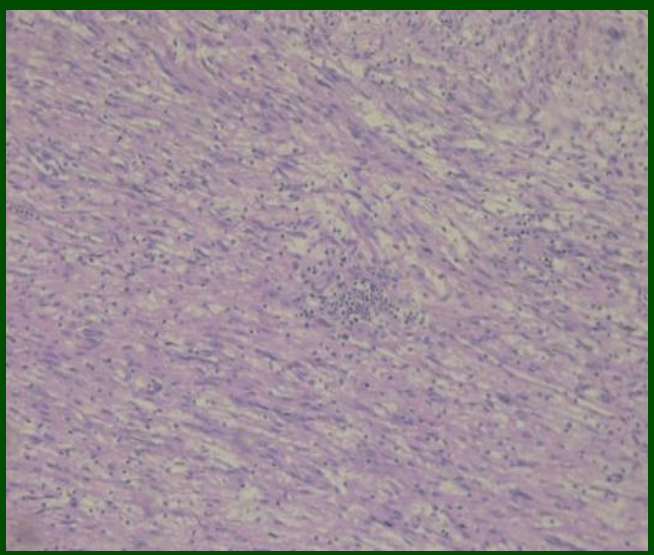
DOAJ DIRECTORY OF OPEN ACCESS JOURNALS

pISSN 0854-0381
eISSN 2598-1013

# Majalah Obstetri & Ginekologi

## JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

Vol. 29 No. 2 August 2021



**Microscopic image showing cigar-like smooth muscle cells in a retroperitoneum parasitic leiomyoma case**



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 Research, Technology, and Higher Education, Republic of Indonesia
No. 30/E/KPT/2018

**Vol. 29 No. 2 August 2021**

**pISSN 0854-0381**
**eISSN 2598-1013**

# Majalah Obstetri & Ginekologi

## JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

**ACCREDITED**
Ministry of Research, Technology, and Higher Education, Republic of Indonesia
**No. 30/E/KPT/2018**

## EDITORIAL TEAM



**Address**

Department of Obstetrics & 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. 29 No. 2 August 2021**

**pISSN 0854-0381**
**eISSN 2598-1013**

# Majalah Obstetri & Ginekologi

## JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

**CONTENT**



Cover :
**Microscopic image showing cigar-like smooth muscle cells in a retroperitoneum parasitic leiomyoma case**

This edition page 74

# AUTHOR GUIDELINES

**Majalah Obstetri & Ginekologi** publishes articles on all aspects of obstetrics and gynecology. Articles can be classified as original articles, case reports, review articles that keep the readers informed of current issues, innovative thinking in obstetrics and gynecology; opinion, letters to the editor; and short communication. Articles are considered for publication with the condition that they have not been published or submitted for publication elsewhere. Manuscript should be written in English. Authors should follow the manuscript preparation guidelines.

## Submission

The submitted manuscript should be addressed to Editor-in-chief of the Majalah Obstetri & Ginekologi. Manuscript must be submitted through online submission by registered users. You can easily register in the journal system. For further question contact us at: mog@journal.unair.ac.id.

## General Principles

As a basic requirement, all articles submitted to the Majalah Obstetri & Ginekologi must be original work, which has never been published previously and is submitted exclusively to the Majalah Obstetri & Ginekologi. The Editorial Board reserves the right to edit all articles in aspects of style, format, and clarity. Authors may be required to revise their manuscripts for reasons of any aspect. Manuscripts with excessive errors in any aspect may be returned to authors for retyping or may be rejected. All manuscripts will be subjected to peer and editorial review.

## Article Types

The journal accept the following types of article:

### a. Original article

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 not exceed 3500 words, references included. Tables and figures are up to six (6) and references up to 15. General structure of the manuscript can be referred to "Structure and Language". The text consists of **Abstract, Introduction, Materials and Methods, Results and Discussion, Conclusion**. The template can be downloaded from the manuscript template in the website (https://e-journal.unair.ac.id/ MOG/pages/view/ Manuscript%20Template)

### b. Case report

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 not exceed 1800 words, references included. Tables and figures are all up to six (6) and references up to 15. The permission should be submitted along with the manuscript. General structure of the manuscript can be referred to "Structure and Language". The structure of the manuscript consists of **Abstract, Introduction, Case Report, Discussion, Conclusion**. The template can be downloaded from the manuscript template in the website (https://e-journal. unair.ac.id/MOG/pages/view/Manuscript%20Template)

### c. Review article

Review article provides a clincial assessment of current evidence covering a broad range of topics of concern. Appropriate methodology should be followed, such as PROSPERO, the online international register for systematic reviews. The manuscript length should be within 3000 words with tables and figures all up to six (6) and references up to 15. General structure of the manuscript can be referred to "Structure and Language". The structure of the manuscript consists of **Abstract, Introduction, Subtitles in keeping with needs, Conclusion**. The template can be downloaded from the manuscript template in the website (https://e-journal. unair.ac.id/MOG/pages/view/Manuscript%20Template)

### d. 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). The template can be downloaded from the manuscript template in the website (https://e-journal.unair.ac.id/MOG/pages/view/ Manuscript%20Template)

### e. Letters to the editor

We also publish short letter delivering information or news relating to articles published recently in Majalah Obstetri & Ginekologi. The letter should have timeliness to the topic of published article, the significance of the point, and the quality of the writing. The letter should be no more than 500 words with five references at most. The letter must include title, which usually contains the title of the article commented, and the names of the persons whose signatories will be published and their affiliations. The template can be downloaded from the manuscript template in the website (https://e-journal.unair.ac.id/MOG/pages/view/Manuscript%20Template)

### f. Short communication

Short communication is a short manuscript presenting new original ideas, controversial issues, focusing, for example, on a particular aspect of a problem or new finding that has a significant impact. The manuscript is limited to 3000 words with abstract of 100 words. The manuscript structure should consist of **Abstract, Text, References** with figures and tables all no more than six (6). The template can be downloaded from the manuscript template in the website (https://e-journal.unair.ac.id/MOG/pages/view/Manuscript%20Template)

Authors must also supply the Disclaimer issued by Majalah Obstetri & Ginekologi, that can be downloaded from the website (https://e-journal.unair.ac.id/MOG/) and be submitted along with the submission of the manuscript.

## Study Ethics

All submitted papers containing animal experiments and/or involving human subjects should have obtained approval from an independent ethics committee in the form of **ethical clearance** for original research and/or **written permission** for case report. The copy of the approval should be submiitted along with the manuscript.

## Publication Ethics

This journal follows guidelines from Committee on Publication Ethics (COPE) in facing all aspects of publication ethics and, in particular, how to handle cases of research and publication misconduct.

## Structure and Language

Articles will be published in US English, following American spelling. Articles in English that are linguistically inadequate may be rejected. Manuscript in general must be submitted in the following structural order: **Title, authors, authors' affiliations, abstract, keywords, correspondence, main text, acknowledgment (if any), conflict of interest, funding, references**. The hierarchy of headings and subheadings is as follows: **BOLD CAPS, Bold lower case, *Bold lower case italics***, Plain text, *Plain text italics*. Tables, figures, and legends are included in the text where they should be placed. The format should refer to the template of the journal.

## Abstract and Keywords

**Abstract** should be prepared in English and Indonesian of approximately 250 words. Abstract should be concise and precise with enough information highlighting the points and importance of the article. Abstract should be structured according to the types of articles as follows:

a. Original Article: **Objective, Materials and Methods, Results, Conclusion**.
b. Case Report: **Objective, Case Report, Conclusion**.
c. Review Article: No structure but **summari-zes the problem** being considered and how the review was conducted.
d. Opinion: not required.
e. Letter to the Editor: not required
f. Short communication: No structure but **summarizes the context** of the manuscipt.

**Keywords** are limited to 3-6 words or short phrases that will allow proper and convenient indexing, separated with semicolon. Keywords should apply terms present in Medical Subject Headings (MeSH).

## Text

The **text** should be structured as explained under the subheading "Article types". Footnotes are not advisable; their contents should rather be incorporated into the text. Use only standard abbreviations; use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement. If a sentence begins with a number, it should be spelled out. Cite in numerical order every reference, figure and table. Use Arabic numerals in superscript to cite references in Vancouver style.

## Statistical Methods

All statistical methods used should be described in detail in the methods section of the manuscript. Avoid

relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

## Acknowledgments

Personal **acknowledgments** should be limited to appropriate professionals who contributed to the paper, including technical help and financial or material support, also general support by a department chair-person.

## Tables and Figures

Total number of tables and figures are advisably **not to exceed 6 (six).** Tables and its title should be included in the text. Tables should be numbered in arabic numerals, captions should be brief, clearly indicating the purpose or content of each table. Provide a footnote to each table, identifying in alphabetical order all abbreviations used. Number tables consecutively in the order of their first citation in the text and supply a brief title for each. Do not use internal horizontal or vertical lines. Give each column a short or an abbreviated heading. Explain all nonstandard abbreviations and explanatory matters in footnotes. Identify statistical measures of variations, such as standard deviation and standard error of the mean. Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

**Figures** should be either professionally drawn or photographed, and in a format (JPEG or TIFF) in the following resolutions [gray-scale or color in RGB (red, green, blue mode) at least 300 dpi (dots per inch)]. Figures should be made as self-explanatory as possible, titles and detailed explanations belong in the legends-not on the figures themselves. Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in the figures should contrast with the background and attached and grouped appropriately to the figures so as to prevent disorganization during figures editing. Photographs of potentially identifiable people must be accompanied by written permission to use the photo-graph.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce the figure. Permission is required irrespective of authorship or publisher except for documents in the public domain. Color figures are allowed, as they will appear in electronic edition of the journal. Since the journal is also printed in black-and-white edition, figures in color should be adjusted in such a way that its printed form in black-and-white will remain be sharp, clear, and lead to no confusion or unclarity. Diagrams and their legends should be in black-and-white to ascertain clarity. If the original size of the figures is too large, the size should be adjusted in order to allow electronic submission of the manuscript.

## Legends for Figures

**Legends for figures** are written with Arabic numerals corresponding to the figures. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

## Units of Measurement

For measurements use S.I. (System International) units. Measurements should be abbreviated (e.g. mm, kcal, etc.) in accordance to the Style Manual for Biological Sciences and using the metric system. Measurements of length, height, weight, and volume should be reported in appropriate scientific units.

## 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. The titles of journals should be abbreviated according to the style used for MEDLINE. 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/cslipublicationsSta/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.virtual-

medical 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 examples:

- 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 ARTICLE

# Diagnostic value of abdominal CT scan in ovarian tumors in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2017 to December 2018

**Ida Bagus Gede Ramayuda[1*], Lies Mardiyana[1], Dyah Erawati[2], Indra Yuliati[2]**
[1]Department of Radiology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia,
[2]Department of Obstetric and Gynecology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

## ABSTRACT

**Objectives:** The purpose of this study was to determine the diagnostic value of contrast-enhanced abdominal CT scan in ovarian tumors in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, to provide scientific and clinical benefits.
**Materials and Methods**: Samples were taken retrospectively by contrast-enhanced abdominal CT scan raw data in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2017 to December 2018. Using inclusion and exclusion criteria, a total of 88 samples were obtained and reviewed blindly by Female Organ Division of Radiology Department, Faculty of Medicine Universitas Airlangga, and by using "tools" (primary and additional findings of modified ovarian tumors malignancy). The data were correlated with histopathological findings and analyzed by statistical tests and the results with and without "tools" were compared.
**Results**: Samples were grouped by age, distributed with a range of 20 years and the group of 41-60 years had the highest age of ovarian tumor samples (46.6%) with 84.1% being ovarian malignant tumors according to their histopathological results. It was dominated by serous, mucinous and endometroid types with sensitivity of 93.3%, specificity of 64.3%, positive predictive value of 93.3% negative predictive value of 69.2%, and accuracy value of 89.8%. More reliable results were obtained by using "tools".
**Conclusion**: Contrast-enhanced abdominal CT scan of ovarian tumors in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, evaluated by "tools" still had a better and more reliable diagnostic value than without tools in determining policy steps in handling ovarian tumors with a note that more in-depth research on pitfalls is needed so it may enrich the characteristic findings in imaging.

**Keywords:** abdominal CT scan; ovarian tumor malignancy; histopathology; primary and additional findings; cancer; maternal health; medicine

## ABSTRAK

**Tujuan:** Tujuan penelitian ini adalah untuk mengetahui nilai diagnostik pemeriksaan CT scan abdomen dengan kontras pada tumor ovarium di RSUD Dr. Soetomo, Surabaya, Indonesia, sehingga memberikan manfaat ilmiah maupun klinis.
**Bahan dan Metode**: Sampel diambil secara retrospektif melalui *raw data* CT scan abdomen dengan kontras di RSUD Dr. Soetomo, Surabaya, Indonesia, antara Januari 2017 hingga Desember 2018, dengan membuat kriteria inklusi dan eksklusi didapatkan sampel sejumlah 88 dan direview oleh divisi female organ Departemen Radiologi FK-Unair-RSUD Dr. Soetomo secara blind dan menggunakan "*tools*" (temuan primer dan tambahan keganasan tumor ovarium termodifikasi) kemudian dikorelasikan dengan temuan histopatologinya dan dianalisa dengan uji statistik serta hasil yang diperoleh dengan dan tanpa "*tools*" diperbandingkan.
**Hasil**: Sampel dikelompokan berdasarkan umur, didapatkan distribusi dengan rentang 20 tahun dan kelompok 41-60 tahun menunjukkan umur sampel tumor ovarium terbanyak (46,6%) dengan 84,1 % merupakan tumor ganas ovarium sesuai hasil histopatologinya. Didominasi oleh keganasan jenis serous, mucinous dan endometroid. Didapatkan sensitivitas 93,3%, spesifisitas 64,3%, nilai duga positif 93,3% nilai duga negatif 69,2%, dan nilai akurasi 89,8% yang hasilnya lebih baik dengan menggunakan *tools*.
**Simpulan**: Pemeriksaan CT scan abdomen dengan kontras pada tumor ovarium di RSUD Dr. Soetomo serta dievaluasi menggunakan *tools* masih memiliki nilai diagnostik yang lebih baik dan dapat diandalkan dibandingkan tanpa *tools* dalam menentukan langkah kebijakan dalam penangan tumor ovarium dengan catatan diperlukan penelitian yang lebih mendalam terhadap timbulnya pitfalls sehingga dapat menambah karakter temuan dalam pencitraan.

**Kata kunci:** CT scan abdomen; keganasan tumor ovarium; histopatologi; *tools*; kanker; kesehatan ibu; perawatan

***Correspondence:** Ida Bagus Gede Ramayuda, Department of Radiology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jalan Prof dr Moestopo 6-8, Surabaya 60286, Indonesia.
E-mail: ida.ramayuda@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.45-52
● Maj Obs Gin. 2021;29:45-52 ● Received 5 Oct 2020 ● Revised 10 Jan 2021 ● Accepted 24 Jan 2021

## INTRODUCTION

Malignancy of ovarian tumors is the 7th most common cause of death in women by cancer, after breast, lung, colorectal, cervical, gastric, liver and pancreatic cancers with 4.4% of 4.2 million deaths from cancer and having an incidence of 3.4% of the 8.6 million new cases in the world.[1] Identifying and assessing the characteristics of ovarian tumor malignancy and female pelvic malignancy is very important before a laparotomy plan is carried out and also associated with 5-year life expectancy in the patients.[2] Contrast-enhanced abdominal CT scan can help clinicians to strengthen diagnostic enforcement of ovarian tumor malignancies before cyto-reduction surgery is performed. Contrast-enhanced abdominal CT scan still a valid tool with good sensitivity and specificity. CT scan provides more extensive and important information in case of gynecological malignancies both as staging determinants and plans for managing the disease. Comprehensive and uniform criteria will increase the diagnostic value of CT scan in ovarian tumors especially in Dr. Soetomo Hospital, Surabaya, Indonesia, and referred to the gold standard diagnostic by histopathological examination.[4,5]

## MATERIALS AND METHODS

This study was approved by the Medical Research Ethics Committee of Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The design of this study was retrospective observational analytic design. There were 213 cases, but most did not have representative histopathological results and incomplete abdominal CT documents. After obtaining inclusion and exclusion criteria, there were 88 cases that met the researcher requirements for sample with the youngest age of 7 years and the oldest age of 79 years. The patients were divided into age groups with a range of 20 years. The results showed that most ovarian tumor patients were in the age group of 41-60 years, namely 46.6% (41 people), 29.5% (26 people) in the age group of 21-40 years, 13.6% (12 people) in the age group of 61-80 years, and 10.2% (9 people) in the age group of 1-20 years. The inclusion criteria were clinical patients suspected of ovarian tumors who had performed contrast-enhanced abdominal CT scan before surgery, raw data of CT scan, and histopathological examination results from January 2017 to December 2018. Exclusion criteria included all who were not included in the inclusion criteria, tumor evaluation (restaging) and prior chemotherapy. All data were collected on contrast-enhanced abdominal CT scan which blindly reviewed by the female organ division of the Radiology Department of Universitas Airlangga using modified "tools" that contain primary findings on CT scan (mass size, septation, septal thickness, cystic component, solid, fat, calcification, contrast enhancement, papillary projection, ovarian artery feeding) and additional findings (ascites, peritoneal implants, lymph node enlargement, normal uterus that could still be identified and the absence of another organ mass). The effectiveness of the diagnostic value with and without the tools was also be compared.

The examination used a 16-slice CT scan machine of the Hitachi brand ECLOS Q1E-BW1545-1 and Siemens SOMATOM Emotion 80476. Abdominal CT scan used non-ionic, water soluble contrast agent of Iopamiro 370 with a dose of 1-1.5mm/body weight and made according to the protocol of Pelvic abdominal CT scan. Raw data of abdominal CT scan was reformed with a thickness of 2 mm. The data was then reviewed using the DCOM file reader application by Female Organ Division of the Radiology Department of the Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Data analysis was performed with Friedman test using SPSS to obtain diagnostic values in the form of sensitivity, specificity, positive and negative predictive values along with accuracy and precision of data. For statistical analysis, the findings of the review results using "tools" was cross tabulated with histopathological findings.

## RESULTS AND DISCUSSION

The results of the comparison test using Friedman test between histopathological examination as the gold standard with CT scan showed p-value of 0.739 ($p > \alpha$).

Table 1. Cross tabulation between abdominal CT scan with histopathological examination in ovarian tumor patients with tools in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

| | | Histopathology | | Total |
|---|---|---|---|---|
| | | Malignant ovarian tumor | Benign ovarian tumor | |
| Ct scan | Malignant ovarian tumor | TP :70 | PF:5 | 75 |
| | Benign ovarian tumor | NF:4 | TN:9 | 13 |
| Total | | 74 | 14 | 88 |

Sensitivity: 93.3%, Specificity: 64.3%, Accuracy: 89.8%, Precision: 93.3%, Recall: 64.3%, Negative predicting value: 69.2%, Positive predicting value: 93.3%

There was no difference between the results of histopathological examination and the results of abdominal CT scan. So the abdominal CT scan was as good as histopathology with a sensitivity value of 93.3% and a specificity of 64.3%. To assess the accuracy of the abdominal CT scan compared to the histopathological results obtained an accuracy value of 89.8%, precision of 93.3%, recall of 64.3% NPV of 69.2%, and PPV of 93.3%.

Table 2. Cross tabulation between abdominal CT scan with histopathological examination in ovarian tumor patients without tools in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

| | | Histopathology | | Total |
|---|---|---|---|---|
| | | Malignant ovarian tumor | Benign ovarian tumor | |
| Ct scan | Malignant ovarian tumor | TP:61 | PF:9 | 70 |
| | Benign ovarian tumor | NF:14 | TN:4 | 18 |
| Total | | 75 | 13 | 88 |

Sensitivity: 87.1%, Specificity: 22.2% Accuracy: 73.8%, Precision: 87.1%

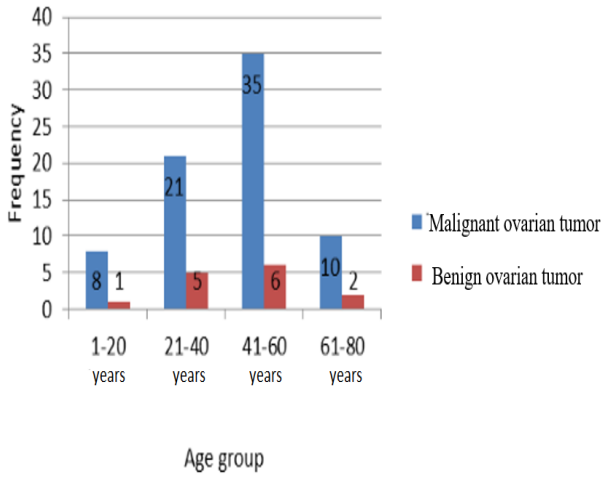



Figure 1. Bar chart of patient's age with malignant and benign findings of ovarian tumors according to histopathology results in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

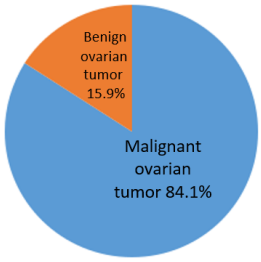



Figure 2. Circle chart of histopathological examination of ovarian tumor patients in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

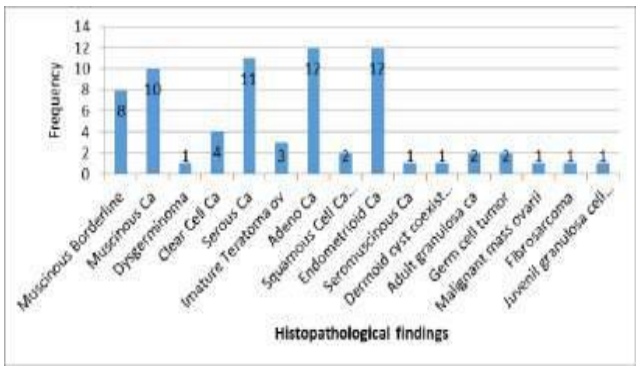



Figure 3. Bar chart of histopathological findings of patients with malignant ovarian tumors in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

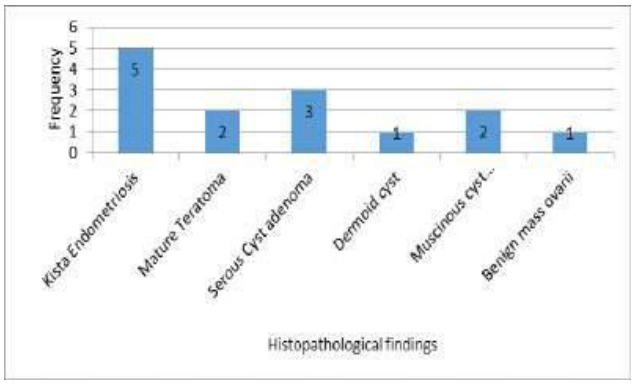



Figure 4. Stem distribution diagram of histopathological findings of patients with benign ovarian tumors in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

Table 3. Primary findings of abdominal CT scan in ovarian tumor patients in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

| Primary findings of abdominal CT scan | | Frequency | Percentage (%) |
|---|---|---|---|
| Lesion size > 4cm | Yes | 87 | 98.9 |
| | No | 1 | 1.1 |
| Septated | Yes | 71 | 80.7 |
| | No | 17 | 19.3 |
| Septa thickness > 3mm | Yes | 71 | 80.7 |
| | No | 17 | 19.3 |
| Cystic | Yes | 86 | 97.7 |
| | No | 2 | 2.3 |
| Solid | Yes | 83 | 94.3 |
| | No | 5 | 5.7 |
| Fat | Yes | 12 | 13.6 |
| | No | 76 | 86.4 |
| Calcification | Yes | 16 | 18.2 |
| | No | 72 | 81.8 |
| Contrast enhancement | Yes | 81 | 92 |
| | No | 7 | 8 |
| Papillary projection | Yes | 35 | 39.8 |
| | No | 53 | 60.2 |
| Feeding artery ovarica | Yes | 72 | 81.8 |
| | No | 16 | 18.2 |

Table 4. Additional findings of abdominal CT scan in ovarian tumor patients in Radiodiagnostic Installation of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, during January 2017 - December 2018

| Primary findings of abdominal CT scan | | Frequency | Percentage (%) |
|---|---|---|---|
| Ascites | Yes | 39 | 44.3 |
| | No | 49 | 55.7 |
| Peritoneal implant | Yes | 5 | 5.7 |
| | No | 83 | 94.3 |
| Enlargement of pelvic lymph node | Yes | 23 | 26.1 |
| | No | 65 | 73.9 |
| Mass of other organs | Yes | 1 | 1.1 |
| | No | 87 | 98.9 |
| Normal uterus identified | Yes | 85 | 96.6 |
| | No | 3 | 3.4 |

This study had 213 cases of ovarian tumor, but most did not have representative histopathological results and incomplete abdominal CT documents and after obtaining inclusion and exclusion criteria, there were 88 cases that met the researcher requirements for analysis. Furthermore, it had the youngest age range of 7 years and the oldest of 79 years with an average age of 43.73 ± 16.02 years so the range was fairly representative as sample, with 46.6% of malignant ovarian tumors in the group age of 41-60 years. It was in accordance with the Kooning PP study in 1989[6] and the National Cancer Institute report which states that ovarian carcinoma occurs most often at the age above 40 years.[7] Most of the lesion had size of more than 4 cm (98.9%), indicating that the character of the tumors was not in the initial phase (Figure 5A).

There were 80.8% of ovarian epithelial tumors which were dominated by mucinous carcinoma, adenocarcinoma and endometroid carcinoma or about 84.1% of malignancies in ovarian tumors. This finding was still lower than the finding of 85% in Koonings PP et al, 1989.[6] The presence of 13.6% fat and 18.2% calcification components showed that lesions with these components originated from germ cell tumors around 10.6%. The increase of contrast enhancement in ovarian tumors is a primary finding that leads to malignancy.[3] This study found that 92% of the samples showed an increase in contrast enhancement (Figure 5C). Papillary projection as a form of protrusion of solid components in complex ovarian cysts leads to a malignancy process (Figure 5D).[8] This study was found that only 39.8% of the samples were described as papilary projection. Kamel (2011) found that 30% of papillary were malignancy in 78% of the sample.[9]

The existence of tumor from an organ can be established by knowing the origin of feeding the arteries that supply nutrients to the mass. Ovarian mass obtains feeding from ovarian arteries, sometimes it can also get an anastomosis from the uterine artery branch because of its anatomic position, so we can still obtain a profile of ovarian mass that seemingly obtains feeding from the uterine artery (Figure 6A). In addition to the primary findings that lead to the malignancy of ovarian tumors, there are also additional findings on contrast abdominal CT scan. These additional findings will strengthen the primary findings towards malignancy. The most common additional finding in this study was ascites, found as many as 44.3% of the sample (Figure 6B). This was similar to the findings of Nimwegen[10] who found that ascites had the same chance of arising in malignant and benign ovarian tumors, so that ascites was not categorized as the primary finding for ovarian tumors.

Peritoneal implants also serve as additional findings in establishing malignancy of an ovarian tumor which indicates the presence of metastases in the peritoneal wall.[11] In this study, it was only 5.7% that were found. This low number was due to the limitations of CT scans to detect the presence of peritoneal lesions of less than 0.5 cm (Figure 6C). Another additional finding referred to the malignancy of an ovarian tumor on CT scan is lymph node enlargement in the pelvis. The amount of ovarian mass in the later phase of the disease also affects the findings of lymph node enlargement because the mass obscures it. Abdominal CT scan also has limitation showing objects smaller than 0.5 cm. These two make lymph node enlargement difficult to evaluate. In this study, 26.1% of the samples were identified with lymph node enlargement in the pelvis (Figure 6D).

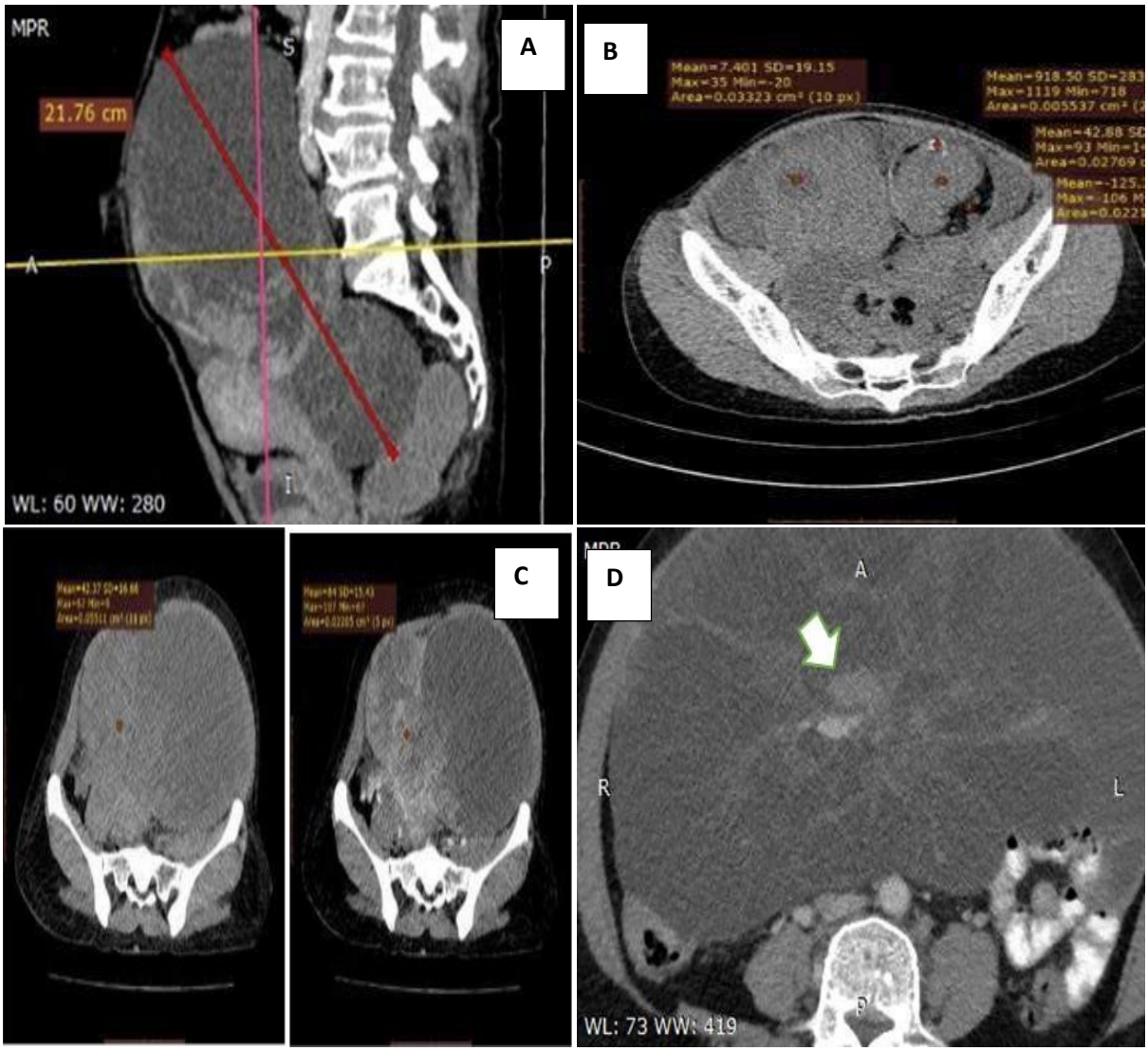



Figure 5. A. Sagittal contrast-enhanced abdominal CT scan, 71-year-old woman with cystic septated mass with the largest size of 21.7 cm which is clear cell carcinoma ovarium on histopathological examination. B. Abdominal CT scan of a woman aged 19 years with the finding of a pelvic mass with calcified, fat, solid and cystic components, on histopathological examination, it was concluded as immature teratoma ovary. C. Examination of contrast-enhanced abdominal CT scan, a 39-year-old woman showed a pattern of increased contrast enhancement in her solid lesions which found as poorly differentiated adenocarcinoma in histopathological examination on adnexa. D. Abdominal CT scan examination of 55-year-old shows a large cystic septated mass with papillary projection (arrow) in the central of the lesion. It was confirmed as mucinous grade II ovarium on histopathological examination.

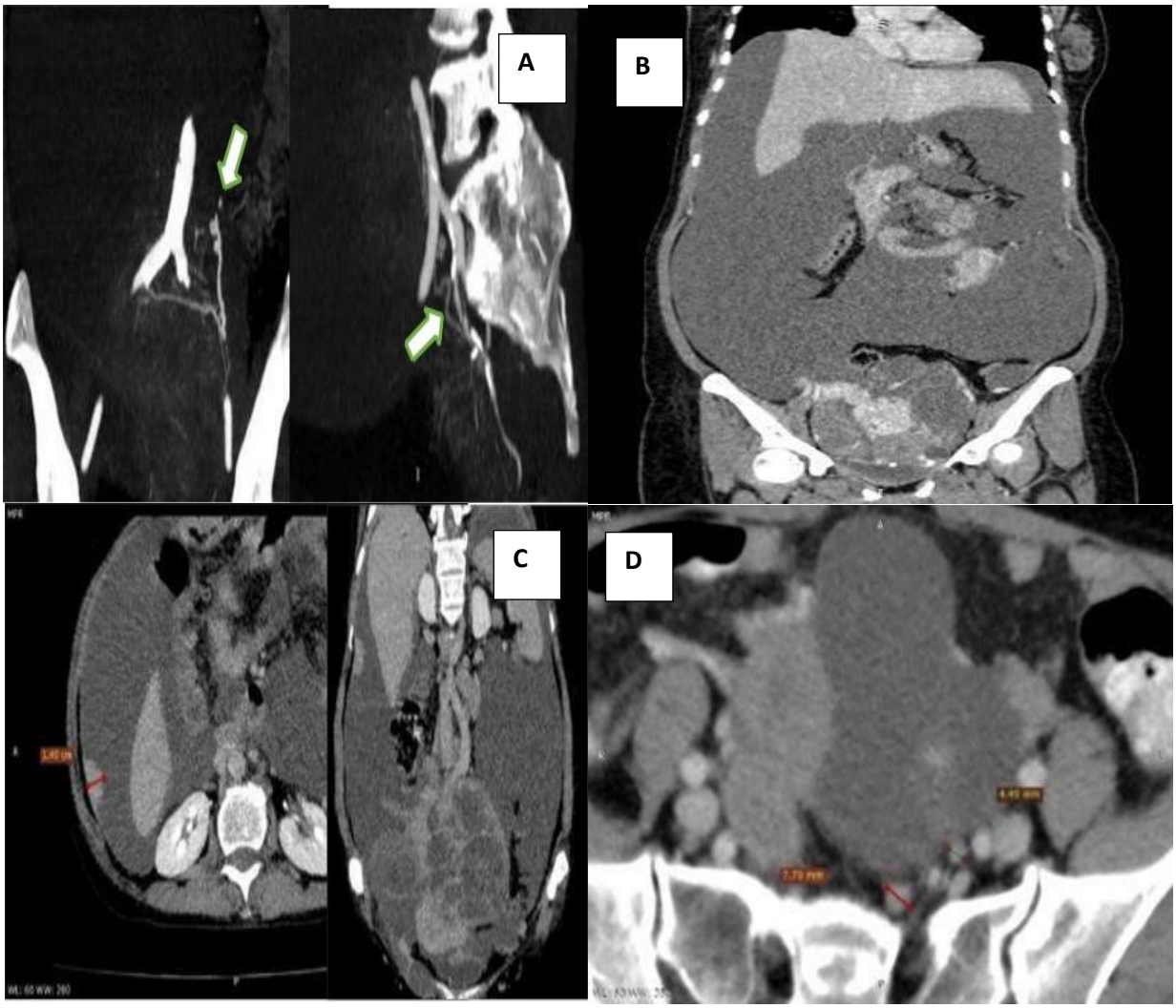



Figure 6. A. Coronal and sagittal abdominal CT scan examination, a 70-year-old woman with a pelvic mass that extends to the abdomen get feeding from the left ovarian artery (white arrow), histopathological examination suggestive of endometrioid carcinoma of ovary. B. Coronal contrast-enhanced abdominal CT scan, 34-year-old woman with serous carcinoma ovary grade II shows ascites that fills the abdominal cavity. C. Axial and coronal contrast enhanced abdominal CT scan of 60-year-old female, shows the presence of ascites with peritoneal implants on the right side lateral abdominal wall which on histopathology examination showed as high grade endometrioid carcinoma. D. Axial abdominal CT scan pelvis showing lymph node enlargement in the pelvis in a 52-year-old female patient of adenocarcinoma ovary.

Finding of mass in other organs should be suspected that the mass in the pelvis is a part or mass expansion of the organs. In this study, 1.1% or 1 sample was found in the presence of a mass in other organ which indicated that the mass in the pelvis was part of the organ (Figure 7A) as stated by Meissnitzer (2012) about abnormalities of other organs that resemble ovarian tumor.[12] Regarding the evaluation of the mass other than adnexa in the diagnosis of ovarian tumors, it is also necessary to determine that normal uterine morphology is still visible. In this study, 96.6% of the samples were obtained with normal uterine morphology (Figure 7B).

The low specificity value in this study was contributed by the magnitude of false positive values in the findings of this study, ie. 5 samples (mucinous cyst adenoma, endometriosis cyst). In this study, the CT appeared to have difficulty in distinguishing malignancy from a benign mass in the advanced phase of the mucinous cyst adenoma ovary, with the character of a mass with usual size of more than 10 cm, attached to the abdominal wall,

multiloculated, septated with septa thickness of 2-3 mm, containing fluid with water to blood density, which is generally found in those of 3rd and 4th decades.[13-15] This was not fully obtained in this sample (Figure 7C). Since the sample was 27 years old, large mass character, thick septa, with solid components, abnormalities obtained in the imaging did not lead to benign abnormalities. Likewise, as endometriosis cysts should show a lesion with a cystic and solid component, unilateral or bilateral with a regular outer wall, sometimes with papillary projection, showing contrast enhancement with ascites and peritoneal implants so, it was very likeky that it was hardly distinguished from malignancy (Figure 7D).

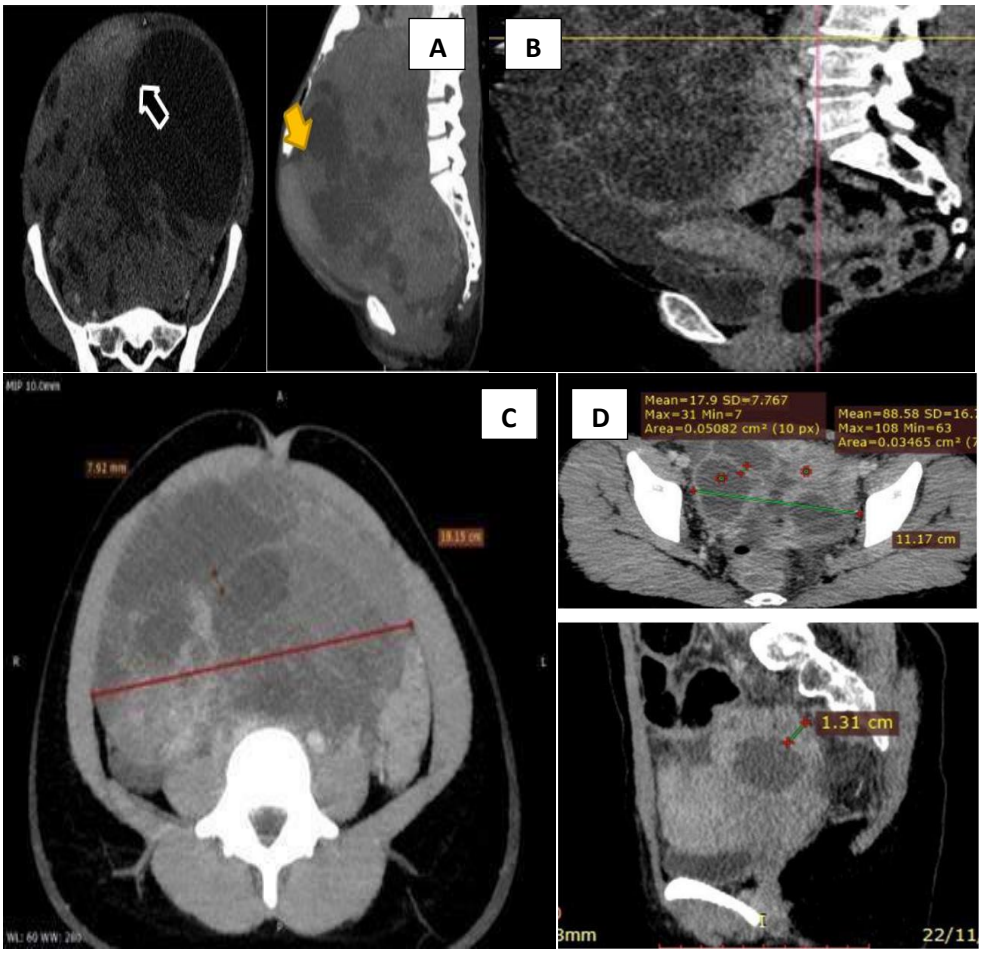



Figure 7A. A 33-year-old woman on axial and sagittal contrast-enhanced abdominal CT scan, showing a large pelvic mass that resembles ovarian malignancy. If observed on sagittal images, the uterine is pushed to the anterosuperior (yellow arrow), with a "claw sign" (white arrow). On histopathological examination, it is suggestive of leiomyosarcoma with differential diagnosis of fibrosarcoma. Figure 7B. Sagittal contrast-enhanced abdominal CT scan, a 55-year-old woman with a pelvic mass that extends into the abdomen. The uterine morphology is still visible and has a well-defined border with a superior mass, showing that the pelvic mass does not originate from the uterine. On histopathology examination, high grade endometrioid carcinoma ovary were obtained. Figure 7C. Axial contrast-enhanced abdominal CT scan of 20 year old woman, showing a multiloculated mass, size exceeding 10 cm, with septa that is more than 3 mm in thickness, with cystic and solid components, leading to the malignancy of ovarian tumors. In fact, on histopathology examination, a mucinous cyst adenoma was shown, which directed to a benign mass. Figure 7D. Contrast-enhanced abdominal CT scan in 27 year old women, obtained a large mass, with cystic and solid components, multiloculated septated with thickness more than 3 mm which urged the uterus, in contrast administration showed contrast enhancement. This finding led to a malignancy. However, the histopathological examination was concluded as an endometriosis cyst.

## CONCLUSION

Diagnostic value of contrast-enhanced abdominal CT scan in ovarian tumors in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2017 to December 2018 for 88 samples that were included in the study criteria using primary findings and additional features modified in "tools" for imaging abdominal CT scans had a sensitivity of 93.3%, specificity of 64.3%, positive predictive value of 93.3%, negative predictive value of 69.2%, and an accuracy value of 89.8%, and shows an increase compared to without tools. The low specificity value can be caused by the findings of the sample are large in size and advanced phase of the disease, so that imaging is difficult to distinguish from malignancy in ovarian tumors.

## REFERENCES


1. 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
2. Elattar A, Bryant A, Winter-Roach BA, et al. Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database Syst Rev. 2011. doi: 10.1002%2F14651858.CD007565. pub2.
3. Suppiah S, Kamal SH, Mohd Zabid AZ, Abu Hassan H. Characterization of adnexal masses using multidetector contrast-enhanced CT scan – Recognising common pitfalls that masquerade as ovarian cancer. Pertanika J Sci Technol. 2017;25(1):337–52.
4. Sahdev A. CT in ovarian cancer staging: How to review and report with emphasis on abdominal and pelvic disease for surgical planning. Cancer Imaging 2016;16(1):1–9. doi: 10.1186/s40644-016-0076-2.
5. Forstner R, Meissnitzer M, Cunha TM. Update on imaging of ovarian cancer. Curr Radiol Rep. 2016;4(6):1–11. doi: 10.1007/s40134-016-0157-9.
6. Masciullo V, Mainenti S, Lorusso D, et al. Lethal clostridium difficile colitis associated with paclitaxel and carboplatin chemotherapy in ovarian carcinoma: Case report and review of the Literature. Int J Gynecol Obstet. 2010;60(2):211–23. doi: 10.1155/2010/749789.
7. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med 2017;14(1):9–32. doi: 10.20892/j.issn.2095-3941. 2016.0084.
8. Abramowicz JS, Timmerman D. Ovarian mass–differentiating benign from malignant: the value of the International Ovarian Tumor Analysis ultrasound rules. American Journal of Obstetrics and Gynecology. 2017;217(6):652-60. doi: 10.1016/ j.ajog.2017.07.019.
9. Hassen K, Ghossain MA, Rousset P, et al. Characterization of papillary projections in benign versus borderline and malignant ovarian masses on conventional and color doppler ultrasound. Am J Roentgenol. 2011;196(6):1444–9. doi: 10.2214/ AJR.10.5014.
10. Nimwegen van LWE, Mavinkurve-Groothuis AMC, Krijger de RR et al. MR imaging in discriminating between benign and malignant pediatric ovarian masses: a systematic review. Eur Radiol. 2019;30:1166–81. doi: 10.1007/s00330-019-06420-4.
11. ACR. Revised 2018. 2018;1–12. [internet] Available from: https://acsearch.acr.org/docs/ 69504/Narrative/
12. Meissnitzer M, Schlattau A, Vasvary I, et al. Mimics of ovarian cancer in imaging. 2012. doi: 10.1594/ecr2012/C-0983.
13. Buy JN, Ghossain M. Gynecological imaging: A reference guide to diagnosis. 2013th edn. Springer; 2013
14. Migda, M., Bartosz, M., Migda, M.S. et al. Diagnostic value of the gynecology imaging reporting and data system (GI-RADS) with the ovarian malignancy marker CA-125 in preoperative adnexal tumor assessment. J Ovarian Res. 2018;11:92. doi: 10.1186/s13048-018-0465-1.
15. Woodfield A. The Usefulness of ultrasound imaging in gynecologic oncology. PET Clinics. 2018;13(2):143-63. doi: 10.1016/j.cpet.2017.11. 003.

## ORIGINAL ARTICLE

# The role of human papillomavirus deoxyribonucleic acid for distinguishing between cervical adenocarcinoma and endometrial adenocarcinoma

**Budi Harjanto*, Suhatno**
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga,
Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

## ABSTRACT

**Objectives:** To analyze the role of HPV DNA for distinguishing between uterine cervical adenocarcinoma and endometrial adenocarcinoma.
**Materials and Methods**: This was a case control study using paraffin block samples from uterine cervix adenocarcinoma and endometrial adenocarcinoma operation at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Each group was tested for HPV DNA using PCR method. Sample size was 18 in each group.
**Results**: A total of 36 samples fulfilled the inclusion criteria in this study. Each group comprised 18 samples. There were 83.3% of uterine cervical adenocarcinoma and 11.1% of endometrial adenocarcinoma that revealed high risk HPV. Chi-Square test result found significant correlation between high risk HPV and uterine cervical adenocarcinoma ($p<0.05$) with Odds Ratio (OR) 40.00 (CI 95%).
**Conclusion**: There was a significant correlation between high risk HPV and uterine cervix adenocarcinoma. High-risk HPV infected patients had a risk to suffer from uterine cervical adenocarcinoma compared to those with endometrial adenocarcinoma. HPV DNA test had a role for distinguishing between uterine cervical adenocarcinoma and endometrial adenocarcinoma.

**Keywords:** Uterine cervical adenocarcinoma; endometrial adenocarcinoma; human papillomavirus; polymerase chain reaction; cancer; maternal health

## ABSTRAK

**Tujuan:** Menganalisis peran pemeriksaan DNA HPV dalam membedakan adenokarsinoma serviks dan adenokarsinoma endometrium.
**Bahan dan Metode**: Penelitian ini adalah penelitian case control dengan sampel berupa blok parafin hasil operasi adenokarsinoma serviks uteri dan adenokarsinoma endometrium di RSUD dr. Soetomo, Surabaya, Indonesia. Masing-masing diperiksa DNA HPV menggunakan metode PCR. Besar sampel 18 pada masing-masing kelompok.
**Hasil**: Sebanyak 36 sampel sesuai kriteria inklusi pada penelitian ini. Setiap kelompok terdiri atas 18 sampel. Sebanyak 83,3% adenokarsinoma serviks dan 11,1% adenokarsinoma endometrium menunjukkan HPV risiko tinggi. Hasil uji Chi Square menunjukkan hubungan bermakna antara HPV risiko tinggi dengan adenokarsinoma serviks uteri ($p<0,05$) dan Odds Ratio (OR) sebesar 40,00 (CI 95%).
**Simpulan**: Terdapat hubungan bermakna antara HPV risiko tinggi dengan adenokarsinoma serviks uteri. Penderita yang terinfeksi HPV risiko tinggi mempunyai risiko menjadi adenokarsinoma serviks uteri dibandingkan adenokarsinoma endometrium. Pemeriksaan DNA HPV dapat berperan dalam membedakan adenokarsinoma serviks uteri dan adenokarsinoma endometrium.

**Kata kunci:** Adenokarsinoma; serviks uteri; adenokarsinoma endometrium; human papillomavirus; polymerase chain reaction; kanker; kesehatan ibu

***Correspondence:** Budi Harjanto, Gynecologic Oncology Division, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jalan Prof dr Moestopo 6-8, Surabaya 60286, Indonesia. E-mail: budijan_obg@yahoo.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.53-56
● Maj Obs Gin. 2021;29:53-56 ● Received 10 Oct 2020 ● Revised 15 Feb 2021 ● Accepted 1 Mar 2021

## INTRODUCTION

Uterine cervical cancer is still the problem of the women's health worldwide. World Health Organization in 2018 has reported that uterine cervical cancer is the fourth most common malignancy in women after breast, colorectal, and lung cancer. It was estimated there were 569.847 new cases and 311.365 deaths caused by cervical cancer in that year. Approximately 80% of those new cases are found in developing countries. Cervical cancer is the second majority in 2018 after breast cancer in Indonesia, followed by ovarian cancer and colorectal cancer. It is estimated there are 32.469 new cases and 18.279 mortalities.[1]

Determining primary tumor between uterine cervical adenocarcinoma and endometrial adenocarcinoma sometimes is more complicated. This can happen due to tiny part of the biopsy or curettage specimen and overlapped histology morphological spectrum.[2] The preoperative distinction is clinically important, because the treatment of endometrial and endocervical adenocarcinoma differs. Uterine cervical adeno-carcinoma and endometrial adenocarcinoma can have similar histopathological description.[3] Immunohisto-chemistry result such vimentin, estrogen reseptor (ER), progesteron reseptor (PR), carcinoembryonic antigen (CEA), and p16 can distinguish tumor origin. Uterine adenocarcinoma has had positive result for p16 and CEA, but negative for ER, PR, and vimentin with accuration of 65-80%.[4] In other researches, there are contradictory result, in which CEA has statistically significant for endometrial carcinoma but not significant for cervical adenocarcinoma, especially for mucinous differentiation.[5] Magnetic Resonance Imaging (MRI) can determine primary tumor by means of considering morphological characteristic and perfusion. MRI can provide information about tumor spreading. MRI accuration to determine endometrial tumor originis quite high (up to 85%) although using limited data. Several researchers found MRI limitation to determine tumor origin with lower sensitivity (21%) especially for determining stage II endometrial cancer.[6,7]

High risk Humanpapilloma virus (HPV) is a main cause of cervical transformation to become malignant, however it does not contribute of endometrial carcinogenesis process.[8] The aim of this research was to find the role of HPV DNA for distinguishing between uterine cervical adenocarcinoma and endometrial adenocarcinoma using case control approach which was conducted in March 2019 at Gynecologic Oncology Outpatient Clinic and Anatomic Pathology Laboratory at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Research samples were paraffin blocks from surgery results, as many as 18 from cervical adenocarcinoma patients and 18 from endometrial adenocarcinoma patients.

## MATERIALS AND METHODS

This study used a case control approach using paraffin block samples from uterine cervix adenocarcinoma and endometrial adenocarcinoma surgery result at Gynecologic Oncology Outpatient Clinic and Anatomic Pathology Laboratory Dr. Soetomo General Academic Hospital,, Surabaya, that fulfilled inclusion and exclusion criteria. Each group was tested for HPV DNA using PCR method. Sample size was 18 from each group. The samples comprised surgery specimens that were surgically removed in 2014–2018. All tumor specimens were fixed in 10% buffered formalin, processed routinely and embedded in paraffin. Therefore, we had 18 paraffin blocks containing cervical adenocarcinoma and 18 blocks containing endometrial adenocarcinoma to investigate the presence of HPV DNA by PCR method. This study was approved by Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (approval No. 1036/KEPK/III/2019).

Paraffin blocks were taken randomly for DNA extraction. The paraffin blocks were cut to pieces of 25 mg. Deparaffinization was done by xylene and rehydration with ethanol. DNA was extracted by using QIAamp DNA Mini Kit according to its manual and used as a template for polymerase chain reaction (PCR) experiments. The heating scheme for the PCR experiments was as follows: activation of the DNA-polymerase for 10 min at 95ºC, followed by 50 cycles of a 30-sec denaturation at 95ºC, a 30-sec annealing at 50oC, and a 30-sec elongation at 72ºC. The PCR experiments were ended with a 5-min final step at 72oC.[9-11] Genotyping of HPV was conducted with Ampliquality HPV-Type Express (AB Analitica) that can detect HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, 87, 89, 90.[12] The type of HPV was reported in the form of band on a blot membrane corresponding to the genotype of HPV.

## RESULTS AND DISCUSSION

This study was performed on 36 paraffin block samples of 18 cervical adenocarcinoma tissue derived from patients with the median age 47.5 years old (range from 35 to 75) and 18 endometrial adenocarcinoma tissue derived from patients with the median age of 57.5 years old (range from 34 to 64). The patients with cervical

adenocarcinoma were younger than endometrial adenocarcinoma.

Table 1. Characteristics of the patients

| | Cervical adenocarcinoma | Endometrial adenocarcinoma | p |
|---|---|---|---|
| Age (year) | 47.5 (35 - 75) | 57.5 (34 - 64) | 0.087 |
| 30-39 | 3 | 2 | |
| 40-49 | 8 | 3 | |
| 50-59 | 4 | 8 | |
| 60-69 | 2 | 5 | |
| 70-79 | 1 | 0 | |

Tumors were evaluated for staging and grading in accordance with the International Federation of Gynaecologic Oncology (FIGO), 2009.[13] Among the cervical adenocarcinomas, eight (44.4%) cases were stage IB1, 3 (16.7%) stage IB2, 2 (11.1%) stage IIA1, 1 (5.6%) stage IIA2, and 4 (22.4%) stage IIB (Table 2). The stage of endometrial adenocarcinoma samples varied from IA to IIIC, with the first majority was stage IB in 5 (27.8%) cases (Table 3).

There were 15 cervical adenocarcinoma patients who had high-risk HPV (HPV 16, 18, 31, 33, 45, dan 66). We found HPV 18 in 11 patients, HPV 16 (2 patients), HPV 66 (2 patients), HPV 31, 33, and 45 in 1 patient respectively. There were 3 patients who had HPV coinfection (HPV 18 and 66, 18 and 33, 45 and 66). There were also low-risk HPV found in this study (HPV 6,11, and 40), although there was no association between low-risk HPV and cervical carcinogenesis process. Of 18 endometrial adenocarcinoma patients, there were 2 patients contained high-risk HPV (HPV 66) and low-risk HPV (HPV 6, 11, and 40) (Table 4).

Table 2. The stages of cervical adenocarcinoma patients

| Stage | n | % |
|---|---|---|
| IB1 | 8 | 44.4 |
| IB2 | 3 | 16.7 |
| IIA1 | 2 | 11.1 |
| IIA2 | 1 | 5.6 |
| IIB | 4 | 22.2 |

Study result showed that 83.3% of uterine cervical adeno-carcinoma had high-risk HPV, while only 11.1% of endometrial adenocarcinoma had high-risk HPV. Chi-square test result found that there was statistically significant difference in the presence of HPV-DNA in uterine cervical adenocarcinoma and endometrial adenocarcinoma (p<0,0001). Analysis using OR (Odds Ratio) revealed 40.00 (5.85-273.62), meaning that high-risk HPV infected patients had probable risk of 40 times to have uterine cervical adenocarcinoma compared to endometrial adenocarcinoma. These data and the results of the present study strongly indicated a causal relationship between HPV infection and the development of primary cervical adenocarcinoma, and that HPV types 18 had a particular predilection for cervical adenocarcinoma, but not endometrial tissues. However, there have been a few reports in which the authors found HPV DNA in endometrial tissues as well. According to a study by Fedrizzi et al, HPV DNA was demonstrated by PCR in 8% of samples.[14] In another study by Giatromanolaki et al, six of 25 endometrial adenocarcinomas were HPV 16-positive (24%), and 5 of 25 (20%) were HPV 18-positive. But, none of the positive cases in the series demonstrated cytological evidence of HPV infection.[15] It appeared that the presence of HPV in the endometrium, as detected by PCR, did not play any role in the initiation or prognosis of endometrial adenocarcinoma.

Table 3. The stages of endometrial adenocarcinoma patients

| Stage | n | % |
|---|---|---|
| IAG1 | 3 | 16.7 |
| IBG1 | 5 | 27.8 |
| IBG2 | 2 | 11.1 |
| IBG3 | 2 | 11.1 |
| II | 2 | 11.1 |
| IIG1 | 1 | 5.6 |
| IIIA | 1 | 5.6 |
| IIIB | 1 | 5.6 |
| IIIC | 1 | 5.6 |

Table 4. HPV analysis among the Patients

| High-risk HPV | Cervical adenocarcinoma | Endometrial adenocarcinoma | p | OR (CI95%) |
|---|---|---|---|---|
| + | 15 (83.3%) | 2 (11.1%) | <0.0001 | 40.00 (5.85 – 273.62) |
| - | 3 (16.7%) | 16 (88.9%) | | |

## CONCLUSIONS

There was a statistically significant difference in the presence of HPV-DNA in uterine cervical adenocarcinoma and endometrial adenocarcinoma. High risk HPV infected patients have probable risk to have uterine cervical adenocarcinoma compared to endometrial adenocarcinoma. HPV DNA test has a role for distinguishing between uterine cervical adenocarcinoma and endometrial adenocarcinoma.

## REFERENCES


1. Globocan IARC 2018. Indonesia fact sheet; 2018. [update 2018; cited 2018 Dec 14]. Available from: gco.iarc.fr/today/fact sheet population.
2. Stewart CJR, Crum CP, McCluggage WG, et al. Guidelines to aid in the distinction of endometrial and endocervical carcinomas, and the distinction of independent primary carcinomas of the endometrium and adnexa from metastatic spread between these and other sites. Int J Gynecol Pathol. 2019;38:75-92. doi: 10.1097/PGP.0000000000000553.
3. Singh N, Hirschowitz L, Zaino R, et al. Pathologic prognostic factors in endometrial carcinoma (other than tumor type and grade), International Journal of Gynecological Patholog. 2019;38:93-113. doi: 10.1097/PGP.0000000000000524.
4. Staebler A, Sherman ME, Zaino RJ, et al. Hormone receptor immunohistochemistry and human papillomavirus in situ hybridization are useful for distinguishing endocervical and endometrial adenocarcinomas. The American Journal of Surgical Pathology. 2002;26(8):998–1006. doi: 10.1097/00000478-200208000-00004.
5. Galic V, Schiavone MB, Herzog TJ, et al. Prognostic significance of mucinous differentiation of endometrioid adenocarcinoma of the endometrium. Cancer Invest. 2013;31(7):500-4. doi: 10.3109/07357907.2013.820321.
6. He H, Bhosale W, Wei W, et al. MRI is highly specific in determining primary cervical versus endometrial cancer when biopsy results are inconclusive. Clin Radiol. 2013;68:1107-13. doi: 10.1016/j.crad.2013.05.095.
7. Ramirez P, Frumovitz M, Milam M, et al. Limited utility of magnetic resonance imaging in determining the primary site of disease in patients with inconclusive endometrial biopsy. Int J of Gynecol Cancer. 2010;20:1344-9. doi: 10.1111/IGC.0b013e3181f30c1b.
8. Chan CK, Aimagambetova G, Ukybassova T, et al. Human papillomavirus infection and cervical cancer: Epidemiology, screening, and vaccination-review of current perspectives. J Oncol. 2019; 2019. doi: 10.1155/2019/3257939.
9. International Agency for Research on Cancer [Internet]. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 100B. Human Papillomaviruses. Lyon, France: IARC; 2012 [update 2012; cited 2018 Sep 23]. Available from: http://monographs.iarc.fr/ENG/ Monographs/vol100B/mono100B.pdf.
10. Mustafa RA, Nancy Santesso N, Khatib R, et al. Systematic reviews andmeta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. International Journal of Gynecology and Obstetrics. 2016; 132:259–65. doi: 10.1016/j.ijgo.2015.07.024.
11. Olesen TB, Svahn MF, Faber MT, et al. Prevalence of human papillomavirus in endometrial cancer: a systematic review and metaanalysis. Gynecol Oncol. 2014;30:1-9. doi: 10.1016/j.ygyno.2014.02.040.
12. Mastutik G, Alia R, Rahniayu A, et al. Genotyping of human papillomavirus in cervical precancerous lesion and squamous cell carcinoma at Dr Soetomo Hospital, Surabaya, Indonesia. Afr J Infect Dis. 2018;12:7-12. doi: 10.21010/Ajid.12v1S.2.
13. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet. 2014;125(2): 97-8. doi: 10.1016/j.ijgo.2014.02.003.
14. Fedrizzi EN, Villa LL, de Souza IV, et al. Does human papillomavirus play a role in endometrial cancinogenesis? Int J Gynecol pathol. 2009;28(4): 322-27. doi: 10.1097/PGP.0b013e318199943b.
15. Giatromanolaki A, Sividis E, Papazoglou D, et al. Human papillomavirus in endometrial adenocarcinomas: Infectious agent or a mere ”passanger”? Infectious Disease in Obstetrics and Gynecology. 2007;60549. doi: 10.1155/2007/60549.

## ORIGINAL ARTICLE

# The correlation of nutritional status with hematology toxicity of adjuvant chemotherapy in ovarian cancer

**Kadek Dharma Widhiarta[1], Brahmana Askandar[2*]**
[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Jember, Jember, Indonesia,
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academy Hospital, Surabaya, Indonesia

## ABSTRACT

**Objectives:** To observe correlation of nutritional status using Nutritional Risk Index with the side effects of adjunctive haematological chemotherapy.
**Materials and Methods**: This study was a retrospective cohort study observing whether or not hematologic side effects occurred during chemotherapy based on medical records of postoperative ovarian cancer patients receiving adjuvant chemotherapy.
**Results**: Sixty-eight subjects with age range of 31-50 years (44.1%) multipara (68.8%), and advanced stage (52.1%) were observed. An increase was found in the diagnosis of malnutrition between the IMT method and NRI, which was 18.7% compared to 43.7%. A significant correlation was found between preoperative malnutrition and the incidence of anaemia after adjuvant chemotherapy for ovarian cancer patients (p=0.002). Whereas, in the event of leukopenia and thrombocytopenia, there were no significant correlations with p=0.675 and p=0.415, respectively.
**Conclusion**: There was an increase in malnutrition rate with the use of NRI compared with BMI and there was a significant correlation between malnutrition and side effects of anaemia in patients with ovarian cancer who underwent surgery and continued with adjuvant chemotherapy.

**Keywords:** ovarian cancer; nutritional status; adjuvant chemotherapy; maternal health

## ABSTRAK

**Tujuan:** Mengetahui hubungan status nutrisi menggunakan Nutritional Risk Index dengan efek samping hematologi kemoterapi ajuvan.
**Bahan dan Metode**: Penelitian ini merupakan suatu studi kohort retrospektif yang mendata terjadi atau tidaknya efek samping hematologi selama kemoterapi berdasarkan data rekam medis penderita kanker ovarium pasca operasi yang mendapat kemoterapi ajuvan.
**Hasil**: Didapatkan 68 subyek dengan rentang usia terbanyak 31-50 tahun (44,1%) multipara (68,8%), dan stadium lanjut (52,1%). Didapatkan peningkatan diagnosis malnutrisi antara metode IMT dengan NRI, yaitu 18,7% dibandingkan 43,7%. Didapatkan hubungan yang bermakna antara malnutrisi pra operasi dengan kejadian anemia pasca kemoterapi ajuvan pasien kanker ovarium (p=0,002). Sedangkan pada kejadian leukopenia dan trombositopenia tidak didapatkan hubungan yang bermakna p= 0,675 dan p=0,415.
**Simpulan**: Didapatkan peningkatan angka malnutrisi dengan penggunaan NRI dibandingkan dengan IMT dan hubungan yang bermakna antara malnutrisi dengan efek samping anemia pada penderita kanker ovarium yang menjalani operasi dan dilanjutkan dengan ajuvan kemoterapi.

**Kata kunci:** kanker ovarium; status nutrisi; kemoterapi ajuvan; kesehatan ibu

***Correspondence:** Brahmana Askandar, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academy Hospital, Jalan Mayjen Prof dr Moestopo 6-8, Surabaya 60286, Indonesia. E-mail: brahmanaaskandar@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.57-62
● Maj Obs Gin. 2021;29:57-62 ● Received 12 Dec 2020 ● Revised 17 Mar 2021 ● Accepted 30 Mar 2021

## INTRODUCTION

Cancer is still a health problem in the world. Each year 240,000 women in the world are diagnosed with ovarian cancer with a five-year survival rate of only about 45%. There are 3 types of ovarian cancer which are named according to the cells they originate from. Ninety percent of ovarian cancers originate from the epithelial lining that covers the surface of the ovary. This group is known as epithelial cancer.[1]

The principles of management of ovarian cancer are the same as the principles of handling other malignant diseases, namely the treatment of primary lesions operatively and the handling of potential sites of tumor metastases with chemotherapy. Handling or main treatment of ovarian cancer to date includes surgery and chemotherapy.[2]

Ovarian cancer sufferers experience changes in body composition as a result of their own disease which causes an increase in energy requirements to meet the increase in body metabolism, but conditions due to cancer also result in decreased appetite so that the body is unable to meet energy needs. This condition causes the catabolic process to increase so that there can be a change in the nutritional status of ovarian cancer patients. Other conditions that can cause changes in nutritional status are therapeutic modalities including chemotherapy.[2]

Chemotherapy is a cancer therapy that involves the use of chemicals or drugs whose purpose is to kill cancer cells. Side effects caused by chemotherapy can cause nausea, vomiting, diarrhea, stomatitis, alopecia, susceptibility to infection, thrombocytopenia, neuropathy and myalgia.[3] Chemotherapy can be done with several chemotherapy drug regimens. Combined chemotherapy regimen Platinum and Taxane is known to increase the life expectancy of ovarian cancer patients. The use of the Taxane class chemotherapy regimen has the effect of leukopenia, neutropenia, and thrombocytopenia.[4]

Cancer therapy including surgery and chemotherapy has the effect of anorexia, nausea, vomiting and diarrhea which will aggravate weight loss. Malnutrition changes physiologically at the organ to cellular level, affecting post-therapy morbidity and quality of life, therefore, a strategy to determine comprehensive nutritional status needs to be found. The results found that patients with good nutritional status since the start of therapy had significantly better survival than those who had poor nutritional status.[5]

Not many studies have looked at the effect of nutritional status on ovarian cancer patients, especially in Dr. Soetomo Hospital, so in this study we tried to find a correlation between nutritional status using the Nutritional Risk Index with the hematological side effects of ovarian cancer patients who received adjuvant chemotherapy.

## MATERIALS AND METHODS

This research is a retrospective cohort study that records whether or not hematologic side effects occur during chemotherapy based on medical records of postoperative ovarian cancer patients receiving adjuvant chemotherapy. The research was conducted at the Gynecology Oncology Clinic and Gynecology Ward, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, by collecting medical records of ovarian cancer patients who underwent surgery and continued with the provision of adjuvant chemotherapy for 3 cycles in January 2018 - December 2018.

Nutritional status calculated by NRI scoring was calculated based on the formula (1.519 x serum albumin gr/L) + (41.7 (current weight/ideal weight)). Then divide the results into 2 groups only not malnutrition (NRI $\geq$97.5) and malnutrition (NRI <97.5). Hematological side effects that occur in ovarian cancer who receive adjuvant chemotherapy based on the National Cancer Institute (NCI) Toxicity Criteria, namely anemia grade 1 (mild): Hb <LLN - 10g/dL, anemia grade 2 (moderate): Hb <10.0- 8.0 g/dL, anemia grade 3 (severe): Hb <8.0 g/dL, grade 1 leukopenia (mild): WBC <LLN-3,000 mm3, leukopenia grade 2 (moderate): WBC <3,000-2,000 mm3, leukopenia grade 3 (weight): WBC <2,000-1,000 mm3, grade 1 thrombocytopenia (mild): PLT <LLN-75,000 µL, grade 2 thrombocytopenia (moderate): PLT <75,000-50,000 µL, grade 3 thrombocytopenia (severe): PLT <50,000-25,000 µL.[6]

## RESULTS AND DISCUSSION

There were 68 ovarian cancer patients who matched the inclusion criteria of the study, namely surgery at Dr. Soetomo Hospital Surabaya and with the results of PA epithelial ovarian cancer during 2018 and continued with adjuvant chemotherapy. Then 20 patients (29.4%) did not undergo further therapy or adjuvant chemotherapy because they did not control or refused chemotherapy.

The age range of study subjects was between 22 and 71 years with a composition of 1 (2.1%) non-malnutrition

group and 2 (4.2%) malnutrition group under 30 years of age, 16 (33.3%) non-malnutrition group and 10 (20.8%) aged between 31 and 50 years, and 10 (20.8%) were not malnourished and 9 (18.8%) were malnourished by more than 51 years. There was no significant difference between the non-malnourished and malnourished groups (p=0.595).

Ovarian cancer is generally found in women of older age or post-menopausal age. Ovarian cancer is rarely found under 40 years of age. The incidence rate increases with increasing age.[7] Increasing age in women may give time for genetic changes to the ovarian surface epithelial cells.[8]

There were 14 (29.2%) of the research subjects with parity 0, 17 (35.4%) with parity 1, 8 (16.7%) with parity 2, 5 (10.4%) with parity 3, and the rest 2 (4.2%) each. The number of live births (parity) is thought to have an effect on reducing the risk of ovarian cancer. Some studies have shown that a first birth can reduce the risk of ovarian cancer compared to subsequent births, but other studies have shown that the protective effect against ovarian cancer increases when there is a second birth.[9]

Early stage cancer staging results based on nutritional status were 13 (27.1%) in the non-malnutrition group, 10 (20.8%) in the malnutrition group. And advance stage 14 (29.2%) were not malnourished and 11 (22.9%) were malnourished and there were no significant differences (p=0.601). The calculation of the Body Mass Index in this study resulted in 9 (18.75%) in the underweight category (undernourished), 27 (56.25%) with normal weight or normal nutritional status, and 12 people (25%). with overweight and obesity. Meanwhile, the calculation of nutritional status using the Nutrition Risk Index/NRI found 27 (56.25%) in the normal category or no malnutrition and 21 (43.75%) obtained malnutrition ovarian cancer. Calculation of nutritional status correctly can reduce delays in identifying malnutrition diagnosis in ovarian cancer patients, thereby reducing morbidity and mortality.[10]

The results of this study indicated that of the 3 parameters of chemotherapy adjuvant side effects, only Hb levels had a significant correlation with the assessment of nutritional status using NRI. Anemia is a common finding in cancer patients, with an incidence between 30% and 90%. Causes of anemia in cancer patients include metabolic disorders and nutrition, chronic disease, kidney disorders, blood loss, decreased production due to bone marrow disease, peripheral destruction due to autoimmune disorders, drug-induced red blood cell aplasia, and chemotherapy-induced anaemia.[11-13] Chemotherapy can cause anaemia through inhibitory mechanisms in normal haematopoiesis and on the action of cytokines. Chemotherapy agents cause anaemia directly by interfering with haematopoiesis, including the synthesis of red blood cell precursors in the bone marrow.[14] The nephrotoxic effect of certain cytotoxic agents (which contain platinum) can also cause anaemia by decreasing erythropoietin production. Platinum based regimen, known as a cause of anaemia due to its toxic effects on bone marrow and kidneys.[15-20]

Table 1. Distribution of nutritional status by age group

| Age | Nutritional Status | | | | *p* |
|---|---|---|---|---|---|
| | No Malnutrition | | Malnutrition | | |
| ≤ 30 th | 1 | 2.1% | 2 | 4.2% | 0.595 |
| 31-50 th | 16 | 33.3% | 10 | 20.8% | |
| ≥ 51 th | 10 | 20.8% | 9 | 18.8% | |

Table 2. Distribution of nutritional status based on parity

| Parity | Nutritional Status | | | | *p* |
|---|---|---|---|---|---|
| | No Malnutrition | | Malnutrition | | |
| Nullipara | 8 | 16.7% | 7 | 14.5% | 0.514 |
| Multiparous | 19 | 39.6% | 14 | 29.2% | |

Table 3. Distribution of nutritional status by stage

| Stage | Nutritional Status | | | | *p* |
|---|---|---|---|---|---|
| | No Malnutrition | | Malnutrition | | |
| Early stage | 13 | 27.1% | 10 | 20.8% | 0.601 |
| Advance stage | 14 | 29.2% | 11 | 22.9% | |

Table 4. Relationship of hematological side effects after adjuvant chemotherapy with nutritional status

| Hematological Side Effects | Nutritional Status | | | | *p* |
|---|---|---|---|---|---|
| | No Malnutrition | | Malnutrition | | |
| Normal HB | 5 | 10.4 % | 3 | 6.3 % | 0.002 |
| Mild Anemia | 18 | 37.5 % | 6 | 12.5 % | |
| Moderate Anemia | 2 | 4.2 % | 12 | 25.0 % | |
| Severe Anemia | 2 | 4.2 % | 0 | 0 | |
| Normal Leukocytes | 24 | 50 % | 18 | 37.5 % | 0.675 |
| Mild Leukopenia | 2 | 4.2 % | 1 | 2.1 % | |
| Moderate Leukopenia | 1 | 2.1 % | 2 | 4.2 % | |
| Normal Platelets | 25 | 52.1 % | 20 | 41.7 % | 0.415 |
| Mild Thrombocytopenia | 1 | 2.1 % | 0 | 0 | |
| Moderate Thrombocytopenia | 1 | 2.1 % | 0 | 0 | |
| Severe Thrombocytopenia | 0 | 0 | 1 | 2.1 % | |

## CONCLUSION

There was an increase in the number of malnutrition with the use of NRI compared to BMI in ovarian cancer patients who underwent surgery and continued with adjuvant chemotherapy. In addition, there was also a significant correlation between nutritional status calculated using NRI and side effects of anemia in ovarian cancer patients who received chemotherapy adjuvant, but there was no significant correlation between leukopenia side effects and thrombocytopenia in ovarian cancer patients who received chemotherapy adjuvant.

## ACKNOWLEDGMENT

This study was supported by the Faculty of Medicine Universitas Airlangga, Dr. Soetomo General Academy Hospital. We would like to thank our colleagues from the Division of Gynecologic Oncology for providing input and further expertise for this study. The authors did not receive any specific grant from any funding agency in the public, commercial, or nonprofit sectors.

## REFERENCES

1. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2017;41:3-14. doi: 10.1016/j.bpobgyn.2016.08.006. Epub 2016 Oct 3. PMID: 27743768.
2. Berek JS, Friedlander M, Hacker NF. Epithelial ovarian, fallopian tube, and peritoneal cancer. In: Berek JS, Hacker NF, eds. Berek and Hacker's Gynecologic Oncology. 5th edition. Philadelphia: Lippincott Williams and Wilkins; 2010. p: 444-495.
3. Sánchez-Lara K, Ugalde-Morales E, Motola-Kuba D, Green D. Gastrointestinal symptoms and weight loss in cancer patients receiving chemotherapy. Br J Nutr. 2013;14;109(5):894-7. doi: 10.1017/S0007114512002073. Epub 2012 Jun 12. PMID: 22691288.
4. Glaze S, Teitelbaum L, Chu P, et al. Dose-dense paclitaxel with carboplatin for advanced ovarian cancer: a feasible treatment alternative. J Obstet Gynaecol Can. 2013;35(1):61-7. doi: 10.1016/s1701-2163(15)31050-1. PMID: 23343799.
5. Gupta D, Lis CG, Vashi PG, Lammersfeld CA. Impact of improved nutritional status on survival in ovarian cancer. Support Care Cancer. 2010;18(3):373-81. doi: 10.1007/s00520-009-0670-y. Epub 2009 May 31. PMID: 19484479.
6. Common Terminology Criteria for Adverse Events (CTCAE). 5.0. US Department of Health and Human Services; 2017.
7. Rambe IR, Asri A, Adrial. Profil tumor ganas ovarium di Laboratorium Patologi Anatomi Fakultas Kedokteran Universitas Andalas periode Januari 2011 Sampai Desember 2012 [Profile of ovarian malignancy at the Laboratory of Anatomic Pathology, Faculty of Medicine, Universitas Andalas, January 2011 – December 2012]. Jurnal Kesehatan Andalas. 2014:3.
8. Simamora RPA., Hanriko R, Sari RDP. Hubungan usia, jumlah paritas, dan usia menarche terhadap derajat histopatologi kanker ovarium di RSUD Dr. H. Abdul Moeloek Bandar Lampung Tahun 2015-2016 [Correlation between age, parity, and menarcheal age on histopathological grade of ovarian cancer at Dr. H. Abdul Moeloek Bandar Lampung year 2015-2016]. Majority 2018;7(2).
9. Sung HK, Ma SH, Choi JY, et al. The effect of breastfeeding duration and parity on the risk of epithelial ovarian cancer: a systematic review and meta-analysis. J Prev Med Public Health. 2016;49(6):349-366. doi: 10.3961/jpmph.16.066. Epub 2016 Sep 8. PMID: 27951628; PMCID: PMC5160134.
10. Paccagnella A, Morello M, Da Mosto MC, et al. Early nutritional intervention improves treatment tolerance and outcomes in head and neck cancer patients undergoing concurrent chemoradiotherapy. Support Care Cancer. 2010;18(7):837-45. doi: 10.1007/s00520-009-0717-0. Epub 2009 Aug 30. PMID: 19727846.
11. Kurtin S. Myeloid toxicity of cancer treatment. J Adv Pract Oncol. 2012 Jul;3(4):209-24. PMID: 25031949; PMCID: PMC4093344.
12. Horowitz KM, Ingardia CJ, Borgida AF. Anemia in pregnancy. Clin Lab Med. 2013;33(2):281-91. doi: 10.1016/j.cll.2013.03.016. Epub 2013 Apr 19. PMID: 23702118.
13. Sun D, McLeod A, Gandhi S, Malinowski AK, Shehata N. Anemia in pregnancy: A pragmatic approach. Obstet Gynecol Surv. 2017;72 (12):730-737. doi: 10.1097/OGX.0000000000000510. PMID: 29280474.
14. Rodgers GM 3rd, Becker PS, Blinder M, et al. Cancer- and chemotherapy-induced anemia. J Natl Compr Canc Netw. 2012;10(5):628-53. doi: 10.6004/jnccn.2012.0064. PMID: 22570293.
15. Lyman G, Glaspy J. Advances in the management of chemotherapy-induced anemia and its treatment. Oncol J. 2006;20(8):1517–25.
16. Oun R, Moussa YE , Wheate NJ . The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans. 2018;47(19):6645-

6653. doi: 10.1039/c8dt00838h. Erratum in: Dalton Trans. 2018 Jun 12;47(23):7848. PMID: 29632935.
17. Walker H, Bell S. Strategies to reduce perioperative nephrotoxicity. Semin Nephrol. 2019;39(5):442-453. doi: 10.1016/j.semnephrol.2019.06.004. PMID: 31514908.
18. Mizuno M, Ito Y, Morgan BP. Exploiting the nephrotoxic effects of venom from the sea anemone, Phyllodiscus semoni, to create a hemolytic uremic syndrome model in the rat. Mar Drugs. 2012;10(7):1582-604. doi: 10.3390/md10071582. Epub 2012 Jul 23. PMID: 22851928; PMCID: PMC3407933.
19. Offurum A, Wagner LA, Gooden T. Adverse safety events in patients with Chronic Kidney Disease (CKD). Expert Opin Drug Saf. 2016 Dec;15(12):1597-1607. doi: 10.1080/14740338.2016.1236909. Epub 2016 Oct 12. PMID: 27648959.
20. Krishnappa V, Gupta M, Manu G, et al. Acute kidney injury in hematopoietic stem cell transplantation: A Review. Int J Nephrol. 2016; 2016:5163789. doi: 10.1155/2016/5163789. Epub 2016 Nov 3. PMID: 27885340; PMCID: PMC5112319.

## ORIGINAL ARTICLE

# The differences of glycodelin and uterus NK cell expression in obese and non-obese rats (*Rattus norvegicus*)

**Diyah Nofita Ofa Ningtriyas*, Arsana Wiyasa, Muhammad Nooryanto**
Department of Obstetrics & Gynecology Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

## ABSTRACT

**Objectives:** To prove the existence of differences in glycodelin levels and uterine NK cell expression in obese and non-obese female white rats of Wistar strain (*Rattus norvegicus*).
**Materials and Methods**: . This study used a randomized post-test only controlled group design. This in vivo study used two groups of female rats (*Rattus norvegicus*). Group 1 was treated with the high obese diet for eight weeks, and group 2 was not treated with the high obese diet. After eight weeks, the rats were weighed, the proestrus phase was synchronized, and then the rats were terminated.
**Results**: In this study, there was no significant difference in glycodelin levels between the obese and non-obese groups with a p= 0.821 (p >0.05). Significant differences were found in uterine NK cell expression between obese dan non-obese groups with p=0.001 (p <0.05). The correlation test of glycodelin levels and uterine NK cell expression showed insignificant results with a correlation coefficient of 0.120 and p=0.513. This proved that there was no significant correlation between glycodelin levels and uterine NK cell expression.
**Conclusion**: There was no significant difference between glycodelin levels and uterine NK cell expression in obese and non-obese female white rats of Wistar strain (*Rattus norvegicus*).

**Keywords:** Obesity; recurrent miscarriage; glycodelin; uterine NK cells

## ABSTRAK

**Tujuan:** Untuk membuktikan adanya perbedaan kadar glikodelin dan ekspresi sel NK uterus pada tikus putih betina (*Rattus norvegicus*) galur Wistar dengan obesitas dan tidak dengan obesitas.
**Bahan dan Metode**: Penelitian ini menggunakan rancangan *randomized post-test only controlled group design*. Penelitian in vivo ini menggunakan dua kelompok tikus betina (*Rattus norvegicus*). Kelompok 1 diberi diet tinggi lemak selama delapan minggu, dan kelompok 2 tidak diberi diet tinggi lemak. Setelah delapan minggu tikus ditimbang dan fase proestrus disinkronisasi. Kemudian tikus diterminasi.
**Hasil**: Dalam penelitian ini, tidak terdapat perbedaan kadar glikodelin yang signifikan antara kelompok dengan obesitas dan tidak dengan obesitas dengan p=0,821 (p>0,05). Perbedaan yang signifikan ditemukan pada ekspresi sel NK rahim antara kelompok dengan obesitas dan tidak dengan obesitas dengan p=0.001 (p <0,05). Uji korelasi kadar glikodelin dengan ekspresi sel NK uteri menunjukkan hasil yang tidak signifikan dengan koefisien korelasi 0,120 dan p=0,513. Hal ini membuktikan bahwa tidak ada hubungan yang signifikan antara kadar glikodelin dengan ekspresi sel NK uteri.
**Simpulan**: Tidak terdapat perbedaan bermakna kadar glikodelin dengan ekspresi sel NK uteri pada tikus putih betina galur Wistar (*Rattus norvegicus*) yang dengan obesitas dan tidak dengan obesitas.

**Kata kunci:** Obesitas; keguguran berulang; glikodelin; sel NK rahim

***Correspondence:** Diyah Nofita Ofa Ningtriyas, Department of Obstetrics & Gynecology Faculty of Medicine, University of Brawijaya, Malang, Indonesia. E-mail: mokhamadfahmi@student.ub.ac.id

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.63-67
● Maj Obs Gin. 2021;29:63-67 ● Received 10 Nov 2020 ● Revised 15 Mar 2021 ● Accepted 30 Mar 2021

## INTRODUCTION

Obesity increases the risk of comorbidities such as diabetes mellitus, high blood pressure, dyslipidemia, cardiovascular disease, obstructive sleep apnea, various types of cancer and death. A study found that obesity was responsible for causing infertility in women by 25% to 50%.[1] The increase in obesity incidence correlates with an increase in the incidence of recurrent pregnancy loss (RPL) or recurrent miscarriage. At least one factor identified recurrent miscarriage in more than half of cases, but no definite cause still unknown. Several conditions are associated with idiopathic recurrent miscarriage, a suspected abnormality including immune system disorders, behavioral and environmental conditions, and obesity. Recent statistics show that two-thirds of women aged >20 years in the United States have a body mass index (BMI) of $\geq$25 kg/m$^2$, indicating that they are overweight or obese, and 36% of people in the United States are classified as overweight (BMI) $\geq$30 kg/m$^2$). Thus, being overweight is a concern for their health because they have a higher risk of causing complications in pregestational period. These complications include miscarriage, fetal death, congenital abnormalities, fetal macrosomia, gestational diabetes, preeclampsia, complications during vaginal delivery, thromboembolism, post-partum infection and difficulty breastfeeding.[1]

The mechanism that causes miscarriage in women who are overweight or obese with a history of recurrent miscarriage and the pathophysiology is still unclear. The high number of women of childbearing age who are overweight and the cause of many cases of recurrent miscarriage is unclear. So this research studied female Wistar strain (*Rattus norvegicus*) white rats in order to determine differences in glycodelin levels and uNK cell expression in obese and non-obese rats.

## MATERIALS AND METHODS

### Study design and subjects

This study used a true experimental design in the laboratory in vivo using a post-test only controlled group design to identify the differences in glycodelin levels and uNK cell expression in obese and non-obese female white Wistar strain rats (*Rattus norvegicus*). This research was conducted at the Parasitology Laboratory, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia, from September 2019 to October 2020. The variables used in this study were obesity as independent variable and glycodelin levels and uNK cell expression as dependent variables.

### Obesity

Obesity, which has a nomical scale, was measured with Lee Index. The Lee Index consists of the division of the cubicle root of the weight in grams by the nasoanal length in millimeters multiplied by 1000.

### Glycodelin examination

Glycodelin was taken from blood in the rat's heart, then centrifuged to obtain pure serum. The serum was then inserted into the Eppendorf tube and then immediately checked by using the ELISA method. Glycodelin has a ratio scale.

### Uterine Natural Killer Cells (uNK cells) examination

uNK cells was evaluated using monoclonal antibodies by immunohistochemical staining of the endometrial tissues. uNK cell expression was measured in the endometrial tissue with total magnification of 400x. uNK cell expression has a ratio scale.

### Data analysis

Data from the calculation of glycodelin levels and uNK cells' expression for each group were processed by tabulation. Based on these tabulations, statistical test was carried out using SPSS 25.0. Before statistical analysis, the existing data were tests for normality using the Sapphiro-Wilk method. If the results were normal, it was continued with the independent t-test. A correlation test was performed to determine the relationship between glycodelin levels and uNK cell expression in obese rats. The statistical test was carried out with 95% degree of confidence with $\alpha$ =0.05. The statistical test results were declared significant if $p < 0.05$.

## RESULTS AND DISCUSSION

### Weight profile and overweight index (Lee Index)

Characteristics of the observed Lee index of the rats indicated that the mean Lee index of the obese group was 313.7 ± 10.8, and the mean Lee index of the non-obese group was 271.6 ± 12.3. Descriptively, the Lee index of the obese rats group was higher than the non-obese group.

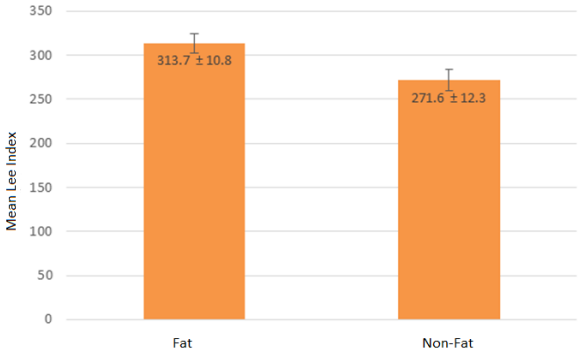



Figure 1. Lee Index characteristics

## Glycodelin profile

The glycodelin level was examined after the rats, whose oestrous phase had been synchronized, were terminated. According to Lee's index, all obese rats with oestrous phase were synchronized with the oestrous phase. If the rats were in proestrus phase, termination and blood samples were taken from the rat's cardiac and uterine organs. The blood sample taken was then put into an EDTA tube and processed to obtain blood serum. The blood serum was examined for glycodelin levels by ELISA using MyBioSource Rat Progestagen-Associated Endometrial Protein (PAEP) ELISA KIT. The absorbance obtained was then converted to determine the glycodelin levels.

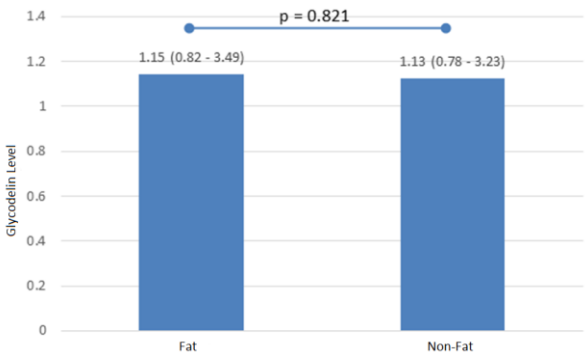



Figure 2. Glycodelin level measurement

## uNK cell expression profiles

The uterus taken at termination was inserted into formalin then processed by cutting and fixation and staining with immunohistochemistry in Anatomic Pathology Laboratory, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia. The finished slides were examined under a microscope at 400x magnification.

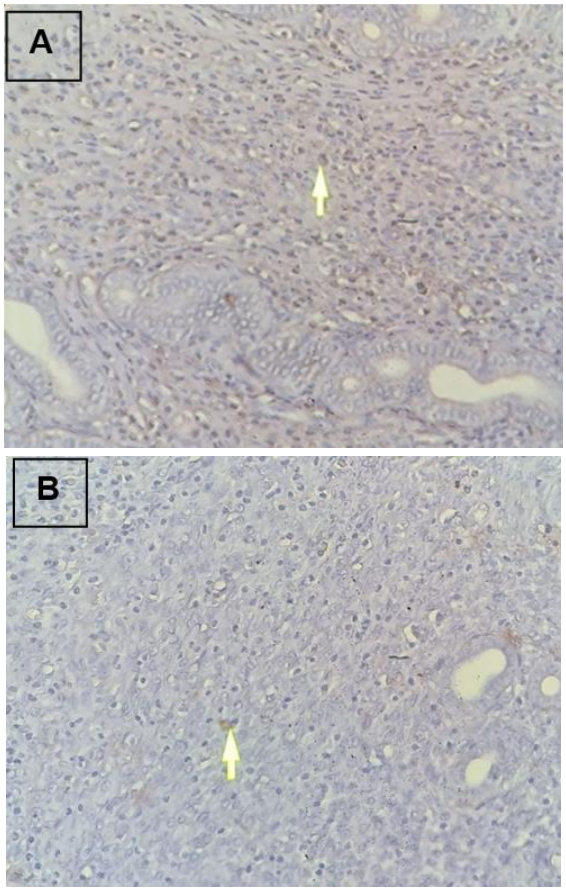



Figure 3. Histopathological profile of uNK cells in obese rat (A) and non-obese rat (B) at 400x magnification

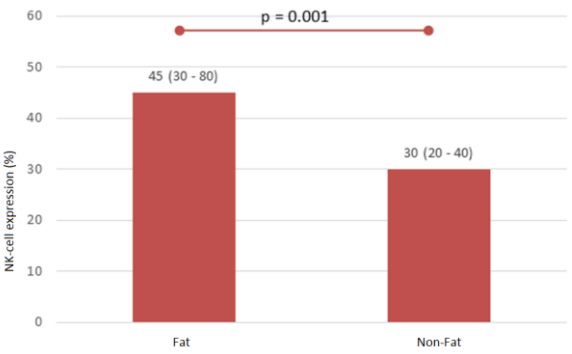



Figure 3. Comparison of uNK cells in obese rats and non-obese rats

## Differences in glycodelin levels in obese and non-obese rats

This study aimed to determine whether there was a difference in glycodelin levels in obese and non-obese female rats. From the research results, the median value

of glycodelin content in the obese group was 1.15 (0.82 - 3.49), and the non-obese group was 1.13 (0.78 - 3.23), indicating that glycodelin content in the obese group of rats was higher than the non-obese group. Based on the Mann-Whitney test analysis results, the p-value was 0.821, more significant than $\alpha = 0.05$ ($p > 0.05$). So from this test, it could be concluded that there was no significant difference in glycodelin levels between the obese and non-obese groups. Overall, it could also be concluded that there was no significant difference in glycodelin levels in obese rats compared to non-obese rats with the median value of glycodelin levels in obese rats being higher than non-obese rats, but it was not statistically significant.

Overweight women, especially with upper-body obesity, have insulin resistance and hyperinsulinaemia, hyperandrogenaemia, increased peripheral aromatization of androgens to estrogen, increased gonadotrophin secretion, decreased SHBG, decreased growth hormone (GH) and (IGFBPs), increased leptin levels and neuroregulatory changes the hypothalamus-pituitary-gonadal axis. This causes ovulation disorders.[2,3]

### The difference uNK cell expression in obese and non-obese rats

The study results and statistical testing showed significant differences in the expression of uNK cells between the obese and non-obese groups of rats. The median value of uNK cell expression in the obese group was 45 (30-80) and in the non-obese group was 30 (20-40). Based on the Mann-Whitney test analysis, the p-value was 0.001, smaller than $\alpha=0.05$ ($p <0.05$). So it was concluded that there was a significant difference in the expression of uNK cells between the obese and non-obese groups of rats. This test proved that the uNK cell expression of the obese rat's group was significantly higher than the non-obese group.

Obesity is a chronic subclinical inflammatory condition. Hypertrophy of obese tissue, causing hypoperfusion, hypoxia and stress on the endoplasmic reticulum are some of the mechanisms by which obesity results in increased obese tissue inflammation.[4-6] The increased release of fatty acids, hormones, and pro-inflammatory molecules in obesity is caused by changes in adipose tissue and peripheral endocrine's metabolic function. Increased peripheral leukocytes and high inflammatory conditions occur in women with obesity.[7,8]

Overweight women were found to have increased systemic inflammation, placental and endocrine function. Failure of decidualization is associated with a high rate of uNK cells, which are nearly 5% in the peri-implantation endometrium.[9] uNK cells in the endometrium are found in the endometrial tissue of women who are not pregnant with more than 30% of the total leukocytes, in contrast to the number in the blood, which is around 5-15% and in conditions of miscarriage, the cells are about 70-80% of lymphocytes.[10]

### Correlation between glycodelin levels and uNK cell expression in obese rats

The results showed that there was no significant relationship between glycodelin levels and uNK cell expression. The correlation coefficient is 0.120, and the p-value is 0.513. The p-value of more than 0.05 ($p> 0.05$) proved no significant relationship between glycodelin levels and uNK cell expression due to the high glycodelin levels in obese rats, although statistically not significant, which did not affect the expression of uNK cells in the obese rats.

Obesity is associated with insulin resistance and hyperinsulinemia. Elevated insulin levels are associated with decreased glycodelin and insulin-like growth factor binding protein (IGFBP1). Low glycodelin levels are associated with recurrent miscarriage. IGFBP1 is an integral molecule involved in adhesion during implantation. Changes in these molecules can decrease endometrial receptivity in obese women.[11-15]

Overweight women were found to have increased systemic inflammation, placental and endocrine function. Failure of decidualization is associated with a high rate of uNK cells, which are nearly 5% in the peri-implantation endometrium.[9] uNK cells are found in the endometrial tissue of women who are not pregnant with more than 30% of total leukocytes, in contrast to the number in the blood, which is around 5-15% and in conditions of miscarriage, the cells are about 70-80% of lymphocytes.[10]

### Limitations

This study had limitations where the dietary treatment in rats was carried out within eight weeks so that the obesity that occurs was not chronic so that insulin resistance had not occurred, which affected the glycodelin levels.

## CONCLUSION

There was no significant difference in glycodelin levels in obese and non-obese female white rats Wistar (*Rattus norvegicus*) in the study. UNK cell expression in obese female Wistar strain rats (*Rattus norvegicus*) was higher than non-obese rats. In the study, there was no correlation between glycodelin levels and uNK cell

expression in obese Wistar (*Rattus norvegicus*) female rats. Further research is needed in this study.

## REFERENCES


1. Giviziez CR, Sanchez EGM, Approbato MS, et al. Obesity and anovulatory infertility: A review. JBRA Assist Reprod. 2016;20(4):240–5. doi: 10.5935/1518-0557.20160046
2. Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. Reprod Camb Engl. 2010;140(3):347–64. doi: 10.1530/ REP-09-0568.
3. Wu S, Divall S, Nwaopara A, et al. Obesity-induced infertility and hyperandrogenism are corrected by deletion of the insulin receptor in the ovarian theca cell. Diabetes. 2014;63(4):1270–82. doi: 10.2337/db13-1514.
4. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, obesity, and leptin resistance: Where are we 25 years later? Nutrients. 2019;11 (11): 2704. doi: 10.3390/nu11112704.
5. Ellulu MS, Patimah I, Khaza'ai H, et al. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci. 2017;13(4):851-63. doi: 10.5114/aoms.2016.58928.
6. Pellegrinelli V, Rouault C, Rodriguez-Cuenca S, et al. Human adipocytes induce inflammation and atrophy in muscle cells during obesity. Diabetes. 2015;64(9):3121-34. doi: 10.2337/db14-0796.
7. Björkström NK, Lindgren T, Stoltz M, et al. Rapid expansion and long-term persistence of elevated NK cell numbers in humans infected with hantavirus. J Exp Med. 2011;208(1):13–21. doi: 10. 1084/jem.20100762.
8. Andersen CJ, Murphy KE, Fernandez ML. Impact of obesity and metabolic syndrome on immunity. Adv Nutr. 2016;7(1):66-75. doi: 10.3945/an.115. 010207.
9. Kuroda K, Venkatakrishnan R, James S, et al. Elevated periimplantation uterine natural killer cell density in human endometrium is associated with impaired corticosteroid signaling in decidualizing stromal cells. J Clin Endocrinol Metab. 2013; 98(11):4429–37. doi: 10.1210/jc.2013-1977.
10. Kofod L, Lindhard A, Hviid TVF. Implications of uterine NK cells and regulatory T cells in the endometrium of infertile women. Hum Immunol. 2018;79(9):693–701. doi: 10.1016/j.humimm.2018. 07.003.
11. Hunter S, Willcox CR, Davey MS, et al. Human liver infiltrating γδ T cells are composed of clonally expanded circulating and tissue-resident populations. J Hepatol. 2018;69(3):654–65. doi: 10.1016/ j.jhep.2018.05.007.
12. Rhee JS, Saben JL, Mayer AL, et al. Diet-induced obesity impairs endometrial stromal cell decidualization: a potential role for impaired autophagy. Hum Reprod. 2016;31(6):1315-26. doi: 10.1093/ humrep/dew048.
13. Haggerty AF, Huepenbecker S, Sarwer DB, et al. The use of novel technology-based weight loss interventions for obese women with endometrial hyperplasia and cancer. Gynecol Oncol. 2016; 140(2):239-44. doi: 10.1016/j.ygyno.2015.11.033.
14. Goetz TG, Mamillapalli R, Taylor HS. Low Body Mass Index in endometriosis is promoted by hepatic metabolic gene dysregulation in mice. Biol Reprod. 2016;95(6):115. doi: 10.1095/biolreprod. 116.142877.
15. Xie Y, Wang JL, Ji M, et al. Regulation of insulin-like growth factor signaling by metformin in endometrial cancer cells. Oncol Lett. 2014;8(5): 1993-9. doi: 10.3892/ol.2014.2466.

## CASE REPORT

# Uterus couvelaire after caesarean section: A challenging case report

**Rendy Singgih[1*], Roy Jansen Sinaga[2], Yanto Hansitongan Sinaga[1]**
[1]Department of Obstetrics and Gynecology, Cimacan General Hospital, Indonesia.
[2]Department of Obstetrics and Gynecology, Fakfak General Hospital, Indonesia

## ABSTRACT

**Objectives:** To discuss the discovery of uterine couvelaire events after the cesarean section without accompanying placental abruption.
**Case Report**: Uterus Couvelaire is a rare occurrence. The incidence of this case is difficult to ascertain and its estimated incidence is as much as 20% and others' estimatation is as low as 5%. It occurs mainly due to complications from placental abruption. When a vascular injury occurs in the placenta, it causes bleeding that infiltrates the wall of the uterus. This case is usually diagnosed accidentally because it is diagnosed only by direct visualization or biopsy. In this case, uterine couvelaire was found in a woman after a cesarean section that had been performed previously. Uterine couvelaire events are usually seen due to complications from placental abruption, but in this case, there was none.
**Conclusion**: It was not known for sure what caused the emergence of the uterine couvelaire in this case. Hysterectomy was performed in this case due to the patient's unstable hemodynamic state.

**Keywords:** Uterus couvelaire; cesarean section; hysterectomy; childbirth complications; maternal health

## ABSTRAK

**Tujuan:** Untuk membahas ditemukannya kejadian *uterus couvelaire* setelah tindakan operasi sesar dan tanpa disertai dengan abrupsio plasenta.
**Laporan Kasus**: *Uterus couvelaire* merupakan kejadian yang jarang terjadi. Insiden kasus ini sulit untuk dipastikan dan diperkirakan kejadiannya terjadi sebanyak 20% dan yang lain memperkirakan serendah 5%. Kejadiannya terutama akibat komplikasi dari abrupsio plasenta. Ketika terjadi cedera vaskular di dalam plasenta menyebabkan perdarahan yang menginfiltasi dinding dari uterus. Kasus ini biasanya terdiagnosis secara tidak sengaja karena didiagnosis hanya dengan visualisasi secara langsung atau biopsi. Pada kasus ini ditemukan kasus *uterus couvelaire* pada seorang wanita setelah sebelumnya dilakukan operasi sesar. Kejadian *uterus couvelaire* biasanya ditemukan akibat komplikasi dari abrupsio plasenta, namun pada kasus ini tidak ada.
**Simpulan**: Tidak diketahui pasti apa yang sebabkan timbulnya *uterus couvelaire* pada kasus ini. Histerektomi dilakukan pada kasus ini karena keadaan hemodinamik pasien yang tidak stabil.

**Kata kunci:** *Uterus couvelaire*; sectio caesarea; histerektomi; komplikasi persalinan; kesehatan ibu

***Correspondence:** Rendy Singgih, Department of Obstetrics and Gynecology, Cimacan General Hospital, Indonesia. E-mail: rendysinggih23@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.68-71
● Maj Obs Gin. 2021;29:68-71 ● Received 24 Jan 2021 ● Revised 29 Apr 2021 ● Accepted 14 Apr 2021


## INTRODUCTION

Uterus couvelaire, also known as uteroplacental apoplexy, is a condition that results from complications from placental abruption.[1] It was first described by a French obstetrician named Alexandre Couvelaire in 1911.[2] The incidence of this case is difficult to ascertain, and the estimated incidence is between 5% and 20%.[1] The profile of this case is the extravasation of extensive blood into the uterine muscle and down the surrounding tissue.[3,4] Distinctive appearance is bluish or purple, speckled by ecchymosis.[1] Thereafter effusion of blood are also visible beneath the tubal serosa, between the leaves of the broad ligament, in the substance of the ovaries, and free in the peritoneal cavity.[5]

The pathophysiology of this case is bleeding in the layer between the decidua-placenta, which then develops and infiltrates into the uterine wall. Characteristically it shows the appearance of ecchymosis on the surface of the uterine serosa. Sometimes bleeding can also occur between large layers of ligaments and infiltrating the uterine wall muscles.[6,7] Sometimes, infiltration can also reach the peritoneal cavity.[8] The resulting effect causes contraction of the myometrium or uterine muscle to become weak and even rupture due to an increase in intrauterine pressure.

Although the etiology is unknown, the uterine couvelaire is associated with placental abruption, placenta previa, coagulopathy, pre-eclampsia, uterine rupture, and amniotic fluid embolism.[2,9,10] The way to make a diagnosis of this case is by direct visual inspection of the uterus or by biopsy or both.[1,10-12] Because of the reason for the diagnosis of uterine couvelaire diagnosis, it can only be identified directly by direct inspection or biopsy, so the incidence of this case is not widely reported and is minimal in the literature search.[4,11]

The management of these cases is usually done immediately conservatively, and hysterectomy is usually unnecessary.[1,6,8,13,14] The uterine couvelaire does not affect the ability of the uterus to contract and decompress, allowing narrowing of the arteries to reach a state of hemostasis. Hysterectomy can be indicated as an act of saving the soul if the process of hemostasis is not achieved so that it can cause disseminated intravascular coagulation.[12]

## CASE REPORT

A 37-year-old woman, G2P1A0, on April 28, 2020, came with a referral from a local midwife because of a history of premature rupture of membranes in the last 24 hours and parturition. While in the hospital, the patient was observed and tried to do a normal delivery, but finally the patient was delivered by section caesarea due to indications of fetal distress. After surgery, the woman's condition was stable and treated in a standard room. Then, two days later, on April 30, 2020 the patient complained of tightness, abdominal pain and so forth. Physical examination was immediately carried out when the vital signs obtained blood pressure of 100/70 mmHg, pulse 136x/m, breath rate 46x/m, temperature 36.6ºC, and 99% SpO2 by administering oxygen via face mask. Other physical and obstetric examination revealed both conjunctival anemias, abdominal tenderness, active vaginal bleeding ± 200 cc, urine output only ± 5 cc (anuria). Investigations in the form of routine blood obtained patient Hb levels of 2.8 g/dL, hematocrit 8.7 g/dL, platelets 215,000/uL and leukocytes 21,900/uL. Immediately the patient was transfused with 4 units of PRC along with other resuscitation fluids in the form of NaCl liquid as much as 1500 cc. Immediate laparotomy surgery with suspicion of intraabdominal bleeding was planned for the following day.

On May 1 2020 the patient was immediately operated for laparotomy under general anesthesia because of a suspected intraabdominal hemorrhage. At the time of laparotomy, when the abdominal cavity was opened, it was found that the size of the uterus was of eight months gestational age. The hematoma in the uterine wall was bluish and uterine contraction was not palpated (Figure 1).

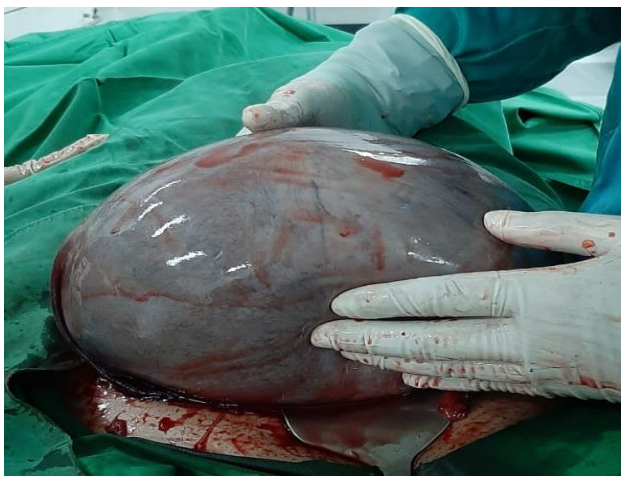


Figure 1. Uterine size during exploratory laparotomy

Then it was decided to do a hysterectomy because of hemodynamic instability (Figure 2). Uterine tissue biopsy was also performed during hysterectomy and then the tissue was taken for anatomic pathology examination. After surgery, the patient was transferred

to the HCU (High Intensive Care) room for 1 day until May 2, 2020. During treatment in the HCU room, the patient's condition was stable so that she was moved to an ordinary ward. When treated in a standard room, patients only complained of pain at the post-operative site and some nausea, no significant complaints or emergencies were found. Routine blood examination was done on May 3, 2020, revealing Hb of 7.7 g/dL, hematocrit 23.7 g/dL, platelets 176,000/uL and leukocytes 11,500/uL.

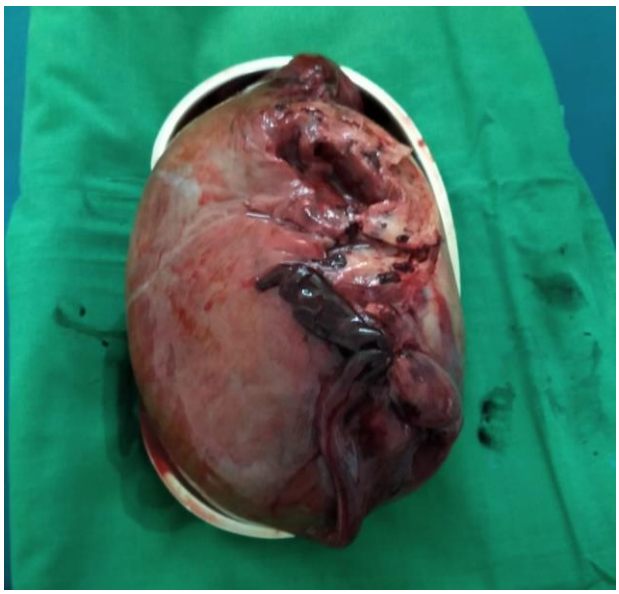


Figure 2. The uterus after hysterectomy

The patient was treated in a ward room until she was allowed to go home on May 5, 2020 with the patient's last vital signs as follows: blood pressure of 120/80 mmHg, pulse 80x/m, breathing rate 21x/m and temperature 36.7ºC. On the pati15ent's discharge date, the histopathological results from the biopsy were released. The conclusion of the results of the specimen obtained was uterine couvelaire. A week after the patient returned from treatment at the hospital, the patient was examined at an obstetric clinic. At that time, the patient was in a stable condition and no complaints were found.

## DISCUSSION

Uterine or uteroplacental couvelaire is a condition in which there is bleeding in the uterine wall. Most of these cases occur because of placental abruption. This case was first described in 1911 by a French obstetrician named Alexandre Couvelaire. The incidence of this case is challenging to ascertain because the diagnosis is found accidentally through direct examination or biopsy. Uterus couvelaire, in addition to placental abruption, is also associated with cases of placenta previa, coagulopathy, pre-eclampsia, uterine rupture and amniotic fluid embolism. In the case of uterine couvelaire that we had found, no placental abruption or other comorbidities were found. This case was like the one reported by Kori et al. who wrote that they found a case of uterine couvelaire without considering the presence of placental abruption.[6] It was not known exactly what had caused this uterine couvelaire, because there was no placental abruption, but the incidence occurred several days after cesarean section. When the cesarean section did not find any signs of uterine couvelaire either, so it was likely due to iatrogenic injury to the uterine wall after the section which had caused extravasation of blood. However, there were no literatures or case reports of uterine couvelaire events after cesarean section. In one case reported by Osial et al., they had a uterine couvelaire after curating and dilating, but not because of a cesarean section.[1]

Management is usually conservative because there will be a natural resolution so that the condition will return to normal. Management of the antenatal and postpartum hemorrhage plays a key role, on one side in the control of the bleeding with blood transfusion and reduce fetal and maternal morbidity and mortality.[15] However, if hemostasis does not occur, hysterectomy needs to be done as an act of saving lives. In this case, it was decided that a hysterectomy was performed because of the patient’s unstable hemo-dynamic and also the consideration of the previous patient had performed a cesarean section with the incision line located in the lower uterine segment by the treating doctor. Similar to this case, in the cases reported by Habek et al. and Osial et al. in 2013, they also performed a hysterectomy because of unstable hemodynamic conditions.[2,11]

## CONCLUSION

The occurrence of uterine couvelaire is found mostly in cases of placental abruption. However, in this case, the abruption case was absent. Cesarean section was performed unconsciously, followed by the emergence of the uterus couvelaire. Then, hysterectomy was performed to maintain the patient's hemodynamic stability.

## REFERENCES

1. Uwagbai ON, Wittich AC. A 30-year-old female found to have a couvelaire uterus with placenta

accreta during planned cesarean delivery. Mil Med. 2017;182(3):e1877-e9. doi: 10.7205/MILMED-D-16-00146.
2. Osial P, Osial P, Atkinson AL, et al. An unreported etiology for couvelaire uterus of case presentation. 2013;2(4):244–8.
3. Mani M, Nidhi A. Couvelaire uterus with concealed abruptio placenta?: A case report. International Journal of Clinical Obstetrics and Gynaecology 2018;2(5):170–1.
4. Senkaya AR, Umut F, Ileri A, et al. Maternal and neonatal outcomes of couvelaire uterus. Med Sci Int Med J Matern. 2021;10(3):775–8.
5. Cunningham FG, Leveno KJ, Bloom SL, Dashe JS, Hoffman BL, Casey BM, et al., editors. Obstetrical Complications. In: William Obstetrics 25th Edition. 25th ed. New York: Mc Graw Hill Education; 2018. p. 771.
6. Kori S, Mudanur SR, Patil N, et al.. Couvelaire uterus without placental abruption: A rare case report. J Evol Med Dent Sci. 2014; 3(38):9787–9.
7. N. Sunanda N, Sruthi T, Sheela SR. Feto-maternal outcome in patients with couvelaire uterus: A 3 year study in a tertiary care hospital in rural Karnataka, India. Int J Reprod Contraception, Obstet Gynecol. 2018;7(2):503. doi: 10.18203/2320-1770.ijrcog20170162.
8. Rathi M, Rathi SK, Purohit M, Pathak A. Couvelaire uterus [Internet]. Case Reports; 2014 [update 2014; cited 2014 Mar 31]. Available from: http://casereports.bmj.com/cgi/doi/10.1136/bcr-2014-204211.
9. Ting JCS, Wong XS, Yong SL, Kang M. A “miracle” pregnancy outcome of severe placental abruption. Hormone Molecular Biology and Clinical Investigation. 2019;38(3):20180059. doi: 10.1515/hmbci-2018-0059.
10. Cipullo LMA, Poto GE, Zullo F, et al. Late complication of a couvelaire uterus?: Case report and literature review. Journal of Pregnancy and Child Health 2019;6(2):6–7. doi: 10.4172/2376-127X.1000407
11. Braila AD, Krastev BM, Mihai-Zamfir E, et al. Uteroplacental apoplexy associated with invasive cervical neoplasm. Rom J Morphol Embryol. 2017;58(4):1465-70. PMID: 29556642.
12. Ming GS, Lee WKR, Tan SQ. An unusual case of placenta abruption leading to couvelaire uterus in a previable pregnancy. J Med Cases. 2020;11(4):103–5. doi: 10.14740/jmc3462.
13. Grohs MA, Kamoune J, Watfeh R, et al. Couvelaire uterus with placental abruption: A striking picture but a normal function. Int. J. of Adv. Res. 2018;6(8): 1028-30. doi:10.21474/IJAR01/7608.
14. Mahendra G, Pukale RS, Vijayalakshmi S. Couvelaire uterus - A case report. Int Arch Integr Med. 2015;2(3):142–5.
15. Cobec IM, Rempen A. Couvelaire-Uterus: literature review and case report. Rom J Mil Med. 2021;124:244–6.

## CASE REPORT

# Retroperitoneum parasitic leiomyoma: Dilemmatic diagnostic

**Setyo Teguh Waluyo, Hariadi Yuseran, Ferry Armanza, Yuvens Richardo Wibowo***
Obstetrics and Gynecology Department, Faculty of Medicine, Lambung Mangkurat University/Ulin Hospital, Banjarmasin, South Kalimantan, Indonesia

## ABSTRACT

**Objectives:** To describe a retroperitoneum parasitic leiomyoma case: a dilemma in diagnosis and operation finding.
**Case Report**: A 38 year-old woman with 3 children visited Ulin Hospital, Banjarmasin, Indonesia, with complaint of mass in lower abdomen and about 4 months before, she underwent biopsy by laparotomy which revealed leiomyoma. Parasitic leiomyoma is a rare type of leiomyoma with predilection area in broad ligament, pelvic peritoneum, pouch of douglas, and omentum. During operation, the tumor was detached from the uterus and located retroperitoneally as high as L4–S1. It had been confirmed intraoperatively and proven histopathologically as a leiomyoma.
**Conclusion**: Retroperitoneal parasitic leiomyoma may cause a dilemma in the diagnosis. Multidiscipline examination and approaches may increase the quality of management.

**Keywords:** Retroperitoneum parasitic leiomyoma; laparotomy; multidisciplinary approach; tumor; cancer; maternal health.

## ABSTRAK

**Tujuan:** Menyajikan laporan kasus tentang Retroperitoneum Parasitic Leiomyoma: dilema dalam diagnosis dan temuan saat operasi.
**Laporan Kasus**: Seorang wanita berusia 38 tahun dengan 3 anak datang ke poli RSUD Ulin, Banjarmasin, Indonesia, dengan keluhan benjolan di perut bawah dan riwayat laparatomi biopsi 4 bulan sebelumnya dengan hasil PA leiomyoma. Parasitic leiomyoma, merupakan jenis leiomyoma yang jarang, biasanya terdapat pada ligamentum latum, peritoneum pelvis, cavum douglas dan omentum. Selama operasi didapatkan massa tumor tidak dari uterus namun terletak retroperitoneal setinggi vertebra L4-S1 dengan hasil histopatologi leiomyoma.
**Simpulan**: Retroperitoneal parasitic leiomyoma dapat menyebabkan dilema dalam membuktikan diagnosis. Pemeriksaan dan pendekatan multidisiplin yang baik akan meningkatkan kualitas manajemen.

**Kata kunci:** Retroperitoneum parasitic leiomyoma; laparotomi; pendekatan multidisiplliner; tumor; kanker; kesehatan ibu.

***Correspondence:** Yuvens Richardo, Obstetrics and Gynecology Department Faculty of Medicine Lambung Mangkurat University/Ulin Hospital, Banjarmasin, South Kalimantan, Indonesia. E-mail: yuventus_as@yahoo.co.id

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.72-75
● Maj Obs Gin. 2021;29:72-75 ● Received 30 Jan 2021 ● Revised 22 May 2021 ● Accepted 5 Jun 2021


## INTRODUCTION

Uterine leiomyomas (uterine fibroid) is one of the most common tumor found in women of reproductive age. The prevalance of leiomyomas is up to 20-30% among women older that 35 years.[1,2] Another study have discovered increases of myoma prevalence in older age, almost 70% among >40 years old, with most incidences in African ethnic at >80% of all population.[3,4] Incidences among Asians and Caucasians are comparable, but some studies have shown that the incidences among Asians are lower. The African American had the higher prevalance, up to 3-fold more than other ethnics.[5,6]

Leiomyoma may develop both intrauterine and extra-uterine. They are known to originate from wherever smooth muscle cells exist. Extrauterine events are rare and may occur in other anatomical locations.[1] Due to the rarity, the development patterns are reported in several works of literature, such as dissemination, benign metastasis, intravenous leiomyoma, retroperito-neal, and parasitic growth. They generally adhere to surrounding tissues, attain additional vascularization from surrounding organs and detach from their initial site as a parasite. Parasitic leiomyomas can also be found on patients with a history of hysterectomy or myomectomy per laparoscopy, especially with morcellator usage for the extraction of myoma tissues.[7,8] The rare condition may present with uncommon clinical symptoms and are prone to preoperative misdiagnosis, even with cutting-edge radiology modalities. We reported a rare case of retroperitoneal parasitic leiomyoma.

## CASE REPORT

A 38 years old female with a history of bearing 3 children came to Obstetric Gyneologic Clinic of Ulin Regional General Hospital, Banjarmasin, Indonesia, presenting a swelling in her lower abdomen. She had a history of biopsy laparotomy 4 months earlier. There was no history of respiratory, digestive, nor urinary symptoms. She had a spontaneous vaginal delivery and two times cesarean section with no history of abortus. Menarche was at 13 years old. The menstrual cycle was orderly every 30 days, with a duration of 4-7 days, with 2-3 times sanitary change daily, no dysmenorrhea history, and no hormonal therapy history. The patient had a tumor biopsy laparotomy 4 months previously with a pathological anatomical examination, revealing that it was a leiomyoma. Physical examinations revealed a prominent, relaxed abdomen. The uterine fundus was unpalpable. A dense, non-bumpy fixated mass of 15x10 cm was palpated in the suprapubic region. The examination did not elicit any pain, and no enlargement of inguinal lymph node or any other abdominal organs were found. The in-speculum examination showed a normal vaginal wall, but an anteriorly pushed cervix. Vaginal toucher revealed an anteriorly pushed portion, enclosing the external uterine orifice. Corpus uterine was unable to be examined, while both the left and right parametrium adnexa were within normal range. The cavum Douglass was protruding with a dense, fixated, non-bumpy tumor mass of 15 x 10 cm. No pain was elicited during the examination. Laboratory values were within normal range. Ultrasound gave an impression of a mass in the cavum Douglass supporting a subserous uterine myoma on the posterior wall of the uterus size of 15 x 10 cm. The CT scan revealed a dense ovarian tumor with the size 9.97 x 14.79 x 13.47 cm in the pelvic cave, extending to the abdominal cave.

Considering both clinical examination and ancillary results, it was concluded that the diagnosis of the patient was a subserous uterine leiomyoma on the posterior uterine wall with a differential diagnosis of dense ovarian tumor. A total hysterectomy–bilateral salphyngo-ophorectomy was then planned. Intra-operative findings revealed that the uterus and both adnexa were normal, but adhesion was present between the abdominal wall and the tumor mass; thus adhesiolysis was conducted. A non-bumpy retroperito-neal mass of 15 x 10 x 13 cm was found adhered on the L4–S1 vertebrae, thus a resection was done, and the sample was sent to the anatomic-pathologist.

### Pathological findings

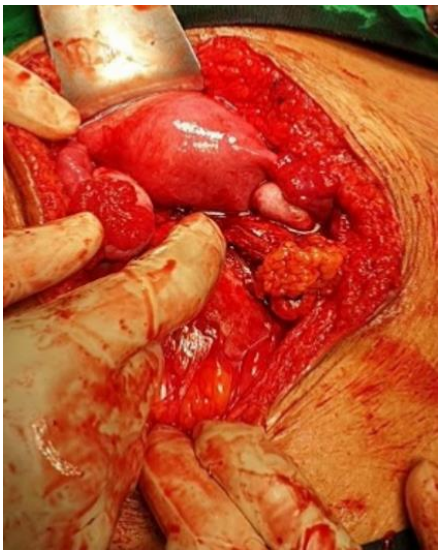


Figure 1. Findings during the operation

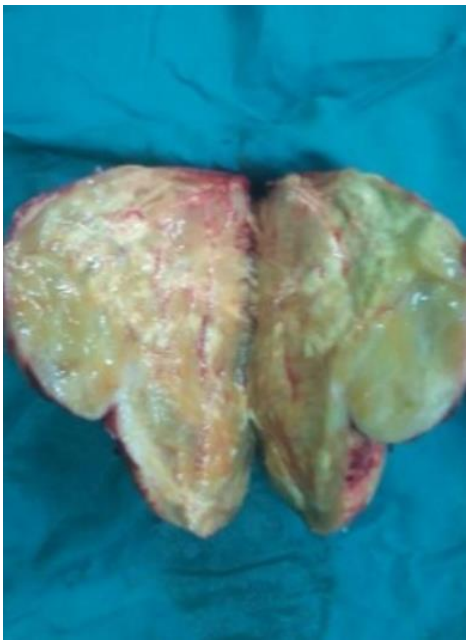


Figure 2. Macroscopic image

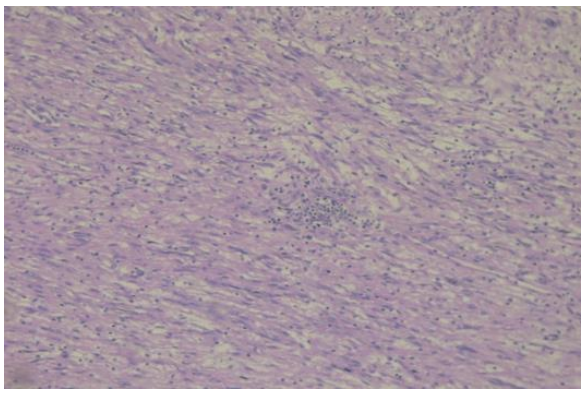


Figure 3. Microscopic image showing cigar-like smooth muscle cells. No malignant signs.

## DISCUSSION

Leiomyoma (uterine fibroid) is the most often benign tumor in female genital organs. A diagnosis is usually able to be confirmed early, but certain circumstances involving pathological changes may increase the difficulty in diagnosing and treating the disease.[9] The growth of subserous leiomyoma is vascularized by blood vessels of the uterus and from surrounding adhered organs' vessels. Like the omentum, the iliac and inferior mesenteric artery will weaken the connection with the uterus. The condition is known as the parasitic leiomyoma. Parasitic leiomyoma is a rare type of leiomyoma, generally occurring on the pelvis and the most dependent parts of the abdominal cavity. Several cases have reported parasitic leiomyomas that occurred on pararectal fossa, omentum, appendix, abdominal wall trocar site, paravesical space, gastric serosa, intestinal serosa, rectus muscle, lumbar region, ovaries, and in the bowel.[10,11] The macroscopic and microscopic findings of the parasitic leiomyoma are very similar to the uterine leiomyoma. Sometimes very peculiar findings such as a necrotizing tumor cell nucleus and radiologically also resemble that of a malignant tumor.[7,11]

Ultrasound and MRI (Magnetic Resonance Imaging) are both the best modalities to diagnose parasitic leiomyoma. The initial investigation, just as in cases of a patient presenting with a pelvic mass, should therefore include a pelvic ultrasound. MRI may further help in distinguishing benign leiomyomas from other solid pelvic and abdominal tumors.[12,13] When the parasitic leiomyoma detached from the uterus, it may result in a misdiagnosis into an adnexal tumor, such as ovarian tumor. In this reported case, the tumor detached from the uterus and was located retroperitoneally as high as L4–S1. It had been confirmed intraoperatively and was proven histopathologically as a leiomyoma.

The retroperitoneum parasitic leiomyoma is a very rare occurrence but should be considered as a differential diagnosis of a female genitalia tumor. Sometimes it grows from the supply of new blood vessels from surrounding organs, involving pathological changes or commonly known as degeneration. The degeneration type most often seen is hyaline, cystic, mucoid and red.[14,15]

## CONCLUSIONS

Retroperitoneal parasitic leiomyoma is a very rare occurrence, often arising dilemma in making a diagnosis. It should be considered as a differential diagnosis for internal female genital tumor. MRI and multidisciplinary approach, hand-to-hand with digestive surgery, will increase the quality of managing this very rare condition.

## REFERENCES

1. Sujatha MS, Mamatha S, Poornima M, et al. Parasitic leiomyoma peritoneum. A rare case. Open Journal of Obstetrics and Gynecology. 2014;04 (14):864. doi: 10.4236/ojog.2014.414121

2. de la Cruz MS, Buchanan EM. Uterine fibroids: Diagnosis and treatment. Am Fam Physician. 2017;95(2):100-7. PMID: 28084714
3. Wechter ME, Stewart EA, Myers ER, et al. Leiomyoma-related hospitalization and surgery: prevalence and predicted growth based on population trends. Am J Obstet Gynecol. 2011; 205:492. doi: 10.1016/j.ajog.2011.07.008.
4. Wise LA, Tommaso SK. Epidemiology of Uterine Fibroids - From Menarche to Menopause. Clin Obstet Gynecol. 2016; 59(1): 2-24. doi: 10.1097/GRF.0000000000000164 .
5. Borah BJ, Nicholson WK, Bradley L, et al. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol. 2013; 209:319. doi: 10.1016/j.ajog.2013.07.017.
6. Brosens I, Parazzini F, Chiaffarino F. The epidemiology of uterine leiomyomata. In: Uterine Leiomyomas. London: CRC Press; 2013. doi: 10.1201/b14628.
7. Lete I, Gonzalez J, Ugarte L, et al. Parasitic leiomyomas: a systematic review. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2016;203:250-9. doi: 10.1016/j.ejogrb. 2016.05.025.
8. Salih AM, Kakamad FH, Dahat AH, et al. Parasitic leiomyoma: A case report with literature review. International Journal of Surgery Case reports. 2017:41:33-5. doi: 10.1016/j.ijscr.2017.10. 003.
9. Ahmed S, El-Agwany, Helmy R, et al. An unusual case of parasitic leiomyoma with serpentine omental blood vessels: A case report. Surgery Journal. 2013;8(2):6-8. doi: 10.36478/sjour.2013. 6.8.
10. Grover A, Bhalla S. Parasitic leiomyoma: A rare complication following laparoscopic myomectomy with review of literature. Curr Med Res Pract. 2015; 5(6):278-81. doi: 10.1016%2Fj.cmrp.2015. 10.002.
11. Bhargava P, Haque K, Vea R, et al. Parasitic leiomyoma presenting as an inguinal hernia in a postmenopausal woman. Radiology case reports. 2018;13(4):767-71. doi: 10.1016%2Fj.radcr.2018. 04.014.
12. Oindi FM, Mutiso SK, Obura T. Port site parasitic leiomyoma after laparoscopic myomectomy: a case report and review of the literature. Journal of medical case reports. 2018;12(1):1-4. doi: 10.1186/ s13256-018-1873-y.
13. Ernest A, Mwakalebela A, Mpondo BC. Uterine leiomyoma in a 19-year-old girl: case report and literature review. Malawi Medical Journal. 2016;28 (1):31-3. PMID: 27217916.
14. Al Manasra ARA, Malkawi AS, Khammash MR. Parasitic leiomyoma: A rare cause of inguinal mass in females. Saudi Med J. 2011;32 (6):633-5. PMID: 21666948.
15. Lim LM, Huang Z, Ilancheran A. Parasitic leiomyoma. Am J Obstet Gynecol. 2016: 1;215(5): 665-e1. doi: 10.1016/j.ajog.2016.07.017.

**REVIEW ARTICLE**

# Examination and counseling of gynecological cases during Corona Virus Disease 2019 (COVID-19) pandemic

**I Gde Sastra Winata*, Clara Amanda**
Obstetrics and Gynecology Department, Medical Faculty of Udayana University, Sanglah Hospital, Denpasar, Indonesia

## ABSTRACT

COVID-19 is a recent pandemic caused by the SARS COV-2 agent with a high incidence and mortality. The disease is transmitted through respiratory droplets and direct contact. Clinically this COVID-19 patient is mainly related to the respiratory tract symptoms. The current clinical classifications are divided into suspected, probable, and confirmed cases. To reduce transmission must pay attention to universal and hierarchical precaution, aseptic standards, and sterile techniques. The types of gynecological examinations during a pandemic are the same as those in general, except that the methods, settings, and priorities are different. The examination begins with screening to assess the risk of transmission so that it can determine the place of examination. The urgency of the examination, history of TOCC, local transmission, provider, and room conditions also need to be considered. Counseling during a pandemic can be done in person or by telemedicine. Counseling is provided for general and case-specific gynecological information. Each gynecological case requires a different focus on counseling.

**Keywords:** COVID-19; examination; counseling; gynecology; virus; communicable disease; health system

## ABSTRAK

COVID-19 merupakan pandemi terbaru yang disebabkan oleh agen SARS COV-2 dengan insidensi dan mortalitas yang tinggi. Penyakit ini ditularkan melalui droplet pernafasan dan kontak langsung. Secara klinis penderita COVID-19 ini terutama berkaitan dengan gejala saluran pernafasan. Klasifikasi klinis saat ini dibagi menjadi kasus yang dicurigai, mungkin, dan dikonfirmasi. Untuk mengurangi penularan harus memperhatikan kewaspadaan universal dan hierarkis, standar aseptik, dan teknik steril. Jenis pemeriksaan ginekologi selama pandemi sama dengan pemeriksaan pada umumnya, kecuali metode, pengaturan, dan prioritasnya berbeda. Pemeriksaan diawali dengan penapisan untuk menilai risiko penularan sehingga dapat menentukan tempat pemeriksaan. Urgensi pemeriksaan, riwayat TOCC, penularan lokal, provider, dan kondisi ruangan juga perlu dipertimbangkan. Konseling selama pandemi dapat dilakukan secara langsung atau melalui telemedicine. Konseling disediakan untuk informasi ginekologi umum dan khusus kasus. Setiap kasus ginekologi membutuhkan fokus yang berbeda pada konseling.

**Kata kunci:** COVID-19; pemeriksaan; konseling; ginekologi; virus; penyakit menular; sistem kesehatan

***Correspondence:** I Gde Sastra Winata, Obstetrics and Gynecology Department, Medical Faculty of Udayana University, Sanglah Hospital, Denpasar, Indonesia. E-mail: dr.sastrawinata@gmail.com

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.76-83
● Maj Obs Gin. 2021;29:76-83 ● Received 8 Mar 2021 ● Revised 15 Jun 2021 ● Accepted 20 Jun 2021

## INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is a disease that is currently spread throughout the world. The World Health Organization (WHO) has declared this disease as a pandemic. Firstly, the disease appeared in Wuhan, Hubei Province, China at the end of 2019. The virus that causes COVID-19 is known as Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS COV-2), which is a type of coronavirus and has a structure that similar to the viruses that cause SARS and the previous Middle East Respiratory Syndrome (MERS). As SARS and MERS, this disease initially presents as clinically acute respiratory and lung infections such as pneumonia. In Indonesia, the first cases of COVID-19 were reported in early February 2020.[1-3]

The incidence and fatality of this disease are quite high. Based on data on August 29, 2020, the global number of cases reached 24,935,559 and nearly a quarter of the total number of cases (6,096,756 cases) was in the United States. However, this number is still increasing. Meanwhile in Indonesia, the number of cases up to the same date reached 169,195 people. The global fatality rate of this disease until 29 August 2020 reached 841,832 people with a fatality rate of 5.00%. Meanwhile, in Indonesia, the number of deaths has reached 7,261. With a fatality rate of 4.29%.[4]

The main transmission of this disease is through respiratory droplets and close contact.[5] This disease has a wide and varied clinical spectrum, ranging from asymptomatic, mild, moderate, severe, critical to fatal. The main clinical symptoms are respiratory system symptoms and fever. Respiratory symptoms are cough, runny nose, and shortness of breath. However, other symptoms that are not related to the respiratory tract can also occur, such as diarrhea, rash, and other systemic symptoms.[1-3,6-7] Currently, the clinical proportion of patients with mild to moderate symptoms is 99% severe and 1% critical.[4]

Based on clinical and contact history, in Indonesia initially classified cases into contacted asymptomatic people, People under Monitoring, Patients under Supervision, and confirmed cases. However, it's been changed into suspected, probable, and confirmed.[8] For medicinal purposes, they are divided into mild, moderate, and severe symptoms. Severe symptoms usually refer the patient to Acute Respiratory Disease Syndrome (ARDS) and a cytokine storm. These severe symptoms are more common in elderly patients or patients with cardiorespiratory or metabolic co-morbidities.

This pandemic has changed the pattern of life habits, including health services. Currently, health services must be adapted to health protocols, including health services in obstetrics and gynecology. All of these protocols aim to reduce the risk of transmission of this disease. Therefore, it is necessary to study further gynecological examinations during this pandemic

## CLINICAL EXAMINATION DURING COVID-19 PANDEMIC

Clinical examination during a pandemic must pay attention to universal and hierarchical precautions, aseptic standards, and sterile techniques. The standard aims to minimize nosocomial infections from blood, body fluids, secretions, skin, and mucous membranes. Hierarchical precautions relate to contact precautions, spray, borne water, etc. Medical personnel should avoid contact without personal protective equipment (PPE).[5]

POGI's recommendation, PPE used in obstetric procedures is divided into levels 1, 2, and 3. Level 1 corresponds to routine PPE. PPE Level 2 is used by officers to work or on duty in the highest risk COVID-19 room. Meanwhile, health workers who take care of COVID-19 patients with PPE level 3.[9] However, all protocols should be adjusted local standard.

## GYNECOLOGICAL EXAMINATION

Principally, the gynecological examination is the same as examinations in other fields including history, physical examination, and investigations. The history includes personal data history, current medical history, complaints of micturition, bowel habit, menstrual history, previous obstetric and gynecological history, sexual history, previous medical history, family and social history.

The physical examination includes a general physical examination and a special gynecological examination. Gynecological examination, palpation of the abdomen, an inspection of the vulva, examination of the speculum, examination, wet mount, examination of bimanual palpation, the examination of rectovaginal, and examination of the breast. Palpation of the abdomen in gynecology includes inspection, the percussion of the four quadrants of the abdomen, and palpation. A vaginal inspection is performed before the speculum examination to check for skin lesions, hirsutism, scarring, vaginal discharge, edema, and prolapse. Speculum examination is carried out in the lithotomy position, with lubrication before the examination. Before this examination, it is important to know the patient's

previous sexual history. This examination allows a deeper examination of the reproductive organs to the cervix and portio.[10]

The wet mount examination mentioned before is taking a sample of the discharge followed by a microscope examination to identify the cause. Examinations may be obtained such as clue cells, trichomonas, sperm cells, or fungi. A vaginal bimanual examination was conducted to examine the cervix, uterus, and adnexa. The cervical examination assesses tenderness, consistency, mobility, or external os. Meanwhile, the uterus examination was conducted to define its axis, size, and consistency of the uterus. In adnexitis, it is necessary to check size, tenderness, and mobility. The rectovaginal examination is not always performed in every patient. This rectovaginal examination is performed on patients with suspicion of malignancy, endometriosis, or a process in the Douglas' cavity.[10]

Examination of the breasts is carried out in two stages, namely inspection and palpation. Inspection tests such as symmetry, location, visible tumor, and changes in the skin. While palpation consists of palpation of lymph nodes and breasts. Palpation of lymph nodes examines cervical, supraclavicular, infraclavicular, axillar, and parasternal lymph nodes. Palpate the breast according to the four quadrants of the breast. All these gynecological physical examinations must pay attention to aspects of patient privacy.[10]

The investigation is often the ultrasound examination (USG). This ultrasound examination can be performed transabdominal or transvaginally. The transabdominal examination was performed in a supine position in a full bladder. Meanwhile, a transvaginal ultrasound is performed in a position like a speculum examination. Breast ultrasound is also performed in a supine position with the arm pulled back from the neck. Other tests include laboratory tests such as complete blood count, urinalysis, urea and creatinine, and pregnancy tests.[10]

## GYNECOLOGICAL EXAMINATION DURING THE COVID-19 PANDEMIC

The special protocol for gynecological examinations during the Covid-19 pandemic was limited because it was adjusted to local protocols. One model of examination approach in gynecology is gynecological cancer. This approach is following Figure 3. In this approach, patients are differentiated into patients who have not been diagnosed but suspect patients with malignancy, have been diagnosed and need treatment, in treatment and cancer survivors. In patients with suspicion of malignancy, diagnostic work-up is still carried out by observing health protocols or remote consultation. Whereas for patients who have been diagnosed, remote consultations can be done, or face to face with health protocols. The same is true of patients who are on treatment and cancer survivors with the principle of long-distance or face-to-face consultation if needed with the medical protocol.

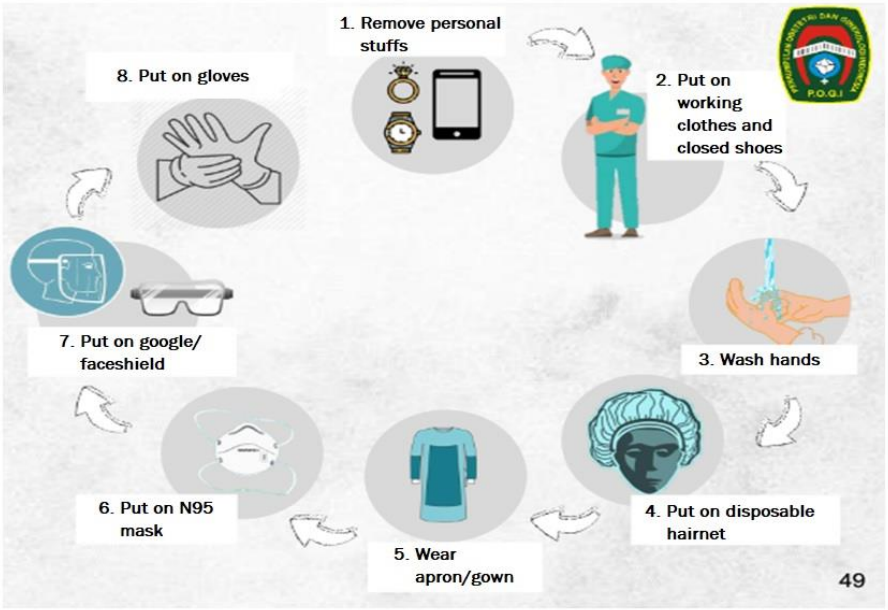



Figure 1. Level 2 PPE and procedure to use.[9]

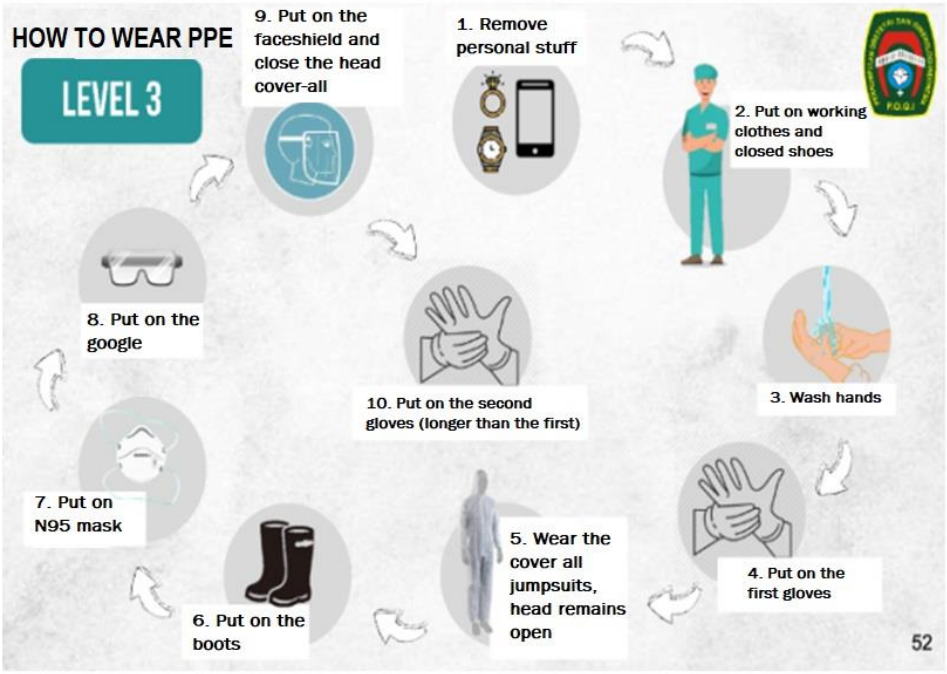



Figure 2. Level 3 PPE and procedure to use.[9]

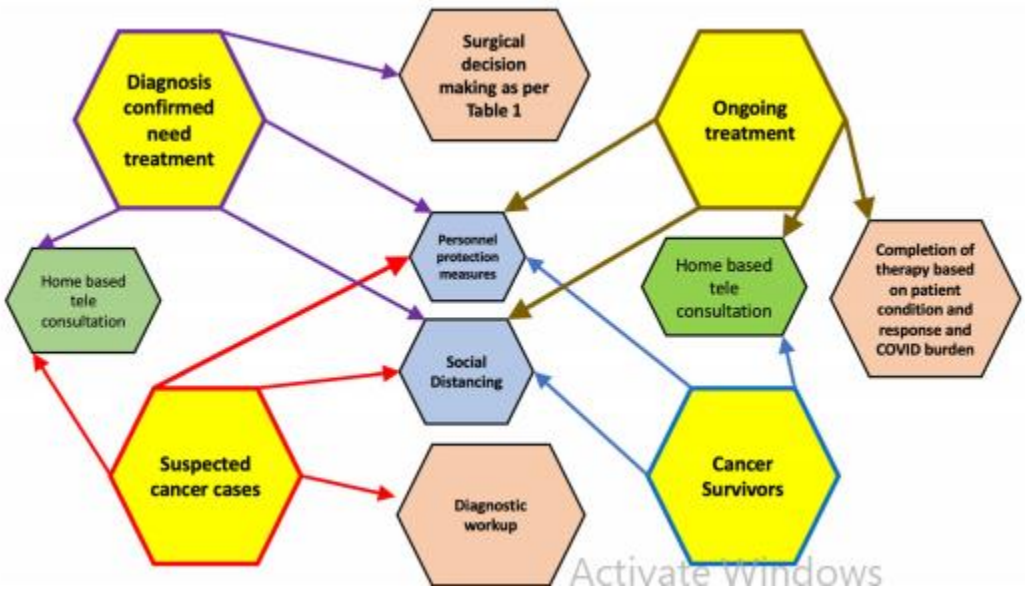



Figure 3. Examination approach model on gynecological cancer.[11]

In patients undergoing face-to-face examinations, screening is necessary before the examination. Screening is carried out by identifying symptoms associated with COVID-19 such as fever, cough, shortness of breath, chills, headache, sore throat, anosmia, weakness, muscle pain, runny nose, nausea, and vomiting, diarrhea, or a history of exposure to a positive patient. If there are no such symptoms, a routine check-up is carried out, with health protocols of course. However, if there are any of these symptoms or history, then proceed with an assessment of its severity. Patients with high risk, do emergency management in the ER or an

equivalent room that has been set. However, if it is not high risk, it is followed by clinical and social risk assessment. The moderate risk with complications or respiratory problems can be treated as high risk, while moderate risk without complications or respiratory problems can be done outpatient as well as low risk. The risk assessment algorithm is following Figure 4.[5,12]

Ultrasound examination in gynecology is one of the risky measures because the examination distance is usually less than 2 meters, the room is usually small, lacks ventilation, often uses air-conditioning, the examination is quite long, about 10-60 minutes, often tells the patient to inhale and exhale deeply. Therapeutic procedures increase the risk of exposure to body fluids, the risk when the patient cough sneezes, or breathes, and the risk of exposure to machines. Therefore, several things must be considered, namely triage, room arrangement, and patients. Triage is carried out to determine the priority of the examination. Suitable room ventilation or the use of high-efficiency particulate air (HEPA) filters in combination with the use of PPE and masks are good ways to reduce the risk of transmission. Meanwhile, the patient needs to do a temperature check and ask for TOCC (travel, occupation, contact, and cluster). The use of masks on patients is also very important and must be considered.[13]

Risk factors for ultrasound providers also need to be considered. Providers who are elderly or with comorbidities should not perform ultrasound examinations on suspected or confirmed patients and must wear complete PPE in local transmission areas even though it is asymptomatic and there is no history of TOCC. The age limit used is 60 years. Meanwhile, comorbidities include hypertension, diabetes mellitus, cardiovascular disease, chronic lung disease, and cancer. ISUOG recommendations are in Table 1.[13]

In reducing contact and establishing a priority scale for examinations, IUSOG divides the examination into "now", "soon", or "later". Examinations that must be done now (now) such as acute pelvic pain, suspicious ovarian torsion, rupture of ovarian cysts, PID or tubo-ovarian abscess, postoperative complications, ovarian hyperstimulation syndrome, symptomatic abdomino-pelvic period, abnormal uterine bleeding (AUB) such as menorrhagia with anemia or hemodynamic instability. The soon category is an examination that can be delayed by 2-4 weeks. These categories include AUB such as postmenopausal bleeding and bleeding after coitus, abdominopelvic mass with a high risk of malignancy, ultrasound staging for biopsy, recurrent gynecological malignancies.[14]

Apart from the above, it is necessary to pay attention to SARS-CoV-2 on dry inanimate objects which can last 48-96 hours. So that the room should be cleaned with a low-level disinfectant every day including the tools and linens, bedding, and towels used during the inspection.[15]

Table 1. PPE use base on symptoms, TOCC and local transmission.[13]

| *PPE* | *Asymptomatic and TOCC negative* | *Asymptomatic and TOCC positive* | *Suspected*/probable/confirmed COVID-19 or where there is widespread community transmission* |
|---|---|---|---|
| Clothing | Dedicated work clothes | Dedicated work clothes | Dedicated work clothes |
| Hand hygiene | Yes | Yes | Yes |
| Surgical facemask | Yes† | Respirator (N95, FFP2/3)‡ | Respirator (N95, FFP2/3)‡ |
| Respirator | No | Yes (N95, FFP2/3)‡ | Yes (N95, FFP2/3)‡ |
| Isolation gown | No | Disposable fluid-resistant and impermeable protective gown (e.g. AAMI level 3) | Disposable fluid-resistant and impermeable protective gown (e.g. AAMI level 3) |
| Disposable gloves | Yes | Yes (two pairs) | Yes (two pairs) |
| Eye protection | No | Goggles or face shield | Goggles or face shield |
| Hair cover | No | Yes | Yes |
| Additional consideration for transvaginal scan or invasive procedures | Standard condom or commercial transducer cover[25] | Standard condom or commercial transducer cover; cover for cable if available[25] | Standard condom or commercial transducer cover; cover for cable if available[25] |
| Staffing/environment | — | — | Ideally scan at bedside rather than in a clinic; minimize number of staff in room and ensure that most senior person is undertaking scan |
| Disinfection/cleaning[26] | Low-level disinfection for external probes; high-level disinfection for internal probes | Low-level disinfection for external probes; high-level disinfection for internal probes; additional low-level disinfection for ultrasound machine and cables | Low-level disinfection for external probes; high-level disinfection for internal probes; additional low-level disinfection for ultrasound machine and cables |

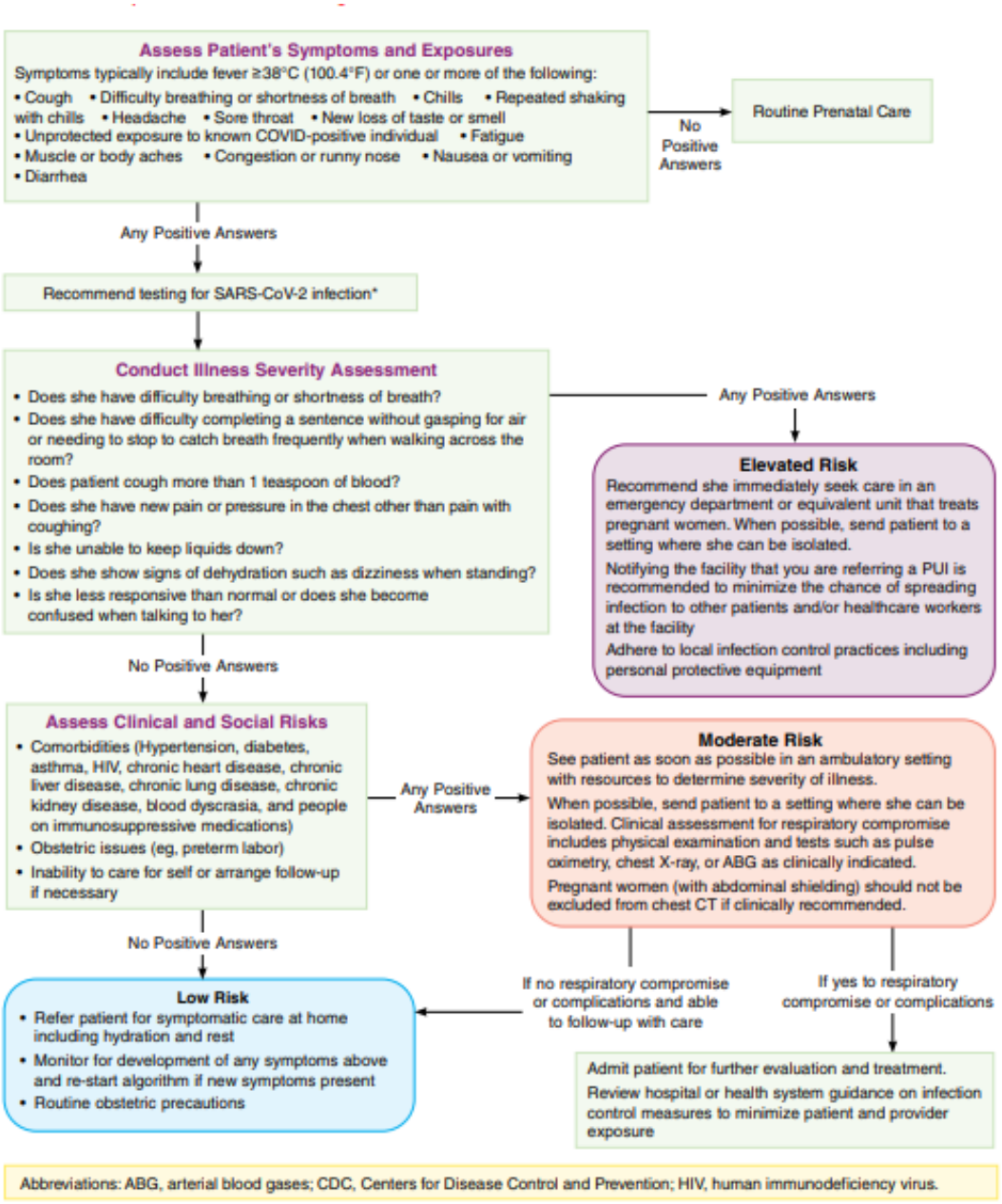



Figure 4. Algorithm of outpatient examination with suspected COVID-19.[17]

Based on the above reviews, gynecological examinations during a pandemic can be carried out by taking into account the need for direct (face-to-face) examinations. If necessary, this should be done with due observance of health protocols. Initial screening is based on low/medium/high-risk principles to determine where the procedure is performed. The principle of the ultrasound examination is also carried out by paying attention to TOCC and local transmissions as well as triage based on the examination findings. The condition of the provider and the room must also be considered. A physical examination in the field of gynecology may also be better performed using these principles.[11-14]

## GYNECOLOGICAL CASE COUNSELING DURING THE COVID-19 PANDEMIC

Patient counseling that will be discussed is the substance of counseling which consists of general and gynecological counseling as well as the telemedicine method. General counseling under WHO guidelines

includes counseling on visit restrictions, transmission routes and prevention, use of masks, hand hygiene, and the environment. Explain the reasons for visit restrictions and the use of masks when entering the room. Transmission routes by direct contact and droplet respiration, incubation 1–4 days, and symptoms are common. The use of masks includes how to use the correct mask and the type of mask according to the circumstances. Keep your hands clean with 7 steps to wash your hands and 5 moments. While the environment includes ventilation and avoiding crowds.[5] Counseling regarding the introduction and education of emergencies in patients is very important. In gynecological cases, it should be differentiated based on case priority (triage) as in ultrasound examination.[14]

Telemedicine is a long-distance method that can be used for counseling during a pandemic. Telemedicine in question is online consultation by telephone or videoconference, telemonitoring/screening using devices used to collect, transform, and evaluate patient data such as blood pressure, respiration, oxygenation, and patient symptoms; use of sensors for GPS for tracing, and Chatbots. Telemedicine is cheaper and reduces the cost of using antiseptics and PPE, is easily accessible, coordinates patient location, and reduces the risk of exposure.[5]

In gynecological cases, Grimes et al. have made recommendations for gynecological cases. Some of the gynecological cases discussed on these recommendations are AUB, chronic pelvic disease and endometriosis, infection and vaginal discharge, and postoperative care. Each case has a different focus on telemedicine counseling. In this recommendation, there are also lengths which are questions and answers that are often asked by patients.[16]

## REFERENCES


1. Working Group on Reproductive Tract Infection: Indonesia Society of Obstetrics and Gynecology. Rekomendasi penanganan infeksi virus corona (Covid-19) pada maternal (hamil, bersalin dan nifas) [Recommendation for coronavirus (Covid-19) infection in mothers (pregnancy, delivery, postpartum)]. 2020.
2. Asadi L, Tabatabaei RS, Safinejad H, Mohammadi M. New Corona Virus (COVID-19) management in pregnancy and childbirth. Arch Clin Infect Dis. 2020;15:e10293. doi: 10.5812/archcid.102938.
3. Rasmussen SA, Smulian JC, Lednicky JA, et al. Corona Virus Disease 2019 (COVID 19) and pregnancy: What obstetric need to know. American Journal of Obstetrics and Gynecology. 2020;222(5):415-26. doi: 10.1016/j.ajog.2020.02.017.
4. COVID 19 Coronavirus Pandemic. [internet] [cited 2020 Aug 2]. Available from: https://www.worldometers.info/coronavirus/
5. Qiu L, Morse A, Di W, et al. Management of gynecology patients during the Coronavirus Disease 2019 pandemic: Chinese expert consensus. American Journal of Obstetric and Gynecology. 2020;223(1):3-8. doi: 10.1016%2Fj.ajog.2020.05.024.
6. Adityo S, Rumende CM. Variasi gambaran klinis COVID 19. Update diagnosis dan tatalaksana. [COVID 19 clinical profile variations. Diagnosis and management update]. Webminar PAPDI 30 March 2020.
7. Boelig RC, Manock T, Oliver E et al. Labor and delivery guidance for COVID-19. Am J Obstet Gynecol MFM. 2020;2(2):100-10. doi: 10.1016/j.ajogmf.2020.100110.
8. Directorate General of Disease Control and Management, Ministry of Health, Republic of Indonesia.. Pedoman kesiapsiagaan menghadapi infeksi Novel Coronavirus (2019-nCoV) [Guidelines for preparedness for infection with Novel Coronavirus (2019-nCoV)]. [internet] [cited 2020 Aug 29]. Available from: https://covid19.kemkes.go.id/downloads/#.Xtva kWgzbIU
9. Personal Protective Equipment (PPE) Guidelines. Indonesian Society of Obstetrics and Gynecology. 2020
10. Unkels R. Gynecological history taking and examination. gynecology for less-resourced locations. [internet] [cited 2020 Aug 29]. Available from: https://www.glowm.com/resource_type/resource/textbook/title/a-textbook-of-gynecology-for-less-resourced-locations/resource_doc/35.
11. Bhatla N, Singhai S. The COVID-19 Pandemic and Implications for Gynaecologic Cancer Care. Indian Journal of Gynecologic Oncology. 2020;18:48.
12. ACOG. Outpatient assessment and management for pregnant women with suspected or confirmed Novel Coronavirus (COVID-19). [internet] [cited 2020 Aug 29]. Available from: https://www.acog.org/topics/covid-19
13. Abramowicz JS, Basseal JM, Brezinka C, et al. ISUOG safety committee position statement on use of personal protective equipment and hazard mitigation in relation to SARS-CoV-2 for practitioners undertaking obstetric and gynecological ultrasound. Ultrasound Obstet Gynecol. 2020;55:886–91. doi: 10.1002/uog.22035.
14. Bourne T, Leonardi M, Kyriacou C, et al. ISUOG consensus statement on rational-ization of gynecological ultrasound services in context of

SARS-CoV-2. Ultrasound Obstet Gynecol. 2020; 55:879–85. doi: 10.1002/uog.22047.
15. Poon LC, Abramowicz JS, Dall'Asta A, et al. ISUOG Safety Committee Position Statement on safe performance of obstetric and gynecological scans and equipment cleaning in context of COVID-19. Ultrasound Obstet Gynecol. 2020;55: 709–12. doi: 10.1002/uog.22027.
16. Grimes CL, Balk EM, Dieter AA. Guidance for gynecologist utilizing telemedicine during Covid-19 pandemic based on expert consensus and rapid literature review. Int Gynecol Obstet. 2020;150: 288-98. doi: 10.1007/s00192-020-04314-4.
17. CDC. Standard Operating Procedure (SOP) for triage of suspected COVID-19 patients in non-US healthcare settings: Early identification and prevention of transmission during triage [internet] [Cited 2020 Aug 29]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/non-us-settings/sop-triage-prevent-transmission.html

**REVIEW ARTICLE**

# Is it time to start COVID-19 vaccination in pregnant women?

**Muhammad Ilham Aldika Akbar***
Department of Obstetrics Gynecology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
Universitas Airlangga Hospital - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

## ABSTRACT

COVID-19 pandemic has been lasting for years, and pregnant women encounter an increased risk of mortality and morbidity. Until now, vaccine COVID-19 has been developed and shows a promising result. Unfortunately, pregnant women are consistently excluded from receiving a new vaccine. Because pregnant women are excluded from participating in a clinical trial of vaccines related to safety issues, this exclusion cycle prevents pregnant women from receiving the vaccine that may benefit them. In this review article, the author provides evidence, data, and the reason why vaccination of pregnant women should be started in Indonesia, at least in a clinical trial, especially for health workers and women with comorbidities.

**Keywords:** Covid-19; vaccine; maternal health; infectious disease; medicine

## ABSTRAK

Pandemi COVID-19 telah berlangsung selama beberapa tahun, dan ibu hamil menghadapi risiko kematian dan kesakitan yang tinggi. Sampai saat ini, vaksin COVID-19 telah dikembangkan dan menunjukkan hasil yang baik. Sayangnya, ibu hamil selalu diekslusi untuk menerima vaksin baru. Karena ibu hamil dieklusi untuk berpartisipasi pada penelitian klinis vaksin terkait isu keamanannya, ini akan menciptakan siklus ekslusi yang mencegah ibu hamil untuk mendapatkan vaksin yang bermanfaat untuk mereka. Pada telaah artikel ini, penulis menunjukkan bukti, data, dan alas an mengapa vaksinasi pada ibu hamil harus dimulai di Indonesia, paling tidak pada uji klinis, terutama pada tenaga Kesehatan dan ibu hamil dengan penyakit penyerta.

**Kata kunci:** Covid-19; vaksin; kesehatan ibu; penyakit infeksi; pengobatan

***Correspondence:** Muhammad Ilham Aldika Akbar, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jalan Prof dr Moestopo 6-8, Surabaya 60286, Indonesia.
E-mail: muhammad-i-a-a@fk.unair.ac.id@fk.unair.ac.id

● pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I22021.84-90
● Maj Obs Gin. 2021;29:84-90 ● Received 14 Apr 2021 ● Revised 21 Jul 2021 ● Accepted 29 Jul 2021

## INTRODUCTION

Since the start of the COVID-19 pandemic, pregnant women became the susceptible group with an increased risk of mortality ad morbidity. Pregnancy outcomes of COVID-19, in general, are better compared to the SARS, MERS, H1N1, Ebola, and Zika infections.[1] However, the risk of ICU admission, mechanical ventilator used, and maternal death is increased compared to normal pregnant women without COVID-19.[2] There has been no official government report about the prevalence, morbidity, and mortality of COVID-19 in pregnancy. Still, our unpublished study result from Universitas Airlangga Hospital show a maternal mortality rate of 9.8% (six maternal death from a total sixty-one confirmed cases). Morbidity presence in this study includes preeclampsia, gestational hypertension, preterm premature rupture of the membrane (PPROM), and preterm birth.

Vaccination (primary prevention) is still the best strategy to overcome any pandemic, including COVID-19.[3] Unfortunately, although pregnant women are a high-risk group, they do not have access to the COVID-19 vaccine. This problem is caused by the fact that pregnant women are permanently excluded from a clinical trial of a new therapy, drugs, including vaccination. The consideration of excluding pregnant women from many clinical trials is primarily related to fetal-neonatal safety and adverse pregnancy outcomes. However, the exclusion of pregnant women from vaccine clinical trials will create a repeated and continuous exclusion cycle. Pregnant women can not participate in a vaccine trial, which leads to no vaccine efficacy and safety data in pregnancy, resulting in no vaccine recommendation in pregnancy.[4] This cycle is unfair for pregnant women: 1. Pregnant women are rejected from vaccine study which may benefit maternal and fetal, and 2. Lack of evidence will decrease vaccine used in pregnant women, lead to decrease protection of the population (pregnant women, fetal) from COVID-19.[4] Therefore a complete review is needed to discuss this problem so that pregnant women and fetuses are not harmed in this pandemic situation. This article will discuss any aspect of the COVID-19 vaccine in pregnancy and why vaccination should be started soon in pregnant women.

## VACCINATION IN PREGNANCY

Since the early 19th century, pregnant women's vaccination has been done to protect mother and baby from smallpox infection, pertussis, and tetanus. The maternal vaccination program has been accelerated since the start of an influenza pandemic in 2009. Vaccination increases the specific antibody vaccine level in maternal blood when the baby is delivered. It can protect until the susceptible periods pass or until the baby has finished their routine immunization program.[5] Until now, three vaccines were recommended in pregnancy: tetanus, pertussis, and influenza. The most critical issue in pregnancy vaccination is the safety concern. The vaccine safety assessment becomes a problem because of adverse events related to pregnancy complication itself. When this event happens in clinical trials, it is essential to examine the association with the vaccine or pregnancy carefully. Many studies have provided evidence of vaccine safety, such as tetanus, influenza, and pertussis[5]. The emerging of the COVID-19 pandemic raises new challenges related to pregnancy vaccination. Considering this is a very recent disease, the lack of evidence from clinical trials makes a vaccination program in pregnancy not yet performed[8].

## COVID-19 VACCINE

Until now, many countries have developed a variety of COVID-19 vaccines. These vaccines can be classified based on the type, mechanism, and media used, including mRNA vaccine, viral vector vaccine, recombinant protein vaccine, and inactivated viral vaccine.[6] Vaccines that used mRNA media are Pfizer-Biotech (BNT162b2) and Moderna (mRNA-1273), the viral vector is AstraZeneca Oxford (AZD1222), and Johnson & Johnson-Janssen Pharmaceuticals (Ad26.COV2.S), a recombinant protein with Baculovirus are Novavax and GSK-Sanofi; also the inactivated viral vaccine is Coronavac-Sinovac Biotech. mRNA vaccine is a relatively new type of vaccine which brings genetic information to create a protein spike SARS-CoV-2, which the maternal immune system will recognize. mRNA vaccine never enters the cell nucleus and merges into the DNA, and in the periods of hours until days, this vaccine will be degraded in the cell cytoplasm. mRNA vaccine does not alter the human DNA, and either causes genetic changes.[7] Theoretically, based on this mechanism, the safety risk to the fetus or newborn is minor. Since Dec 13, 2020, FDA has approved the Emergency Use of Authorization (EUA) for the Pfizer dan Moderna vaccine to be used in the community in an emergency state. The EUA approval needs a tight review and test from four agencies/panels and has shown that the benefit of vaccine exceeds the risk from phase 3 clinical trial[6-8].

Astra Zeneca and Johnson & Johnson vaccine mechanism involve a modified viral vector that gives a protein spike SARS-CoV-2 into the cell and induces an immune response. This monovalent vaccine contains a recombinant human adenovirus type 26 (Ad26) vector,

which encodes a stabilized form of protein spike (S) SARS-CoV-2. The vector vaccine is not a live virus so that it unable to replicate in human body cells. This mechanism has been used in the Ebola HIV vaccine, which has been applied to pregnant women and shows a tolerable safety profile and reactogenicity.[3,7] Two adenovirus vector vaccine COVID-19 studies (phase 1/2 dan phase 2) show a neutralizing antibody and T-cell response to the protein spike SARS-CoV-2.[8] ChAdOx1, a viral platform that uses a chimpanzee adenovirus vector used in the Oxford study, shows an ability to safely induce a cellular and humoral immune response and protect pregnant sheep. They were vaccinated in the first trimester against Rift Valley fever disease, without risk of maternal viremia or miscarriage.[8]

Coronavac vaccine (China Sinovac Biotech) receive a EUA from The Food and Drugs Monitoring Agency Indonesia (BPOM) to be used in Indonesia.[9] Phase 3 clinical trials in Indonesia, Turkey, and Brazil show that the Coronavac is safe with minor-moderate adverse effects in the form of local impact (pain, induration, redness, and edema in injection site) and systemic effect (fever, myalgia, and fatigue). The Coronavac has also shown efficacy in three clinical trials Indonesia (65.3%), Turkey (91.25%), and Brazil (78%).[9] This vaccine uses the additional platform of inactivated virus, which has been proven a safety profile in pregnancy as shown in an influenza vaccine.[10–12] Coronavac has shown immunogenicity reactogenicity to mice, rats, and non-humans primates by inducing antibody SARS-CoV-2 who neutralized ten strains of SARS-CoV-2. The study shows Coronavac gives partials/complete protection on macaques from severe interstitial pneumonia interstitial after intentionally infected by SARS-CoV-2, which supports the next step to human clinical trial.[13] Indonesia is developing a national vaccine (Merah Putih vaccine - Eijkman Institute -Biofarma) in phase 1 clinical trial. The trial is expected complete in September-October 2021.[14]

### Evidence of COVID-19 vaccine in pregnancy

COVID-19 pandemic has shown the risk and susceptibility of pregnant women when excluded from vaccine trials and limits their access to vaccines. Vaccination on pregnant women protects the pregnancy outcomes, mother and baby, simultaneously.[15] However, because pregnant women are permanently excluded from vaccine trial cause lack of evidence for the recommendation of COVID-19 vaccine to this susceptible group. Fetal safety issues always become the first consideration to exclude vaccination to pregnant women. Many proposals have been sent to NIH and US FDA to permit pregnant women involves in the clinical trial with a tight protocol and prioritize their pregnancy safety.

### Evidence from previous used of similar vaccine

Inactivated viral vaccine (SINOVAC's Coronavac) is an established vaccine platform that has been used for a long time. This vaccine type has a proven safety profile in pregnant women and fetuses. The safety profile of Coronavac presumed will be similar to other inactivated viral vaccines such as the influenza vaccine. Inactivated influenza vaccine has been proven safe to the fetal-neonatal and does not increase the risk of adverse pregnancy outcomes such as preeclampsia, preterm birth, IUGR, and congenital malformation.[16] The most frequent adverse effect found are injection site pain and edema, fever, and myalgia. The absolute contra-indication is a severe allergic reaction to the vaccine or its ingredients.[16] Oppermann et al. evaluate the safety profile and pregnancy outcomes after influenza vaccination A (H1N1)v2009 on 323 pregnant women compared to 1329 control. The study shows no difference between both groups in risk of spontaneous miscarriages, major fetal malformation from exposure in any trimester, or first trimester only, or preconception periods.

Moreover, the risk of preeclampsia, preterm delivery, and IUGR are not increased in the vaccinated group. Oppermann et al. conclude that the H1N1 vaccine does not increase maternal and fetal risk.[10] From this study, the safety profile of Coronavac is expected to be similar. Pregnant women should have a chance to participate in the inactivated viral vaccine's clinical trial because this vaccine type's safety profile is already established.

## DEVELOPMENTAL AND REPRODUCTIVE TOXICOLOGY STUDY

FDA recommends a developmental and reproductive toxicology study (DART) on the animal to evaluate the vaccine's adverse effect potential on a reproductive function.[6] So far, only Moderna that already submit their DART study and indicate that mRNA1273 vaccine, which is given to mice before or during pregnancy with a dose of 100 ug do not show a poor effect on the female reproductive system or interfere with fetal, embryonal, or postnatal development except general skeletal variations which can be resolved without intervention after delivery.[6,7] A DART study of a rabbit who gave a 1 ml injection of Janssen COVID-19 vaccine shows no poor adverse effect on female fertility or developmental problems in fetal, neonatal, and postnatal until day 28.[7] At the same time, the Ad26 vector vaccine is already used in HIV, Ebola on

pregnant women and has been proven its safety profile and reactogenicity. These DART study results indicate the first safety data of the COVID-19 vaccine used in pregnancy.

## V-SAFE PREGNANCY REGISTRY DATA

Although pregnant women are permanently excluded from vaccine trials, many reproductive ages women who are vaccinated became pregnant. In US, in a group of women who were vaccinated with Pfizer-Biotech, there are 12 pregnancies and in Moderna vaccinated group, there is 13 pregnancy. Pregnancy outcomes still in observation, and until now, there are no signs of disturbance in fetal development.[6] In UK, there is 53 accidental pregnancy after vaccination. The miscarriage rate is similar between vaccinated and unvaccinated groups, as seen in Table 1.[1]

Until Feb 16, 2021, 30.494 pregnancy has been reported to CDC v-safe post-vaccination health checker and shows no sign of specific safety issues.[7] CDC has include pregnancy in the v-safe pregnancy registry study and, up to Feb 19, 2021, already recruit 1800 pregnant women.[17] This study aims to evaluate the safety profile of Pfizer-Biotech and Moderna vaccine in pregnancy in the US. As far the reactogenicity and adverse event in pregnancy do not show a significant safety problem. The adverse event is also similar between pregnant and non-pregnant women. There is no difference in adverse pregnancy outcomes between pregnant women who participate in the v-safe pregnancy registry and the general pregnant women population. This preliminary result can be seen in Table 2.[17]

## CLINICAL TRIAL

Phase 1/2 clinical trial already performed to evaluate safety, tolerability, and immunogenicity of Coronavac to 18-59 years old healthy adult in China.[18] In this randomized, double-blind, placebo-controlled trial, 144 participants are recruited in the phase 1 trial and 600 participants in the phase 2 trial. Zhang et al. show that two doses of Coronavac given in a different concentration and schedule are well tolerated and indicate moderate immunogenicity in a healthy adult. The incidence of adverse reaction between 3 ug and six ug doses is not different and shows no dose-effect safety concern. However, long-term follow-up is needed to ascertain this finding. The majority side effect found in this study is primarily mild pain in the injection site. Compared to another COVID-19 vaccine, such as viral vector and mRNA, fever incidence in Coronavac is lower.[18]

Table 1. Miscarriages rate in accidental pregnancy after COVID-19 vaccine in UK.[1]

| Vaccine | Control Group | | Vaccinated Group | |
|---|---|---|---|---|
| | Miscarriages n (%) | Pregnancies/ Total Participants | Miscarriages n (%) | Pregnancies/ Total Participants |
| Pfizer-Biotech | 1 (8) | 12/18.846 | 0 | 11/18.860 |
| Moderna | 1 (14) | 7/15.170 | 0 | 6/15.181 |
| AstraZeneca | 3 (33) | 9/5.829 | 2 (17%) | 12/5.807 |

Table 2. V-safe pregnancy registry outcomes in COVID-19 vaccinated pregnant women.[17]

| Outcomes | Background Rates (%) | V-safe Pregnancy Registry Overall (%) |
|---|---|---|
| Pregnancy Outcomes | | |
| Miscarriage (< 20 weeks) | 26 | 15 |
| Stillbirth (≥ 20 weeks) | 0.6 | 1 |
| Pregnancy Complications | | |
| Gestational Diabetes | 7-14 | 10 |
| Preeclampsia or gestational hypertension | 10-15 | 15 |
| Eclampsia | 0.27 | 0 |
| Intrauterine Growth Restriction | 3-7 | 1 |
| Neonatal Outcomes | | |
| Preterm birth | 10.1 | 10 |
| Congenital Anomalies | 3 | 4 |
| Small for Gestational Age | 3-7 | 4 |
| Neonatal death | 0..38 | 0 |

Coronavac also shows a humoral immune response and produces sufficient neutralizing antibodies, which supports the emergency use of this vaccine in China, and phase 3 trial in Indonesia, Turkey, and Brazil. Phase 1/2 trial has also been done in older adults (>60 years old), show a good safety profile, tolerability, and induce an excellent humoral immune response.[19] Pregnancy vaccination with Coronavac is predicted to show a similar safety and immunogenicity result.

Clinical vaccine trials on pregnant women are now in progress. Kathryn et al. study evaluate the immunogenicity and reactogenicity of mRNA COVID-19 vaccine on pregnant and lactating women compared to 1. control unpregnant women, 2. control pregnant women who are infected naturally.[20] This study involves 131 reproductive-age women who were vaccinated, consisting of 84 pregnant women, 31 breastfeeding women, and 16 non-pregnant women. The study shows that antibody titer post-vaccination is not different between pregnant, breastfeeding, and non-pregnant women (5.59 vs. 5.74 vs. 5.62). However, all titers are still higher compare to antibody titers induced by natural infection of COVID-19. Vaccine-induced antibodies are also found in the umbilical blood cord and breastmilk. Second doses vaccine increase Ig G SARS-CoV-2 titer but not the Ig A, in maternal blood and breastmilk. The adverse effect found in pregnant and lactating women are relatively lower compare to non--pregnant group, include pain and redness in the injection site, headache, myalgia, fatigue, and fever. During study periods, only 13 pregnant women gave birth, one patient experienced spontaneous preterm birth, and no other complication was found, such as preeclampsia and IUGR. Newborn morbidity was found to include one case of transient tachypnea of the newborn (TTN), and two babies need NICU admission. In general, this study shows that the mRNA COVID-19 vaccine shows good immunogenicity, reactogenicity, and safety profile, although the sample size is small.

Pfizer-Biotech already starts a phase 2/3 trial to evaluate the safety, tolerability, and immunogenicity COVID-19 vaccine (BNT162b2) on healthy pregnant women over 18 years old. On Feb 18, 2021, the first participant received the first dose of vaccine for this trial. At the end of the study, the sample is expected to reach 4000 pregnant women.[21,22] This study completes the initial phase 1/2 trial, which has shown a good safety result.[22] This study hopefully will give evidence about the safety of the mRNA vaccine in pregnancy soon.

## CONSIDERATION OF VACCINATION IN PREGNANCY

The primary consideration of vaccination on pregnant women is the balance between risk and benefit. COVID-19 significantly increases maternal, neonatal mortality and morbidity and the risk of adverse pregnancy outcomes.[23] The clinical trial has shown a vaccine efficacy of around 55-95%, depend on vaccine type.[6,9,24] Vaccination in pregnant women will significantly decrease pregnancy complications, adverse pregnancy outcomes, and maternal death risk. Vaccine COVID-19 may potentially give early protection to the newborn, based on Ig anti spike SARS-CoV-2 finding in a baby born from a vaccinated mother.[25] However, further study is needed to evaluate this antibody's protective role in newborns from COVID-19 infection.

In addition to efficacy/effectivity, vaccine safety always becomes a priority consideration for pregnancy vaccination. Based on the type and mechanism of the existing COVID-19 vaccine, theoretically, it is safe for pregnancy. All vaccines do not consist of living viruses, so they do not replicate in the human body either change genetic material.[6] Adenovirus 26 vector has been proven as safe as it used in Ebola vaccination in pregnancy.[26] The inactivated vaccine has also been established as a safe platform vaccine in pregnancy, as used in an influenza vaccine.[10,11,27] An animal study, DART study, clinical phase 1/2 trial of the COVID-19 vaccine shows a promising result in terms of safety and tolerability.[21,22,28] Clinical phase 3 trial is still in progress in many countries, and the official result is not published yet. However, clinical phase 3 trials in healthy non-pregnant women show a reassuring safety profile, and no significant safety issues arise.[17,21,22] The summary of consideration matter in COVID-19 vaccination in pregnancy can be seen in table 3.

The available data about the risk and benefit of COVID-19 vaccination can be used to determine our next step in managing this pandemic, especially in pregnant women. The clinical phase 3 vaccine trial involving pregnant women should be started in Indonesia, parallel with many other countries. The pregnant health workers and pregnant women with comorbidities need to be the first prioritized participant in this vaccine trial before a more extensive scale trial involving the population are performed. Meanwhile, health workers should support pregnant women who want to be vaccinated after full informed consent about the risks and benefits. Health workers should not obstruct the pregnant women's will to have a COVID-19 vaccine for their (maternal & fetal) own benefit.

Table 3. Summary consideration of COVID-19 vaccination in pregnant women

| |
|---|
| COVID-19 Infection Risk in Pregnancy |
| 1. Pregnancy increase the risk of severe COVID-19, ICU admission, mechanical ventilator used, and maternal death<br>2. COVID-19 complications risk increase if pregnant women have a comorbid/underlying disease such as obesity, hypertension, diabetes, older age, cardiovascular disease, and autoimmune disease<br>3. Vertical transmission risk to fetal (although small and rare)<br>4. Pregnancy complication risk (preterm birth and intrauterine growth restriction) |
| Safety of COVID-19 Vaccine |
| 1. Theoretical risk based on the COVID-19 vaccine mechanism is small<br>2. The use of a similar type of COVID-19 vaccine has been proven safe in pregnancy (adenovirus vector, inactivated viral vaccine)<br>3. DART study on Moderna and Pfizer-Biotech vaccine have shown a good safety profile<br>4. Phase 1/2 clinical trial on COVID-19 vaccine shows a good tolerability and safety profile<br>5. Phase 3 clinical trial is in progress, and a pre-preliminary result of the V-safe pregnancy registry study shows no increase in the risk of adverse pregnancy outcome in vaccinated women<br>6. The risk of vaccine reactogenicity includes fever may affect fetal in the first trimester. This problem can be resolved with the addition of antipyretic drugs. |
| Efficacy of COVID-19 Vaccine |
| 1. Limited data on pregnancy; however, vaccine efficacy are expected to be similar with healthy unpregnant women (55% - 95%)<br>2. Decrease risk of adverse pregnancy outcomes, maternal morbidity, and mortality<br>3. Prevent severe manifestation of COVID-19<br>4. Protective potential of antibody transfer through placenta to the fetal |

## CONCLUSION

Pregnant women and medical staff shall use the limited data available dan consider the risk and benefit of the COVID-19 vaccine in pregnancy, including specific individual patients risk exposed to SARS-CoV-2. Available data show reassuring evidence about the possibility of safe COVID-19 vaccination in pregnant women. CDC, ACOG, and SMFM recommend COVID-19 vaccination for pregnancy, considering its benefit outweighs the risk. Pregnancy medical staff should be the priority to obtain the COVID-19 vaccine. While waiting for the result of phase 3 clinical trial in many countries, Indonesia can start the vaccine trial involving pregnant medical staff or pregnant women with comorbidities before performing a larger scale study in the population. In addition, pregnant women who want to get the COVID-19 vaccine should be supported after complete informed consent of the risk and benefit.

## REFERENCES


1. Male V. Are COVID-19 vaccines safe in pregnancy? Nat Rev Immunol [Internet]. 2021;0123456789. doi: 10.1038/s41577-021-00525-y
2. Allotey J, Stallings E, Bonet M, et al. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. BMJ. 2020;370. doi: 10.1136/bmj.m3320.
3. Society for Maternal-Fetal Medicine (SMFM). Society for Maternal-Fetal Medicine (SMFM) Statement: SARS-CoV-2 Vaccination in Pregnancy [Internet]. SMFM website. 2020 [update 2020; cited 2021 Apr 3]. Available from: https://www.smfm.org/ publications/339-society-for-maternal-fetal-medicine-smfm- statement-sars-cov-2-vaccination-in-pregnancy%0A17.
4. Beigi RH, Krubiner C, Jamieson DJ, et al. The need for inclusion of pregnant women in COVID-19 vaccine trials. Vaccine [Internet]. 2021 ;39(6):868–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0264410X20316716
5. Jones CE, Calvert A, Le Doare K. Vaccination in pregnancy - Recent developments. Pediatr Infect Dis J. 2018;37(2):191–3. doi: 10.1097/INF.0000000000001822.
6. Rasmussen SA, Kelley CF, Horton JP, et al. Coronavirus Disease 2019 (COVID-19) vaccines and pregnancy: What obstetricians need to know. Obstet Gynecol. 2021;137(3):408–14. doi: 10.1097/AOG.0000000000004290.
7. American Colleague of Obstetrics and Gynecology. Vaccinating pregnant and lactating patients against summary of key information and recommendations [Internet]. ACOG web. 2021 [update 2021; cited 2021 Apr 3]. Available from: https://www.acog.org/clinical/clinical-guidance/ practice-advisory/articles/2020/12/vaccinating-pregnant-and-lactating-patients- against-covid-19%0A18.
8. Dashraath P, Nielsen-Saines K, Madhi SA, et al. COVID-19 vaccines and neglected pregnancy. Lancet [Internet]. 2020;396(10252):e22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673620318225
9. Office of Assistant to Deputy Cabinet Secretary for State Documents & Translation. BPOM Issues EUA for Sinovac COVID- 19 Vaccine [Internet]. 2021 [update 2021; cited 2021 Apr 7]. Available from: https://setkab.go.id/en/bpom-issues-eua-for-sinovac-covid-19-vaccine/
10. Oppermann M, Fritzsche J, Weber-Schoendorfer C, et al. A(H1N1)v2009: A controlled observational prospective cohort study on vaccine safety in

pregnancy. Vaccine 2012;30(30):4445–52. doi: 10.1016/j.vaccine.2012.04.081.
11. Giles ML, Krishnaswamy S, Macartney K, et al. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccines Immunother. 2019;15(3):687–99. doi: 10.1080/21645515.2018.1540807.
12. Swamy GK, Heine RP. Vaccinations for pregnant women. Obstet Gynecol. 2015;125(1):212–26. doi: 10.1097/AOG.0000000000000581.
13. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 2020;369(6499):77–81. doi: 10.1126/science.abc1932.
14. CNN. Vaksin Merah Putih Uji Klinis Akhir 2021 [Internet]. CNN Indonesia. 2021 [update 2021; cited 2021 Apr 8]. p. 2021. Available from: https://www.cnnindonesia.com/teknologi/20210324131843-199-621466/disusul-thailand-vaksin-merah-putih-uji-klinis-akhir-2021
15. Whitehead C, Walker SP. Consider pregnancy in COVID-19 therapeutic drug and vaccine trials. Lancet. 2020;395:e92. doi: 10.1016/S0140-6736(20)31029-1.
16. Psarris A, Sindos M, Daskalakis G, et al. Immunizations during pregnancy: How, when and why. Eur J Obstet Gynecol Reprod Biol. 2019;240:29–35. doi: 10.1016/j.ejogrb.2019.06.019.
17. Advisory Committee on Immunization Practices. COVID-19 vaccine safety update [Internet]. 2021. 2021. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-02/28-03-01/05-covid-Shimabukuro.pdf
18. Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis. 2021;21(2):181–92. doi: 10.1016/S1473-3099(20)30843-4.
19. Wu Z, Hu Y, Xu M, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy adults aged 60 years and older: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. Lancet Infect Dis 2021;3099(20):1–9. doi: 10.1016/S1473-3099(20)30987-7.
20. Gray KJ, Bordt EA, Atyeo C, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. Am J Obstet Gynecol. 2021:19–21.
21. Pfizer. Pfizer and BioNTech Commence Global Clinical Trial to Evaluate COVID-19 Vaccine in Pregnant Women | Pfizer [Internet]. 2021 [update 2021; cited 2021 Apr 7]. Available from: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-commence-global-clinical-trial-evaluate
22. Pfizer. Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older [Internet]. ClinicalTrials.gov. 2021. Available from: https://www.clinicaltrials.gov/ct2/show/NCT04754594?term=NCT04754594&draw=2&rank=1
23. CDC. COVID-19 People with Certain Medical Conditions [Internet]. [update 2021; cited 2021 Apr 7]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html
24. ACOG. COVID-19 Vaccines and Pregnancy?: Conversation Guide for Clinicians [Internet]. ACOG web. 2021 [update 2021; cited 2021 Apr 7]. p. 1–2. Available from: http://www.cmsdocs.org/COVID19VaccineconversationguideACOG.pdf
25. Gilbert P, Rudnick C. Newborn Antibodies to SARS-CoV-2 detected in cord blood after maternal vaccination. medRxiv [Internet]. 2021. Available from: https://www.medrxiv.org/content/ 10.1101/2021.02.03.21250579v1.full.pdf
26. Tapia MD, Sow SO, Ndiaye BP, et al. Safety, reactogenicity, and immunogenicity of a chimpanzee adenovirus vectored Ebola vaccine in adults in Africa: a randomised, observer-blind, placebo-controlled, phase 2 trial. Lancet Infect Dis. 2020;20(6):707–18. doi: 10.1016/S1473-3099(20)30019-0.
27. Marshall H, McMillan M, Andrews RM, et al. Vaccines in pregnancy: The dual benefit for pregnant women and infants. Hum Vaccines Immunother. 2016;12(4):848–56. doi: 10.1080/21645515.2015.1127485.
28. US Food and Drug Administration. Vaccines. FDA Briefing Document Moderna COVID-19 Vaccine. 2020;1–54. Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM583779.pdf

# ACKNOWLEDGMENT OF REVIEWERS 2021

The editors are greatly indebted and highly appreciate the assistance of the following reviewers of Majalah Obstetri & Ginekologi vol. 29 no. 1-2, 2021 :

Aan Anantasika

Ashon Sa'adi

Budi Iman Santoso

Eddy Suparman

Erry Dachlan

Fery Yusrizal

Freddy Wagey

Hari Nugroho

Hari Paraton

Heru Priyanto

I Wayan Wiyasa

Johannes Mose

Ketut Suwiyoga

Kusnarman Keman

Mirza Iskandar

Muhammad Dikman Angsar

Nusratuddin Abdullah

Sri Sulistyowati

Syahrul Rauf

Syarief Hidayat

Tjok Suwardewa

# MAJALAH OBSTETRI & GINEKOLOGI

## INDEX

## Volume 29, April, August 2021

## AUTHORS



## SUBJECTS

# 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