive babies, while vaginal delivery was 10.3%. In addition, asymptomatic infants from infected mothers have a strong immune response to COVID-19 in the second trimester of pregnancy because of IgG formation potential.[11]

Based on the condition of women with positive COVID-19 confirmed by RT-PCR who died in this study, neonate IgM antibodies were found in one baby (2.3%) and neonate IgG antibodies were also found in one baby (2.3%). A study of 9 third-trimester pregnant women with COVID-19 discovered that none of the patients had severe COVID-19 or died, and that there were no severe outcomes in neonates or fetal infections that could have been caused by intrauterine vertical transmission.[12] A review of 26 journals on neonate COVID-19 infection stated that demographically, 44 neonates from 35 confirmed COVID-19 mothers, only 1 neonate with confirmed COVID-19 was found and the rest had higher IgM and IgG serology levels than normal, and overall, the mothers were able to recover completely.[13]

In this study, from neonates of pregnant women with positive COVID-19 confirmed by RT-PCR who underwent immunoserological examination, one (2.3%) had reactive IgM, seven (15.9%) had reactive IgG, and one (2.3%) had reactive IgM and IgG, but all tested negative for COVID-19 on RT-PCR swab examination. Zhu et al. studied neonates of 9 pregnant women with confirmed COVID-19 with various mild-moderate symptoms. Of these neonates, 6 had a Pediatric Critical Illness Score (PCIS) of less than 90.

Clinically, symptoms encountered in neonates were shortness of breath, fever, thrombocytopenia, abnormal liver function, tachycardia, vomiting, and pneumo-thorax. All of the neonates had pharyngeal swabs and the results were negative for COVID-19, but the possibility of false-negative results could not be ruled out.[14]

This is in line with a case report by Dong et al. in which IgM, IgG, and RT-PCR swab examinations were carried out on neonates from a mother with confirmed COVID-19. The results found that the neonates had high serological levels, but swab results were negative.[15] In contrast to Liu et al.'s study, who examined 51 neonates, neither IgG, IgM, nor positive RT-PCR swab results were found.[16] Yang et al. also found that none of the 23 infants had a positive nasopharyngeal swab; one preterm infant was found to have a positive result for IgM anti-SARS-CoV-2 within 2 hours of birth.[17]

This study showed that there was potential for antibodies inherited from pregnant women to provide protection for neonates against SARS-CoV-2 infection. Another evidence suggests that vertical transmission in the uterus is responsible for COVID-19 in neonates that makes neonatal infection through the umbilical cord unlikely.[18-20] Further studies are needed to determine whether COVID-19 antibodies protect neonates from COVID-19 infection; the concentration of IgG that can provide prevention; and whether the transplacental kinetics of vaccine-derived antibodies are similar to

those obtained naturally. In addition, the results of this study were expected to be useful in determining the management of neonates from mothers infected with COVID-19.

There were limitations in this study because it was an observational one, therefore it could not draw some conclusions in terms of testing and two-group comparison. Therefore, further research is needed to provide an in-depth review of COVID-19 outcomes among mothers and neonates in Type A hospital scale.

CONCLUSION

The neonatal umbilical cord serology results from the mothers confirmed with positive COVID-19 revealed that the majority (79%) of the samples, comprising 35 mothers, had nonreactive IgG and IgM; seven (15.9%) had reactive IgG, and one (2%) had reactive IgM. All the babies' PCR swab results were negative. Therefore, research with different methods is needed to assess potential vertical transmission of COVID-19.

DISCLOSURES

Acknowledgment

The present study was conducted in collaboration with University of North Sumatra and RSUP H. Adam Malik General Hospital, Medan, Indonesia.

Conflict of interest

All authors have no conflict of interest.

Funding

This research has received no external funding.

Author Contribution

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

REFERENCES

1. Liu H, Wang LL, Zhao SJ, et al. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 2020;139:103122. doi: 10.1016/j.jri.2020.103122. Epub 2020 Mar 19. PMID: 32244166; PMCID: PMC7156163.
2. Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, et al. Vertical transmission of Coronavirus Disease 19 (COVID-19) from infected pregnant mothers to neonates: A Review. Fetal Pediatr Pathol. 2020;39(3):246-50. doi: 10.1080/15513815.2020.1747120. Epub 2020 Apr 2. PMID: 32238084; PMCID: PMC7157948.
3. Benski C, Di Filippo D, Taraschi G, et al. Guidelines for pregnancy management during the COVID-19 pandemic: A public health conundrum. Int J Environ Res Public Health. 2020;17(21):8277. doi: 10.3390/ijerph17218277. PMID: 33182412; PMCID: PMC7664946.
4. Yuliana, Y. Corona virus diseases (COVID-19): Sebuah tinjauan literatur. Wellness and Healthy Magazine. 2020;2(1):187-92. doi: 10.30604/well.95212020
5. Fenizia C, Biasin M, Cetin I, et al. Analysis of SARS-CoV-2 vertical transmission during pregnancy. Nat Commun. 2020;11(1):5128. doi: 10.1038/s41467-020-18933-4. PMID: 33046695; PMCID: PMC7552412.
6. Alberca RW, Pereira NZ, Oliveira LMDS, et al. Pregnancy, viral infection, and COVID-19. Front Immunol. 2020;11:1672. doi: 10.3389/fimmu.2020.01672. PMID: 32733490; PMCID: PMC7358375.
7. Mahyuddin AP, Kanneganti A, Wong JJL, et al. Mechanisms and evidence of vertical transmission of infections in pregnancy including SARS-CoV-2s. Prenat Diagn. 2020;40(13):1655-70. doi: 10.1002/pd.5765. Epub 2020 Oct 4. PMID: 32529643; PMCID: PMC7307070.
8. Zeng H, Xu C, Fan J, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. JAMA. 2020;323(18):1848-49. doi: 10.1001/jama.2020.4861. PMID: 32215589; PMCID: PMC7099444.
9. Kohler PF, Farr RS. Elevation of cord over maternal IgG immunoglobulin: evidence for an active placental IgG transport. Nature. 1966210(5040):1070-1. doi: 10.1038/2101070a0. PMID: 5950290.
10. Kotlyar AM, Grechukhina O, Chen A, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol. 2021;224(1):35-53.e3. doi: 10.1016/j.ajog.2020.07.049. Epub 2020 Jul 31. PMID: 32739398; PMCID: PMC7392880.
11. Mo H, Wang M, Wang M, et al. Detectable antibodies against SARS-CoV-2 in newborns from mothers infected with COVID-19 at different gestational ages. Pediatr Neonatol. 2021;62(3):321-3. doi: 10.1016/j.pedneo.2021.03.011. Epub 2021 Mar 26. PMID: 33836982; PMCID: PMC7997304.
12. Chen H, Guo J, Wang C, et al. Clinical characteristics and intrauterine vertical transmission

potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet. 2020;395(10226):809-15. doi: 10.1016/S0140-6736(20)30360-3. Epub 2020 Feb 12. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. Erratum in: Lancet. 2020 Mar 28;395(10229):1038. PMID: 32151335; PMCID: PMC7159281.

13. Trevisanuto D, Cavallin F, Cavicchiolo ME, et al. Coronavirus infection in neonates: a systematic review. Arch Dis Child Fetal Neonatal Ed. 2021; 106(3):330-5. doi: 10.1136/archdischild-2020-319837. Epub 2020 Sep 17. PMID: 32943533.
14. Zhu H, Wang L, Fang C, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Transl Pediatr. 2020;9(1):51-60. doi: 10.21037/tp.2020.02.06. PMID: 32154135; PMC ID: PMC7036645.
15. Dong L, Tian J, He S, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA. 2020;323(18) :1846-8. doi: 10.1001/jama.2020. 4621. PMID: 32215581; PMCID: PMC7099527.
16. Liu P, Zheng J, Yang P, et al. The immunologic status of newborns born to SARS-CoV-2-infected mothers in Wuhan, China. J Allergy Clin Immunol. 2020;146(1):101-9.e1. doi: 10.1016/j.jaci.2020.04.038. Epub 2020 May 11. PMID: 32437740; PMCID: PMC7211641.
17. Yang H, Hu B, Zhan S, et al. Effects of Severe Acute Respiratory Syndrome Coronavirus 2 infection on pregnant women and their infants. Arch Pathol Lab Med. 2020;144(10):1217-22. doi: 10.5858/arpa.2020-0232-SA. PMID: 32422078.
18. Gidlöf S, Savchenko J, Brune T, et al. COVID-19 in pregnancy with comorbidities: More liberal testing strategy is needed. Acta Obstet Gynecol Scand. 2020;99(7):948-9. doi: 10.1111/aogs.13862. Epub 2020 Apr 17. PMID: 32249924.
19. Li Y, Zhao R, Zheng S, et al. Lack of vertical transmission of Severe Acute Respiratory Syndrome Coronavirus 2, China. Emerg Infect Dis. 2020;26(6):1335-6. doi: 10.3201/eid2606.200287. Epub 2020 Jun 17. PMID: 32134381; PMCID: PMC7258467.
20. Khan S, Peng L, Siddique R, et al. Impact of COVID-19 infection on pregnancy outcomes and the risk of maternal-to-neonatal intrapartum transmission of COVID-19 during natural birth. Infect Control Hosp Epidemiol. 2020;41(6):748-50. doi: 10.1017/ice.2020.84. PMID: 32279693; PM CID: PMC7156579.

CASE REPORT

Comprehensive management of pregnant woman with Sjögren's syndrome

Giovanny Azalia Gunawan*, Adinda Ayu Dyah Rahadina, Budi Prasetyo
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga,
Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Article Info
Received Mar 19, 2022
Revised May 17, 2022
Accepted Jun 20, 2022
Published Dec 1, 2022

Corresponding author:
Giovanny Azalia Gunawan
giogunawan95
@gmail.com

Keywords:
Sjögren syndrome
Pregnancy
Autoimmune disease
Comprehensive management
Preeclampsia

ABSTRACT

Objective: To illustrate the comprehensive management of pregnant women with Sjögren syndrome.

Case Report: A 24 years old women came to Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, due to Sjögren syndrome in 35/36 weeks of gestasional age for routine examination. She was first diagnosed with Sjögren syndrome in February 2018 because she complained of dry eyes and hair fall out. This was her first pregnancy. Laboratory result showed positive ANA test. The patient had hypertension with controlled blood preasure and dry eyes. The patient was diagnosed with primigravida 35-36 weeks of pregnancy, single live intrauterine, head presentation, IUGR, screening preeclampsia was positive, and there was complication with Sjögren's syndrome. The patient was treated by multidisciplinary team consisting of obstetricians, internists, ophthalmologists and neonatologists.

Conclusion: Sjögren's syndrome is a chronic autoimmune disease that attacks the exocrine glands, especially lacrimal and salivary glands. The exact cause of Sjögren's syndrome is still not known. Women with Sjögren's syndrome should have clinical and laboratory examination, risk assessment and also preconception counseling before planning pregnancy because Sjögren syndrome was a rare case during pregnancy. Close monitoring and proper management was imperative to detect the early complication.

Cite this as : Gunawan, G.A., Rahadina, A.A.D., & Prasetyo, B. (2022). Comprehensive management of pregnant woman with Sjögren's syndrome. Majalah Obstetri & Ginekologi, 30(3), 134-138. https://doi.org/10.20473/mog.V30I32022.134-138.

INTRODUCTION

Sjögren's syndrome is a chronic systemic autoimmune disease caused by lymphocyte infiltration in the exocrine glands, the lacrimal and salivary glands.[1] Sjögren's syndrome is divided into primary and secondary. Secondary Sjögren's syndrome occurs with other autoimmune diseases, most commonly are rheumatoid arthritis and systemic lupus erythematous.[2-5]

Sjögren's syndrome is mostly prevalent in women, with a ratio of women and men from 20 : 1 to 9 : 1. It generally appears in the 4-5 decade, at the age of perimenopause.[1-5] Immune-mediated inflammation causes secretory dysfunction of the glands and causes sicca symptoms.[6] The main symptom of Sjögren's syndrome is dryness of eyes caused by lacrimal hypo-function and dry mouth because of hyposalivation.[4,7] Physical examination will reveal keratoconjunctivitis sicca and xerostomia.[1] The symptoms sometimes had extra-glandular involvement, such as joints, skin, lungs, GI tract, nervous system, and kidneys.

Hormonal and immunological changes during pregnancy can modulate the expression of autoimmune disease.[8] Autoimmune disease itself will affect maternal and fetal development. Women with Sjögren's syndrome can get pregnant and have healthy babies but it is a good idea to get advice from a specialist because there is risk of complications for some women such as abortion, preterm delivery, preeclampsia and etc. Careful patient management and control is important to detect complications early and provide early therapy.[9]

CASE REPORT

A 24-year-old primigravida at 35-36 weeks of gestational age visited the obstetrics gynecology clinic for routine examination. The patient had no complaints.

Current medical history

The patient was diagnosed with Sjögren's syndrome since February 2018. She complained dry eyes and hair fall out. Since positive for pregnancy, she had routine examination at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, and received methyl-prednisolone 4 mg every 24 hours, azathioprine 2 mg every 12 hours, folic acid 1 tablet, aspirin 1 tablet every 24 hours and calc 1 tablet every 24 hours.

This was the first pregnancy for the patient. She had her first menarche at age 13, having regular cycle every month, with duration of menstruation about 5 days. The patient got cramp pain every month before and after menstruation. This was her first marriage and she never used any contraception. There was no family member who had autoimmune disease similar to the patient's.

Physical examination

From vital sign examination, the patient looked healthy with GCS 456. There was no pain with Visual Analog Scale (VAS) score of 0. The patient's body weight was 60 kg, body height 160 cm, with a body mass index of 23.4 kg/m^2 (normal). From the head and neck examination, there was non-anemic conjunctiva, non-icteric sclera, no cyanosis, no dyspnea. There was no increase in jugular venous pressure nor any enlargement of the neck lymph nodes.

From the chest examination, we obtained symmetrical chest wall movement, without intercostalis or supraclavicular retraction. On cardiac examination, we found single S1 and S2 heart sound, regular, without additional hearts sounds, gallop, or pericardial friction rub. In lung examination, vesicular breath sounds were obtained on both hemithorax, no additional breath sounds, either rhonchi or wheezing, in both lung fields.

Table 1. Vital sign examination

Pre gestational		Blood pressure 135/70 mmHg Pulse 99 x/minute Respiratory rate 22 x/minute Temperature 36.6 ºC Saturation 98 % free air
Trimester I		Blood pressure 130/80 mmHg Pulse 91 x/minute Respiratory rate 20 x/ minute Temperature 36.9 ºC Saturation 98 % free air
Trimester II	1st	Blood pressure 145/90 mmHg Pulse 88 x/minute Respiratory rate 18 x/minute Temperature 36.7 ºC Saturation 99% free air
	2nd	Blood pressure 148/89 mmHg Pulse 90 x/minute Respiratory rate 21 x/minute Temperature 36.4 ºC Saturation 99% free air
Trimester III		Blood pressure 140/80 mmHg Pulse 97 x/minute Respiratory rate 20 x/minute Temperature 36.7ºC Saturation 97% free air

From the abdominal examination, we found no surgery scar. From extremities examination, they felt warm, dry, and looked red. There was no edema on both extremities. From obstetric examination, we obtained protuberance abdomen with striae gravidarum. We could palpate the fetus, single live intrauterine with head presentation, fundus height 24 cm, fetal heart rate 144 x/minute, regular rhythm.

Additional examinations

From laboratory examination, we found Hb 12.6 g/dl, Hct 36/6%, leucocytes 4.870/µL, and platelets 226,000, with non-reactive HbsAg, HIV, and syphilis. An immunology panel showed high titers of antinuclear antibody levels 211,60 units (normal range <20 units), normal complement levels, C3 level of 63.1 mg/dL (normal range 50-120 mg/dL), C4 of 20.5 mg/dL (20-50 mg/dL). A diagnosis of autoimmune disease was made.

From obstetric sonography, we found intrauterine single living fetus, approximately 35/36 weeks of pregnancy, placenta on fundus, enough amnion fluid, with estimated fetal weight 2050 g. There was no congenital heart block.

Assessment and management

Based on the history, physical and additional examinations, the patient was assessed with primigravida 35-

36 weeks of pregnancy, single live intrauterine, head presentation, IUGR, positive preeclampsia, and complicated with Sjögren's syndrome. The patient was planned to have fetomaternal sonography routinely to detect any abnormality. The patient was treated by multidisciplinary team consisting of obstetricians, internists, ophthalmologists and neonatologists. The therapy given to the patient was methylprednisolone 4 mg every 24 hours, azathioprine 2 mg every 12 hours, folic acid 1 tablet, calc 1 tablet every 24 hours and aspirin 1 tablet every 24 hours. The patient was planned to have vaginal labor.

Outcome

The baby was born vaginally at 39 weeks with birth weight 2200 g with apgar score 8. There were no complications found in the mother and the baby.

DISCUSSION

Sjögren's syndrome is a chronic systemic autoimmune disease caused by lymphocyte infiltration in the exocrine glands, namely the lacrimal and salivary glands.[10] This syndrome was first discovered by an ophthalmologist from Sweden named Henrik Sjögren in 1933.[19] The exact cause is unknown. Hormonal and immunological changes can occur during pregnancy and affect the patient's autoimmune disease activity.[9] Sjögren's syndrome patient tends to experience worsening during pregnancy and post partum mainly due to worsening pulmonary hypertension.[20]

The most common complications in pregnancy with Sjögren's syndrome include spontaneous abortion, preterm delivery, preeclampsia, and IUGR. Neonatal lupus and congenital heart block (CHB) are the most common complications in the fetus.[12] The incidence of neonatal lupus in mothers with positive anti-SSA is 1-2%.[4] Prenatal screening of anti-SSA/Ro and anti-SSB/La antibodies is needed before conception or as soon as possible, especially in patients with known Sjögren's syndrome.[11]

The main symptom of this disease is Sicca syndrome.[17] A person suffering from Sjögren's syndrome will feel dryness on mouth and eye. This is due to the decreasing secretions of the salivary and tear glands that act as moisturizers. In addition to the two symptoms above, there can also be complaints of dry throat and nose, numb tongue, digestive complaints, joint pain and frequent fatigue. Complaints that arise in each individual tends to be more varied.[13]

Women with Sjögren's syndrome should undergo clinical examination, laboratory examination, risk assessment and also preconception counseling before planning pregnancy.

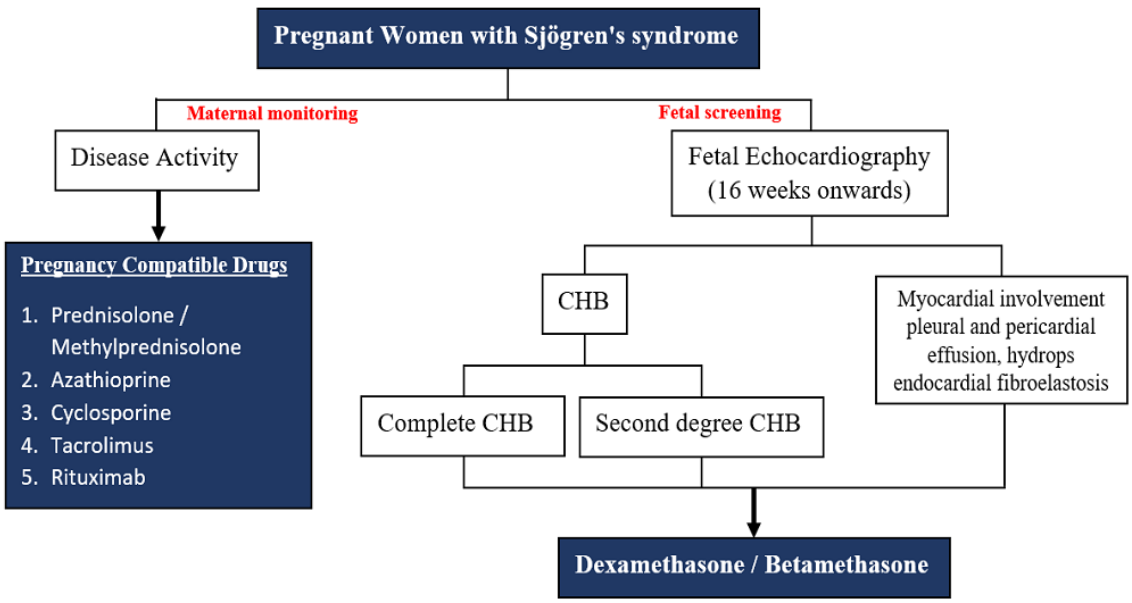


Figure 1. Overview of Sjögren's syndrome management in pregnancy.[14]

Ideally, disease activity should be well controlled at least 3- 6 months before conception. Teratogenic drugs such as methotrexate, cyclophosphamide, and mycophenolate should be discontinued at preconception and replaced by other drugs safe for pregnancy. Pregnancy is contraindicated in CKD, severe PAH, severe ILD, and heart failure.[4,9]

CHB is caused by damage to the AV node by anti-SS-A and/or anti-SSB.[15] Congenital heart block generally occurs at 18-24 weeks of gestation, can appear as fetal bradycardia which can be detected by routine fetal auscultation, ultrasound, or pulsed Doppler echocardiography.[16] There is no guideline on the frequency of examinations, some carry out Doppler examinations for 18-26 weeks and every 2 weeks after 32 weeks of age.[11]

The therapy is expected to reduce maternal autoantibodies, thereby reducing placental transfer and reducing inflammation before permanent fibrosis and irreversible CHB occur. Early diagnosis and therapy are expected to improve prognosis, especially in cases of incomplete CHB.[4] Therapy with fluorinated steroids, such as dexamethasone and betamethasone, can reduce damage caused by inflammation because of antibodies.[18] Thirty percent of cases of second-degree block return to the sinus rhythm after steroid administration. If after 1 week there is progression to grade 3, then the therapy is stopped. There is still a lot of controversy for giving steroid on the 1st degree block. Few studies claim that steroid therapy can reverse to sinus rhythm. These studies are not enough and some considered conservative therapy.[11]

CONCLUSION

Sjögren's syndrome is an autoimmune disease that attacks the exocrine glands and causes sicca symptoms. The exact cause of Sjögren's syndrome is still not known. The diagnosis begins with anamnesis of the complaints of dry eye and mouth symptoms with examination for antibody levels. Pregnant women accompanied by Sjögren's syndrome has risk of complications such as death of the fetus in the womb, spontaneous abortion, and premature birth. Close monitoring and proper management are imperative to detect early complication. Management of Sjögren's syndrome is supportive and symptomatic to prevent complications. Immunosuppresives such as corticosteroid is one of the therapies for Sjögren's syndrome. As for pregnant women accompanied Sjögren's syndrome, apart from getting corticosteroid therapy, they are advised to do regular pregnancy ultrasound to determine the presence of organ abnormalities in the fetus (congenital heart block).

DISCLOSURES

Acknowledgment

I like to thank Adinda Ayu Dyah Rahadina for her contribution in working together with this case report. I also want to thank Dr. Budi Prasetyo for his comments, suggestions and fruitful discussions as well as his support and encouragement.

Conflict of interest

All authors have no conflict of interest.

Patient consent for publication

The patient signed the informed consent form and agreed that this case report is published.

Funding

This research has received no external funding.

Author contribution

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

REFERENCES

1. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. Clin Epidemiol. 2014;6:247-55. doi: 10.2147/CLEP.S47399. PMID: 25114590; PMCID: PMC4122257.
2. Gupta S, Gupta N. Sjögren Syndrome and pregnancy: A literature review. Perm J. 2017;21:16-047. doi: 10.7812/TPP/16-047. Epub 2016 Nov 9. PMID: 28080954; PMCID: PMC5267941.
3. Hussein SZ, Jacobsson LT, Lindquist PG, et al. Pregnancy and fetal outcome in women with primary Sjogren's syndrome compared with women in the general population: a nested case-control study. Rheumatology (Oxford). 2011;50(9):1612-7. doi: 10.1093/rheumatology/ker077. Epub 2011 Apr 29. PMID: 21531959.
4. Meena A, Hema T. Successful management of a case of pregnancy with Sjögren Syndrome.

International Journal of Scientific Research 2020;9:11-2. doi: 10.36106/ijsr.
5. Pasoto SG, Adriano de Oliveira Martins V, Bonfa E. Sjögren's syndrome and systemic lupus erythematosus: links and risks. Open Access Rheumatol. 2019;11:33-45. doi: 10.2147/OARRR.S167783. PMID: 30774485; PMCID: PMC6357904.
6. Tong L, Koh V, Thong BY. Review of autoantigens in Sjögren's syndrome: an update. J Inflamm Res. 2017;10:97-105. doi: 10.2147/JIR.S137024. PMID: 28848359; PMCID: PMC5557906.
7. Khalele BAEO. Sjögren's syndrome in a 25-year-old female: A case study. Future Dental Journal of Egypt. 2016;2:94-8. doi: 10.1016/j.fdj.2016.10.001.
8. Brandt JE, Priori R, Valesini G, et al. Sex differences in Sjögren's syndrome: a comprehensive review of immune mechanisms. Biol Sex Differ. 2015;6:19. doi: 10.1186/s13293-015-0037-7. PMID: 26535108; PMCID: PMC4630965.
9. Elliott B, Spence AR, Czuzoj-Shulman N, et al. Effect of Sjögren's syndrome on maternal and neonatal outcomes of pregnancy. J Perinat Med. 2019;47(6):637-42. doi: 10.1515/jpm-2019-0034. PMID: 31287800.
10. Mavragani CP, Moutsopoulos HM. Sjögren's syndrome: Old and new therapeutic targets. J Autoimmun. 2020;110:102364. doi: 10.1016/j.jaut.2019.102364. Epub 2019 Dec 9. PMID: 31831255.
11. Nasef N, Hafez M, Bakr A. Neonatal lupus erythematosus. Journal of Neonatology & Clinical Pediatrics. 2014;1:002. doi: 10.24966/NCP-878X/100002
12. Ambrosi A, Wahren-Herlenius M. Congenital heart block: evidence for a pathogenic role of maternal autoantibodies. Arthritis Res Ther. 2012;14(2):208. doi: 10.1186/ar3787. PMID: 22546326; PMCID: PMC3446439.
13. Tarn JR, Tripp NH, Lendrem DW, et al. Symptom-based stratification of patients with primary Sjögren's syndrome: Multi-Dimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials. The Lancet Rheumatology. 2019;1(2):85-94. doi: 10.1016/S2665-9913(19)30042-6.
14. Sandhya, P. Management of Sjögren's syndrome During Pregnancy. In: Sharma, S. (eds) Women's Health in Autoimmune Diseases, 2020:187-96. Springer, Singapore. doi: 10.1007/978-981-15-0114-2_18.
15. Tam WK, Hsu HC, Hsieh MH, et al. Association of Anti-Ro/Sjögren's syndrome type A Antibodies and Complete Atrioventricular Block in an Adult With Sjögren's syndrome. Arch Rheumatol. 2017;33(2):225-9. doi: 10.5606/ArchRheumatol.2018.6492. PMID: 30207577; PMCID: PMC 6117129.
16. Batra AS, Balaji S. Fetal arrhythmias: Diagnosis and management. Indian Pacing Electrophysiol J. 2019;19(3):104-9 doi: 10.1016/j.ipej.2019.02.007. Epub 2019 Feb 25. PMID: 30817991; PMCID: PMC6531664.
17. Lester S, Rischmueller M, Tan L, et al. Sicca symptoms and their association with chronic rhinosinusitis in a community sample. Open Rheumatol J. 2012;6:170-4. doi: 10.2174/1874312901206010170. Epub 2012 Jun 28. PMID: 22802916; PMCID: PMC3396280.
18. Putra RS, Najirman. Treatment of Systemic Lupus Erythematosus with Anti-SSA and SSB positive pregnancies. Bioscientia Medicina: Journal of Biomedicine and Translational Research. 2022;6(3):1523-29. doi: 10.37275/bsm.v6i3.470.
19. Akpek EK, Bunya VY, Saldanha IJ. Sjögren's syndrome: More than just dry eye. Cornea. 2019 May;38(5):658-61. doi: 10.1097/ICO.0000000000001865. PMID: 30681523; PMCID: PMC6482458.
20. Gayed M, Gordon C. Pregnancy and rheumatic diseases. Rheumatology (Oxford). 2007;46(11):1634-40. doi: 10.1093/rheumatology/kem156. Epub 2007 Jul 10. PMID: 17623748.

CASE REPORT

Psychological aspects of precocious puberty child during the COVID-19 pandemic

Nurul Ima Suciwiyati[1], Nur Rochmah[2]*, Muhammad Faizi[2], Fadhil Abiyyu[1]
[1]Faculty of Medicine, Universitas Airlangga, Dr Soetomo General Academic Hospital, Surabaya, Indonesia.
[2]Department of Child Health, Faculty of Medicine, Universitas Airlangga, Dr Soetomo General Academic Hospital, Surabaya, Indonesia.

Article Info
Received Apr 23, 2022
Revised Jun 17, 2022
Accepted Jul 20, 2022
Published Dec 1, 2022

Corresponding author:
Nur Rochmah
nur-r@fk.unair.ac.id

Keywords:
Precocious Puberty (PP)
Psychological aspect
COVID-19
Mental health

ABSTRACT

Objective: To present a longitudinal case of a child with organic Central Precocious Puberty (CPP) that focused on medical, growth and development, and parent's psychological aspect during the COVID-19 pandemic.

Case Report: A 14-month old girl attended with major complaints of breasts enlargement and menstruation. The Tanner's stage was at A1M3P1 and the vagina showed reddish-brown spots. The patient's bone age was advanced (3 years and 6 months). USG examination showed a corpus uterine: cervix ratio of 2:1. GnRH stimulation test showed an elevated of FSH/LH and estradiol. MRI showed an extra-axial dense mass that leads to Hypothalamic Hamartoma (HH). The definitive diagnosis of this patient was organic CPP with HH. The patient was managed with GnRH analog. Precocious puberty (PP) becomes a financial and psychosocial burden for parents. The COVID-19 pandemic adds a double burden for the parents.

Conclusion: During the COVID-19 pandemic, parents with PP children had a good psychological aspect if the child was comprehensively handled with adequate motivation and psychoeducation.

Cite this as : Suciwiyati, N.I., Rochmah, N., Faizi, M., et al. (2022). Psychological aspects of precocious puberty child during the COVID-19 pandemic. Majalah Obstetri & Ginekologi, 30(3), 139-145. https://doi.org/10.20473/mog.V30I32022.139-145.

INTRODUCTION

Precocious puberty (PP) is a common condition in pediatric endocrinology cases. It is defined as the development of pubertal changes before 8 years old in girls. PP is responsible for early progression of secondary sexual characteristics, rapid bone maturation, final height reduction, inappropriate body appearance, and psychological behavioral abnormalities.[1,2]

It is classified into central precocious puberty (CPP) and peripheral precocious puberty (PPP) types. CPP accounts for 80% of patients with PP. The frequency of CPP ranges between 1/5.000 – 1/10.000 and more frequent in girls. Gender ratio for girls:boys is between 3 : 1.[3] Based on the data, 13 CPP cases were reported in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from January 2012 to June 2015 with girls : boys proportion was 10 : 3.

PP becomes a financial and psychosocial burdens for parents. Furthermore, the COVID-19 pandemic worsens the situation. An Italian study described that during and after the COVID-19 lockdown, the incidence of newly diagnosed and pubertal progression of CPP increased.[4] A previous study explained that psychological stress caused by parents or parental conflicts could induce early puberty. The impact of COVID-19 increased stress and behavioral changes due to quarantine or social isolation.[5] Parents may also pass their psychological

distress to children, leading to improper parenting behaviors, which may affect medical treatment and the outcome of children with PP.[6]

In this case report, we reported the monitoring of a child with organic CPP with Hypothalamic Hamartoma (HH) that focused on medical, growth and development, and parent's psychological aspect.

CASE REPORT

A 14-month-old girl attended the pediatric endocrinology outpatient, Dr. Soetomo General Hospital, on June 26, 2019 with major complaints of breasts enlargement and menstruation. The mother reported that she realized her daughter had breast development since six months of age and early menstruation was observed at 9-month of age for 3 days, then stopped, and happened again at 1-year of age. It started with brown blood and then bright red blood with mucus. Pubic and armpit hair were not found. There was no history of disease, trauma and drug or corticosteroid use in long time.

She was the third daughter and there was no history of taking any medicine nor radiation exposure during pregnancy. She was delivered spontaneously by midwife. The birth weight and length was 3100 gr and 49 cm. The patient had exclusive breastfeeding until 22-month-old then continued with formula milk. The immunization was up to date. She was able to stand at age 11-month-old and walk by herself at age 13-month-old, talk fluently at age 17-month-old. The mother reported her first menstruating when she was 11-year-old and her father got bed wetting when he was 13-year-old. The father and the mother height are 160 cm and 150 cm. The mid parental height was 164 cm and the child predictive adult height was 140 – 157 cm.

Physical examination presented an alert girl, with body weight and height were 10 kg and 83 cm. Percentage of ideal body weight was classified as good nutrition. Growth velocity was 7.6 - 8.3 cm/year. Blood pressure was 90/50 mmHg, heart rate was 110 beats/minute, respiratory rate was 24 beats/minute, and axillary temperature was 36ºC. Examination of head, neck, lungs, heart, abdomen and extremities were within normal limits. WHO Z-score plotting showed normal WAZ, WLZ, HcAZ and LAZ >2SD.

The patient had tanner stage 1 of armpit hair development, tanner stage 3 of breast development, and tanner stage 1 of pubic hair and genital development (A1M3P1). There were sign of vaginal discharge, labia minor development, and menstruation. Based on history taking and physical examination the working diagnose of this patient was suspicious PP. The patient was examined for bone age using Greulich and Pyle method and it was found that the predicted patient age was 3-year and 6-month with chronological age of 14 month. Ultrasonography (USG) showed a corpus uterine : cervix ratio was 2 : 1 (normal ratio <1).

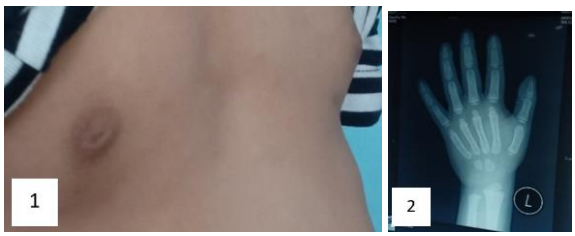


Figure 1 & 2. (1) Patient's breasts (Stage 3 breast development). (2) X-Ray of patient's left palm

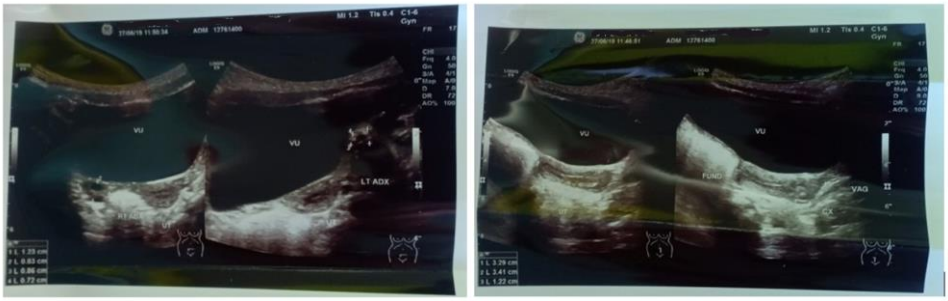


Figure 3. USG of patient's uterus and cervix

Table 1. Hormonal examination (GnRH Stimulation Test)

	Basal		2 hours after Leuprorelin		Normal
	N	Interpretation	N	Interpretation	value
LH	6.55	Elevated	23.33	Elevated	0.1 - 3.1
FSH	5.23	Normal	12.69	Elevated	0.46 - 5.98
Estradiol	28.67	Elevated	39.03	Elevated	6.00 - 27.00

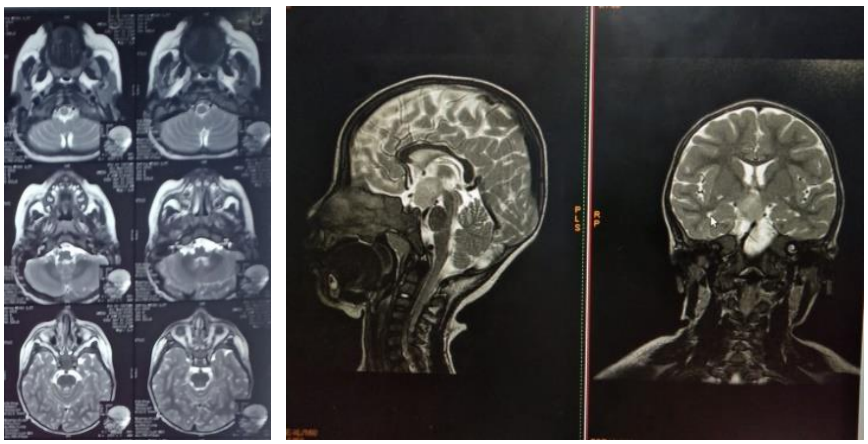


Figure 4. Patient's head MRI

A Gonadotropin-Releasing Hormone (GnRH) stimulation test is needed to differentiate CPP and PPP. CPP theoretically has hormonal abnormality and high level of estradiol, Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) after GnRH stimulation test.[7] The genes GABRA1, LIN28B, NPYR, TAC3, and TACR3 are associated with CPP.[8] Laboratory examination after GnRH stimulation test found a high level of FSH/LH, FSH and LH ratio >1, and high level of estrogen. Head Magnetic Resonance Imaging (MRI) showed an extra-axial dense mass, 2.2 x 1.5 x 1.7 cm, in supra-cellar (from tuburus cinereum) that leads to HH. The definitive diagnosis of this patient was organic CPP with HH. The patient was in good condition after medication, and no adverse event occurred. Moreover, the patient had an MRI for follow-up.

DISCUSSION

Medical aspect

The patient was monitored for medical aspects from February - August 2020. Diagnosis of PP underlies on the growth spurt, advanced bone age, secondary sexual characteristic and an elevated LH, FSH, estradiol after GnRH stimulation test.[1,9] At the final follow-up at 28-month, the patient had a good treatment compliance, LH and FSH level was 0.16 and 1.15, and 4-year old of bone age (chronological age was 28-month).

Puberty is the developmental process that causes the secondary sexual characteristics and the capacity to reproduce. Breast development is one of the secondary sexual characteristics which normally (thelarche: the onset of breast buds) starts between 8 and 13 years of age, followed within a few years by pubic hair growth (pubarche: the onset of pubic hair).[1,9] It begins with the activation of the hypothalamic-pituitary-gonadal axis and ends with the attainment of reproductive capability and the acquisition of adult body in terms of composition and habitus.

Pathological conditions in which puberty occurs early are divided into PP, premature adrenarche, McCune-Albright syndrome, and premature thelarche.[10] Menstruation is an important phase which is influenced by the psychological (signs of adulthood, female identity) and physiological factors (normal hypothalamus-pituitary-ovarian axis, basis for fertility and reproduction).[11] Early menarche is menarche which occurs at the age before 10-year old and part of PP. Early menarche increases the risk of obesity, hypertension, type 2 diabetes mellitus, ischemic heart disease, stroke, cardiovascular disease, and cancer.[11,12]

Table 2. Patient's medical aspect monitoring schedule

Parameters	Month of observation					
	1	2	3	4	5	6
Patient's complaints	✓	✓	✓	✓	✓	✓
Vital signs and clinical symptoms	✓	✓	✓	✓	✓	✓
Bone age	✓					✓
Laboratory Results						
LH	✓					✓
FSH	✓					✓
Estradiol						✓
Regularity of drug injection	✓	✓	✓	✓	✓	✓
No drug side effect	✓	✓	✓	✓	✓	✓

The patient's bone age (3-year and 6-month) increased because the increasing bone age in PP is ≥2,5 SD or ≥2 years from chronological age and bone age/chronological age ratio is >1.[9] Sex steroid hormone (estradiol) influences growth stimulation in girls. Hence, it stimulates bone maturation and at the end of the puberty, the bone stops growing. To assess the extent a child has grown, it is necessary to calculate the stage of sexual development, height, and bone age.[7,13]

GnRH stimulation test is a gold standard to identify CPP. The results of the GnRH stimulation test that showed a LH and FSH ratio >1 and an increase in LH 5-8 IU/liter confirmed the diagnosis of CPP.[14] Head MRI intends to evaluate intracranial lesion in CPP. Most causes of CPP are idiopathic and in selective cases are resulted by organic causes.[15,16] HH is a disorder of the central nervous system (CNS) and relates to endocrinological and neurological disorders. HH as progenitor hypothalamus-pituitary-gonad axis, which contains normal neuron (astrocytes), expresses TgF alpha and beta to produce GnRH. The appearance of endocrinology symptoms are PP, obesity, acromegaly, and hypopituitarism.[17] The incidence of HH has increased with the use of MRI.[10] Kumar et al., mentioned that the HH prevalence on CPP was around 21% - 49%.[18]

HH without neurological symptoms does not require surgery, thus long-term medical therapy is a must. Medical therapy is a GnRH analog to suppress the hypothalamus-pituitary-gonad pathway by giving constant stimulation to gonadotroph pituitary cells. The stimulation will result in the desensitization of gonadotroph cells and the suppression of gonadotropin (LH and FSH) production which in the end will reduce sex hormone production from gonad (ovarium).[19] The goals of the therapy are to slow down the growth rate and the bone maturation, prevent short adult height, avoid emotional and psychological stress.[7] The patient received an intramuscular injection of leuprorelin acetate 1.8 mg every 4 weeks. In general, the treatment can be stopped at the age of physiological puberty (10 – 11 years old for girls). Development of puberty will reoccur about one year (± 18-month) after stopping the treatment. In idiopathic CPP, the earlier therapy is started, the better the prognosis will be. In organic CPP, the prognosis depends on the cause and location of the lesion in the CNS.[20]

Growth and development aspect

The patient was monitored for growth and development aspects from February - August 2020. During the observation, it showed that the patient's height did not increase significantly (<5 cm/year) and the height curve started to slope and corresponded to the mid parental height. Tanner's stage regressed to A1M2P1. The aspects of language development, fine and gross motor skills, social personal, and cognitive-intelligence functions were good.

Growing up is a hallmark of puberty with the height rate becomes sudden (height spurt). Premature puberty will lead to a decrease in adult height to compensate for premature maturation of the bones. PP shortens the duration of prepubertal and pubertal growth so that they can not reach the maximum peak amplitude. The therapy is aimed to restore the duration of prepubertal in order to reach the target of the height prediction.[20,21] Tanner's stage is a parameter that is used to determine the sex maturity rating from a value of 1 to 5.[14] The development of breasts and pubic hair is the main concern in girls during puberty. Development of secondary sex characteristics, which are ovarian and uterine size, growth rate, and bone maturation are monitored by clinically, sonographycally, and radiologically. In most of the patients, the reduction occurred after 6 months of treatment.[22]

Table 3. Patient's growth and development aspect monitoring schedule

Parameters	Month of observation					
	1	2	3	4	5	6
Growth Aspect						
Height	✓	✓	✓	✓	✓	✓
Weight	✓	✓	✓	✓	✓	✓
Head Circumference	✓					✓
Development Aspect						
Denver II	✓			✓		✓
CAT CLAMS	✓			✓		✓

Developmental Quotient (DQ) is a scoring system that describes the proportion of normal children's development at that age. The development of children is said to be normal if DQ in language and visual-motor skills and Full Scale DQ are >85.[23] The patient has Denver II and FSDQ >85. According to some studies, there is no intellectual function and academic score difference between PP patient and normal child. However, there is a difference in performance IQ, which the former scores lower. This is presumably because early maturation is associated with lower spatial development due to weakness in the function of the right hemisphere.[24] Early puberty is linked with a higher risk of mental health and behavior problems. Maturation abnormality due to early puberty is influenced by sudden hormonal changes that lead to emotional overload and behavioral changes.[25]

Parent's psychological aspect in COVID-19 pandemic era

The parent's psychological aspect was measured by the Parental Stress Scale (PSS). The PSS is developed by Berry and Jones in 1995 to measure the levels of stress experienced by the parents. The tool consists of 18 self-report scale items that represent positive and negative themes of parenthood. Respondents agree or disagree in terms of their typical relationship with their children with a 5-point scale. Overall possible score on the scale range from 18 – 90 and the higher the score, the higher the level of parental stress. Higher level of parental stress relates to lower level of parental sensitivity to the child, poorer child behavior, and lower quality of parent-child relationships. The validity of PSS scores was supported by predicted correlations with measures of relevant emotions and role satisfaction and significant discrimination between mothers of children in treatment for emotional/behavioral problems and developmental disabilities and mothers of children not receiving treatment.[26] COVID-19 pandemic led to community-wide measures, affecting parents and children. Parents of children with PP were reported having a higher level of stress, worse mental health, and a financial burden.[27,28] Psychoeducation and motivation from heath workers at all levels of health facilities are urgently needed.

In this case, the PSS is presented. The questionnaire was filled out by the patient's parents (parent-reported). The result of PSS score was 24 which is a low level of PSS. It indicates that PP patients who are treated have a good influence on the psychosocial condition of the parents. The existence of good psychoeducation and government health insurance to get the convenience of treatment have an effect on the psychology of the parents. Children with abnormal puberty may have an early evaluation to improve patients prognosis and quality of life. The limitation of this case report was that it only presented one case, so there was a lack of ability to generalize.

CONCLUSION

We presented a longitudinal case of 14-month old girl with organic CPP with HH, in which long term GnRH analog was chosen as the main therapy. From the result of 6-month observation, it obtained a good medical and growth and development aspect outcomes. The parent's psychological aspect which measured by the PSS score showed a good score when the PP patient handled comprehensively with good motivation and psycho-education during the COVID-19 pandemic.

DISCLOSURES

Acknowledgment

Thanks to all the study participants and the endocrine team of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, for their support.

Conflict of interest

The authors report there are no competing interests to declare.

Patient's consent for publication

The patient's parents signed the informed consent form and agreed that this case report is published.

Funding

This research has received no external funding.

Author contribution

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

REFERENCES

1. Fuqua JS. Treatment and outcomes of precocious puberty: an update. J Clin Endocrinol Metab. 2013;98(6):2198-207. doi: 10.1210/jc.2013-1024. Epub 2013 Mar 20. PMID: 23515450.
2. Berberoğlu M. Precocious puberty and normal variant puberty: definition, etiology, diagnosis and current management. J Clin Res Pediatr Endocrinol. 2009;1(4):164-74. doi: 10.4274/jcrpe.v1i4.3. Epub 2009 May 2. PMID: 21274291; PMCID: PMC 3005651.
3. Phillip M, Lazar L. Precocious puberty: growth and genetics. Horm Res. 2005;64 Suppl 2:56-61. doi: 10.1159/000087760. PMID: 16286772.
4. Stagi S, De Masi S, Bencini E, et al. Increased incidence of precocious and accelerated puberty in females during and after the Italian lockdown for the coronavirus 2019 (COVID-19) pandemic. Ital J Pediatr. 2020;46(1):165. doi: 10.1186/s13052-020-00931-3. PMID: 33148304; PMCID: PMC 7609833.
5. Chioma L, Bizzarri C, Verzani M, et al. Sedentary lifestyle and precocious puberty in girls during the COVID-19 pandemic: an Italian experience. Endocr Connect. 2022;11(2):e210650. doi: 10.1530/EC-21-0650. PMID: 35029543; PMCID: PMC8859940.
6. Demaria F, Vicari S. COVID-19 quarantine: Psychological impact and support for children and parents. Ital J Pediatr. 2021;47(1):58. doi: 10.1186/s13052-021-01005-8. PMID: 33750452; PMCID: PMC7941406.
7. Kim HK, Kee SJ, Seo JY, et al. Gonadotropin-releasing hormone stimulation test for precocious puberty. Korean J Lab Med. 2011;31(4):244-9. doi: 10.3343/kjlm.2011.31.4.244. Epub 2011 Oct 3. PMID: 22016677; PMCID: PMC3190002.
8. Shim YS, Lee HS, Hwang JS. Genetic factors in precocious puberty. Clin Exp Pediatr. 2022;65(4) :172-81. doi: 10.3345/cep.2021.00521. Epub 2021 Oct 18. PMID: 34665958; PMCID: PMC8990949.
9. Faizi M, Artati RD, Pulungan AB. Diagnosis dan tata laksana pubertas prekoks sentral. Pedoman Praktek Klinik Ikatan Dokter Anak Indonesia. [Internet]. 2017. Available from: http://spesialis1.ika.fk.unair.ac.id/wp-content/uploads/2018/03/PPK-Pubertas-Prekoks-Sentral.pdf
10. Kotwal N, Yanamandra U, Menon AS, et al. Central precocious puberty due to hypothalamic hamartoma in a six-month-old infant girl. Indian J Endocrinol Metab. 2012;16(4):627-30. doi: 10.4103/2230-8210.98027. PMID: 22837930; PMCID: PMC3401770.
11. Manjila S, Vogel TW, Chen Y, et al. Hypothalamic hamartoma simulating a suprasellar arachnoid cyst: resolution of precocious puberty following micro-surgical lesion resection. J Neurosurg Pediatr. 2014;14(1):101-7. doi: 10.3171/2014.4.PEDS 13371. Epub 2014 May 16. PMID: 24835046.
12. Batubara JR, Bambang Tridjaja AAP, Pulungan AB. Buku ajar endokrinologi anak [Textbook on pediatric endocrinology]. Edisi I. Jakarta: Badan Penerbit IDAI; 2010.
13. Caillet P, Laurent M, Bastuji-Garin S, et al. Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. Clin Interv Aging. 2014;9:1645-60. doi: 10.2147/CIA.S57849. PMID: 25302022; PMCID: PMC4189720.
14. Hochberg Z. Practical algorithms in pediatric endocrinology. Karger Medical and Scientific Publishers; 2007.
15. Chalumeau M, Chemaitilly W, Trivin C, et al. Central precocious puberty in girls: an evidence-based diagnosis tree to predict central nervous system abnormalities. Pediatrics. 2002;109(1):61-7. doi: 10.1542/peds.109.1.61. PMID: 11773542.
16. Brown JJ, Warne GL. Growth in precocious puberty. Indian J Pediatr. 2006;73(1):81-8. doi: 10.1007/BF02758267. PMID: 16444068.
17. García H, Youlton R, Burrows R, et al.; Rama de Endocrinologia Pediatrica de la Sociedad Chilena de Pediatria. Consenso sobre el diagnóstico y tratamiento de la pubertad precoz central [Consensus on the diagnosis and treatment of central early puberty]. Rev Med Chil. 2003;131(1):95-110. Spanish. PMID: 12643227.

18. Ng SM, Kumar Y, Cody D, et al. Cranial MRI scans are indicated in all girls with central precocious puberty. Arch Dis Child. 2003;88(5): 414-8; discussion 414-8. doi: 10.1136/adc.88.5.414. PMID: 12716713; PMCID: PMC1719560.
19. Léger J, Reynaud R, Czernichow P. Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? J Pediatr. 2000;137(6):819-25. doi: 10.1067/mpd .2000.109201. PMID: 11113839.
20. Léger J, Carel JC. Central Precocious Puberty - Management and Long-term Outcomes. Eur Endocrinol. 2015;11(1):45-6. doi: 10.17925/EE .2015.11.01.45. Epub 2015 Apr 11. PMID: 29632569; PMCID: PMC5819064.
21. Xhrouet-Heinrichs D, Lagrou K, Heinrichs C, et al. Longitudinal study of behavioral and affective patterns in girls with central precocious puberty during long-acting triptorelin therapy. Acta Paediatr. 1997;86(8):808-15. doi: 10.1111/j.1651-2227.1997.tb08602.x. PMID: 9307158.
22. Stoppelbein L, Greening L, Moll G, et al. Factor analyses of the Pediatric Symptom Checklist-17 with African-American and Caucasian pediatric populations. J Pediatr Psychol. 2012;37(3):348-57. doi: 10.1093/jpepsy/jsr103. Epub 2011 Dec 14. PMID: 22171075.
23. Mensah FK, Bayer JK, Wake M, et al. Early puberty and childhood social and behavioral adjustment. J Adolesc Health. 2013;53(1):118-24. doi: 10.1016/j.jadohealth.2012.12.018. Epub 2013 Apr 1. PMID: 23558038.
24. Mendle J, Turkheimer E, Emery RE. Detrimental psychological outcomes associated with early pubertal timing in adolescent girls. Dev Rev. 2007;27(2):151-71. doi: 10.1016/j.dr.2006.11.001. PMID: 20740062; PMCID: PMC2927128.
25. Williams VSL, Soliman AM, Barrett AM, et al. Review and evaluation of patient-centered psycho-social assessments for children with central precocious puberty or early puberty. J Pediatr Endocrinol Metab. 2018;31(5):485-95. doi: 10. 1515/jpem-2017-0465. PMID: 29649000.
26. Berry JO, Jones WH. The parental stress scale: Initial psychometric evidence. J Soc Pers Relat. 1995;12(3):463-472. doi:10.1177/0265407595123 009.
27. A L van Tilburg M, Edlynn E, Maddaloni M, et al. High levels of stress due to the SARS-CoV-2 pandemic among parents of children with and without chronic conditions across the USA. Children (Basel). 2020;7(10):193. doi: 10.3390/ children7100193. PMID: 33096787; PMCID: PMC 7589303.
28. Kaltiala-Heino R, Marttunen M, Rantanen P, et al. Early puberty is associated with mental health problems in middle adolescence. Soc Sci Med. 2003;57(6):1055-64. doi: 10.1016/s0277-9536(02) 00480-x. PMID: 12878105.

REVIEW ARTICLE

The role of antihypertensive drugs in patients with preeclampsia and how to prevent it

I Gde Sastra Winata[1], I Wayan Agus Surya Pradnyana[2], Maria Septiana Parmonang Aroean[2]
[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Udayana, Sanglah General Hospital, Denpasar, Bali, Indonesia.
[2]Faculty of Medicine, Universitas Udayana, Denpasar, Bali, Indonesia.

Article Info
Received Oct 22, 2021
Revised Feb 17, 2022
Accepted Mar 20, 2022
Published Dec 1, 2022

Corresponding author:
I Gde Sastra Winata
sastra@unud.ac.id

Keywords:
Preeclampsia
Antihypertensive
Methyldopa
Nifedipine
Maternal health

ABSTRACT

Treatment of hypertension in pregnancy, such as preeclampsia (PE), is still a difficult issue with negative short and long-term consequences for both the mother and the baby. Screening for preeclampsia at 11-13 weeks' gestation using a combination of maternal demographic characteristics and medical history with biomarker measurements can identify approximately 75% of women who develop premature preeclampsia with delivery at 37 weeks gestation and 90% of those with early preeclampsia. Preeclampsia has a 10% positive screen rate at 32 weeks. Another important worry on the use of antihypertensive medications during pregnancy is the potential harm to the fetus. Methyldopa, hydralazine, labetalol, and nifedipine are some common antihypertensive medications. Aspirin use is frequently related to a decrease in the prevention of early preeclampsia, but it must be accompanied by medication adherence. Aspirin can be coupled with heparin. Recent investigations on the use of furosemide and nifedipine in preeclampsia have also revealed a new combination.

Cite this as : Winata, I.G.S., Pradnyana, I.W.A.S., & Aroean, M.S.P., (2022). The role of antihypertensive drugs in patients with preeclampsia and how to prevent it. Majalah Obstetri & Ginekologi, 30(3), 146-153. https://doi.org/10.20473/mog.V30I32022.146-153.

INTRODUCTION

Severe hypertension in pregnancy is defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥90 mmHg. The most common cause of severe hypertension in pregnancy is pre-eclampsia (PE), which is presenting after 20 weeks' gestation. Severe hypertension happened before 20 weeks' gestation is rare, usually due to chronic hypertension and need a rapid control of blood pressure due to risk of hemorrhagic stroke, and other target organ damage.[1]

PE is a condition resulting in hypertension, proteinuria, and end-organ damage. One of the most typical cases of pregnancy-related hypertension might develop after giving delivery. Other clinical signs and symptoms include thrombocytopenia, epigastric discomfort, altered eyesight, headache, and reduced liver function.[2] These clinical symptoms are brought on by mild to severe microangiopathy in target organs like the brain, liver, kidneys, and placenta. The effects on the mother could include pneumoedema, cerebral hemorrhage, hepatic failure, renal failure, and even death. Fetal issues

brought on by placental hypoperfusion or the need for an early birth.[3]

In affluent countries, preeclampsia affects 3 to 5 percent of pregnancies and is characterized by hypertension, the onset of proteinuria, or organ failure after 20 weeks of pregnancy.[4,5] The signs and symptoms of severe preeclampsia include organ damage or restricted prenatal development.[6]

Delivery of the fetus was the definite therapy for PE, but the mainstay of the treatment is the use of antihypertensive drug to control the blood pressure when indicated. Many antihypertensive drugs have been used in the management of severe PE and have an acceptable safety profile in pregnancy. The choice of therapy also depends on the severity of the hypertension. However, there was no clear recommendation for the use of combined antihypertensive drugs.[4]

Preeclampsia also increases the risk of cardiovascular disease over the long run in addition to the short-term risks of morbidity and mother and child deaths (CVD). Future CVD is up to seven times more likely to affect severe preeclamptic women than normotensive pregnant women. PE patients had an elevated postpartum cardiovascular risk, according to recent research. As a result, people with hypertension during pregnancy should be watched for the development of additional cardiovascular problems postpartum.

In this review article, we discuss the antihypertensive medicines that are currently used to treat patients with PE, as well as the benefits and drawbacks of utilizing these drugs during pregnancy.

DIAGNOSIS

According to International Society for the Study of Hypertension in Pregnancy (ISSHP)7 in 2018, hypertension is defined as systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg; and severe Hypertension defined as SBP of ≥160 mmHg and/or DPB of ≥110 mmHg. Hypertension arising de novo minimum at 20 weeks' of gestation was classified into Transient Gestational Hypertension (TGH), Gestational Hypertension (GH), and Pre-eclampsia–de novo or superimposed on chronic hypertension.

TGH is a de novo hypertension that develops at any gestation and resolves without any treatment during pregnancy. GH is a persistent de novo hypertension in the absence of features of pre-eclampsia. Meanwhile, PE is defined as a GH which is accompanied by one or more of the following onset conditions minimum at 20 weeks' of gestation: proteinuria (positive if ≥1+ or 30 mg/dL), maternal organ dysfunction – such as acute kidney injury (creatinine ≥90 µmol/L or 1 mg/dL), liver involvement (elevated ALT or AST >40 IU/L) with or without right upper quadrant or epigastric abdominal pain, neurological complications (eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata), hematological complication (thrombocytopenia <150.000/µL, DIC, hemolysis); and uteroplacental dysfunction – such as fetal growth restriction, abnormal umbilical artery Doppler wave form analysis or stillbirth. In certain circumstances, PE can be diagnosed without proteinuria. However, some people showed signs of multiorgan disease without it.[8]

According to a 2013 report from the American College of Obstetricians and Gynecologists (ACOG) Task Force on Hypertension in Pregnancy, PE can be identified when, in previously normotensive patients, either the systolic blood pressure is greater than or equal to 160 mm or the diastolic blood pressure is greater than or equal to 90 mmHg on two separate assessments at least 4 hours apart.[2,9] A protein ratio more than or equal to 0.3, a urine dipstick protein level of greater than 1, or more than 300 mg of protein per 24-hour urine samples should be considered proteinuria in addition to hypertension (if quantitative measurement is not available).[3]

CLASSIFICATION

PE used to be classified as either mild, moderate, or severe. Both ISSHP and ACOG Task Force on Hypertension in Pregnancy recently recommended against using this categorization because to the substantial morbidity and mortality associated with severe asymptomatic PE.[3] They also agree that PE may become a major threat to both mother and fetus at any stage of pregnancy, and so classification of PE into mild or severe disease might be misleading to less experienced clinician. They recommended to use PE with or without severe features as a more practical approach rather than using severe PE as a diagnosis.

Generally speaking, PE can be divided into two groups: those with symptoms appearing before 34 weeks of pregnancy (early-onset PE) and those with symptoms appearing later in pregnancy (late-onset PE), such as new-onset hypertension and proteinuria before 34 weeks of pregnancy (late-onset PE), and sometimes after labor (Table 1). Despite the lack of evidence, it has been hypothesized that preeclampsia subgroups have different rates of maternal and perinatal death.[10,11] Ten

percent of all PE cases are classified as having an early onset, and placental dysfunction is more prevalent in this group than in the more common late onset PE group.

The effects of PE might be compounded in patients with preexisting conditions such chronic hypertension or chronic renal failure. Both the mother and the unborn child have a dismal prognosis when chronic hypertension is present.[12] Diagnosis is made when a pregnant woman who has chronic hypertension or who has been previously diagnosed develops proteinuria and/or end-organ failure after 20 weeks of pregnancy.

Women with chronic preexisting hypertension/ previously diagnosed who have proteinuria before or in early pregnancy are at increased risk of being misdiagnosed with preeclampsia if their hypertension worsens suddenly or if they need to increase their antihypertensives.

Despite the well-established association between preeclampsia and renal disease, distinguishing between CKD and PE during pregnancy can be challenging due to the fact that both conditions can coexist with hypertension and proteinuria. Uteroplacental flow and tyrosine kinase-1, such as the soluble tyrosine kinase-1 in maternal circulation to placental growth factor ratio, are two of the methods being explored to differentiate CKD from PE.[13] Protection of high-risk individuals and, in the event of PE, stabilization of the mother and fetus before timely delivery are the cornerstones of care.[14]

TREATMENT

All antihypertensive drugs are able to cross the placenta safely. To yet, no randomized controlled trials have shown any clear benefit from one antihypertensive over another. However, there are drugs that can reduce blood pressure while still being safe for the mother and unborn child. The severity of hypertension is a major factor in deciding the course of treatment. Additionally, the question of whether a patient would prefer parenteral or oral treatment needs to be addressed before a medication can be selected.

Methyldopa

The neurotransmitter (-methylnorepinephrine) decreases sympathetic outflow of norepinephrine to the heart, kidneys, and peripheral blood vessels by stimulating central alpha-adrenergic receptors. Methyldopa is commonly prescribed to manage hypertension in pregnant women. Additionally, its safety for the developing baby over time has been demonstrated. Women with preeclampsia who were given methyldopa in the CHIPS (Control of Hypertension in Pregnancy Study) trial may have fared better than those given Labetalol.[15] In contrast, methyldopa's antihypertensive effects are mild and gradual in onset (3 to 6 hours). It is unlikely that the majority of preeclamptic women will be able to achieve the desired blood pressure levels using only oral drugs.

Labetalol

Specifically, labetalol blocks alpha-1 and alpha-2 adrenergic receptors, which results in a decrease in blood pressure. The blood flow between the uterus and the placenta can be maintained for a longer period of time than with other blockers. It starts working more quickly than methyldopa (2 hours). Safe labetalol during pregnancy has been demonstrated in randomized clinical trials where the drug was compared to methyldopa and nifedipine.[16,17] Maternal hepatotoxicity from labetalol has been described. This adverse effect warrants close attention because it can be easily mistaken for HELLP syndrome. However, there have been fatalities associated with labetalol, despite the fact that hepatotoxicity is usually reversible.[18]

Table 1. Characteristics of the preeclampsia subgroup

Preeclampsia Subgroup	Signs and Symptoms
Early-onset PE (<34 weeks of gestation)	Only ± PE case Often due to placental dysfunction, increased IUGR, and maternal and perinatal mortality. Renal function indicators (Cr, BUN, and Uric Acid) increased significantly, but alkaline phosphate was low
Late-onset PE (≥34 weeks gestation)	Most cases of PE Severe during normal or large-term labor

Nifedipine

Nifedipine, a kind of calcium channel blocker, has been used successfully during pregnancy. Since short-acting nifedipine can cause a significant reduction in blood pressure, long-acting nifedipine is recommended. Short-acting oral nifedipine may be investigated for safely decreasing blood pressure, according to the findings of certain recent trials. Once daily dosing of 30-90 mg is appropriate for long-acting nifedipine. The highest recommended daily dose is 120 mg, and it can be raised by 20 mg every 7 to 14 days.[19]

Hydralazine

The arteriolar vasculature is immediately dilated by hydralazine. Hydralazine is commonly used intravenously to treat severe hypertension related to pregnancy. Although meta-analyses showed that the risk of adverse events was somewhat greater with hydralazine than with labetalol, there is not enough information to recommend one drug over the other.[20] But the hypotensive effect of hydralazine is less predictable than that of other parenteral medications. Hypertension caused by pregnancy can be managed with oral hydralazine. However, it has several drawbacks, including edema in the lower limbs and a tachycardia reflex.[19]

There is less consensus on the best way to manage PE in individuals with chronic hypertension or CKD who do not have severe hypertension. Patients with PE who also have high hypertension may benefit from antihypertensives (sustained systolic blood pressure of at least 160 mmHg or diastolic blood pressure of at least 110 mmHg).[3] Medications including labetalol, nifedipine, and methyldopa are commonly recommended as first treatments. Nifedipine, a calcium channel blocker, may also be first-line treatment, as shown by recent studies, especially in its rapid-onset oral release form.[20-26]

First-line treatment, especially in the absence of intravenous access, should consist of oral-rapid onset nifedipine, according to the 2017 Committee Opinion of the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. You should stay away from the renin-angiotensin-aldosterone system inhibitors such angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and mineralocorticoid receptor antagonists. A blood pressure reading between 120/80 mm Hg to 160/105 mm Hg is considered normal.

Likewise, it is not known whether or not antihypertensives can help prevent eclampsia. Magnesium sulfate has long been used to control recurrent seizures in eclampsia and prevent seizures in preeclamptic women with severe symptoms. However, it is not advised as an antihypertensive medication. In a small double-blind, placebo-controlled study, individuals with severe asymptomatic preeclampsia who were given magnesium sulfate had the same rate of eclampsia progression as those who were given a dummy treatment.[27]

Magnesium sulfate should not be administered to all women with preeclampsia who have systolic blood pressure less than 160 mmHg and diastolic blood pressure less than 110 mmHg and no maternal symptoms, as per 2013 recommendations from the American College of Obstetricians and Gynecologists (ACOG). Magnesium sulfate is only recommended for the prevention of eclampsia by the ACOG in patients with blood pressure of 160/110 or higher, or in patients with blood pressure of less than 160/110 who also exhibit additional severe symptoms that typically precede seizures. Compared to other common anticonvulsants like phenytoin and diazepam or lytic combinations, research show that magnesium sulfate is more effective at avoiding recurrent seizures in eclampsia.[27-28]

Preventing seizures with magnesium sulfate is associated with its effects on the central nervous system, maybe through NMDA receptors, calcium channels, and acetylcholine, although the exact mechanism of action is uncertain. While there is limited information, it is safe to say that taking magnesium sulfate and nifedipine together will not result in serious side effects, including hypotension and neuromuscular inhibition.[29]

During the postpartum period, 108 women with severe preeclampsia had two readings of 150/100 mmHg or above within the first 24 hours after giving birth. These patients were randomly split in half (Group A: furosemide 20 mg OD plus nifedipine; Group B: nifedipine alone). Women in Group B took antihypertensives at a much higher rate than those in Group A did (26.0 percent versus 8.0 percent, p = 0.017). There were no significant differences between the groups in terms of length of hospital and postpartum stays or the prevalence of antihypertensives prescribed upon release.[30]

Table 2. Antihypertensive drugs frequently used in severe preeclampsia

Drugs	Indications	Doses
First Line		
Methyldopa	PE with severe symptoms Hypertension in pregnancy	0.5-3 g/day PO in 2 divided doses
Labetalol	PE with severe symptoms, usually IV formulation	Starting with 20 mg IV bolus May require double dose 10 minutes later
Hydralazine	PE with severe symptoms, usually IV formulation.	5 mg IV slowly over 1 to 2 minutes
	Long acting nifedipine	30-90 mg once daily. It can increased at 7 to 14-day intervals, up to a maximum dose of 120 mg daily
Nifedipine	PE with severe symptoms, immediate release of an oral formulation	Start with 10 mg PO May repeat 30 minutes later
Second Line		
Nicardipine	Severe acute-onset hypertension that is resistant when first-line fails	Give IV infusion of 3 to 9 mg/hour
Sodium Nitroprusside	Life-threatening acute hypertension associated with PE	Start with 0.24 g/kg/min. Can be titrated until maximum dose of 5 g/kg/min

PREVENTION

There are three levels of protection against pre-eclampsia, known as primary, secondary, and tertiary.[8] Primary prevention is taking measures to decrease disease prevalence, such as modifying one's lifestyle or dietary habits, or improving one's overall dietary intake. That is why it is quite improbable that we will be able to stop a case of PE in its tracks.[31]

Women who are overweight, have dyslipidemia (especially hypertriglyceridemia and hypercholesterol-emia), uncontrolled diabetes mellitus, or obstructive sleep apnea are at a higher risk for developing preeclampsia (chronic hypoxemia).[32,33] High-risk individuals should have surgical therapy for sleep apnea in addition to weight loss, correction of an aberrant lipid profile, blood sugar management, and other lifestyle changes. While the preventive benefit of adding low molecular weight heparin to aspirin is minimal, it may be amplified when used in conjunction with other preventative medications.[34]

Recent studies have shown that the use of l-arginine or isosorbide mononitrate (both of which improve endothelial nitric oxide production) can lower the risk of preeclampsia and boost intrauterine growth and fetal development. Therefore, boosting nitric oxide product-ion need to be a part of the preventive strategy.[35] Statins have been shown to have beneficial benefits in initiating the HO pathway and reducing the risk of preeclampsia, and, therefore, they should be included in the preventive strategy even in individuals who do not have preexisting dyslipidemia.[36]

Preeclampsia can be avoided by taking aspirin, according to one study. For aspirin, the odds ratio for preeclampsia was 0.24 (95% CI, 0.09-0.65) at 90% adherence and 0.59 (95% CI, 0.23-1.53) at 90% adherence. Preeclampsia prevalence increased with maternal age, and decreased with smoking, being of African-American or South Asian descent, or having a previous pregnancy complicated by preeclampsia. Benefits from medication are contingent on patients being compliant with their dosing schedules, a study found.[37]

Aspirin use during pregnancy reduced the need for neonatal intensive care unit admissions by nearly 70%, according to another study of high-risk pregnancies. In particular, earlier preeclampsia avoidance is responsible for the decline in 32-week birth rates. These results have implications for newborn mortality and disability, as well as immediate medical expenses.[38]

There were 1620 people that took part in the study, and 1571 live births occurred. Length of time spent in newborn intensive care was higher in the placebo group compared to the aspirin group (1696 vs 531 days). This is because aspirin significantly decreased the median length of stay in the neonatal intensive care unit from 31.4 days to 11.1 days (95% CI, 7.0-38.6; P =.008).[39]

Aspirin and heparin together have been shown to be effective in a recent study. Aspirin combined with LMWH has been shown to improve clinical efficacy, coagulation function, renal function, and blood pressure levels in patients with severe preeclampsia, and to reduce the risk of adverse pregnancy outcomes. As a result of the intervention, the overall effective rate was

94.44% in the study group and 76.00% in the control group. It was statistically proven that the overall effective rate of patients in the study group was much greater than in the control group after treatment (P 0.05).[40]

CONCLUSION

Many variables complicate PE case prevention. The majority are linked to an unclear etiology, the low predictive value of current screening tools, and diverse illness presentations. Interventions that define a small risk reduction imply that a large number of women must be treated to prevent a single instance. For the time being, the definitive treatment is placental delivery and expulsion. At this time, no effective PE prophylaxis is officially suggested. However, because PE is seen as a global health issue, with relatively high maternal and newborn morbidity and mortality rates in many countries, prophylactic measures with minimal or moderate impact may be beneficial.

DISCLOSURES

Acknowledgment

The authors would like to thank William Alexander Setiawan for his excellent contribution in assisting this review.

Conflict of interest

The authors report there are no competing interests to declare.

Funding

This research has received no external funding.

Author contribution

The 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. Wiles K, Damodaram M, Frise C. Severe hypertension in pregnancy. Clin Med (Lond). 2021;21(5):e451-e456. doi: 10.7861/clinmed.2021-0508. PMID: 34507929; PMCID: PMC8439512.
2. Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. JAMA. 2002;287(24):3183-6. doi: 10.1001/jama.287.24.3183. PMID: 12076198.
3. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-31. doi: 10.1097/01.AOG.0000437382.03963.88. PMID: 24150027.
4. Odigboegwu O, Pan LJ, Chatterjee P. Use of antihypertensive drugs during preeclampsia. Front Cardiovasc Med. 2018;5:50. doi: 10.3389/fcvm.2018.00050. PMID: 29896480; PMCID: PMC5987086.
5. Mol BWJ, Roberts CT, Thangaratinam S, et al. Pre-eclampsia. Lancet. 2016;387(10022):999-1011. doi: 10.1016/S0140-6736(15)00070-7. Epub 2015 Sep 2. PMID: 26342729.
6. Steegers EA, von Dadelszen P, Duvekot JJ, et al. Pre-eclampsia. Lancet. 2010;376(9741):631-44. doi: 10.1016/S0140-6736(10)60279-6. Epub 2010 Jul 2. PMID: 20598363.
7. Brown MA, Magee LA, Kenny LC, et al.; International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertens. 2018;13:291-310. doi: 10.1016/j.preghy.2018.05.004. Epub 2018 May 24. PMID: 29803330.
8. ACOG Committee on Practice Bulletins--Obstetrics. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. Obstet Gynecol. 2002;99(1):159-67. doi: 10.1016/s0029-7844(01)01747-1. PMID: 16175681.
9. Bellamy L, Casas JP, Hingorani AD, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007;335(7627):974. doi: 10.1136/bmj.39335.385301.BE. Epub 2007 Nov 1. PMID: 17975258; PMCID: PMC2072042.
10. Li XL, Guo PL, Xue Y, et al. An analysis of the differences between early and late preeclampsia with severe hypertension. Pregnancy Hypertens. 2016;6(1):47-52. doi: 10.1016/j.preghy.2015.12.003. Epub 2015 Dec 17. PMID: 26955772.
11. Cunningham FG, Lindheimer MD. Hypertension in pregnancy. N Engl J Med. 1992;326(14):927-32. doi: 10.1056/NEJM199204023261405. PMID: 1542342.
12. Dekker GA. Risk factors for preeclampsia. Clin Obstet Gynecol. 1999;42(3):422-35. doi: 10.1097/00003081-199909000-00002. PMID: 10451762.
13. Rolfo A, Attini R, Tavassoli E, et al. Is it possible to differentiate chronic kidney disease and

preeclampsia by means of new and old biomarkers? A Prospective Study. Dis Markers. 2015;2015 :127083. doi: 10.1155/2015/127083. Epub 2015 Oct 8. PMID: 26557728; PMCID: PMC4618113.
14. Mol BWJ, Roberts CT, Thangaratinam S, et al. Pre-eclampsia. Lancet. 2016;387(10022):999-1011. doi: 10.1016/S0140-6736(15)00070-7. Epub 2015 Sep 2. PMID: 26342729.
15. Magee LA; CHIPS Study Group, von Dadelszen P, et al. Do labetalol and methyldopa have different effects on pregnancy outcome? Analysis of data from the Control of Hypertension In Pregnancy Study (CHIPS) trial. BJOG. 2016;123(7):1143-51. doi: 10.1111/1471-0528.13569. Epub 2015 Aug 11. PMID: 26265372.
16. Peacock WF 4th, Hilleman DE, Levy PD, et al. A systematic review of nicardipine vs labetalol for the management of hypertensive crises. Am J Emerg Med. 2012;30(6):981-93. doi: 10.1016/j.ajem.2011. 06.040. Epub 2011 Sep 9. PMID: 21908132.
17. Molvi SN, Mir S, Rana VS, et al. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Arch Gynecol Obstet. 2012;285(6) :1553-62. doi: 10.1007/s00404-011-2205-2. Epub 2012 Jan 15. PMID: 22249781.
18. Clark JA, Zimmerman HJ, Tanner LA. Labetalol hepatotoxicity. Ann Intern Med. 1990;113(3):210-3. doi: 10.7326/0003-4819-113-3-210. Erratum in: Ann Intern Med 1990 Sep 15;113(6):485. PMID: 2375555.
19. Smith P, Anthony J, Johanson R. Nifedipine in pregnancy. BJOG. 2000;107(3):299-307. doi: 10.1111/j.1471-0528.2000.tb13222.x. PMID: 1074 0323.
20. Magee LA, Cham C, Waterman EJ, et al. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. BMJ. 2003;327(7421): 955-60. doi: 10.1136/bmj.327.7421.955. PMID: 14576246; PMCID: PMC259162.
21. Raheem IA, Saaid R, Omar SZ, et al. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial. BJOG. 2012; 119(1):78-85. doi: 10.1111/j.1471-0528.2011. 03151.x. Epub 2011 Oct 10. PMID: 21985500.
22. Shekhar S, Sharma C, Thakur S, et al. Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial. Obstet Gynecol. 2013;122(5):1057-63. doi: 10.1097/AOG.0b013e3182a9ea68. PMID: 2410 4790.
23. Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy. Cochrane Database Syst Rev. 2013;2013(7) :CD001449. doi: 10.1002/14651858 .CD001449 .pub3. PMID: 23900968; PMCID: PMC 7073408.
24. Rezaei Z, Sharbaf FR, Pourmojieb M, et al. Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy. Acta Med Iran. 2011;49(11):701-6. PMID: 2213 1238.
25. Magee LA, Miremadi S, Li J, et al. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. Am J Obstet Gynecol. 2005;193(1):153-63. doi: 10.1016/j.ajog.2004.11.059. PMID: 16021073.
26. Paauw ND, Luijken K, Franx A, et al. Long-term renal and cardiovascular risk after preeclampsia: towards screening and prevention. Clin Sci (Lond). 2016;130(4):239-46. doi: 10.1042/CS20150567. PMID: 26769659.
27. Vikse BE, Irgens LM, Leivestad T, et al. Preeclampsia and the risk of end-stage renal disease. N Engl J Med. 2008;359(8):800-9. doi: 10.1056/NEJMoa0706790. PMID: 18716297.
28. McDonald SD, Han Z, Walsh MW, et al. Kidney disease after preeclampsia: a systematic review and meta-analysis. Am J Kidney Dis. 2010;55(6):1026-39. doi: 10.1053/j.ajkd.2009.12.036. Epub 2010 Mar 25. PMID: 20346562.
29. Dekker G, Sibai B. Primary, secondary, and tertiary prevention of pre-eclampsia. Lancet. 2001;357 (9251):209-15. doi: 10.1016/S0140-6736(00) 03599-6. PMID: 11213110.
30. Spradley FT. Metabolic abnormalities and obesity's impact on the risk for developing preeclampsia. Am J Physiol Regul Integr Comp Physiol. 2017 ;312(1):R5-R12. doi: 10.1152/ajpregu.00440.2016. Epub 2016 Nov 30. PMID: 27903516; PMCID: PMC5283940.
31. El Khouly NI, Sanad ZF, Saleh SA, et al. Value of first-trimester serum lipid profile in early prediction of preeclampsia and its severity: A prospective cohort study. Hypertens Pregnancy. 2016;35(1):73-81. doi: 10.3109/10641955.2015.1115060. Epub 2016 Feb 1. PMID: 26829675.
32. Mastrolia SA, Novack L, Thachil J, et al. LMWH in the prevention of preeclampsia and fetal growth restriction in women without thrombophilia. A systematic review and meta-analysis. Thromb Haemost. 2016;116(5):868-78. doi: 10.1160/TH16-02-0169. Epub 2016 Jul 21. PMID: 27440387.
33. Camarena Pulido EE, García Benavides L, Panduro Barón JG, et al. Efficacy of L-arginine for preventing preeclampsia in high-risk pregnancies: A double-blind, randomized, clinical trial. Hypertens Pregnancy. 2016;35(2):217-25. doi: 10.3109/10641955.2015.1137586. Epub 2016 Mar 22. PMID: 27003763.

34. Abdel Razik M, El-Berry S, Abosereah M, et al. Prophylactic treatment for preeclampsia in high-risk teenage primigravidae with nitric oxide donors: a pilot study. J Matern Fetal Neonatal Med. 2016 ;29(16):2617-20. doi: 10.3109/14767058.2015 .1094793. Epub 2015 Oct 12. PMID: 26456672.
35. Marrs CC, Costantine MM. Should we add pravastatin to aspirin for preeclampsia prevention in high-risk women? Clin Obstet Gynecol. 2017;60(1):161-8. doi: 10.1097/GRF.0000000000 000248. PMID: 27906745; PMCID: PMC5250542.
36. Wright D, Poon LC, Rolnik DL, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: influence of compliance on beneficial effect of aspirin in prevention of preterm preeclampsia. Am J Obstet Gynecol. 2017;217(6):685.e1-685.e5. doi: 10.1016/j.ajog.2017.08.110. Epub 2017 Sep 6. PMID: 28888591.
37. Wright D, Rolnik DL, Syngelaki A, et al. Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol. 2018 ;218(6):612.e1-612.e6. doi: 10.1016/j.ajog.2018 .02.014. Epub 2018 Mar 2. PMID: 29505771.
38. Wang X, Gao H. Prevention of preeclampsia in high-risk patients with low-molecular-weight heparin: a meta-analysis. J Matern Fetal Neonatal Med. 2020;33(13):2202-8. doi: 10.1080/14767058. 2018.1543656. Epub 2018 Nov 20. PMID: 30458652.
39. Chang L, Liu Y, Zhang X, et al. The clinical effect of aspirin combined with low-molecular-weight heparin in the treatment of severe preeclampsia and the combination's effect on pregnancy outcomes. Am J Transl Res. 2021;13(8):9113-21. PMID: 34540025; PMCID: PMC8430098.
40. Veena P, Perivela L, Raghavan SS. Furosemide in postpartum management of severe preeclampsia: A randomized controlled trial. Hypertens Pregnancy. 2017;36(1):84-9. doi: 10.1080/10641955.2016.123 9735. Epub 2016 Nov 11. PMID: 27835048.

SYSTEMATIC REVIEW

The role of adequate vitamin D levels in the menstrual cycle of reproductive-age women

Ahila Meliana[1#], Hana Salsabila[1#], Bendix Samarta Witarto[1], Manik Retno Wahyunitisari[2*]
[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Medical Microbiology, Universitas Airlangga, Surabaya, Indonesia.
[#]Equal first author

Article Info
Received Nov 2, 2021
Revised May 17, 2022
Accepted Jun 20, 2022
Published Dec 1, 2022

Corresponding author:
Manik Retno Wahyunitisari
manik-r-w@fk.unair.ac.id

Keywords:
Human & health
Menstrual cycle
Reproductive age
Women
Vitamin D

ABSTRACT

Objective: This study investigated the role of adequate vitamin D levels in the menstrual cycle of reproductive-age women.
Materials and Methods: We systematically searched using certain key words in PubMed and ScienceDirect for English articles, full articles, published between August 2013 - August 2022 that evaluated the effect of vitamin D levels on the menstrual cycle of women in reproductive age. The results were analyzed qualitatively.
Results: Eight studies from 653 recorded articles were eligible for review. Decreased vitamin D levels can cause menstrual cycle irregularities, which are related to a decrease in the hormone estradiol, affecting the menstrual cycle. In addition, lower levels of vitamin D lead to longer menstrual cycles.
Conclusion: Vitamin D is vital in the menstrual cycle because it influences the frequency and duration of menstruation.

Cite this as : Meliana, A., Salsabila, H., Witarto, S., et al. (2022). The role of adequate vitamin D levels in the menstrual cycle of reproductive-age women. Majalah Obstetri & Ginekologi, 30(2), 154-160. https://doi.org/10.20473/mog.V30I32022.154-160.

INTRODUCTION

Menstrual cycles are one sign of women's physiological well-being.[1] It occurs as a feedback process of the hypothalamus-pituitary-ovarian (HPO) axis.[2] The average menstrual cycle ranges from 18–35 days, and the intervals might differ for each.[3] Approximately 64% of females have at least one menstrual issue. These issues include irregular menstrual cycle, oligomenorrhea, and menorrhagia.[4] It is suggested that metabolic mechanisms play a role in disrupting menstrual regularity.[5] Numerous physiological and metabolic processes rely on vitamin D as a crucial element.[6] To achieve ion-calcium balance and bone mineral metabolism, Vitamin D is necessary.[7] Vitamin D's importance in calcium homeostasis and bone mineralization is generally acknowledged.[8] Furthermore, it significantly impacts reproductive hormone regulation and the menstrual cycle.[9] Inside reproductive organs, which includes, ovaries, endometrium, myometrium, uterus, and placenta there are sites/organs where vitamin D can also be found.[10,11] Accordingly, a range of clinical reproductive consequences are associated with vitamin D inadequacy.[8,12,13] Vitamin D is correlated with women-menstrual cycle, particularly

in its regularity and length, since it affects the metabolism of reproductive hormones.[14]

However, the mechanism whereby vitamin D impacts the menstrual cycle is still unclear.[15] The hypothesis of significant correlation between vitamin D and Anti-Mullerian Hormone (AMH), insulin, androgen hormones, and other yet-to-be-identified key mechanisms have been studied.[10] This association correlates with the active form of vitamin D, 25-hydroxyvitamin D (25(OH)D) which inducing menstrual problems if minimum amount of 25(OH)D is not reached. The correlated menstrual cycle problems are including menstrual cycle irregularities,[10] endometriosis,[16] menstrual cycle lengthening,[17] and polycystic ovary syndrome (PCOS).[18] Moreover, 25(OH)D insufficience increases the symptoms of premenstrual syndromes, such as tenderness and pain.[19] During the menstrual cycle, vitamin D level fluctuations might impact estradiol.[14,20] Estradiol levels decrease when 25(OH)D is inadequate.[1,20] Therefore, this study aimed to investigate the role of adequate vitamin D levels in the menstrual cycle of reproductive-age women.

MATERIALS AND METHODS

Search strategy

We performed systematic literature search on Pubmed and ScienceDirect for articles published from August 2013 to August 2022 that evaluated 25(OH)D level in the menstrual cycle of reproductive-age women following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[21] The following search term was constructed using Medical Subject Headings (MeSH) terms and Boolean operators: ("Menstrual Cycle" OR "Cycle, menstrual" OR "Menstrual cycles") AND ("Adult" OR "Adolescent") AND ("Woman" OR "Women" OR "Girls" OR "Female") AND ("Ergocalciferol" OR "Cholecalciferol" OR "Calciferol" OR "25-Hydroxyvitamin D" OR "1,25-Dihydrocholecalciferol" OR "25-Hydroxycholecalciferol" OR "Vitamin D" OR "D3, Vitamin"). Potential studies were also found in the reference lists of the papers included in this investigation. The overall study selection process was conducted by two reviewers (AM and HS) and any disagreements or conflicts were accomplished through discussion with a third reviewer (BS) to determine the final resolution.

Eligibility criteria and quality assessment

Eligibility criteria was formulated using Population, Intervention, Comparison, and Outcome (PICO) framework as shown in Table 1. We included studies that: (1) investigated association between 25(OH)D levels and menstrual cycle; (2) included women aged 12 to 55 years as subjects; and (3) published in English language. The exclusion criteria were: (1) duplicates; (2) studies with irretrievable full-text; or (3) review articles, case reports, case series, and conference abstracts. Afterwards we assessed the included methodological quality using the Joanna Briggs Institute (JBI) critical appraisal checklist[22,23] conducted by two reviewers (AM and HS), and only studies with ≥50% score will be further included.

Data extraction

Data extraction was conducted by two reviewers (AM and HS). The following data were extracted from each included study: (1) name of the first author and year of publication; (2) study design; (3) sample size; (4) age; (5) serum 25(OH)D level (ng/ml); and (6) study outcomes and results.

RESULTS AND DISCUSSION

Study selection

The initial search from the two databases returned 653 records and excluded 637 articles based on duplication, title, and abstract. In addition, a study was identified from citation searching. Ultimately, 16 eligible studies were assessed, and eight of these were included for a full review.[14,17,20,24–28] Articles were excluded for the following reasons: duplicate paper, irrelevant title, wrong study design and population based on abstracts, and wrong outcomes based on full-text review. Figure 1 illustrates the overall process of the study selection.

Study characteristics and quality assesment

Six of the eight reviewed studies were observational studies.[14,17,20,24,27,28] and the rest were randomized control trials (RCTs).[25,26] The studies included a range of 60 to 1,133 women aged 12 to 55 years. This study assessed the correlation of study subjects' serum 25(OH)D levels on their menstrual cycles outcomes. Serum 25(OH)D level parameters were classified as deficient (<20–30 ng/ml) and sufficient (≥20 ng/ml). Seven studies measured serum 25(OH)D levels which are the deficiency or lower levels associated with the longer menstrual cycle, short follicular phases or long luteal phases, and irregular cycles. Meanwhile, another study had shown that vitamin D status was not correlated with a woman's menstrual cycle.[20] Data extraction and methodological assessment score are summarized in Table 2.

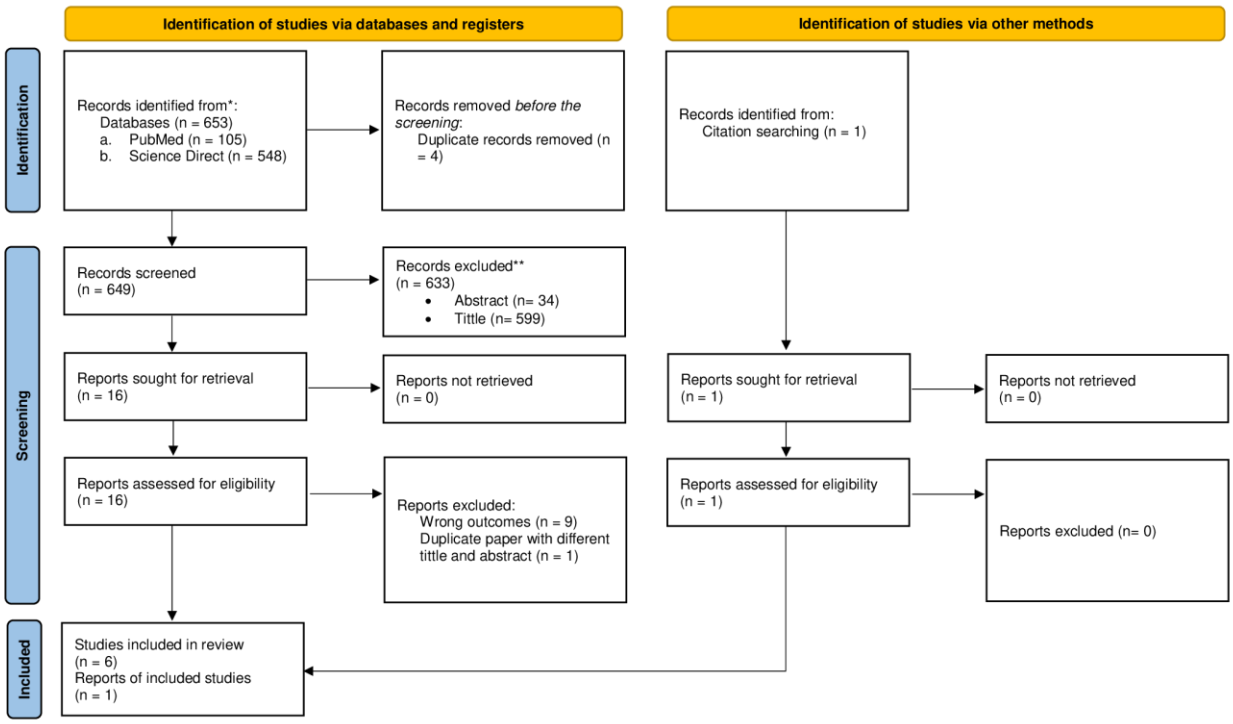


Figure 1. PRISMA flowchart showing the screening process and final articles included.

Table 1. PICO framework

Components of PICO	Definition
Population	Reproductive-age women
Intervention	Serum vitamin D levels
Comparison	None
Outcome	The regularity and length of the menstrual cycle

Outcome variables

Decreased 25(OH)D levels can cause menstrual cycle irregularities. This is related to a decrease in the hormone estradiol which affects the menstrual cycle. Furthermore, reduced levels of 25(OH)D result in prolonged menstrual periods.

Our findings are similar to those several studies[17,27] who reported that inadequate vitamin D levels are linked to longer menstrual periods[17,27] and cause oligomenorrhea or amenorrhea.[27] Women with sufficient 25(OH)D had around half the probability of having extended cycles as women with insufficient status.[27] In the other study with 531 participants (29–44 years), Jukic et al[24] stated that lower 25(OH)D contributed to a longer menstrual cycle and follicular phase. 25(OH)D deficiency status has the strongest correlated with longer menstrual cycle. However, insufficiency status contributed with high risk of prolonged menstrual cycle.[24] Singh et al[28] found the vitamin D status on 166 women 18–40 years who have menstrual irregularities on a cross-sectional study and showed a decrease in 25(OH)D levels was correlated with a higher risk of irregular menstrual cycles.[28]

PICO, Population, intervention, comparison, outcome

Table 2. Summary of included studies showing the effect of serum vitamin D levels on the menstrual cycle.

First Author (Year)	Study Design	Age (range in years)	Sample size	Serum 25(OH)D levels (ng/ml)	Outcomes	Results	JBI score
Bahrami (2018)[14]	Prospective study	12–18	897	<50:deficiency; 50–74.9: insufficiency; and 75: sufficiency	The supplementation of high dose vitamin D and menstrual cycle	• Vitamin D supplementation was linked to a lengthy menstrual cycle • Normal 25(OH)D levels were positively correlated with total subjects elevation which are normal menstrual cycle length (p=0.015) • Increased normal cycle from 71,8% to 78% • Decreased short length cycle from 23,6% to 18,0%, and long length cycle from 4,7% to 4,0%	73%
Jukic (2018)[24]	A prospective cohort study	29–44	531	<20: deficiency; 20-<30: insufficiency	Serum 25(OH)D levels and follicular phase length.	• 25(OH)D is linked with prolonged menstrual cycles, short follicular phases, and extended luteal phases • Long menstrual cycles were three times more likely to occur in people with 25(OH)D deficiency. (OR(CI): 2.8 (1.0, 7.5)) • 25(OH)D insufficiency was related to double the likelihood of prolonged menstrual cycles (OR(CI): 1.9 (1,1, 3.5).	91%
Jukic (2016)[17]	Prospective study	23–34	1,133	≤20: deficiency; >20:sufficiency	Vitamin D with menstrual cycle length and regularity	Serum vitamin D levels amelioration were linked to reduced oods and probability of long menstrual cycles.	91%
Al-Bayyari (2020)[25]	A prospective, randomized, double-blind, placebo-controlled clinical study	18–49	60	<20: deficiency	Serum 25(OH)D levels and regularity of the menstrual cycle	Vitamin D_3 supplementation at 50.000 IU increased serum 25(OH)D levels and normalized menstrual cycles.	100%
Harmon (2020)[20]	A prospective cohort study	18–44	89	<20: deficiency	Three calciotropic hormones (25(OH)D, 1,25(OH)2D, iPTH) to evaluate LH and FSH cycle	• No differences in the cyclic reproductive hormone pattern were compared with higher and lower 1,25(OH)2D. • 25(OH)D <30ng/ml on FSH (95% CI: -0.2, 0.2) and LH (95% CI: -0.08, 0.4) • 1,25(OH)2D <105pmol/L on FSH (95% CI: -0.5, 0.01) and LH (95% CI: -0.5, -0.02)	82%
Jafari-Sfidvajani (2018)[26]	A double-blind, randomized, placebo-controlled trial	20–40	60	<20; deficiency	Vitamin D_3 supplementation towards "Vitamin D" group and "Placebo" group to evaluate the menstrual cycle	• Normalizing the vitamin D level serum increases the regularity of menstruation (p=0.01), and decreases amenorrhea and oligomenorrhea (p=0.01). • Significantly increased the median vitamin D levels from 18,5 ng/ml to 42.69 ng/ml and improvement in the frequency of regular menstrual cycle	100%
Lagowska (2018)[27]	Prospective cohort study	-	77	<30: deficiency; >30: sufficiency	Serum 25(OH)D levels and menstrual cycle	25(OH)D deficiency (<30 ng/mL) were correlated with longer cycles (oligomenorrhea or amenorrhea) (OR(CI): 5.0 (1.047 to 23.871), p = 0.04)	73%
Singh (2021)[28]	Cross-sectional study	18–≥ 40	166	<20: deficiency; ≥20: sufficiency	25(OH)D and menstrual cycle characteristics (long and short cycle length and cycle irregularity)	• A decreased 25(OH)D levels were associated with 13.3 times the odds of an irregular cycle (OR (95% CI): 13.30 (5.79-30.60), p<0.001) • There were a significant difference in mean 25(OH)D levels between individuals with irregular (14.56 ± 8.76) and regular (21.90 ± 6.15) menstrual cycles which were difference significant (p<0.0001) • The mean 25(OH)D levels of females with infrequent and frequent cycles are not significantly different	100%

25(OH)D, 25 Hydroxyvitamin D; CI, Confidence Interval; IU, International Unit; 1,25(OH)2D, 1,25-Dihydroxyvitamin D; 25(OH)D; 25-hydroxyvitamin D; FSH, Follicle-Stimulating Hormone; iPTH, Intact Para Thyroid Hormone; JBI, Joanna Briggs Institute; LH, Luteinizing Hormone

Vitamin D intake normalized the 25(OH)D levels of the participants (12–18 years) and normal menstrual length (p=0.015).[14] This study implied that vitamin D 50.000 IU for nine weeks of supplementation helps to normalize 25(OH)D level serum and affects the normal menstrual period.[14] This study in line with a randomized placebo-controlled clinical trial conducted by Al-Bayyari et al[25], which found vitamin D intake 50,000 IU for 12 weeks ameliorated the menstrual length in 60 participants (18–49 years) (p=0.001).[25] A variety of

studies, although not all, have shown vitamin D fluctuations during the menstrual cycle, as well as differences in gonadal hormone levels during the luteal phase.[29–31] However, how vitamin D affects this phase mechanism remains unclear. This is assumed to be connected to vitamin D's action on AMH, a glycoprotein hormone generated by granulosa cells during the folliculogenesis process, which plays a role in ovulation and oocyte maturation.[32] A randomized placebo-controlled clinical trial study conducted by Jafari-Sfidvajani et al.[26] showed that normalizing the vitamin D level serum increases the regularity of menstruation (p=0.01) and decreases amenorrhea and oligomenorrhea (p=0.01). Unlike the other two trials, this investigation integrated 50,000 IU vitamin D intake with a low-calorie diet for a week.[26]

Vitamin D is categorized as corticosteroid[33] which modulates many beneficial reproductive processes, such as menstrual cycle regulation and sex hormone regulation.[34] It has several receptors in the nucleus of the body's organ tissue, one of which is in the hypothalamic-hypophysis-ovarium system; hence, it impacts the menstrual cycle.[20] Vitamin D is correlated with steroidogenesis and follicle development because its receptor is exist in ovarian cells.[35] Vitamin D influences sex steroid hormones forming process and human immune system regulation by interacting with progesterone through the induction of T cells and vitamin D receptors. It affects estradiol and estrogen biosynthesis which are correlated with aromatase gene expression and calcium metabolism.[1,27] In addition, this vitamin affects folliculogenesis and the production of the hormone progesterone by affecting the sensitivity of follicle stimulating hormone (FSH).[1] AMH may be associated with 25(OH)D metabolism because it decreases primordial follicle recruitment, leading to a significant decrease in follicular development and further delaying atresia. In the AMH gene's promoter region is a domain for the vitamin D signaling pathway. Therefore, vitamin D are hypothesized as responsible for controlling AMH production.[36] This mechanism may explain how vitamin D has an essential role in menstrual regulation.

This study had several limitations. Several studies used a small population size. Some studies did not provide mean and standard deviation values of 25(OH)D. Therefore, we were unable to identify the general classification of the baseline population characteristics before intervention. The included studies were also undertaken mainly in high-income countries, limiting the generalizability of the study findings. Furthermore, only a few studies recorded menstrual phase testing previous to the intervention, which might lead to varied 25(OH)Dlevels interpretations among participants due to fluctuations across the menstrual phases.

CONCLUSION

The results of both observational studies and randomized controlled trials included in this review imply that serum vitamin D levels influence the length and the frequency of the menstrual cycle. This findings are due to the effect of serum vitamin D on female reproductive hormones that play a role on menstrual cycle regulation. Given the limitations of the current review, future studies, possibly with a randomized controlled design, are required to further confirm our findings.

DISCLOSURES

Acknowledgment

None

Conflict of interest

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

Funding

There was no source of financial assistance for this study.

Author contribution

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

REFERENCES

1. Draper CF, Duisters K, Weger B, et al. Menstrual cycle rhythmicity: metabolic patterns in healthy women. Sci Rep 2018;8(1):1–15.
2. Park YJ, Shin H, Jeon S, et al. Menstrual cycle patterns and the prevalence of premenstrual syndrome and Polycystic Ovary Syndrome in Korean young adult women. Healthcare (Basel). 2021;9(1):56. doi: 10.3390/healthcare9010056. PMID: 33430265; PMCID: PMC7825721.
3. Bull JR, Rowland SP, Scherwitzl EB, et al. Real-world menstrual cycle characteristics of more than 600,000 menstrual cycles. NPJ Digit Med. 2019;

2:83. doi: 10.1038/s41746-019-0152-7. PMID: 31482137; PMCID: PMC6710244.
4. Singh M, Rajoura OP, Honnakamble RA. Menstrual patterns and problems in association with body mass index among adolescent school girls. J Family Med Prim Care. 2019;8(9):2855-8. doi: 10.4103/jfmpc.jfmpc_474_19. PMID: 31681655; PMCID: PMC6820408.
5. Wang YX, Arvizu M, Rich-Edwards JW, et al. Menstrual cycle regularity and length across the reproductive lifespan and risk of premature mortality: prospective cohort study. BMJ. 2020;371:m3464. doi: 10.1136/bmj.m3464. PMID: 32998909; PMCID: PMC7526082.
6. Dimitrov V, Barbier C, Ismailova A, et al Vitamin D-regulated Gene Expression Profiles: Species-specificity and Cell-specific Effects on Metabolism and Immunity. Endocrinology. 2021;162(2):bqaa218. doi: 10.1210/endocr/bqaa218. PMID: 33249469; PMCID: PMC7751191.
7. Saponaro F, Saba A, Zucchi R. An update on vitamin D metabolism. Int J Mol Sci. 2020;21(18):6573. doi: 10.3390/ijms21186573. PMID: 32911795; PMCID: PMC7554947.
8. Lerchbaum E, Rabe T. Vitamin D and female fertility. Curr Opin Obstet Gynecol. 2014;26(3):145-50. doi: 10.1097/GCO.0000000000000065. PMID: 24717915.
9. Arslan S, Akdevelioğlu Y. The relationship between female reproductive functions and vitamin D. J Am Coll Nutr. 2018;37(6):546-51. doi: 10.1080/07315724.2018.1431160. Epub 2018 Mar 13. PMID: 29533153.
10. Jukic AM, Steiner AZ, Baird DD. Lower plasma 25-hydroxyvitamin D is associated with irregular menstrual cycles in a cross-sectional study. Reprod Biol Endocrinol. 2015;13:20. doi: 10.1186/s12958-015-0012-5. PMID: 25879830; PMCID: PMC4359493.
11. Paffoni A, Ferrari S, Viganò P, et al. Vitamin D deficiency and infertility: insights from in vitro fertilization cycles. J Clin Endocrinol Metab. 2014;99(11):E2372-6. doi: 10.1210/jc.2014-1802. Epub 2014 Aug 14. PMID: 25121462.
12. Pagliardini L, Vigano' P, Molgora M, et al. High prevalence of vitamin D deficiency in infertile women referring for assisted reproduction. nutrients. 2015;7(12):9972-84. doi: 10.3390/nu7125516. PMID: 26633484; PMCID: PMC4690068.
13. Bikle D, Christakos S. New aspects of vitamin D metabolism and action - addressing the skin as source and target. Nat Rev Endocrinol. 2020;16(4):234-52. doi: 10.1038/s41574-019-0312-5. Epub 2020 Feb 6. PMID: 32029884.
14. Bahrami A, Avan A, Sadeghnia HR, et al. High dose vitamin D supplementation can improve menstrual problems, dysmenorrhea, and premenstrual syndrome in adolescents. Gynecol Endocrinol. 2018;34(8):659-63. doi: 10.1080/09513590.2017.1423466. Epub 2018 Feb 15. PMID: 29447494.
15. Drakopoulos P, van de Vijver A, Schutyser V, et al. The effect of serum vitamin D levels on ovarian reserve markers: a prospective cross-sectional study. Hum Reprod. 2017;32(1):208-14. doi: 10.1093/humrep/dew304. Epub 2016 Dec 6. PMID: 27927849.
16. Harris HR, Chavarro JE, Malspeis S, et al. Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. Am J Epidemiol. 2013;177(5):420-30. doi: 10.1093/aje/kws247. Epub 2013 Feb 3. PMID: 23380045; PMCID: PMC3626048.
17. Jukic AMZ, Upson K, Harmon QE, et al. Increasing serum 25-hydroxyvitamin D is associated with reduced odds of long menstrual cycles in a cross-sectional study of African American women. Fertil Steril. 2016;106(1):172-9.e2. doi: 10.1016/j.fertnstert.2016.03.004. Epub 2016 Mar 18. PMID: 26997249; PMCID: PMC4930882.
18. Drakopoulos P, van de Vijver A, Schutyser V, et al. The effect of serum vitamin D levels on ovarian reserve markers: a prospective cross-sectional study. Hum Reprod. 2017;32(1):208-14. doi: 10.1093/humrep/dew304. Epub 2016 Dec 6. PMID: 27927849.
19. Alkhalaf Z, Kim K, Kuhr DL, et al. Markers of vitamin D metabolism and premenstrual symptoms in healthy women with regular cycles. Hum Reprod. 2021;36(7):1808-20. doi: 10.1093/humrep/deab089. PMID: 33864070; PMCID: PMC 8530167.
20. Harmon QE, Kissell K, Jukic AMZ, et al. Vitamin D and reproductive hormones across the menstrual cycle. Hum Reprod. 2020;35(2):413-23. doi: 10.1093/humrep/dez283. PMID: 32068843; PMCID: PMC7986370.
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71. PMID: 33782057; PMCID: PMC8005924.
22. Moola S, Munn Z, Tufanaru C, et al. JBI manual for evidence synthesis [Internet]. JBI, 2020. Available from: https://synthesismanual.jbi.global
23. Tufanaru C, Munn Z, Aromataris E, et al. JBI manual for evidence synthesis [Internet]. JBI, 2020. Available from: https://synthesismanual.jbi.global

24. Jukic AMZ, Wilcox AJ, McConnaughey DR, et al. 25-hydroxyvitamin D and long menstrual cycles in a prospective cohort study. Epidemiology. 2018 ;29(3):388-96. doi: 10.1097/EDE.0000000000 000804. PMID: 29337846; PMCID: PMC5882585.
25. Al-Bayyari N, Al-Domi H, Zayed F, et al. Androgens and hirsutism score of overweight women with polycystic ovary syndrome improved after vitamin D treatment: A randomized placebo controlled clinical trial. Clin Nutr. 2021;40(3):870-8. doi: 10.1016/j.clnu.2020.09.024. Epub 2020 Sep 24. PMID: 33010974.
26. Jafari-Sfidvajani S, Ahangari R, Hozoori M, et al. The effect of vitamin D supplementation in combination with low-calorie diet on anthropometric indices and androgen hormones in women with polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. J Endocrinol Invest. 2018;41(5):597-607. doi: 10.1007/s40618-017-0785-9. Epub 2017 Nov 6. PMID: 29110281.
27. Łagowska K. The relationship between vitamin D status and the menstrual cycle in young women: A preliminary study. Nutrients. 2018;10(11):1729. doi: 10.3390/nu10111729. PMID: 30423869; PM CID: PMC6265788.
28. Singh V, Tamar N, Lone Z, et al. Association between serum 25-hydroxy vitamin D level and menstrual cycle length and regularity: A cross-sectional observational study. Int J Reprod Biomed. 2021;19(11):979-86. doi: 10.18502/ijrm.v19i11. 9913. PMID: 34977455; PMCID: PMC8717082.
29. Tartagni M, Cicinelli MV, Tartagni MV, et al. Vitamin D supplementation for premenstrual syndrome-related mood disorders in adolescents with severe hypovitaminosis D. J Pediatr Adolesc Gynecol. 2016;29(4):357-61. doi: 10.1016/j.jpag. 2015.12.006. Epub 2015 Dec 24. PMID: 26724745.
30. Franasiak JM, Wang X, Molinaro TA, et al Free vitamin D does not vary through the follicular phase of the menstrual cycle. Endocrine. 2016 ;53(1):322-6. doi: 10.1007/s12020-016-0946-1. Epub 2016 Apr 6. PMID: 27052515.
31. Tehrani HG, Mostajeran F, Shahsavari S. The effect of calcium and vitamin D supplementation on menstrual cycle, body mass index and hyperandrogenism state of women with poly cystic ovarian syndrome. J Res Med Sci. 2014;19(9):875-80. PMID: 25535503; PMCID: PMC4268197.
32. Kadoura S, Alhalabi M, Nattouf AH. Effect of calcium and vitamin D supplements as an adjuvant therapy to metformin on menstrual cycle abnormalities, hormonal profile, and IGF-1 system in Polycystic Ovary Syndrome patients: A randomized, placebo-controlled clinical trial. Adv Pharmacol Sci. 2019;2019:9680390. doi: 10.1155/ 2019/9680390. PMID: 31354810; PMCID: PMC 6636596.
33. Jenkinson C. The vitamin D metabolome: An update on analysis and function. Cell Biochem Funct. 2019;37(6):408-23. doi: 10.1002/cbf.3421. Epub 2019 Jul 22. PMID: 31328813.
34. Wieder-Huszla S, Jurczak A, Szkup M, et al. Relationships between vitamin D_3 and metabolic syndrome. Int J Environ Res Public Health. 2019 ;16(2):175. doi: 10.3390/ijerph16020175. PMID: 30634516; PMCID: PMC6352038.
35. Muscogiuri G, Altieri B, de Angelis C, et al. Shedding new light on female fertility: The role of vitamin D. Rev Endocr Metab Disord. 2017;18(3) :273-83. doi: 10.1007/s11154-017-9407-2. PMID: 28102491.
36. Subramanian A, Gernand AD. Vitamin D metabolites across the menstrual cycle: a systematic review. BMC Womens Health. 2019;19(1):19. doi: 10.1186/s12905-019-0721-6. PMID: 30691458; PMCID: PMC6348668.

MAJALAH OBSTETRI & GINEKOLOGI

INDEX

Volume 30, April, August, December 2022

AUTHORS

Abiyyu, F	3 : 139-145
Aditiawarman	1 : 10-16
Alda, K	1 : 42-47
Aldiansyah, D	2 : 78-83
Amru, SN	3 : 122-127
Andrijono	3 : 116-121
Anggayana, AD	1 : 42-47
Anindya PA, Fadhila	1 : 24-31
Ardiansyah, E	3 : 128-133
Aroean, MSP	3 : 145-153
Aryana, MBD	2 : 101-107
Atmaja, PDAP	2 : 84-91
Atnil, E	2 : 66-71
Brahmana, NR	2 : 58-65
Budinurdjaja, P	2 : 92-100
Cilik, RM	2 : 72-77
Danianto, A	2 : 84-91
Effendi, IH	3 : 128-133
Ernawati	1 : 17-23
Faizah, Z	2 : 72-77
Faizi, M	3 : 139-145
Fatmawati, W	1 : 24-31
Febri, RR	2 : 66-71
Gunawan, GA	3 : 134-138
Hendarto, H	1 : 1-9
Hestiantoro, A	2 : 66-71
Hikmah, R	1 : 1-9
Ibrahim, RC	1 : 36-41
Indarti, J	1 : 42-47
Izzati, D	3 : 108-115
Kamajaya, IGNAT	2 : 101-107
Karuniawaty, TP	2 : 84-91
Kekalih, A	3 : 116-121
Khoiri, MA	2 : 78-83
Kulsum, U	3 : 108-115
Kurniawati, EM	3 : 108-115
Larasati, S	1 : 36-41
Lestari, P	1 : 10-16, 2 : 52-57
Lumbanraja, SN	2 : 78-83, 3 : 128-133
Lumentut, AM	1 : 32-35
Meliana, A	3 : 154-160
Mulawardhana, P	2 : 52-57
Muna, N	2 : 66-71
Noor, MS	2 : 92-100
Nurcahyawati, WAS	2 : 92-100
Pangestu, S	1 : 42-47
Permadi, V	1 : 10-16
Pradnyana, IWAS	3 : 145-153
Prameswari, N	1 : 42-47
Pramono, N	1 : 36-41
Prasetyo, B	3 : 134-138
Rahadina, AAD	3 : 134-138
Ramlan, D	1 : 36-41
Riayati, O	2 : 66-71
Rifiranda, C	1 : 42-47
Rochmah, N	3 : 139-145
Sa'adi, A	2 : 58-65
Salsabila, H	3 : 154-160
Sandhika, W	2 : 72-77
Sari, DJ	2 : 52-57
Sari, RA	1 : 17-23
Setiawan, P	3 : 122-127
Sihite, B	3 : 128-133
Siregar, MFG	2 : 78-83
Sitepu, M	2 : 78-83, 3 : 128-133
Sondakh, JMM	1 : 32-35
Suardi, L	2 : 92-100
Suciwiyati, NI	3 : 139-145
Sukatendel, K	3 : 128-133
Sukowati, EG	1 : 24-31
Sulistiawati	1 : 17-23, 3 : 108-115
Tala, MR	2 : 78-83
Taufiq, M	1 : 48-51
Tendean, HMM	1 : 32-35
Wahyunitisari, MR	3 : 154-160
Widjiati	1 : 1-9
Winata, IGS	1 : 48-51, 3 : 145-153
Witarto, BS	3 : 154-160
Wityawan, I	3 : 116-121
Yaznil, R	3 : 128-133
Yudiwati, R	2 : 58-65
Yuliati, I	3 : 122-127

SUBJECTS

Acceptance 3 : 108-115
Acetic acid 2 : 52-57
Acid, acetic 2 : 52-57
Acid, trichloroacetic 1 : 48-51
Age, gestational 2 : 72-77
  reproductive 3 : 153-160
Antepartum hemorrhage 3 : 122-127
Antihypertensive 3 : 146-153
Autoimmune disease 3 : 134-138
Calcium serum 2 : 78-83
Candidiasis, vulvovaginal 2 : 72-77
Cardiomyopathy 2 : 101-107
Cardiovascular disease 2 : 101-107
Cervical cancer 1 : 48-51, 2 : 52-57
  3 : 108-115
Cobas® 4800 HPV Test 3 : 116-121
Compress, herbal 1 : 36-41
Contraception 1 : 42-47
Coping process 3 : 108-115
COVID-19 2 : 84-91, 3 : 128-133
  3 : 139-145
Delivery method 1 : 42-47
Detection, early 2 : 52-57
Dyslipidemia 2 : 66-71
E2 2 : 92-100
Early detection 2 : 52-57
Eclampsia 1 : 32-35
Endometrial implant 1 : 1-9
Follicle Stimulating
  Hormone 2 : 92-100
Genotyping 3 : 116-121
Gestational age 2 : 72-77
Hemorrhage, antepartum 3 : 122-127
Herbal compress 1 : 36-41
HIV 1 : 42-47
Human Papillomavirus 3 : 116-121
IgG 3 : 128-133
IgM 3 : 128-133
Implant, endometrial 1 : 1-9
In Vitro Fertilization 2 : 58-65
Infertility score 2 : 58-65
Inflammatory markers 2 : 66-71
IUD 1 : 42-47
Labor pain 1 : 36-41
Lesion, cervical cancer 1 : 48-51
Leuprolide 1 : 1-9
Magnesium sulfate 1 : 17-23
Marker, inflammatory 2 : 66-71
Maternal mortality 1 : 32-35
Menopause 2 : 92-100
Menstrual cycle 3 : 153-160
Methyldopa 3 : 146-153
Midwives 2 : 52-57, 2 : 72-77
Mortality, maternal 1 : 32-35
NF-kappaB 1 : 1-9
Nifedipine 3 : 146-153
Outcomes, maternal 1 : 24-31, 3 : 122-127
  neonatal 3 : 122-127
  perinatal 1 : 24-31
Pain, labor 1 : 36-41
Pandanus conoideus, Lam 1 : 1-9
Peripartum 2 : 101-107
Placenta previa 3 : 122-127
Polycystic Ovary
  Syndrome 2 : 66-71
Precocious Puberty 3 : 139-145
Preeclampsia 1 : 10-16, 1 : 17-23
  1 : 24-31, 2 : 101-107
  3 : 134-138, 3 : 146-153
Pregnancy 3 : 134-138
  termination 1 : 10-16
  with COVID-19 2 : 84-91
  with HIV 1 : 42-47
Primigravida 1 : 36-41
Psychological aspects 3 : 139-145
Red fruit 1 : 1-9
Reproductive age 3 : 153-160
RT-PCR 3 : 128-133
Score, infertility 2 : 58-65
Serology 3 : 128-133
Serum, calcium 2 : 78-83
Sjogren syndrome 3 : 134-138
Stress Urinary
  Incontinence 2 : 92-100
Termination of pregnancy 1 : 10-16
Test, visual inspection 2 : 52-57
Transmission, vertical 3 : 128-133
Trichloroacetic acid 1 : 48-51
Trimester 2 : 78-83
Umbilical cord 3 : 128-133
Urine samples 3 : 116-121
Visual inspection test 2 : 52-57
Vitamin D 3 : 153-160
Vulvovaginal candidiasis 2 : 72-77

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