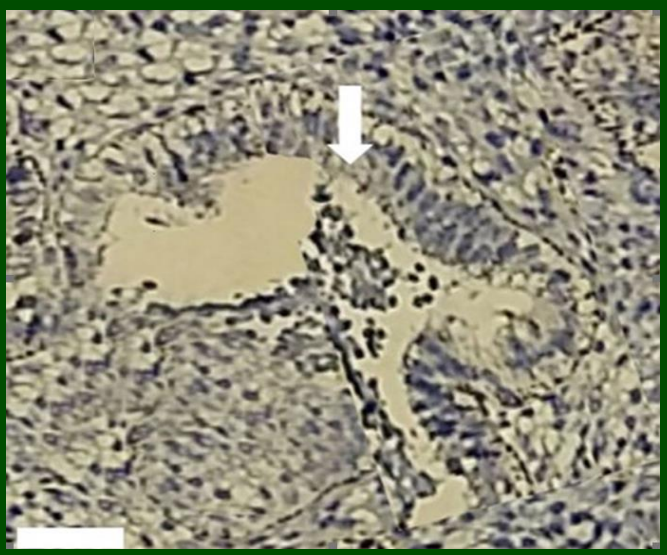
DOAJ DIRECTORY OF OPEN ACCESS JOURNALS

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

Vol. 29 No. 1 April 2021



Leukemia Inhibitory Factor (LIF) expression in the endometrium of PCOS patients (white arrow)

Original Research

- Correlation between response time and infant outcome in pregnant women with fetal distress undergoing caesarean section in two tertiary hospitals
- Emergency maternal referral worksheet as a clinical decision-making tool
- Comparison of pregnancy rates on day 3 and day 5 embryo transfer in In Vitro Fertilization (IVF)
- Antibiotic sensitivity on pathogenic bacteria causing bacterial vaginosis
- Changes in LIF expression on PCOS as biomarker implantation
- Prevention of vaginal vault prolapse occurrences post vaginal and abdominal hysterectomy. An evidence based case report

Case Reports

- Maternal and perinatal outcomes of hyperthyroidsm in pregnancy at Dr. Cipto Mangunkusumo Hospital, Jakarta, period of January 2015 - December 2016
- Acute Respiratory Distress Syndrome and septic shock in pregnant woman with COVID-19

Published by
Department of Obstetrics& Gynecology,Faculty of Medicine, Universitas Airlangga
In Collaboration withIndonesian Society of Obstetrics& Gynecology

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

Vol. 29 No. 1 April 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 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. 1 April 2021

pISSN 0854-0381
eISSN 2598-1013

Majalah Obstetri & Ginekologi

JOURNAL OF OBSTETRICS & GYNECOLOGY SCIENCE

CONTENT

ORIGINAL RESEARCH :

1. Correlation between response time and infant outcome in pregnant women with fetal distress undergoing caesarean section in two tertiary hospitals
Raditya Ery Pratama, M Ardian CL ..... **1 – 6**

2. Emergency maternal referral worksheet as a clinical decision-making tool
Mochammad Hud Suhargono ..... **7 – 13**

3. Comparison of pregnancy rates on day 3 and day 5 embryo transfer in In Vitro Fertilization (IVF)
Audia Mumtaz Rifasky, Puspa Wardhani, Ashon Sa'adi, Ninik Darsini, Hamdani Lunardhi, Zakiyatul Faizah ..... **14 – 17**

4. Antibiotic sensitivity on pathogenic bacteria causing bacterial vaginosis
Shiwi Linggarjati, Dita Diana Parti, Elly Nurus Sakinah ..... **18 – 22**

5. Changes in LIF expression on PCOS as biomarker implantation
Uki Retno Budihastuti, Eriana Melinawati, Sri Sulistyowati, Tanti Arianti ..... **23 – 27**

6. Prevention of vaginal vault prolapse occurrences post vaginal and abdominal hysterectomy. An evidence based case report
Suskhan Djusad ..... **28 – 35**

CASE REPORTS :

7. Maternal and perinatal outcomes of hyperthyroidsm in pregnancy at Dr. Cipto Mangunkusumo Hospital, Jakarta, period of January 2015 - December 2016
Fita Maulina, M Adya F Dilmy, Ali Sungkar ..... **36 – 40**

8. Acute Respiratory Distress Syndrome and septic shock in pregnant woman with COVID-19
Jesselyn Kristanti, Fransiscus OH Prasetyadi ..... **41 – 44**

Cover :
Leukemia Inhibitory Factor (LIF) expression in the endometrium of PCOS patients (white arrow)
This edition page 25

AUTHOR GUIDELINES

Majalah Obstetri & Ginekologi publishes articles on all aspects of obstetrics and gynecology. Articles can be classified as research reports, case reports and literature reviews that keep the readers informed of current issues, innovative thinking in obstetrics and gynecology. Articles are considered for publication with the condition that they have not been published or submitted for publication elsewhere. Manuscript should be written in English or in Indonesian. 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 reseach

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 **Helsinki Declaration 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 10. 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. Literature Review

Literature review 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 research: **Objective, Materials and Methods, Results, Conclusion**.
b. Case Report: **Objective, Case Report, Conclusion**.
c. Literature Review: No structure but **summarizes 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 nonstandard 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 writing of the manuscript**. 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 RESEARCH:

Correlation between response time and infant outcome in pregnant women with fetal distress undergoing caesarean section in two tertiary hospitals

Raditya Ery Pratama,[1] M Ardian CL[2*]
[1]Ibnu Sina Hospital, Gresik, Indonesia, [2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr Soetomo Hospital, Surabaya, Indonesia

ABSTRACT

Objectives: This study aimed to illustrate the response time of pregnant women with fetal distress undergoing caesarean section at dr. Soetomo Hospital and Universitas Airlangga Hospital during 2015-2017.
Materials and Methods: This was a non-experimental descriptive observational study using medical records at dr. Soetomo Hospital and Universitas Airlangga Hospital during 2015-2017. Samples of the study were enrolled using total sampling.
Results: Data at dr. Soetomo Hospital revealed 103 patients: the age characteristics of >30 year were 48 patients (38%), underlying diseases with hypertension 68 cases (66%), use of general anesthesia with 65 cases (63%). Caesarean section response time >30 minutes was in 85 cases (83%), from which 58 babies (56.3%) had severe asphyxia. At Universitas Airlangga Hospital there were 5 patients, from whom those of 20-30 years were 4 (80%), and those with underlying diseases of hypertension were 3 patients (60%), and those using general anesthesia were 4 (80%). caesarean section response time of >30 minutes were in 3 cases (60%) where all 5 babies (100%) had moderate asphyxia. Age data processing with Chi-square test revealed $p = 0.534$ ($p>0.05$), indicating no significant relationship between age group with fetal outcome. Response time of the caesarean section showed $p = 0.027$ ($p<0.05$), indicating significant relationship between caesarean section response time and fetal outcome.
Conclusion: Response time of pregnant women with fetal distress performed caesarean section at dr. Soetomo Hospital and Universitas Airlangga Hospital period 2015-2017 was still more than 30 minutes and the baby's was found to have moderate-severe asphyxia. These were due to delayed informed consent, patient stabilization, as well as anesthesia, operating room and pediatrics preparation.

Keywords: Pregnant women with fetal distress; response time; baby outcome

ABSTRAK

Tujuan: Mengetahui hubungan waktu respon pasien gawat janin yang dilakukan seksio sesarea dengan luaran bayi di RSUD dr. Soetomo dan di RS Universitas Airlangga Surabaya periode tahun 2015-2017.
Bahan dan Metode: Metode non eksperimental (observasional) deskriptif menggunakan rekam medis RSUD dr. Soetomo dan RS Universitas Airlangga Surabaya tahun 2015-2017. Pengambilan sampel penelitian menggunakan total sampling.
Hasil: Dari data di RSUD dr Soetomo didapatkan 103 pasien, karakteristik usia >30 tahun 48 pasien (38%), penyakit terbanyak ibu hamil yaitu hipertensi 68 kasus (66%). Anestesi yang paling banyak digunakan yaitu general 65 kasus (63%). Waktu respon diambilnya keputusan sampai lahirnya bayi >30 menit yaitu 85 kasus (83%), dimana 58 bayi (56,3%) asfiksia berat. Sementara di RS. Universitas Airlangga didapatkan 5 pasien dengan karakteristik: usia 20-30 tahun sebanyak 4 pasien (80%), penyakit mendasari ibu hamil yaitu hipertensi 3 pasien (60%). Penggunaan anestesi terbanyak dengan general 4 kasus (80%), waktu respon >30 menit sebanyak 3 kasus (60%) dengan 5 bayi (100%) asfiksia sedang. Pengolahan data dengan Chi-square didapatkan nilai p 0,534 ($p>0,05$) diartikan tidak ada hubungan signifikan kelompok umur dengan luaran janin, sementara waktu respon operasi seksio nilai p 0,027 ($p<0,05$), diartikan terdapat hubungan signifikan waktu respon operasi seksio pada bayi gawat janin dengan luarannya.
Simpulan: Waktu respon pasien hamil dengan gawat janin yang dilakukan operasi seksio di RSUD dr. Soetomo dan RS Universitas Airlangga periode tahun 2015-2017 masih kurang, yaitu >30 menit. Luaran bayi banyak mengalami asfiksia sedang-berat. Hal ini disebabkan antara lain hambatan pengambilan informed consent, stabilisasi pasien, persiapan anestesi, persiapan ruang operasi dan persiapan pediatri.

Kata kunci: Ibu hamil dengan gawat janin; waktu respon; luaran bayi

***Correspondence:** M. Ardian CL, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr Soetomo Hospital, Jalan Prof dr Moestopo 6-8, Surabaya 60286, Indonesia. E-mail: m.ardian@fk.unair.ac.id

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.1-5
● Maj Obs Gin. 2021;29:1-6 ● Received 24 Nov 2020 ● Revised 6 Jan 2021 ● Accepted 22 Jan 2021

INTRODUCTION

Maternal Mortality Rate (MMR) and Infant Mortality Rate (IMR) are indicators of health development in the 2015-2019 National Mid-Term Development Plan and the SDGs. According to the Indonesian Health Data Survey, the Maternal Mortality Rate has decreased in the period 1994-2012, namely in 1994 of 390 per 100,000 live births, in 1997 it was 334 per 100,000 live births, in 2002 it was 307 per 100,000 live births, and in 2007 amounting to 228 per 100,000 live births. However, in 2012 the Maternal Mortality Rate increased again to 359 per 100,000 live births. In the IDHS 2012, the Infant Mortality Rate shows 32/1,000 live births (IDHS 2012), and in 2015, the 2015 Basic Health Research showed a decrease in MMR and IMR (MMR 305/100,000 live births; IMR 23/1000 live births). The highest cause of maternal mortality in 2016 was bleeding (32%) and 26% due to hypertension which causes seizures, and pregnancy poisoning so that the mother dies.[1]

Infant Mortality Rate is an indicator commonly used to determine the level of public health, both at provincial and national levels. IMR refers to the number of babies who die in the phase between birth and before reaching age 1 year per 1,000 live births. Currently, the Infant Mortality Rate (IMR) in Indonesia is the highest compared to other ASEAN countries. According to 2007 Indonesian Demographic and Health Survey (IDHS) data, the Infant Mortality Rate (IMR) in Indonesia is 34 per 1000 live births (Ministry of Health, 2009). According to the Ministry of Health of the Republic of Indonesia in 2008, one of the causes of newborn mortality is asphyxia (27%) which is the second cause of death for newborns after LBW. In 2009, the incidence of asphyxia in the world according to the World Health Organization (WHO) was 19%.[1]

This high maternal and infant mortality rate is due to the lack of health services in Indonesia. This is related to human resources (health workers), health infrastructure (health facilities), and the level of awareness of women of reproductive age in Indonesia regarding pregnancy planning and reproductive health. One of the factors associated with incorrect health services is the response time in diagnosing diseases of a pregnant woman and making decisions regarding the delivery process that will be taken. In general, the problems faced in meeting the response time are preparation for surgery (from informed consent to the operating room), anesthesia consultation, transportation of patients to the operating room, preparation for anesthesia, waiting time for the effectiveness of anesthetic action, the presence of operating personnel (obstetricians, anesthetists, pediatricians/neonatal officers, and surgical nurses) and the operation team cooperation.[2]

Decision to delivery interval (DDI) or response time is defined as the time interval in minutes from the time of cesarean section decision until the baby is born. The NICE RCOG (Royal College of Obstetrician and Gynecologist) Caesarean Section Guidelines states that the response time for category 1 cesarean section is 30 minutes and category 2 is between 30-75 minutes.[3]

In Indonesia, especially at dr. Soetomo Hospital Surabaya and at Universitas Airlangga Hospital Surabaya, there was no data on the response time of caesarea section in fetal distress patients. This study aims to determine the response time of cesarean section in fetal distress patients in both hospitals in order to reduce infant mortality.

MATERIALS AND METHODS

This study was an observational analytic study with cross-sectional design using medical records at dr. Soetomo and Universitas Airlangga Hospitals, Surabaya, Indonesia, in 2015-2017. The sample of this study was taken by total random sampling of all pregnant women with fetal distress who then underwent emergency cesarean section in 2015-2017. Furthermore, from these data the response time was calculated from the decision to operate until the birth of the baby based on the classification in Figure 1 in the process of delivery of fetal distress, which lasts 30 minutes.

RESULTS

Characteristics of the age of pregnant women with fetal distress undergoing cesarean section at dr. Soetomo Hospital, Surabaya

From 2015-2017 pregnant women with fetal distress who underwent cesarean section at dr. Soetomo Hospital, Surabaya, were as many as 103 patients with the characteristics of mostly aged >30 years (48 patients or 47% of all cases), then 20-30 years of age of 40 patients (38%) and the least were 15 patients (15%) aged of <20 years.

Characteristics of the age of pregnant women with fetal distress undergoing cesarean section at Universitas Airlangga Hospital

Between 2015-2017 pregnant women with fetal distress who underwent cesarean section at Universitas Airlangga Hospital, Surabaya were 5 patients with

mostly 20-30 years of age (4 or 80% of all cases), then 1 case of age >30 years (20%) and there were no patients aged <20 years.

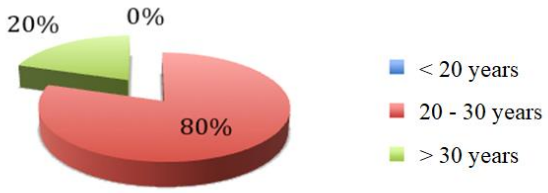


Figure 1. Age characteristics of pregnant women with fetal distress undergoing cesarean section at dr. Soetomo Hospital Surabaya

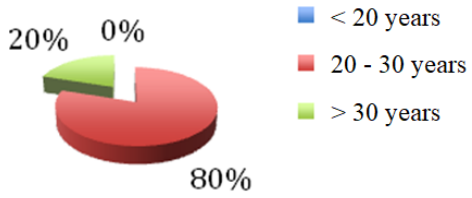


Figure 2. Age characteristics of pregnant women with fetal distress undergoing cesarean section at Universitas Airlangga Hospital

Characteristics of diseases of pregnant women with fetal distress undergoing cesarean section at dr. Soetomo Hospital, Surabaya

These data indicate that the most fetal distress cases occurred in pregnant women with hypertension (68 cases/66%) and total placenta previa with bleeding in 4 cases (4%), and 7 cases of heart disease (7%).

Table 1. Disease characteristics of pregnant women with fetal distress undergoing cesarean section at dr. Soetomo Hospital, Surabaya

No	Type of disease	Total
1	Hypertension	68
2	APB ec PPT	4
3	Heart disease	7
4	DM	2
5	Others	22
	Total	103

Characteristics of disease in pregnant women with fetal distress undergoing cesarean section at Universitas Airlangga Hospital

Three out of five cases of fetal distress pregnant women suffered from hypertension, whereas premature rupture of membranes was found in one case, and mal-presentation of vertex position in one case.

Table 2. Disease characteristics of pregnant women with fetal distress undergoing cesarean section at Universitas Airlangga Hospital

No	Type of disease	Total
1	Hypertension	3
2	PRM	1
3	Malpresentation	1
	Total	5

Selection of anesthesia for pregnant women with fetal distress undergoing cesarean section at dr. Soetomo Hospital Surabaya

Cesarean section procedure in pregnant women with fetal distress can be performed with two choices of anesthesia, the general anesthesia and regional anesthesia. This study found 63% of the cases underwent cesarean section using general anesthesia, while 37% used regional anesthesia.

Table 3. Selection of anesthesia for pregnant women with fetal distress undergoing cesarean section at dr. Soetomo Hospital, Surabaya

No	Type of Anesthesia	Total
1	General Anesthesia	65 (63%)
2	Regional Anesthesia	38 (37%)
	Total	103

Selection of the type of anesthesia for pregnant women with fetal distress undergoing cesarean section at Universitas Airlangga Hospital

Cesarean section in pregnant women with fetal distress can be performed with 2 choices of anesthesia, the general anesthesia and regional anesthesia. It was found that 80% of caesarean sections were performed with general anesthesia, while 20% used regional anesthesia.

Table 4. Selection of types of anesthesia for pregnant women with fetal distress undergoing cesarean section at Universitas Airlangga Hospital

No	Type of Anesthesia	Total
1	General Anesthesia	4 (80%)
2	Regional Anesthesia	1 (20%)
	Total	5

Response time of pregnant women with fetal distress undergoing emergency cesarean section at dr. Soetomo Hospital, Surabaya

This study found that the response time for the implementation of cesarean section in pregnant women with fetal distress mostly (83%) still needed >30 minutes, while the remaining 17% required <30 minutes.

Table 5. Response times of pregnant women with fetal distress undergoing emergency cesarean section at dr. Soetomo Hospital, Surabaya

No	Response Time	Total
1	< 30 minutes	18 (17%)
2	> 30 minutes	85 (83%)
	Total	103

Response time of pregnant women patients with fetal distress undergoing emergency cesarean section at Universitas Airlangga Hospital

This study found that the response time for the implementation of cesarean section in pregnant women with fetal distress was mostly (60%) more than >30 minutes, while the remaining 40% was performed <30 minutes.

Table 6. Response times of pregnant women with fetal distress undergoing emergency cesarean section at Universitas Airlangga Hospital

No	Response Time	Total
1	< 30 minutes	2 (40%)
2	> 30 minutes	3 (60%)
	Total	5

Infant outcome from pregnant women with fetal distress at dr. Soetomo Hospital, Surabaya

Most of infant outcomes from mothers with fetal distress who undergoing cesarean section at dr. Soetomo Hospital Surabaya was severe asphyxia with Apgar Score 1-3 in 58 cases (56.3%), moderate asphyxia in 37 cases (35.9%), and mild asphyxia in 10 cases (9.7%).

Table 7. Infant outcomes from cases of fetal distress at dr. Soetomo Hospital Surabaya

No	APGAR Scores	Total
1	Mild asphyxia (7-10)	10 (9,7%)
2	Moderate asphyxia (4-6)	37 (35,9%)
3	Severe asphyxia (1-3)	58 (56,3%)
	Total	103

Table 8. Infant outcomes from cases of fetal distress in dr. Universitas Airlangga Hospital.

No	Nilai APGAR	Jumlah
1	Mild asphyxia (7-10)	0
2	Moderate asphyxia (4-6)	5
3	Severe asphyxia (1-3)	0
	Total	5

DISCUSSION

Characteristics of pregnant women with fetal distress undergoing cesarean section and infant output at dr. Soetomo Hospital, Surabaya

In this study, at dr. Soetomo Hospital we found that, from 103 patients, most of them were in the age range of >30 years, which were as many as 48 patients (47%), and the gestational age was mostly less than 37 weeks (premature), which was in 55 patients (53%). This was related to the underlying disease of the pregnant women, the hypertension, so that the delivery process did not wait for a full-term pregnancy. The babies were born at 34-37 weeks of gestation.[4]

As many as 66% of fetal distress cases occurred in mothers with hypertension and 12% in mothers with total placenta previa accompanied by bleeding. Apart from hypertension, total placenta previa, especially those with active flux, often results in fetal distress incidence. Hypertension is closely related to the incidence of chronic utero-placental flow insufficiency which may cause intrauterine fetal hypoxia, resulting in decreased fetal heart rate, leading to fetal emergency. In total placenta praevia totalis that is accompanied by bleeding, there is acute insufficiency of utero-placental flow which may lead to fetal distress.[4]

The most common type of anesthesia was general anesthesia which was performed in 65 patients (63%) compared to regional anesthesia in 38 patients (37%). Of the two types of anesthesia, general anesthesia is the main choice of anesthesia in cesarean section of pregnant women with fetal distress because general anesthesia does not require a long time to start the incision when compared to regional anesthesia.[6]

Response time for the implementation of cesarean section at dr. Soetomo Hospital was >30 minutes, which was experienced by 85 patients (83%) while patients who underwent the operation for <30 minutes were 18 (17%). This differs from the defined time for classification of grade 1 emergency cesarean section in other cases, such as those with fetal bradycardia, umbilical cord prolapse, uterine rupture, placental abruption and pathological cardiotocography, which

may take 30 minutes.[6] The infant outcome at dr. Soetomo Hospital for the period 2015-2017 showed that most of the infants experienced severe asphyxia, consisting of 57 patients (56.3%).

Characteristics of pregnant women with fetal distress undergoing cesarean section and infant outcomes at Universitas Airlangga Hospital

In Universitas Airlangga Hospital, most patients had an age range of 20-30 years, as many as 4 patients (80%). All patients had gestational age at term (>37 weeks). The most common disease among pregnant women was hypertension in 3 patients (60%). Although most of the patients had hypertension, the patients arrived at >37 weeks' gestation age so the pregnancy termination was carried out at that time.

Like at dr. Soetomo Hospital, in the most common type of anesthesia was general anesthesia in 4 patients (80%), while regional anesthesia was performed in 1 patient (20%). This is in accordance with a previous study which found that the choice of anesthesia in cesarean section in pregnant women with fetal distress is the general anesthesia because it does not require a long time to wait for the onset of drug action.[6]

Response time for cesarean section in the hospital. Universitas Airlangga was> 30 minutes in 3 patients (60%) and <30 minutes in 2 patients (40%). This differs from the time requirements for classification of grade 1 emergency cesarean section in cases including fetal bradycardia, umbilical cord prolapse, uterine rupture, placental abruption and pathological cardiotocography, which is 30 minutes.[7] Out of the baby at the hospital. Universitas Airlangga for the period 2015-2017 showed that all of them had moderate asphyxia.

Relation of response time for cesarean section with infant outcome

Data processing response time for cesarean section has a value of $p = 0.027$ ($p < 0.05$) which shows a significant relationship between the response time of cesarean section in fetal distress infants with fetal output, while between age and outcome the baby does not show a significant relationship with $p = 0.534$ ($p > 0.05$).

One of the factors that can affect the response time in our study is related to the condition of the pregnant women when they arrived at the hospital.[8-10] From the data obtained from dr. Soetomo Hospital, there were 20 pregnant women with fetal distress and underlying hypertension (preeclampsia, eclampsia, chronic HT) accompanied by pulmonary edema, while there were as many as 20 patients with heart defects. This caused delayed response time to carry out the procedure, which might be due to time needed to obtain supporting data such as laboratory examinations, chest radiographs and echocardiography. This additional examinations is highly necessary for the safety of the patient before surgery.[11-15] However, we did not obtain the data on the time needed for anesthetic preparations related to preoperative anesthesia, time to obtain effective action of the anesthetic agent, time for pediatrics time to arrive to the operating room, time for transportation for the patient to the operating room, and preparation time for the operating room, so this was a weakness of this study.

CONCLUSION

The response time obtained this study from both hospitals was more than 30 minutes, which indicates a low response time. The outcome of infants in both hospitals that showed varying degrees of asphyxia indicated that a long response time (> 30 minutes) could have an effect on infant outcome. Further research is needed to analyze the response time associated with cesarean section in pregnant women with fetal distress using more valid and accurate data involving the time for anesthesia and pediatric preparation, patient transportation to the operating room, and preparation of the operating room.

REFERENCES

1. Survei Demografi Kesehatan Indonesia; Angka Kematian Ibu dan Bayi; 2016.
2. Xiaolei X, Jingshan L, Swartz CH, DePriest P. Improving response-time performance in acute care delivery: A systems approach. Transactions on Automation Science and Engineering. 2014; 11(4).
3. National Collaborating Centre for Women's and Children's Health: Decision to delivery interval, 2011.
4. Pandya T, Mangalampally K. Critical care in obstetrics. Indian J Anaesth. 2018 Sep; 62(9): 724–733..
5. Departement of Health Royal Australian College of GP. Guidelines for Shared Maternity Care Affiliates. State of Victoria: Department of Health Royal Australiasn College of GP, 2010.
6. Miheso J, Burns S. Care of women undergoing emergency caesarean section; Emergency Cesarean Section Classification: 2015.
7. Tashfeen K, Patel M, Hamdi IM, et al. Decision-to-delivery time intervals in emergency caesarean

section cases. Sultan Qaboos Univ Med J. 2017 Feb; 17(1): e38–e42.
8. Gately R, San A. Kurtkoti J, Parnham A. Life-threatening pregnancy- associated atypical haemolytic uraemic syndrome and its response to eculizumab. Nephrology, 2017.
9. Morton CH, Van Otterloo RL, Marla J, et al. Translating maternal mortality review into quality improvement opportunities in response to pregnancy-related deaths in california. 2019;48(3): 252-62
10. Punches BE, Johnson KD, Acquavita SP, et al. Patient perspectives of pregnancy loss in the emergency department. International Emergency Nursing. 2019;43:61-6.
11. Williams AC, Craig KD. Updating the definition of pain. Pain. 2016;157(11):2420–3.
12. Duncan LG, Cohn MA, Chao MT et al. Benefits of preparing for childbirth with mindfulness training: a randomized controlled trial with active comparison. BMC Pregnancy Childbirth. 2017;17 (140)
13. Coates D, Makris A, Catling C, et al. A systematic scoping review of clinical indications for induction of labour. PLoS ONE. 2020;15(1): e0228196.
14. Sitras V, Šaltytė Benth J, Eberhard-Gran M. Obstetric and psychological characteristics of women choosing epidural analgesia during labour: A cohort study. PLoS ONE. 2017;12(10): e0186564.
15. Hatamleh R, Abujilban S, Shaker A, et al. The effects of a childbirth preparation course on birth outcomes among nulliparous Jordanian women. Midwifery. 2019;72:23-9.

ORIGINAL RESEARCH:

Emergency maternal referral worksheet as a clinical decision-making tool

Mochammad Hud Suhargono*
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Objective: This study aimed at discovering some different delivery outcomes from maternal emergency referral cases in referral health facilities (RHF) for those who used did not use Emergency Maternal Referral Worksheet (EMRW) at public health facilities (PHF).
Materials and Methods: This study was a quantitative research with observational case control. It used in-depth interviews to several health centers in Tuban by using Mann Whitney statistic test.
Results: The results of statistical test Mann Whitney, 161 referral cases were found to have p value of 0.036. It indicated significant differences in delivery outcomes. The differences were found in groups of mothers in mortality, high morbidity, and survived groups who used and did not use EMRW. Supporting and resisting factors from 22 respondents examined were socialization and technical support, leadership and supervision by the heads of PHF and Regional Health Ministry, as well as coordination and synergy among policy makers and related parties.
Conclusion: The use of EMRW affects the outcome of patients so that EMRW can be used as a clinical decision making tool in other maternal and non-maternal health services.

Keywords: Maternal mortality rate; EMRW; clinical decision making tools; referral decision support tools.

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk menemukan hasil persalinan yang berbeda dari kasus rujukan kegawatdaruratan ibu di rumah sakit rujukan bagi mereka yang menggunakan dan tidak menggunakan Emergency Maternal Referral Worksheet (EMRW) di puskesmas.
Bahan dan Metode: penelitian ini adalah penelitian kuantitatif dengan kontrol kasus observasional. Penelitian ini menggunakan wawancara mendalam ke beberapa puskesmas di Tuban dengan menggunakan uji statistik Mann Whitney.
Hasil: Pada 161 kasus rujukan, uji statistik Mann Whitney menunjukkan nilai p=0,036, yang berarti ada perbedaan signifikan pada hasil persalinan dalam kelompok ibu mortalitas, morbiditas tinggi, dan kelompok ibu yang bertahan hidup yang menggunakan EMRW dan tidak menggunakan EMRW. Faktor pendukung dan menolak dari 22 responden yang diteliti meliputi sosialisasi dan dukungan teknis, kepemimpinan dan pengawasan oleh kepala puskesmas dan Dinas Kesehatan Daerah, serta koordinasi dan sinergi di antara pembuat kebijakan dan pihak terkait.
Kesimpulan: Penggunaan EMRW mempengaruhi hasil pasien sehingga EMRW dapat digunakan sebagai alat pengambilan keputusan klinis di layanan kesehatan ibu dan layanan kesehatan lainnya.

Kata Kunci: AKI; EMRW; alat pengambil keputusan klinis; alat penunjang keputusan rujukan

***Correspondence:** Mochammad Hud Suhargono, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga, Dr Soetomo Hospital, Jl. Mayjen Prof. Dr. Moestopo 6-8, Surabaya 60286, Indonesia.
E-mail: drhudspog@gmail.com

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.6-12
● Maj Obs Gin. 2021;29:7-13 ● Received 30 Nov 2020 ● Revised 21 Jan 2021 ● Accepted 5 Feb 2021

INTRODUCTION

Maternal Mortality Ratio (MMR) in Indonesia is still high, especially in East Java Province. The high MMR reflects the low quality of health services especially maternal health services. The decline of maternal mortality occurred, but at the same time, the decline of life births in East Java was significant from 92.04 / 100, 000 in 2016 to 92.34/100,000 in 2017.[1]

One of the efforts to reduce significant MMR is by handling maternal complications especially quick and adequate treatment for emergencies.[2] Efforts to reduce MMR require an effective referral system, especially for emergency cases. One fundamental aspect of the referral system is an effective reciprocal communication between the first health facility and a higher referral health facility as it is reflected in an effective referral system in the area.[3]

Around 15% of pregnancies and deliveries will experience complications as maternal emergency cases. Even, some of them will cause mortality. Complications treated by hospitals require a continuum of care, such as a reciprocal service from community, primary health-care to the referral hospitals.

Adequate hospital services will not help much patients who had inadequate referral pre-treatment and arrived at the hospitals in bad conditions. A retrospective review of maternal mortality cases conducted by POGI in 2015 found that pre-referral stabilization in the first-level health facility was very low, only 50% of referral cases which had been pre-stabilized or adequately treated. Handling maternal emergency cases in the first-level health facility requires adequate clinical decision-making. If health staffs at the first-level healthcare fail to provide adequate treatment, it can cause severe maternal morbidity and even death.[4]

The Indonesian Ministry of Health in 2013 made an action plan to reduce the maternal mortality rate in Indonesia. One of the programs and activities is the Guaranteed Effective Referral Implementation Program for complication cases to ensure the availability of the referral guidelines by developing clear regional referral guidelines and operations in the first-level health facility.[5]

EMAS (Expanding Maternal and Neonatal Survival) program was introduced in Tuban District in 2015. Then, Antenatal Emergency Referral Worksheet was introduced as a clinical decision-making tool and written referral communication tool in 2016 at the first-level health facility. As a result, first-level health facilities can provide treatment based on the standards for maternal emergency cases.

The referral worksheet contains steps for handling pregnant women with complications in a form of check-lists to ease health staffs assess. In the first part of the check-list, they need to identify early symptoms of complications, initial structurally stable treatDment according to the medication standard, observation stages and final conditions referring to higher health facilities. The Antenatal Emergency Referral Worksheet is used as a medical record sheet and means of communication with the referral health facilities.

MATERIALS AND METHODS

The study was conducted in Tuban District, East Java in 2017 and invited pregnant mothers who were referred to a referral hospitals from 2016 to 2017. Maternity cases with emergency complication were referred to the referral public or private hospitals. These maternity cases were classified into survived pregnant mother, maternal morbidity, and maternal mortality.

The technique of data collection was random sampling with 161 samples including maternal cases with emergency complications (survived maternity, maternal morbidity, and maternal mortality) referred to the referral public or private hospitals. The quantitative data were collected by exploring the documentation data of medical records of pregnant women with emergency cases referred to the referral hospitals inside and outside Tuban District from 2016 to 2017. The observation was done by identifying the referring public health centers, prior referred patients' condition and the evidence of EMRW use in the hospital's archives.

Furthermore, the research collected qualitative data by crosschecking with the referee and patients with interview method. The interview was conducted in two stages. The early stage was conducted to 161 patients, and with the second stage was conducted to 22 public health staffs as referees and hospital officers as the referral health facilities.

The statistical test for observational case control assessed the correlation between nominal/categorical data of survived mother, high maternal morbidity and maternal mortality and the use of Antenatal Emergency Referral Worksheet by using the Mann-Whitney statistical test.

This research had passed ethic code test by the Ethics Committee of the Health Researchers of the Medical Faculty of Universitas Airlangga, Surabaya No.7/EC/

KEPK/FKUA/2018 with the title "The Analysis of Antenatal Emergency Referral Worksheet Associated with Delivery Outcomes in the Referral Hospitals: A Mix-method Research in Tuban District from 2016 to 2017.

RESULTS AND DISCUSSION

This study collected emergency cases of referral maternity at the first-level health services to three referral hospitals in Tuban from 2016 to 2017. The total samples who met the criteria were 161 cases consisting of 61 cases which did not use EMRW for referral pregnant mothers and 100 cases which used EMRW for referral pregnant mothers.

Quantitative Research Results

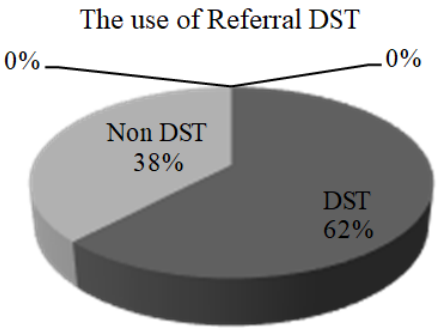


Figure 1. Percentage of EMRW usage (EMRW Referral) in Tuban District.

Based on Diagram 1, It can be interpreted that out of 161 referral cases that met the criteria, there were 61 cases (38%) which did not use EMRW referrals and 100 cases (62%) which had used EMRW referrals when referring to the referral hospitals. Distribution of referral cases in three referral hospitals in Tuban District shows that Koesmo Hospital had 53 referral cases, NU Hospital had 85 referral cases, and Muhammadiyah Hospital had 23 referral cases.

Based on Diagram 2, it illustrates the distribution and details of referral cases using or not using EMRW. At Koesmo Regional Hospital, out of 33% referral cases, only 16% cases did not use EMRW, and 17% cases used EMRW referred by public health centers or independently practical midwife. At NU Hospital, there were 14% cases that used EMRW out of 53% referral cases that met the criteria. Meanwhile, 8% referral cases at Muhammadiyah Hospital used EMRW, and 6% cases did not use EMRW.

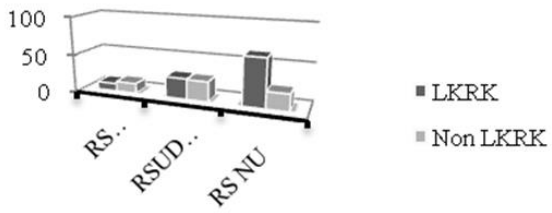


Figure 2. Distribution of referrals in three hospitals in Tuban District.

Table 1. Overview of cases referred to referral hospitals

	EMRW Use		
	Non EMRW	EMRW	Total Percentage %
Ages			
< 20	5 (3%)	11 (7%)	16 (10%)
20-30	34 (21%)	61 (37%)	95 (58%)
30-40	21 (13%)	26 (16%)	47 (29%)
40<	1 (1%)	2 (2%)	3 (3%)
Parity			
Primi	39 (24%)	75 (47%)	114 (71%)
2-3	17 (11%)	20 (12%)	37 (23%)
3<	5 (3%)	5 (3%)	10 (6%)
	EMRW Use		
	Non EMRW	EMRW	Total Percentage %
At the referral			
Ante Partum	31 (19%)	62 (38%)	93 (57%)
Intra Partum	25 (16%)	36 (22%)	61 (38%)
Post Partum	5 (3%)	2 (2%)	7 (5%)
Origin of referral			
Non Poned/BPM	48 (30%)	39 (24%)	87 (54%)
Poned	13 (8%)	61 (38%)	74 (46%)

Table 1 shows that 54% cases originally came from Non-PONED hospitals and 46% from BPM or Non-Poned. 24% of poned public health centers used EMRW, and 38% non-poned public health centers also used EMRW. 30% of non-poned public health centers have not used EMRW while only 8% of poned public health centers have not used EMRW.

Out of 57% cases were referred in ante partum stage, 38% were referred in intrapartum stage, and the remaining 5% was referred in post-partum stage. 38% cases referred in Antepartum mostly had used EMRW while the remaining 19% had not used EMRW referrals. In terms of age, there were 58% of 20-30 year-old patients, 29% of those aged 30-40 years old, 10% of those aged less than 20 years old, and 3% of those aged 40 years old at the referrals. In terms of parity, there were 71% primigravida cases, 23% parity 2-3 cases and 6% parity more than 3 cases. In terms of primigravida cases, 47% primigravida cases had used EMRW referrals.

Table 2. Referral cases that used EMRW and did not use EMRW for delivery outcomes

	Delivery outcome			
	Save	Morbidity	Mortality	Total Percentage %
Non DST	32 (20%)	23 (14%)	6 (4%)	61 (38%)
DST	54 (33%)	44 (27%)	2 (2%)	100 (62%)
Total	86 (53%)	67 (41%)	8 (6%)	161(100%)

Table 2 illustrates the delivery outcomes in using EMRW rather than without EMRW. There were three groups of delivery outcomes observed, namely survived pregnant mother, high maternal morbidity, and maternal mortality. From the total emergency referral cases, pregnant women who delivered safely were 53% which 33% used EMRW while 20% did not use EMRW for the referral. 27% pregnant women experienced high morbidity and used EMRW while 14% of those did not use EMRW. 6% cases came to mortality with only 2% cases using EMRW and 4% cases without EMRW at the referrals.

Qualitative research results

The result of quantitative case control study found that some public health centers used EMRW, but others did not in receiving patients to be referred to the referral hospitals. Both issues carried a qualitative research to identify the supporting factors and resisting factors in using EMRW.

This qualitative study involved 22 informants consisting of 8 informants from two out-patient and non-poned public health centers who had not used EMRW consisting of executive midwives, coordinating midwives, general doctors in charge and head of public health centers. Seven informants came from two inpatient and PONED public health centers that used EMRW referrals. These informant consist of executive midwives, independently practical midwives as a cadre of public health centers, regional coordinator midwives, general doctors in charge and head of public health centers. Seven informants from two referral hospitals consist of midwives in charge of maternity room and general doctors in charge of the maternity room and emergency installation.

Out of 15 respondents at the referral public health centers, the usage pattern, supporting factors, and resisting factors in using EMRW were found. Viewed from the use of EMRW, most of them have been actively using EMRW for referring to the hospitals. However, there are also respondents who used EMRW to refer patients, but the use of EMRW was still rare or ineffective. Meanwhile, there was a small percentage of those that never used EMRW in making referrals. They used maternal forms instead.

In terms of socialization, the majority had already got socialization as a support for the usage effectiveness and understanding of EMRW by midwife coordinators and team EMAS or Health Department of Tuban. Some also stated that they had already received socialization, but had a little knowledge about EMRW usage. In addition some respondents stated already god socialization, but did not understand about the use of EMRW. Even, some respondents never got a good socialization from the Health Department or midwife coordinator.

Based on the worksheet procurement as a running tool for ERMW, some respondents stated that EMRW procurement had been duplicated by the public health centers or midwife coordinator. In fact, the procurement was not available at the village health center or independent midwife's clinic. Whereas, most respondents stated that EMRW procurement had been duplicated and disseminated by the midwife coordinator as the stock could be found in their clinics.

Based on filling form of EMRW, few of them could not and did not know how to fill out and use EMRW. However, some of them already knew about EMRW sheet, but still have no idea how to use. They claimed to not refer patients when EMAS program was currently implemented. Some of them also ever heard about EMRW, but never saw EMRW sheet. However, most of them already knew and understood the use of EMRW sheets.

Based on archiving and reporting, most respondents stated that they had never filed EMRW either at the hospitals or in the first-level health facilities. However, few of them stated that they left the EMRW sheet in the hospitals and did not bring it back to the first-level health facilities, or they took from the public health centers and brought it back there. When the investigation was conducted, some data of EMRW in the hospitals were found, but they were not found in the public health centers as the first-level health facilities. However, some respondents also stated that they archived the data of EMRW in the public health centers and hospitals.

In terms of leadership role to enhance the use of EMRW, some respondents stated that the heads of the health centers still do not really support or monitor the use of EMRW in the first-level health facilities. However, some respondents stated that the heads supported the use of EMRW, but did not monitor its use. Most of respondents stated that the heads supported and monitored the use of EMRW in each health center.

Based on the hospital staff's response, most respondents stated that the staffs did not ask for EMRW referral, but they asked for only the maternal referral. Likewise, few respondents gave a good feedback since they understood about EMRW. Some respondents gave feedback by using EMRW as a treatment guidance. Nevertheless, some of them did not give any feedback since they never received patients who brought EMRW referral.

Based on the outcome of the patient, a number of respondents stated that the patients experienced mortality. A small proportion of respondents stated that patients had morbidity status after being referred to EMRW, and most respondents stated that the patients survived after being referred to EMRW.

Regarding the response towards the implementation of EMRW, some respondents said that using EMRW only add more duties to midwives who referred a patient. Meanwhile, a small part of respondents did not feel burdened when using EMRW. Most of respondents got easier and not burdened at all for using EMRW during the referral.

Based on the interview with the referral hospitals, in terms of input, such as referee's knowledge and understanding of EMRW, only a small percentage of respondents understood or knew the information, functions and uses. Meanwhile, most of them only knew information, but did not understand the function and use. There were also respondents who did not know the information about EMRW.

Based on the hospital's response, only a small proportion of respondents gave perfect feedback because they really understood EMRW. Nevertheless, there were also respondents who gave feedback by using EMRW as a guide for action, and some did not provide feedback because they did not know or never had patients bringing EMRW at the referral. Based on the usefulness of EMRW, the majority of respondents could monitor the treatment given by the referees, but some said EMRW was not that helpful.

In Table 3, the calculations of Mann-Whitney test showed H1 was accepted due to p value 0.036 <0.005, which means there was any significant difference between the use of EMRW with delivery outcomes.

In this study, there were different delivery outcomes between maternal emergency referral cases with EMRW and without EMRW having alpha <0.05. The observed delivery outcomes include survived pregnant mother, maternal morbidity and maternal mortality. Similar to research about the effect of using a surgical checklist, the decline of mortality was amounted from 1.5 % to 0.8%.[6]

Table 3. Results of Mann-Whitney statistical test analysis

Ranks

	DST Use	N	Mean Rank	Sum of Ranks
Delivery outcome	DST	100	75.81	7581.00
	Non DST	61	89.51	5460.00
	Total	161		

Statistical Test

	Maternal delivery outcome
Mann-Whitney U	2531.000
Wilcoxon W	7581.000
Z	-2.097
Asymp. Sig. (2-tailed)	0.36

a. Grouping variable: DST Use

This research also analyzed the data by using decision-making tools to determine non-Valvular Atrial Fibrillation patients who require anticoagulant or not. In conclusion, atrial fibrillation decision support tools were very helpful to predict the bleeding risk in the use of anticoagulants.[7] In addition, there was a study about the use of decision-making tools to determine which patients need implant defibrillators recommending their use.[8]

In qualitative research, the use of EMRW was proven to improve delivery outcomes from maternal emergency referral cases of survived pregnant mothers, maternal morbidity and maternal mortality. Therefore, it is expected that EMRW can be used in maternal emergency referral cases from the first-level health facilities to the referral hospitals. Until the end of 2017, 62% maternal emergency referral cases used EMRW referrals, so data were needed to find out the supporting factors and resisting factors for the use of EMRW.

Qualitative research was conducted to identify supporting and resisting factors from those that used EMRW and did not use EMRW referrals and maternal emergency referral cases at the hospitals. In transcribing the interview results from health staffs at the public health centers and referral hospitals, keywords of each issue were identified in terms of input, process, and output due to the use of EMRW.

The socialization and technical guidance for the use of EMRW at the public health centers were conducted to find out the supporting and existing factors on the use of EMRW. It showed that this was indispensable for the successful use of EMRW in all Tuban Districts. There were some differences of the method and socialization

frequency as well as the technical guide at the PONED PONED public health centers and non-PONED and non-treatment public health centers.

In the PONED public health centers, socialization and technical guide were better and were accomplished by all health staffs who were mentored by Health Department of Tuban and mentors from EMAS program in handling some cases. The mentoring program was carried out once year. When the program ended, EMRW was still being used due to an internalization process and had become a part of the standard steps for handling emergency cases at the public healt centers.

Unlike the non-PONED public health centers, the socialization from Health Department of Tuban was only conducted to representatives (the heads or senior midwives) from the public health centers, so the activity could vary widely in each public health center. For non-PONED public health centers, they did not get special technical guidance for real use of EMRW so that most health staffs did not understand the use of EMRW when there was an emergency patient in the public health centers.

Data about EMRW usage show that 54% of all referral cases came from non-PONED public health centers. Thus, socialization and technical guidance should not be differentiated for all public health centers in Tuban District. It is in accordance with the recommendations of the JHPIEGO-USAID 2000 Quality Assurance which said although EMRW as a Job Aids can improve the performance of health staffs, but organizational policy is needed as the most important factor that supports its successful implementation. The policy starts from the effort to get job aids from all health teams in all health facilities, improves the feedback process. There was theoretical and practical technical guidance for the implementation, and the development of job aids was tailored to the real conditions.[9]

Head of public health centers also supervised the implementation of EMRW to discover the supporting and resisting factor as important indicators to determine how successful the use of EMRW was at the public health centers. The leadership factor possessed by the heads of public health centers is needed to share vision in terms of motivating health staffs, providing understanding, supervising and monitoring the use of EMRW and as well as providing responses and solutions if there are obstacles in the implementation. The head of public health centers need to carry out budget allocation for the availability of RKRK sheet. The Society for Maternal-Fetal Medicine 2017 also recommended to periodically review the output of EMRW usage as a checklist of decision making tool at health facilities over the district as a top management level.[10]

In terms of emergency response by emergency team at a health facility, the American College of Obstetrician and Gynecologsts recommended the heads of health facilities have to prepare emergency equipment in one place (Trolly Emergency), build a responsive emergency team and effective communication aids among emergency teams in health facilities and referral health facilities, conduct emergency drills and emergency case simulations by using EMRW as a decision aid tool according to standards.[11]

The role of peer supervision in terms of health personnel compliance with health service guidelines is very important. Bedwell et al. studied the use of partograph as a clinical decision making tool by the midwives on-duty. They concluded that the knowledge, behavior of midwives and supervision from superiors greatly influence their performance in giving treatment to patients.[12]

A study by Islami concluded that the level of education, managerial function of the head at the public health centers and the personal motivation of midwives had a significant effect on the low implementation of the Standard Operating Procedure for early detection of preeclampsia at the public health centers in Surabaya.[13] Setiyana et al. in their study suggested to improve the head's perception about supervision by improving supervision techniques, preparation, and schedule.[14]

The synergy and synchronization EMRW with the standard flow of referrals and previous referral administration issues may be a resisting factor that also needs attention and resolution by coordinating with relevant institutions or creating new rules. Another study on the factors influencing healthcare service quality mentioned that leadership role at the policy-maker level and collaboration with other institutions are needed to develop coordination and program synchron-ization.[15]

The design and content of EMRW material that become an obstacle must also be continuously improved and monitored and evaluated for its use. From the quantitative data on the referral causes, it turns out that the case of Dystocia or Power Passage Passanger disorder during the delivery process was 14 % of all referral cases. There were also 14% other cases out of the total 28% cases unlisted in EMRW material Updated and redesign of EMRW should be executed to suit the needs of users. Periodic studies, assessment of the results of EMRW implementation, assessing compliance

and adaptation of health workers in the field need to be carried out.[16]

The results show the relationship between pregnant mothers who used EMRW as a referral and those with high morbidity and mortality. It illustrates that the use of EMRW can improve the quality of maternal delivery outcomes so that it is useful in improving emergency services in the first-level health facilities. In the implementation, not all first-level health facilities used EMRW. Some factors that influence the success and development of EMRW can be considered by improving socialization and technical guidance, leadership and supervision from the head of the public health centers and Health Department, coordination and synergy between policies and related institutions, the design and contents of EMRW material according to the users' needs of health staffs based on the results of regular evaluation and monitoring.

CONCLUSION

This study conclude from the Mann-Whitney statistical test that t there was a difference between the use of EMRW and patient output, with accepted H1 and p value 0.036 <0.005. There were significant differences in delivery outcomes between users of antenatal emergency referral worksheet and those who did not use it. The delivery outcomes observed in the study include survived pregnant mothers, severe maternal morbidity, and maternal mortality.

REFERENCES

1. Committee Opinion No. 683: Behavior that undermines a culture of safety. Obstet Gynecol. 2017; 129(1):e1-e4.
2. ACOG Committee Opinion No. 447: Patient safety in obstetrics and gynecology. Obstet Gynecol. 2009;114(6):1424-1427.
3. EMAS-USAID Program, 2015, Program Brief: Retrospective Review of Cases and Factors Associated with 112 Maternal Deaths in 12 Hospitals 2015
4. Dogma M, Fournier P. Human resource and the quality of emergency obstetric care in developing countries: a systematic review of the literature. Human Resources for Health.2009;7:7
5. Health Office of East Java Province. Kematian ibu dan bayi di Jawa Timur [Infant and maternal death in East Java]. Surabaya: Health Office of East Java Province; 2017
6. Haynes AB et al, 2009. A surgical checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009;360:491-9
7. Wess ML et al. Application of a decision support tool for anticoagulation in patients with non-valvular atrial fibrilation. J Gen Intern.Med 2007; 23(4):611-7
8. Caroll SL, McGillion M, Stacey D, et al. 2013, Development and feasibility testing of decision support for patients who are candidates for a prophylactic implantable defibrillator: a study protocol for a pilot randomized controlled trial. Trials 2014;14:346
9. Knebel E, Lundahl S, Wilson N, et al. The use of manual job aids by health care providers, What do we know? Quality Assurance Project. 2000:1.
10. Ash JS, Stavri PZ, Kuperman GJ. A concensus statement on consideration for a succesful CPOE implementation. J Am Med Inform Assoc. 2003;10:229-34.
11. ACOG Committee Opinion No. 487: Preparing for clinical emergencies in obstetrics and gynecology. Obstet Gynecol. 2011;117(4):1032-34.
12. Bedwell C, Levin K, Pett Celia, 2017. A realist review of the Partograph: when and how does it work of labour monitoring? BMC Pregnancy and Cildbirth. 2017;17:31.
13. Islami D. Faktor yang mempengaruhi kepatuhan bidan terhadap pelaksanaan SOP deteksi dini preeklamsia di Puskesmas Kota Surabaya [Factors affecting midwives' compliance to preeclampsia early detection procedure at PHF in Surabaya] [Thesis]. Surabaya: Universitas Airlangga; 2016.
14. Subekti SS, et al, 2014, Faktor-faktor yang mempengaruhi kinerja bidan desa dalam penerapan standar asuhan kebidanan ibu bersalin di Kabupaten Semarang [Factors affecting village midwives' performance in applying midwivery care standard for partus mothers in Semarang District]. Jurnal Manajemen Kesehatan Indonesia. 2014;2(2):116-22.
15. Mosadeghard AM. Factors influencing healthcare service quality. Int J Health Policy Manag. 2014; 3(2):72-89.
16. Bernstein PS et al. The development and implementation of checklist in obstetrics. Society for Maternal-Fetal Medicine (SMFM) Special Report. 2017. Elsevier Inc.

ORIGINAL RESEARCH:

Comparison of pregnancy rates on day 3 and day 5 embryo transfer in In Vitro Fertilization (IVF)

Audia Mumtaz Rifasky[1], Puspa Wardhani[2], Ashon Sa'adi[3], Ninik Darsini[4], Hamdani Lunardhi[4], Zakiyatul Faizah*[4]

[1]Medical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia [2]Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia. [3]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga Dr. Soetomo General Hospital, Surabaya, Surabaya, Indonesia.[4]Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

ABSTRACT

Objectives: To identify the success rates of pregnancy on the third and fifth day embryo transfer at Graha Amerta Hospital, Surabaya, Indonesia.
Materials and Methods: This study used comparative cross sectional design. Data were taken from medical record of IVF participants who met the inclusion and exclusion criteria at Graha Amerta Hospital for the period of January 2016 - December 2016.
Results: Successful pregnancy rates were found in this research. The embryo transfer on the third day and the fifth day were 35% and 49.3% respectively. In other words, the rates of pregnancy success were not affected by embryo transfer on the third day and the fifth day in the medical record sample as it had p value of 0.090.
Conclusion: Embryo transfer on the third and fifth days had the same rates of pregnancy success in IVF participants at Graha Amerta Hospital, Surabaya, Indonesia.

Keywords: IVF; day 3; day 5; embryo transfer

ABSTRAK

Tujuan: untuk mengetahui tingkat keberhasilan kehamilan pada embrio transfer hari ketiga dan kelima di RS Graha Amerta, Surabaya, Indonesia.
Bahan dan Metode: Penelitian ini menggunakan studi analisis komparasi n (comparative study) cross section. Data yang digunakan yaitu rekam medis peserta IVF yang memenuhi kriteria inklusi dan eksklusi di RS Graha Amerta periode Januari 2016 – Desember 2016.
Hasil: Tingkat kehamilan yang berhasil ditunjukkan dalam penelitian ini, yaitu transfer embrio pada hari ketiga dan hari kelima adalah 35% dan 49,3% masing-masing. Dengan kata lain tingkat keberhasilan kehamilan tidak terpengaruh oleh transfer embrio pada hari ketiga dan hari kelima dalam sampel rekam medis. Hal ini dapat dilihat dari nilai P yang bernilai 0,090. jika diambil 0,05.
Simpulan: Transfer embrio pada hari ketiga dan kelima memiliki tingkat keberhasilan kehamilan tidak bermakna pada peserta IVF di RS Graha Amerta, Surabaya, Indonesia.

Kata kunci: IVF; hari ke 3; hari ke 5; transfer embrio

***Correspondence:** Zakiyatul Faizah, Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Jalan Prof dr Moestopo 47, Surabaya 60131, Indonesia. E-mail: faizbiomed@yahoo.com

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.13-16
● Maj Obs Gin. 2021;29:14-17 ● Received 29 Dec 2020 ● Revised 9 Feb 2021 ● Accepted 26 Feb 2021

INTRODUCTION

Currently, infertility rate in Indonesia is 10-20% of married couples, and from the 10% it turns out that 10% -20% need Assisted Reproductive Technology (ART), including the newly developed In-Vitro Fertilization (IVF), which is now widely used for infertility treatment.[1] Infertility is defined as a condition marked by attempts to have regular sexual relations by not using protector and establishing a clinical pregnancy for 12 months but ending in failure and also because an individual or the partner has disability to reproduce.[2] The simple understanding of IVF is the removal of the ovum out from the ovary and then integrating it with the sperm cells in the laboratory to become an embryo.[1] In its implementation, embryo transfer is the phase that is considered to determine the success, while the pre- or post transfer activities are also very influential in its success. In general, embryo transfer is carried out on 5th day when the embryo enters blastocyst stage.[3] Because the longer the IVF process, the more difficult to breed the embryo until day 5, the embryo transfer is carried out on day 3, although at that time the implant rate is relatively low.[4] One study suggest that pregnancy rates and high implantation can be achieved by embryo transfer on day 3 and day 5. The level of implantation on third and fifth day of transfer is the same.[5] These studies were conducted to observe IVF outcomes where high positive success rate of beta-hCG and embryo transfer played an important role for this success. Thus, the best most suitable embryos were planted on day 3 and day 5. The main aim of this study was to analyze the success rates of pregnancy on the third and fifth day embryo transfer at Graha Amerta Hospital, Surabaya, Indonesia.

MATERIALS AND METHODS

This study used a comparative cross-sectional design, which used total sampling of IVF participants at Graha Amerta Hospital, Surabaya, in 2016. Data were collected using medical records, which had been subjected to inclusion and exclusion criteria. The data were entered in Microsoft Excel and analyzed statistically using SPSS 16. This study received ethical approval from the Health Research Ethics Commission of the Dr. Soetomo Hospital, Surabaya, with ethical clearance letter number: 0705/KEPK/X/2018.

RESULTS AND DISCUSSION

From medical records of January 2016 - December 2016, 256 data were obtained but only 139 samples of IVF participants in Graha Amerta Hospital, Surabaya, Indonesia, who had completed medical record data and matched the inclusion and exclusion criteria. The sample needed were those with details of beta-hCG transfer embryos on third day and beta-hCG embryo transfer on fifth day. Data on IVF participants are presented in Table 1 and Table 2, showing p value of >0.05 that there are no significant difference between embryos transfer on third day and embryos transfer on fifth day with pregnancy success rates in medical record samples. This finding was in line with a study by Dahiya et al. who found that embryo transfer day did not affect initial beta-hCG value.[6] However, another previous study did show that the stage of embryo development was affected significantly by embryo transfer day 3 or embryo transfer day 5.[7]

The embryonic cell division stage, which divided into 8 cells, 10 cells, 12 cells, 16 cells, morula and blastosis when it met the time of embryo transfer in IVF process, also does not affect the success rate of pregnancy. The same response was also shared by other researchers that live births and pregnancy success rates for embryo transfer at the blastocyst phase were the same as embryo transfer during the cleavage phase.[8] However, there are also other studies that proved that the blastocyst phase could produce higher pregnancy success rates compared to other stages of embryonic cell division.[9] Other studies suggest that the quality of embryo seen on the third day is one of the most effective predictors for determining pregnancy success, but the combination of parameters would be better as a predictor of pregnancy success.[10,11] The same opinion shows that implantation in embryo transfer on the third day significantly illustrates better outcomes at clinical pregnancy rates and is a good benchmark for providing information and helps in distinguishing good embryonic morphology as candidates for embryos transfer.[12]

Because the third day can be expressed as a predictor, if the embryo produced is good and abundant on the third day, it can be waited for and developed until the blastocyst stage and then the embryo transfer can be carried out. However, if on the third day the embryos are produced less and of poor quality, it is better to transfer embryo at that stage since the condition of embryonal development in the endometrium is much better than outside. Therefore, the embryo can be planted before the blastocyst stage and still be successful because the embryo and endometrium are in a good condition. However, other studies have suggested that pregnancy outcomes after the fifth day embryo transfer resulted in a higher value than the third day embryo transfer.[13,14] There is a similarity in opinion that the transfer of blastocysts or embryo to day 5 transfers produce fewer embryo transferred. It results in a higher implantation rate, and increases clinical

pregnancy rates.[15] This was in line with other studies which found that extending embryo culture to day 5 can be a better strategy for identifying and selecting groups of embryos with a higher overall probability of success for implantation.[16] Embryo implantation is a complex process. Improved clinical results have been seen with blastocyst transfer compared to cleavage phase embryos. Given the available evidence, improved results are seen after the 5th day embryo transfer.[17]

Table 1. Data embryo transfers on the 3rd and 5th day of IVF process with the success rate of pregnancy

Embryo Transfer 3rd day or 5th day	β-hcg positive (≥ 25 IU)	β-hcg negative (≤ 25 IU)	p
ET day 3	21(9.06)	39(16.8)	
ET day 5	39(22.1)	40(22.7)	0.090

Table 2. Data on pregnancy success rates and the stage of division in the embryo of the IVF process

Pregnancy	β-hcg positive (≥ 25 IU)	β-hcg negative (≤ 25 IU)	p
Blastosis	34(17.6)	36	
Morula	2(0.05)	2(0.05)	
16 cells	3(0.06)	0(0)	0.298
12 cells	9(1.73)	17(3.27)	
10 cells	1(0.01)	1(0.01)	
8 cells	9(1.67)	16(2.96)	

CONCLUSION

It was found that embryo transfer on third and fifth day lead to the same rates of pregnancy success in IVF participants in Graha Amerta Hospital, Surabaya.

ACKNOWLEDGMENT

We express our gratitude to the Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Airlangga ,Dr. Soetomo Hospital, Surabaya and to the Infertility Clinic, Graha Amerta Hospital, Surabaya.

REFERENCES

1. World Health Organization (WHO). WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge: Cambridge University Press; 2000.
2. Van der Borght M, Wyns C. (2018). Fertility and infertility: Definition and epidemiology. Clinical Biochemistry. 2018;62:2-10.
3. Spitzer D, Haidbauer R, Corn C, et al. Effects of embryo transfer quality on pregnancy and live birth delivery rates. Journal of Assisted Reproduction and Genetics. 2011;29(2):131-5.
4. Edwards RG, Brody SA. History and ethics of assisted human conception. In: Principles and practice of assisted human reproduction. Philadelphia: Saunders; 1995, p. 17–47.
5. Hatırnaz Ş, Kanat Pektaş M. Day 3 embryo transfer versus day 5 blastocyst transfers: A prospective randomized controlled trial. Turk J Obstet Gynecol. 2017;14(2):82-8.
6. Dahiya M, Rupani K, Yu S, et al. Embryo transfer day does not affect the initial maternal serum beta-hCG levels: A retrospective cohort study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2017;212:75-9.
7. Papanikolaou. Rbmojournal; 2018 [cited 2018 Oct 18] Available from https://www.rbmo journal. com/article/S1472-6483(10)60981-9/pdf
8. Martins WP, Nastri CO, Rienzi L, et al. Blastocyst vs cleavage-stage embryo transfer: systematic review and meta-analysis of reproductive out-comes. Ultrasound Obstet Gynecol. 2017;49(5): 583-91.
9. Kaartinen N, Das P, Kananen K, et al. (2015). Can repeated IVF–ICSI-cycles be avoided by using blastocysts developing from poor-quality cleavage stage embryos? Reproductive BioMedicine Online. 2015;30(3):241-7.
10. Lee C, Lee T, Huang C, et al. Detection of early cleavage embryos improves pregnancy and delivery rates of Day 3 embryo transfer during I in vitro fertil-ization. Taiwanese Journal of Obstetrics and Gynecology. 2016;55(4):558-62.
11. Herbemont C, Sarandi S, Boujenah J, et al. Should we consider day-2 and day-3 embryo morphology before day-5 transfer when blastocysts reach a similar good quality? Reproductive BioMedicine Online. 2017;35(5):521-8.
12. Adamson G, Abusief M, Palao L, et al. (2016). Improved implantation rates of day 3 embryo transfers with the use of an automated time-lapse–enabled test to aid in embryo selection. Fertility and Sterility. 2016:105(2);369-375.e6.
13. Kumbak B, Oral E, Karlikaya G, et al. Serum oestradiol and beta-HCG measurements after day 3 or 5 embryo transfers in interpreting pregnancy outcome. Reprod Biomed Online. 2006;13(4):459-64.
14. Racowsky. rbmonline.com. [internet] Rbmonline. com. [cited 2018 Oct 18] Available at: http://www. rbmonline.com/Article/807
15. Revelli A, Canosa S, Carosso A, et al. Impact of the addition of Early Embryo Viability Assessment to morphological evaluation on the accuracy of

embryo selection on day 3 or day 5: a retrospective analysis. J Ovarian Res. 2019;12(1):73.
16. Mastenbroek S, van der Veen F, Aflatoonian Aet al. Embryo selection in IVF. Hum Reprod. 2011;26(5):964-6.
17. Tiegs A, Franasiak J. The embryo day 3 versus day 5 ET. Encyclopedia of Reproduction. 2018; p. 278-83.

ORIGINAL RESEARCH:

Antibiotic sensitivity on pathogenic bacteria causing bacterial vaginosis

Shiwi Linggarjati[1*], Dita Diana Parti[2], Elly Nurus Sakinah[3*]
[1]Medical Program, University of Jember, Jember, Indonesia, [2]Laboratory of Obstetrics Gynecology, Faculty of Medicine, University of Jember, Jember, Indonesia, [3]Laboratory of Pharmacology, Faculty of Medicine, University of Jember, Jember, Indonesia

ABSTRACT

Objectives: To identify the sensitivity of antibiotics to pathogenic bacteria that cause Bacterial Vaginosis (BV).
Materials and Methods: This type of research was an observational study with a sample of six specimens. The data were taken using primary data from patients who were swabbed in the vagina and then diagnosed BV with amsel criteria on vaginal secretion specimens carried out at Tanggul health center on January 23-February 23, 2020. The specimens were sent to Parahita Clinical Laboratory for bacterial identification and adjusted for sensitivity with CLSI using vitek 2 compact tool.
Results: The results of this study identified the bacteria that caused bacterial vaginosis, the *E. coli* and *K. pneumoniae* with one sample of suspected ESBL. ESBL is a beta lactamase enzyme produced by bacteria and can induce bacterial resistance to penicillin, cephalosporin generation 1, 2, and 3. The types of bacteria found were *E. coli* and *K. pneumoniae* with high sensitivity antibiotics tested including piperacillin/tazobactam, ceftazidime, cefepime, ertapenem, meropenem, amikacin, gentamicin, tigecycline, and nitrofurantoin. Antibiotics with high levels of resistance tested against these bacteria included: ampicillin, amoxicillin, and ampicillin/sulbactam due to the mechanism of beta-lactam antibiotic resistance in the production of beta lactamase from bacteria.
Conclusion: The type of bacteria found was *E. coli* and *K. pneumoniae* with high resistance levels in beta lactam antibiotics.

Keywords: Bacterial vaginosis; sensitivity; antibiotics; amsel criteria

ABSTRAK

Tujuan: Mengetahui sensitivitas antibiotik terhadap bakteri patogen penyebab Vaginosis Bakterialis khususnya Jember.
Bahan dan Metode: Jenis penelitian yang digunakan merupakan penelitian observasional dengan jumlah sampel 6 spesimen. Data diambil menggunakan data primer dari pasien yang di swab vaginanya lalu didiagnosis BV dengan kriteria amsel pada spesimen sekret vagina yang dilakukan di Puskesmas Tanggul pada tanggal 23 Januari-23 Februari 2020. Spesimen kemudian dikirim ke Laboratorium Klinik Parahita untuk identifikasi bakteri serta melihat sensitivitasnya yang disesuaikan dengan CLSI menggunakan alat vitek 2 compact
Hasil: Hasil penelitian ini teridentifikasi bakteri penyebab vaginosis bakterialis yaitu *E. coli* dan *K. pneumoniae* dengan terdapat satu sampel suspek ESBL dimana ESBL merupakan enzim beta laktamase yang diproduksi oleh bakteri dan dapat menginduksi resistensi bakteri terhadap penisilin, sefalosporin generasi 1, 2, dan 3. Jenis bakteri yang ditemukan adalah *E. coli* dan *K. pneumoniae* dengan antibiotik dengan sensitivitas tinggi yang diujikan antara lain: piperacilin/tazobactam, ceftazidime, cefepime, ertapenem, meropenem, amikacin, gentamicin, tigecycline, dan nitrofurantoin. Antibiotik dengan tingkat resistensi tinggi yang diujikan terhadap bakteri tersebut antara lain: ampicillin, amoxicillin, dan ampicillin/sulbactam akibat mekanisme resistensi antibiotik beta-laktam pada produksi beta lactamase dari bakteri.
Simpulan: Jenis bakteri yang ditemukan adalah *E. coli* dan *K. pneumoniae* dengan tingkat resistensi tinggi pada antibiotik golongan beta lactam.

Kata kunci: Vaginosis bakterialis; sensitivitas; antibiotik; kriteria amsel

***Correspondence:** Elly Nurus Sakinah, ellyns.fk@unej.ac.id ; Shiwi Linggarjati, Cempaka Street No. 17A, E-mail: shiwilinggarjati@gmail.com

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.17-21
● Maj Obs Gin. 2021;29:18-22 ● Received 5 Jan 2021 ● Revised 17 Feb 2021 ● Accepted 5 Mar 2021

INTRODUCTION

Bacterial vaginosis (BV) is a disease in vaginal infections caused by infection with a group of pathogenic bacteria due to an imbalance of the normal flora in the vaginal mucosa in the form of a shift in the number of *Lactobacillus bacteria* colonies that are replaced with various pathogenic bacteria such as *E. coli, Gardenella vaginalis, Mycoplasma hominis,* and *Mycoplasma curtisii*.[1] The first-line therapy in BV management is metronidazole and can also use clindamycin as a second-line therapy.[2] The prevalence and distribution of bacteria that cause BV varies in populations throughout the world. 20-30% of women with vaginal discharge experience BV even though the prevalence can increase to 50-60% in populations of high-risk sexual behavior.[3] Success rates for therapy are often low due to antibiotic resistance or the use of antibiotics that are not in accordance with the etiology so an antibiotic sensitivity test is needed.[4] This study aims to determine the sensitivity of antibiotics to pathogenic bacteria that cause Bacterial Vaginosis, especially in Jember so that it can be a guideline for clinicians in using the medical choice as a choice of empirical BV therapy and can reduce antibiotic resistance caused besides to determine the characteristics of age, occupation, use of tools contraception, and personal hygiene of BV patients.

MATERIALS AND METHODS

This type of research was an observational study with a sample of 6 specimens that had inclusion criteria as follows: married, did not take antibiotics for fourteen days, and signed an informed consent. The exclusion criteria were damaged and unreadable sample.[5] Data were taken using primary data from patients who were swabbed in the vagina and then diagnosed with BV with amsel criteria, namely by looking at the color of abnormal vaginal secretions, pH, whiff tests, and clue cells in vaginal secretion specimens on vaginal secretion specimens conducted at Tanggul Public Health Center on January 23 - February 23, 2020.[6] The specimens are then sent to the Parahita Clinical Laboratory for bacterial identification and see which sensitivity is said to be sensitive if the bacteria are able to be inhibited by antibiotics with minimal concentrations (MIC) adjusted to CLSI using vitek-2 compact tool.[7]

RESULTS AND DISCUSSION

This research was conducted on January 23 to February 23, 2020 at Tanggul public health center and Parahita Jember Clinical Laboratory. The characteristics of the sample were obtained from six patients who met the criteria of the study sample with the largest age range of four people (66.6%) at the age of 46-55 years. The most occupational distribution of BV patients was found four people (66.7%) had jobs as housewives. Diagnosis with amsel criteria is positive if 3 out of 4 positive criteria are obtained. Table 3 shows six colors of 100% homogeneous white vaginal discharge, pH above 4.5 (100%), positive whiff test (16.7%), negative whiff test (83.3%), and positive clue cell (100%).

Table 1. Distribution of characteristics of the study sample

Characteristics	Total (n)	Percentage (%)
Ages		
26-35	1	16.7
36-45	1	16.7
46-55	4	66.6
Occupation		
Housewife	4	66.7
Farmer	2	33.3
Amsel criteria		
Vaginal discharge color		
Clear	0	0
Yellowish white and homogeneous	6	100%
pH		
<4.5	0	0
>4.5	6	100%
Whiff test		
Positive	1	16.7%
Negative	5	83.3%
Clue Cell		
Positive	6	100%
Negative	0	0
Type of contraception		
IUD	0	-
Hormonal	4	66.7%
No contraception	2	33.3%
Personal Hyegine		
Smoke		
Yes	0	0%
No	6	100%
Douching		
Yes	3	50%
No	3	50%
Change panties		
≥3x a day	0	0%
<3x a day	6	100%
Use of antibiotic		
Metronidazole	3	50%
Amoxicillin	1	16.6%
Not given antibiotic	2	33.3%

The results of the most use contraceptives in BV patients found four people using hormonal contraception by 66.7. The distribution of personal hygiene risk factors for BV patients found as many as six patients did not smoke (100%), as many as 50% of patients did douching, as well as the frequency of changing panties every day <3x a day by 100%. There are 2 types of antibiotics given to patients, namely metronidazole

(50%) and amoxicillin (16.6%) and not given antibiotics as many as 2 people (33.3%) which can be seen in Table 1.

In this study obtained two bacterial species from culture results with positive growth which can be seen in Table 2. The culture results from vaginal secretion specimens found five species of *E. coli* bacteria (83.3%) and one species of bacteria *K. pneumoniae* (16.6%). Based on gram staining obtained overall six gram negative bacteria.

Table 2. Types of bacteria that cause vaginosis bacterialis

Bacterial species	Total	Percentage
E. coli	5	83.3%
K. pneumoniaee	1	16.6%

The results of the sensitivity test of bacteria that grew came from the results of bacterial culture using vitek 2 compact. The antibiotics tested were different for each bacterial species as shown in Table 3. Of the five species of *E. coli* identified, two *E. coli* bacteria are sensitive to Amoxicillin, Ampicillin, Ampicillin/ Sulbactam, and Trimethoprim/Sulfamethoxazole. Three out of five bacteria are sensitive to Ciprofloxacin. Four of the five bacteria are sensitive to Cefazolin Urine, Cefotaxime, Ceftriaxone, and Azretonam. Five *E. coli* bacteria are sensitive to Piperacillin/Tacobactam, Ceftazidine, Cefepime, Ertapenem, Meropenem, Amikacin, Gentamicin, Tigecyline, and Nitrofurantoin. Four of the five *E. coli* bacteria found to have intermediate sensitivity levels to other cefazolin antibiotics. While one in five bacteria have resistance to urine Cefazolin, Cefazolin other, cefotaxime, ceftriaxone, and azretonam. Two out of five bacteria have resistance to ciprofloxacin, and three out of five bacteria have resistance to amoxicillin, ampicillin, ampicillin/ sulbactam, and trimethoprim/sulfamethoxazole. One in five *E. coli* bacteria suspected ESBL.

The results of the bacterial sensitivity test for *K. pneumoniae* to bacteria are shown in Table 3. In this bacterium found resistance to Amoxicillin and Amicillin. The sensitivity results showed intermediates on other cefazolin antibiotics as well as being sensitive to antibiotics Ampicillin/Sulbactam, Piperacillin/ Tazobactam, cefazolin urine, cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam, ertapenilin, meropenem, cefazolin tincture, cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam, ertapenem, meropenem, cefazolin tint, cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam, ertapenem, meropenem, amylacinline, cefotazidime, amikacin line, cycloxin, cycloxin/sulfamethoxazole. The bacterium *K. Pneumoniae* is also negative for ESBL suspects.

Overall the sensitivity level of *E. coli* bacteria to antibiotics is 75.79%, the intermediate level is 4.21%, and the resistance level is 20% with a positive suspicion of ESBL of 20% and negative ESBL of 80% while the sensitivity level of bacteria *K. pneumoniae* for antibiotics at 84.21%, intermediate levels at 5.26%, and resistance levels at 20% with positive ESBL suspects of 0% and negative ESBL at 100% as shown in Tabel 4.

Table 3. Results for bacterial sensitivity to antibiotics

Antibiotic		*E. coli*					*K. pneumoniae*
ESBL		NEG	NEG	POS	NEG	NEG	NEG
AMC	Amoxicillin	R	S	R	S	R	R
AMP	Ampicillin	R	S	R	S	R	R
AMS	Ampicillin/Sulbactam	R	S	R	S	R	S
PTZ	Piperacilin/Tazobactam	S	S	S	S	S	S
CFZ URINE	Cefazolin Urine	S	S	R	S	S	S
CFZ OTHER	Cefazolin Other	I	I	R	I	I	I
CTZ	Cefotaxime	S	S	R	S	S	S
CAZ	Ceftazidime	S	S	S	S	S	S
CTR	Ceftriaxone	S	S	R	S	S	S
CPM	Cefepime	S	S	S	S	S	S
AZT	Aztreonam	S	S	R	S	S	S
ETP	Ertapenem	S	S	S	S	S	S
MEM	Meropenem	S	S	S	S	S	S
AMK	Amikacin	S	S	S	S	S	S
GM	Gentamicin	S	S	S	S	S	S
CIP	Ciprofloxacin	S	S	R	S	R	S
TGC	Tigecycline	S	S	S	S	S	S
FD	Nitrofurantoin	S	S	S	S	S	S
SXT	Trimethoprim/Sulfamethoxazole	S	R	R	S	R	S

Table 4. Antibiotic sensitivity level

Bacterial species	S (%)	I (%)	R (%)	ESBL + (%)	ESBL - (%)
E. coli	75.79	4.21	20	20	80
K. pneumoniaee	84.21	5.26	20	0	100

This study was conducted in patients with a diagnosis of bacterial vaginosis at the Tanggul Health Center in Jember. The number of research samples with female sex 46 years and over (66.6%) more than the age of 46 years and under. This is supported by a research by Bitew et al. (2017) which states that the proportion of bacterial vaginosis is highest in women aged over 46 years.[5]

In the distribution of amsel criteria, the color of yellowish white to gray secretions is found as well as homogeneous white color, this is supported by the theoretical basis stated.[8] In the pH criteria it is found that the pH is more than 4.5, the positive result is supported by the research of Mohammadzadeh et al. (2015) which states that the measurement of pH ≥4.5 is the second highest sensitivity after the presence of a clue cell with a sensitivity value of 97% this is due to a decrease in the number of normal flora of Lactobacillus. The clue cell criteria were obtained 100% in 6 samples where the clue cell was a buildup of bacteria in the vaginal epithelium so that the vaginal epithelium appeared granulated under a microscope. In the research of Mohammadzadeh et al. (2015) stated that clue cells in vaginal secretions have the highest sensitivity for diagnosis of BV, which is 97.6%.[6,8]

In the results obtained the use of vaginal douching by (50%). This is consistent with research by Ranjit et al., 2018 which states that douching was found in 55.8% of cases of BV with a significant result of 0.015%. The use of vaginal douching on a regular basis can cause disruption of the normal vaginal flora ecosystem, Lactobacillus so that it can increase vaginal pH and be a risk factor for bacterial vaginosis.[8] The results obtained as many as 100% of samples to change the underwear ≤3x a day. This is supported by research by Ernawati et al. (2013) about the risk of changing underpants to the incidence of bacterial vaginosis which shows a significant relationship with the specific frequency of changing underpants at least 3 times a day with the incidence of BV.[9,10]

The use of antibiotics in the samples examined is in accordance with the theory of using metronidazole (75%). Research conducted by Ara et al. (2017) states that metronidazole resistance in *Gardnerella vaginalis* is 52.63% where this resistance is quite high and always increases every day, this can be caused by the use of antibiotics that are not rational or due to the use of antibiotics that are not in accordance with the etiology due to the presence of pathogenic bacteria other. In this study the pathogenic bacteria found were *E. coli* and *K. pneumoniae*. Research on the sensitivity of metronidazole to *E. coli* has been carried out and the results obtained from 31 samples examined, only 5 samples that are sensitive to metronidazole, while 26 others are resistant so that in the treatment of metronidazole against *E. coli* can often recur.[11,12]

The highest levels of *E. coli* resistance found in this study were broad spectrum antibiotics that were often used including amoxicillin (60%), ampicillin (60%), Ampicillin/sulbactam (60%), and trimethoprim sulfamethoxazole (60%). High levels of resistance to amoxicillin, ampicillin, or ampicillin/sulbactam are supported by Anago et al. (2015) in which the study mentioned resistance to amoxicillin (95.2%) and ampicillin (97.6%) due to the mechanism of beta-lactam antibiotic resistance in the production of beta lactamase from *E. coli*. In addition to the beta lactam group, it was also mentioned in the results that the resistance of *E. coli* to ciprofloxacin was (40%). Ciprofloxacin resistance to Gram-negative bacteria has been reported to increase in recent years due to excessive and inappropriate use of drugs, especially at low doses and single therapy.[13,14]

K. pneumoniae is one of the bacteria that currently has a high level of antibiotic resistance due to changes in the genome of the organism's core and can produce beta-lactamase which can cause hydrolysis of beta-lactam ring on antibiotics, this is found in the results that isolate *K. pneumoniae* is resistant against amoxicillin and ampicillin (20%). In addition, ESBL in *K. pneumoniae* has also been reported in Europe in 1983 and the United States in 1989 where this ESBL can hydrolyze oxyimino cephalosporin which causes third generation cephalosporins are no longer effective against ESBL treatment.[15]

In the identification results found a suspicion of ESBL (Extended-spectrum -lactamase) positive where ESBL is a beta lactamase enzyme produced by bacteria and can induce bacterial resistance to penicillin, generation 1, 2, and 3 cephalosporins, and aztreonam (except cephwhiff and carbapenem) by hydrolyzing antibiotics where the antibiotic can inhibit β-lactamase with β-lactamase inhibitors for example clavulanic acid. ESBL ESBL is produced by gram-negative bacteria, for

example the family Enterobacteriaceae which is a normal intestinal flora where this bacterium has been resistant to beta lactam antibiotics and is one of the main causes of bacterial infections in hospitals or in the community.[16]

CONCLUSION

The types of bacteria that cause bacterial vaginosis found were *E. coli* (83.3%) and *Klebsiella pneumoniae* (16, 6%). High sensitivity antibiotics tested against *E. coli* and *Klebsiella pneumoniae* bacteria include piperacillin/tazobactam, ceftazidime, cefepime, ertapenem, meropenem, amikacin, gentamicin, tigecycline, and nitrofurantoin. Antibiotics with a high level of resistance tested against *E. coli* and *Klebsiella pneumoniae* bacteria include ampicillin, amoxicillin, trimethoprim/sulfamethoxazole, and ampicillin/sulbactam.

ACKNOWLEDGMENT

Thank you to the Tanggul Public health center staff who have given permission to conduct research there and thank the Medical Faculty, Jember University for the opportunities and facilities provided so that this thesis can be completed.

REFERENCES

1. Kumar K, Behera B, Sagiri SS, et al. Bacterial vaginosis: Etiology and modalities of treatment-abrief note. Journal of Pharmacy and Broallied Science. 2011;3(4):496-503.
2. Machado D, Castro J, Palmeira-de-Olieveira A, et al. Bacterial vaginosis biofilms: Challenges to current therapies and emerging solutions. Frontiers in Microbiology. 2016;6(1528):1-13.
3. Bautista CT, Wurapa E, Sateren WB, et al. Bacterial vaginosis: a synthesis of the literature on etiology, prevalence, risk factors, and relationship with chlamydia and gonorrhea infections. Military Medical Research. 2016;3(4):1-10.
4. Permanasari DA, Sakinah EN, Santosa A. Aktivitas ekstrak etanol daun cincau hijau (*Cyclea barbata* Miers) sebagai penghambat pembentukan biofilm bakteri *Salmonella typhi*. Journal of Agromedicine and Medical Science. 2016;2(2): 24-27.
5. Bitew A, Abebaw Y, Bekele D, et al. Prevalence of bacterial vaginosis and associated risk factors among women complaining of genital tract infection. International Journal of Microbiology. 2017:1-8.
6. Mohammadzadeh F, Dolatian M, Jorjani M, et al. Diagnostic value of amsel's clinical criteria for diagnosis of bacterial vaginosis. Global Journal of Health Science. 2015;7(3):7-14.
7. Prihatini, Aryanti, Hetty. Identifikasi cepat mikroorganisme menggunakan alat Vitek-2. Majalah Patologi Klinik dan Laboratorium Medik. 2007;13(3):129-32.
8. Pujiastuti AT, Murtiastutik D. Studi retrospektif: Vaginosis bakterial. Berkala Ilmu Kesehatan Kulit dan Kelamin. 2014;26(2):127-33.
9. Ranjit E, Raghubanshi BR, Maskey S, Parajuli P. Prevalence of bacterial vaginosis and its association with risk factors among nonpregnant women: A hospital based study. Int J Microbiol. 2018;2018:8349601
10. Ernawati. Faktor determinan terjadinya vaginosis bakterial pada wanita usia subur di kota Makassar. STIKES Nani Hasanuddin Makassar. 2013;3(5):70-7.
11. Ara NNR, Husain MA, Akter N, et al. Detection and antibiotic sensitivity pattern of *Gardnerella vaginalis* isolated from bacterial vaginosis patients attending Chittagong Medical College Hospital. Chattagram Maa-O-Shishu Hospital College Journal. 2017;16(1):48-53.
12. Iswara, A. Pola sensitivitas *Eschericia coli* terhadap antibiotik metronidazole. The 2nd University Research Coloquium 2015. 273-377.
13. Anago E, Ayi-Fanou L, Akpovi CD, et al. Antibiotik resistance and genotype of beta-lactamase producing *Escherichia coli* in nosocomial infections in Cotonou, Benin. Annals of Clinical Microbiology and Antimicrobials. 2015;14(5):1-6.
14. Drago L, Nicola L, Mattina R, et al. In vitro selection of resistance in *Escherichia coli* and *Klebsiella spp*. at in vivo fluoroquinolone concentrations. BMC Microbiology. 2010;10:119.
15. StatPearls [Internet]. *Klebsiella pneumoniae* [Updated 2020 March 25; cited 2020 February 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519004/
16. Naelasari DN, Koendhori EB, Dewanti L, et al. The prevalence of Extended Spectrum Beta-Lactamase (ESBL) producing gut bacterial flora among patients in Dr. Soetomo Hospital and Primary Health Center in Surabaya. Fol Med Indones. 2018;54(4):256-262.

ORIGINAL RESEARCH:

Changes in LIF expression on PCOS as biomarker implantation

Uki Retno Budihastuti[1,2],*, Eriana Melinawati[1,2], Sri Sulistyowati[1,2], Tanti Arianti[3]
[1]Medical Faculty of Universitas Sebelas Maret, Surakarta, Central Java, Indonesia, [2]Department of Obstetric Gynecology General Hospital Dr. Moewardi, Surakarta, Central Java, Indonesia, [3]Obstetric and Gynecology Study Program of Universitas Sebelas Maret, Surakarta, Central Java, Indonesia

ABSTRACT

Objectives: This study aimed to compare the endometrial expression of LIF PCOS compared to normal and determine the effect of PCOS and external variables that affect LIF expression.
Materials and Methods: This retrospective case control study with a correlational approach was conducted at Sekar Clinic, General Hospital Dr. Moewardi Surakarta. Subject were taken by consecutive sampling starting from September 2018 –. Februari 2019. External variable: age, occupation, family history PCOS, menarche, and BMI were recorded. The research samples were 60 subjects consisting of 30 PCOS patients based on Rotterdam criteria and 30 fertile women. In the luteinizing hormone (LH) secretion phase at LH + 5 days - LH + 10 days, an endometrial biopsy is performed with pipelle curettage, then it is examined by immunohistochemistry. Statistical analysis was performed using the Mann-Whitney, linier regression test.
Results: Mean of LIF expression was found significantly lower in PCOS group (1.53±3.65) compared to control group (35.33±21.04, with p=<0.001). Multivariate analysis linear regression in the effect of PCOS and external variables to endometrial LIF expression models showed PCOS (b=-1.14; 95% CI=-1.56 – -0.72; p=<0.001) and occupation (b = 0.32; 95% CI=0.14 – 0.52; p=0.001) significantly decreases LIF expression. PCOS (B=-1.14) is more important than Occupation (B=0.33) in decreasing LIF expression.
Conclusion: LIF expression decreased in the endometrium of PCOS patients and occupations compared to normal group, with considering all existing variables.

Keywords: Endometrial Receptivity, Leukemia Inhibitory Factor, Polycystic Ovary Syndrome

ABSTRAK

Tujuan: Penelitian ini bertujuan untuk membandingkan ekspresi endometrium LIF PCOS dibanding normal dan mengetahui pengaruh PCOS dan variabel luar yang mempengaruhi ekspresi LIF.
Bahan dan Metode: Studi kontrol kasus retrospektif ini dengan pendekatan korelasional dilakukan di Klinik Sekar, Rumah Sakit Umum Dr. Moewardi Surakarta. Subjek diambil secara consecutive sampling mulai dari September 2018 –. Februari 2019. Variabel eksternal: usia, pekerjaan, riwayat keluarga PCOS, menarche, dan BMI dicatat. Subjek penelitian adalah 60 subjek yang terdiri dari 30 pasien PCOS berdasarkan kriteria Rotterdam dan 30 wanita subur. Pada fase sekresi hormon luteinizing (LH) LH + 5 hari hingga LH + 10 hari dilakukan biopsi endometrium dengan kuret pipelle, kemudian diperiksa dengan imuno-histokimia. Analisis statistik dilakukan menggunakan Mann-Whitney, uji regresi linier.
Hasil: Rata-rata ekspresi LIF ditemukan secara signifikan lebih rendah pada kelompok PCOS (1.53±3.65) dibandingkan dengan kelompok kontrol (35.33±21.04, dengan p=<0.001). Analisis multivariat linear regression pengaruh PCOS dan variabel eksternal terhadap ekspresi LIF endometrium menunjukkan PCOS (b=-1.14; 95% CI=-1.56 – -0.72; p=<0.001) dan pekerjaan (b=0.32; 95% CI=0.14 – 0.52; p=0.001) secara signifikan menurunkan ekspresi LIF. PCOS (B=-1.14) lebih penting dibandingkan Pekerjaan (B=0.33) dalam penurunan ekspresi LIF.
Simpulan: Ekspresi LIF menurun pada endometrium pasien PCOS dan pekerjaan dibandingkan dengan kelompok normal, dengan mempertimbangkan variabel yang ada.

Kata kunci: Reseptivitas endometrium, LIF, SOPK

***Correspondence:** Uki Retno Budihastuti, Jl. Kol Sutarto No. 132, Jebres, Surakarta, 57126, E-mail: ukiretno@staff.uns.ac.id

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.22-27
● Maj Obs Gin. 2021;29:23-27 ● Received 20 Jan 2021 ● Revised 4 Mar 2021 ● Accepted 19 Mar 2021
 Available at https://e-journal.unair.ac.id/MOG/

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is one of the most common gynecological problems in reproductive age women that contributes to 15-20% infertility cases.[1,2] PCOS is known as an endocrine disorder that often occurs in women of childbearing age throughout the world.[3] Based on the Rotterdam ESHRE/ASRM, criteria of PCOS diagnosis must include at least two of the following three criteria: oligo or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovary features on ultrasound.[4]

The etiology of infertility in patients with PCOS is unknown. In many cases, PCOS infertility is often caused by anovulation. Some researchers think that endometrial receptivity has no effect on implantation. Meanwhile, other researchers also state that endometrial receptivity has an effect on implantation. Endometrial dysfunction is characterized by histomorphological disorders and disturbances in endometrial receptivity during the implantation phase.[5] Endometrial receptivity is a requirement for embryo implantation, starting from apposition, adhesion, and invasion. One embryo has been implanted, then endometrium is transformed into decidual tissues until placenta formation is complete.[6] Endometrial receptivity disorders in patients with PCOS are associated with the regulation of cytokine expression, resulting in down regulation of growth factors for embryo implantation.[7] Furthermore, the relationship between PCOS infertility and endometrial receptivity disorders are complex.[8]

Leukemia Inhibitory Factor (LIF) is a member of the cytokine IL-6 family this is produced and secreted by epithelial cells and endometrial stromal cells during implantation. This cytokine plays a vital role in endometrial receptivity during the invasion process by modulating trophoblast differentiation. The trophoblasts have two layers (syncytiotrophoblast and inner cytotrophoblast) of placenta formation, and before increasing maternal blood flow in the apposition to develop blood vessels in embryonic villi, induction of uterine spiral arteries is required.[9] Therefore, this study aimed to investigate LIF expression in endometrial receptivity of patients with PCOS affecting a uterine dysfunction and adverse reproductive outcomes.

MATERIALS AND METHODS

Research design

This cross-sectional study was conducted using PCOS patients and fertile women at the Sekar Clinic, General Hospital Dr. Moewardi Surakarta from September 2018 until Februari 2019.

Research subject

Research subjects consisted of ages 23-40 years, subjects were divided into 2 groups: 30 PCOS patients who are in accordance with Rotterdam criteria such as menstrual disorders, clinical hyperandrogen and polycystic ovary features on ultrasound and 30 fertile women undergoing sterilization, history and gynecological examination not suspected of having PCOS (fertility and clinical examination of normal gynecology) as control group. Exclusion criteria were normal women who have malignancy, use of contraception hormones and refuse to be research subjects.

Variables

The dependent variable was LIF expression. The independent variable was endometrial receptivity in PCOS and fertile women, while the external variables were age, cater occupation, family history PCOS, menarche, and body mass index (BMI).

Immunohistochemistry

Immunohistochemical examination for LIF expression using Anti Leukemia Inhibitory Factor (LIF, Cholinergic Differentiation Factor, CDF, DIA, Differentiation-stimulating Factor, D Factor, HILDA, Melanoma-derived LPL Inhibitor, MLPLI) with number L2024-01D, produced by United States Biological. All groups who met the inclusion and exclusion criteria signed the informed consent. In the luteinizing hormone (LH) secretion phase at LH + 5 days - LH + 10 days, PCOS patients undergo an endometrial biopsy with pipelle curettage about 2-3 cm below the uterine fundus. In fertile women the same procedure is performed, but previously the patient underwent female surgery method (MOW), permission to biopsy with pipelle curettage which did not cause bleeding. After that, the endometrium from the biopsy is put into a bottle with formalin buffer. The bottle label is written number, name, age, date of birth, sex and address of the patient. The biopsy results were sent to the Pathological Anatomy department of Dr. Sardjito Yogyakarta for immunohistochemical examination (IHC) to examine the expression of LIF. Calculation of LIF expression is through observing a number of 200 cytoplasmic epithelial cells, luminal epithelium and glandular epithelium using a microscope at 40x10 magnification, then counting positive cells that are brown in color. The measurement results are expressed as a percentage.

Data analysis

Bivariate analysis to identify the correlation between variables using chi-square test and Mann-whitney test. Multivariat analysis using linear regression. Statistical analysis was performed using SPSS 22.0.

Ethical clearance

Ethical clearance was obtained from the the commission of ethical health research of Dr. Moewardi General Hospital in Central Java, and the medical faculty of Sebelas Maret University, Surakarta, Central Java, Indonesia, Number: 650/VIII/HREC/2018.

RESULTS AND DISCUSSION

Table 1 showed that the percentage of PCOS is higher in patients aged <37, occupation status (no), without family history of PCOS, menarche ≥14, and normal BMI.

Table 1. Subjects Characteristics

Variable		N	(%)
Age	<37 years old	39	65
	≥37 years old	21	35
Occupation	No	36	60
	Yes	24	40
Family history PCOS	No	48	80
	Yes	12	20
Menarche	<14	20	33.3
	≥14	40	66.6
BMI	Normal	48	80
	Obesity	12	20

In table 2 of the age group, the highest percentage of PCOS sufferers are those aged <37 years with the number of PCOS patients at 58.9%. It was also shown in the table that the majority of those in the PCOS group were women employed 21 (87.5%). Job differences, family history of PCOS, and menarche in the PCOS group were compared with the normal group which was statistically significant with p <0.05. Homogeneity between the PCOS group and the control group in age and BMI was not statistically significant, with p> 0.05.

Both images were immunohistochemical results of LIF expression in the luminal epithelium and the glandular endometrial secretion phase and then analyzed visually using 40x10 magnification microscope. In Figure 1 (A) the glandular cytoplasm and brownish stroma show more LIF expression. Whereas in figure 1 (B) the LIF expression is limpid and only a few brownish LIF expressions are found.

Comparison of LIF expression between the two groups using bivariate analysis with the Mann-Whitney Test. The comparison results are shown in the table 3, where the mean LIF expression is lower on PCOS compared to the normal group. This difference was statistically significant with p ≤0.001.

Table 2. Bivariate analysis

Variables	Groups				Total		OR	p
	PCOS		Control					
	n	%	n	%	n	%		
Age								
<37 years old	23	58.9	16	41.1	39	100	0.35	0.058
≥37 years old	7	33.3	14	66.7	21	100		
Occupation								
No	9	25.0	27	75.0	36	100	21.00	<0.001*
Yes	21	87.5	3	12.5	24	100		
Family History of PCOS								
No	20	41.7	28	58.3	48	100	7.00	0.010*
Yes	10	83.3	2	16.7	12	100		
Menarche (year)								
<14	6	30.0	14	70.0	20	100	3.50	0.028*
≥14	24	60.0	16	40.0	40	100		
BMI								
Normal	21	43.8	27	56.2	48	100	3.86	0.053
Obesity	9	75.0	3	25.0	12	100		

*Significant : p<0.05

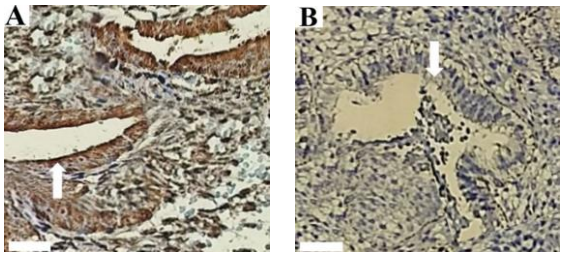


Figure 1. LIF expression in endometrium. The white arrows indicate endometrium in fertile women (A); and endometrium in PCOS patients (B). White bar: 10 µm
⇧: LIF Expression

Table 3. Difference in LIF expression in two groups

Groups	N	Mean	SD	p
LIF with PCOS	30	1.53	3.65	<0.001*
LIF with Normal	30	35.33	21.04	

*Significant : p<0.05

Table 4. Multivariate Analysis Linear Regression in The Effect of PCOS and External Variables to Endometrial LIF Expression

Variable	LIF expression to PCOS				LIF expression to PCOS and external variable			
	Unstand. Coeff. B	Stand. Coeff. b	95%CI	p	Unstand. Coeff. B	Stand. Coeff. b	95%CI	p
PCOS	-1.67	-0.75	-2.06 – -1.28	<0.001*	-1.14	-0.51	-1.56 – -0.72	<0.001*
Age					-0.13	-0.13	-0.31 – 0.04	0.123
Occupation					0.33	0.32	0.14 – 0.52	0.001*
Family history PCOS					0.16	0.13	-0.04 – 0.36	0.112
Menarche					-0.07	-0.07	-0.26 – 0.12	0.444
BMI					0.17	0.14	-0.03 – 0.38	0.090

* Significant : p<0.05

Multivariate analysis in table 4 was performed to see the correlation between variables with linear regression. In table 4 model 1 shows a statistically significant effect between PCOS and LIF expression. LIF expression on PCOS decreased as much as -1.67 times with p <0.001 and 95% CI (-2.06 - -1.28). Likewise, in PCOS table 4 model 2 also shows the effect of PCOS on LIF expressions after considering all external variables (age, occupation, family history PCOS, menarche, BMI), where LIF expression on PCOS decreased as much as -1.14 times with p values <0.001 and 95% CI (-1.56 - 0.72). The most common cause of infertility in women with PCOS is anovulation or ovarian dysfunction. Although it can still be cured by inducing ovulation, the rate of miscarriage and implantation failure is higher in women with PCOS.[10,11] Previous studies have shown that LIF decreases in serum and follicular fluid in women with PCOS compared to women without PCOS.[12] This is an important factor that disrupts foliculogenesis.[13] LIF is expressed in many endometrial glands at the time of blastocyst formation and before implantation, and this is most likely the result of increasing estrogen levels during the menstrual cycle.[14]

The effect of increasing levels of estrogen in the proliferative phase (follicles) due to the increase of ovarian follicles leads to blood vessel endothelium, epithelial proliferation and stroma for endometrioma regeneration.[7,15] The success of pregnancy depends on endometrial epithelium and blastocyst trophoblasts synchronized temporally and spatially. Here, LIF has an important role in the process of trophoblast invasion.[16,17] The shift from the proliferative status of the luminial epithelium to be differentiated is mediated by LIF through regulation of cell molecules that act as barriers to embryo invasion.[7] In the epithelial immunostaining, LIF is detected maximally in the middle and end of the secretory phase, but it is also detected with lower levels in other phases.

Meanwhile, stromal immunostaining is detected in all cycles.[18] The mechanism of LIF in regulating the function of uterine implantation is uncertain.[19] In this study LIF in PCOS patients decreased if it was compared to fertile women. This was in line with previous studies which reported that the level of LIF secretion in the endometrium decreased significantly under conditions of infertility as in PCOS patients.[9] This condition showed that LIF could be used for infertility therapy in women and, conversely, LIF antagonists could be used as a contraception. In addition, HOXA-10, HOXA-11, and LIF levels were reported to be significantly lower in PCOS patients who might contribute to PCOS related to infertility.[20] However, it is different from the results of studies that LIF expression increases significantly in the endometrium three months after laparoscopic ovarian dirlling (LOD).[21] Possibly one of the mechanisms underlying increased LIF expression after LOD is progesterone resistance, because LOD in the ovaries of PCOS can restore progesterone resistance so that it can increase LIF expression.[21,22]

The results showed that there was a decrease of LIF expression in women with PCOS compared to fertile women. Thus, this could be concluded that LIF played a role on endometrial receptivity. Therefore, it was necessary to do an early detection of LIF since a biomarker of endometrial reception was also necessary to avoid a uterine dysfunction and adverse reproductive outcomes.

However, the limitation in this study was the size of the uterine cavity, the elongated luteal phase, confirmation of ovulation, estrogen and progesterone levels were not measured. This is a limitation of research.

CONCLUSION

There are differences of LIF expression in PCOS patients and fertile women. LIF expression in PCOS patients decreases significantly compared to fertile women.

ACKNOWLEDGMENT

We thanks all participants and acknowledge the work of Pathological Anatomy Laboratory of Dr. Sardjito Hospital, Yogyakarta and Sekar Clinic of General Hospital Dr. Moewardi – Universitas Sebelas Maret.

CONFLICT OF INTEREST

Authors declare that there were no financial conflicts of interest existing in this study.

REFERENCES

1. Nandi A, Chen Z, Patel R, Poretsky L. Polycystic Ovary Syndrome. Endocrinol Metab Clin North Am [Internet]. 2014 Mar;43(1):123–47. Available from: http://dx.doi.org/10.1016/j.ecl.2013.10.003
2. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2014;1–13.
3. Goodman NF, Cobin RH, Futterweit W, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Androgen Excess and Pcos Society Disease State Clinical Review: Guide To the Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome - Part 2. Endocr Pract. 2015;21(12): 1415–26.
4. Azziz R. Diagnosis of polycystic ovarian syndrome: The Rotterdam criteria are premature. J Clin Endocrinol Metab. 2006;91(3):781–5.
5. Benagiano G, Bianchi P, Brosens I. Endometrial receptivity in PCOS. In: Infertility in Women with Polycystic Ovary Syndrome. 2018. p. 41–61.
6. Sourial S, Tempest N, Hapangama DK. Theories on the Pathogenesis of Endometriosis. 2014;2014.
7. Kim SM, Kim JS. A review of mechanisms of implantation. Natl Cent Biotechnol Inf. 2017;4: 351–9.
8. Garrido-Gomez T, Ruiz-Alonso M, Blesa D, et al. Profiling the gene signature of endometrial receptivity?: clinical results. Fertil Steril. 2013;99(4):1078–85.
9. Nicola NA, Babon JJ. Cytokine & growth factor reviews leukemia inhibitory factor (LIF). Cytokine Growth Factor Rev [Internet]. 2015; Available from:
10. Franks S, Stark J, Hardy K. Follicle dynamics and anovulation in polycystic ovary syndrome. Hum Reprod Update. 2008;14(4):367–78.
11. Li S, Song Z, Song M, et al. Impaired receptivity and decidualization in DHEA-induced PCOS mice. 2016;1–10.
12. Li Z, Zhu Y, Li H, et al. Leukaemia inhibitory factor in serum and follicular fluid of women with polycystic ovary syndrome and its correlation with IVF outcome. Reprod Biomed Online [Internet]. 2018;36(4):483–9. Available from: https://doi.org/10.1016/j.rbmo. 2017.12.020
13. Aghajanova L. Update on the role of leukemia inhibitory factor in assisted reproduction. Curr Opin Obstet Gynecol. 2010;22(3):213–9.
14. Nicola NA, Babon JJ. Leukemia inhibitory factor (LIF). Cytokine Growth Factor Rev. 2015;26(5):533–44.
15. Cha J, Sun X, Dey SK. review Mechanisms of implantation?: strategies for successful pregnancy. Nat Med [Internet]. 2012;18(12):1754–67. Available from: http://dx.doi.org/10.1038/nm.3012
16. Salleh N, Giribabu N. Leukemia inhibitory factor: Roles in embryo implantation and in nonhormonal contraception. Sci World J. 2014;2014.
17. d'Hauterive SP, Charlet-Renard C, Berndt S, et al. Human chorionic gonadotropin and growth factors at the embryonic-endometrial interface control leukemia inhibitory factor (LIF) and interleukin 6 (IL-6) secretion by human endometrial epithelium. Hum Reprod. 2004;19(11):2633–43.
18. Vogiagis D, Marsh MM, Fry RC, Salamonsen LA. Leukaemia inhibitory factor in human endometrium throughout the menstrual cycle. J Endocrinol. 1996;148(1):95–102.
19. Chen DB, Hilsenrath R, Yang ZM, et al. Implantation: Leukaemia inhibitory factor in human endometrium during the menstrual cycle: Cellular origin and action on production of glandular epithelial cell prosta-glandin in vitro. Hum Reprod. 1995;10(4): 911–8.
20. Kara M, Ozcan SS, Aran T, et al. Intraoperative and postoperative clinical evaluation of the hysteroscopic morcellator system for endometrial polypectomy: a prospective, randomized, single-blind, parallel group comparison study. Gynecol Minim Invasive Ther 2018; 7(1):1–5.
21. Zan E, Durant B. Laparoscopic ovarian drilling regulates endometrial LIF and integrin expression in PCOS. EC Endocrinol Metab Res. 2020;5(1):1–5.
22. Savaris RF, Groll JM, Young SL, DeMayo FJ, Jeong JW, Hamilton AE, et al. Progesterone resistance in PCOS endometrium: A microarray analysis in clomiphene citrate-treated and artificial menstrual cycles. J Clin Endocrinol Metab. 2011;96(6):1737–46.

ORIGINAL RESEARCH:

Prevention of vaginal vault prolapse occurrences post vaginal and abdominal hysterectomy. An evidence based case report.

Suskhan Djusad
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia,
Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ABSTRACT

Objectives: To determine efficacy of the procedures which were performed during hysterectomy in preventing any complication, in the form of vaginal vault prolapse.
Materials and Methods: Articles were searched through the databases, such as PubMed, Scopus, EBSCO-host, and Cochrane Library; resulting in three full text articles which were relevant to be critically reviewed. Those articles then were critically reviewed based on validity, importance, and applicability based on critical review tools from University of Oxford Centre-for Evidence Based Medicine (CEBM) 2011.
Results: Findings from the articles showed that prevention procedures during hysterectomy such as McCall culdoplasty, Shull suspension, laparoscopic USP and ULS were effective in preventing future vaginal vault prolapse in women who underwent hysterectomy. Among the four procedures; McCall culdoplasty and Shull suspension provide the highest efficacy as prevention procedures. Other than that, both methods were capable to increase quality of life and sexual function post hysterectomy.
Conclusion: Vaginal vault prolapse prevention procedures such as McCall culdoplasty, Shull suspension, laparoscopic USP and ULS were effective in preventing a vaginal vault prolapse. However, additional literatures are needed to support the utilization of these methods in clinical setting.

Keywords: Prevention; vaginal vault prolapse; vaginal hysterectomy; abdominal hysterectomy

ABSTRAK

Tujuan: Menilai efektifitas tindakan pencegahan selama proses histerektomi dalam mencegah terjadinya komplikasi berupa vaginal vault prolapse.
Bahan dan Metode: Pencarian literatur dengan menggunakan database PubMed, Scopus, EBSCO-host, serta Cochrane Library yang menghasilkan 3 artikel full text yang relevan untuk dilakukan telaah kritis lebih lanjut. Ketiga artikel tersebut kemudian ditelaah secara kritis berdasarkan kriteria validity, importance, serta applicability berdasarkan alat telaah kritis keluaran Centre-for Evidence Based Medicine (CEBM) University of Oxford tahun 2011.
Hasil: Pencarian literatur menunjukkan hasil bahwa prosedur pencegahan selama proses histerektomi seperti McCall culdoplasty, Shull suspension, laparoskopik USP, serta ULS memiliki efektivitas dalam mencegah vaginal vault prolapse dikemudian hari pada wanita yang menjalani prosedur histerektomi. Diantara ke-4 metode tersebut, McCall culdoplasty dan Shull suspension memberikan efektivitas yang paling tinggi dalam pencegahan. Selain itu, kedua metode tersebut juga mampu meningkatkan kualitas hidup dan fungsi seksual pasca histerektomi.
Simpulan: Prosedur pencegahan vaginal vault prolapse seperti McCall culdoplasty, Shull suspension, laparoskopik USP, serta ULS ditemukan memiliki efektivitas dalam mencegah vaginal vault prolapse. Akan tetapi, dibutuhkan literatur tambahan untuk mendukung penggunaan metode-metode ini pada setting klinis.

Kata kunci: Pencegahan; vaginal vault prolapse; histerektomi vaginal; histerektomi abdominal

Correspondence: Suskhan Djusad, Department of Obstetrics and Gynecology, Dr. Cipto Mangunkusumo Hospital, Faculty of Medicine, Universitas Indonesia, Email: suskhan007@yahoo.co.id

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.28-35
● Maj Obs Gin. 2021;29:28-35 ● Received 31 May 2020 ● Revised 16 Jul 2020 ● Accepted 15 Oct 2020

INTRODUCTION

Vaginal vault prolapse is a condition in which the top of the vagina loses its normal shape or position, resulting in sagging or dropping of the part down into the vaginal canal or outside the vagina.[1] International Continence Society defined vaginal vault prolapse as descent of the vaginal cuff below a point that is 2 cm less than total length of the vagina above the hymen.[2] Vaginal vault prolapse may occur as a complication of vaginal or abdominal hysterectomy procedure. Hysterectomy can increase vaginal vault prolapse occurrence risk up to 5.5 times higher than other etiologies. The incidence of this complication was about 0.2-43%.[1,3] Other than hysterectomy, the vaginal vault prolapse incidence due to other etiologies was about 1.8%.[4]

In a normal condition, during an increased abdominal pressure, the vagina is held in its proper position by supporting structures such as levator plate and endopelvic fascia (cardinal and uterosacral ligaments). A vaginal vault prolapse develops if there is laceration, stretching, or other causes that are generally weakened those supporting structures. Because of these, the vagina loses its original axis position during an increased intraabdominal pressure, then the prolapse occurs.[1] Vaginal vault prolapse shows as a medium or long term failure of the supporting mechanisms and results from a amalgamation of intrinsic defects such as weakness of tissue collagen and impairment of pelvic floor along with its nerve supply during childbirth.[5] A vaginal vault prolapse is frequently related with other part abnormalities such as cystocele, rectocele, or enterocele.[6] It can lead to anorectal, sexual, and urinary dysfunction; thus reducing the patient's quality of life.[2] Vaginal vault prolapse symptoms consist of dyspareunia, bulging sensation in the vagina, low back pain, recurrent urinary tract infections, voiding and penetration difficulties. Other symptoms related to defecation problems include encopresis, constipation, and incomplete evacuation. The severity of prolapse can be evaluated through abdominal and pelvic examination and objectively assessed by POP-Q scoring system.[4]

Up until now, no agreement has been established yet about the right curative procedure to manage a vaginal vault prolapse. There is still an ongoing debate about whether a vaginal, abdominal, or combined hysterectomy procedure is the most appropriate one in treating the complication. Each procedure has its own advantages, weaknesses, and specific indications. Therefore, it is better to perform prevention procedures before a vaginal vault prolapse is seen. Vaginal vault prolapse prevention can be done by attaching pelvic supporting structures such as cardinal and uterosacral ligament to vaginal membrane post vaginal hysterectomy. Other than preventing a vaginal vault prolapse, this procedure can also prevent enterocele formation along reducing the patient's discomfort after surgery.[1] Another procedure can be performed to prevent vaginal vault prolapse occurrences. This literature review was made to assess the efficacy of vaginal vault prevention procedures. Hopefully, this literature review can give an illustration related to proper action needed to be done in order to avoid the development of a vaginal vault prolapse post vaginal or abdominal hysterectomy.

Clinical scenario

A 35-year-old woman will undergo a hysterectomy procedure. A hysterectomy procedure may lead to several complications; one of those is a vaginal vault prolapse. As an obstetrician and gynaecologist, you have read that a vaginal vault prolapse can be prevented by performing prevention procedures during hysterectomy. You want to know the efficacy of those prevention procedures in preventing vaginal vault prolapse in the future.

MATERIALS AND METHODS

In order to obtain knowledge related to the efficacy of vaginal vault prolapse prevention procedures which were performed during hysterectomy, a literature search was carried out based on the clinical question mentioned. The literature search was performed through online databases, such as PubMed, Cochrane, Scopus, and EBSCO-host in June 8th, 2019. The keywords and synonyms used in the literature search were as follows: "hysterectomy", vaginal or abdominal hysterectomy or vaginal hysterectomy", "prevention and control or secondary prevention or avoidance", "pelvic organ prolapse or vaginal vault prolapse". Those keywords then were used in the literature searching strategy as shown as in Table 2.

Table 1. PICO for Clinical Question

Population	Intervention	Control	Outcome
Women who are planned to undergo hysterectomy	Vaginal vault prolapse prevention procedure	Without prevention procedure or other vaginal vault prolapse prevention procedures	Vaginal vault prolapse occurrence

Table 2. Literature searching strategy

Database	Keywords	Results
PubMed	(((((((("Hysterectomy"[Mesh]) OR "Hysterectomy, Vaginal"[Mesh]) OR Hysterectomy abdominal[Title/Abstract]) OR abdominal hysterectomy[Title/Abstract]) OR vaginal hysterectomy[Title/Abstract])) OR hysterectomy[Title/Abstract])) AND ((((((("Pelvic Organ Prolapse/prevention and control"[Mesh])) OR "Secondary Prevention"[Mesh]) OR ("prevention and control" [Subheading])) OR prevention[Title/Abstract]) OR avoidance[Title/Abstract]) OR secondary prevention[Title/Abstract])) AND ((("Pelvic Organ Prolapse"[Mesh]) OR pelvic organ prolapse[Title/Abstract]) OR vaginal vault prolapse[Title/Abstract])	142
Scopus	(TITLE-ABS-KEY (hysterectomy OR vaginal AND hysterectomy OR abdominal AND hysterectomy OR hysterectomy AND vaginal OR hysterectomy AND abdominal) AND TITLE-ABS-KEY (prevention OR prevention AND control OR secondary AND prevention OR avoidance) AND TITLE-ABS-KEY (pelvic AND organ AND prolapse OR vaginal AND vault AND prolapse))	1
EBSCO-host	AB (hysterectomy OR vaginal hysterectomy OR abdominal hysterectomy OR hysterectomy vaginal OR hysterectomy abdominal) AND AB (prevention OR prevention and control OR secondary prevention OR avoidance) AND AB (pelvic organ prolapse OR vaginal vault prolapse)	13
Cochrane Library	"hysterectomies" OR hysterectomy OR vaginal hysterectomy OR abdominal hysterectomy OR hysterectomy vaginal OR hysterectomy abdominal in Title Abstract Keyword AND "preventional" OR prevention OR prevention and control OR secondary prevention OR avoidance in Title Abstract Keyword AND "pelvic organ prolapse" OR pelvic-organ prolapse OR vaginal vault prolapse in Title Abstract Keyword - (Word variations have been searched)	37

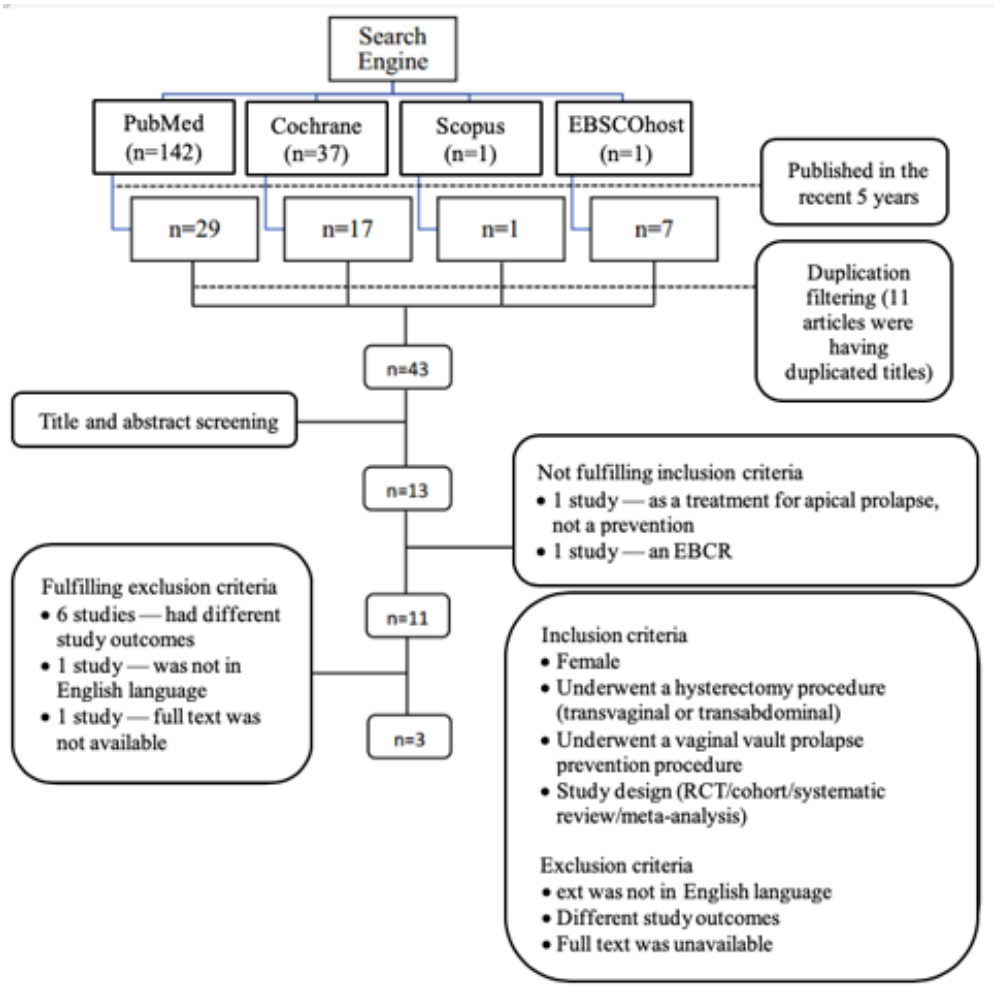


Figure 1. Literature Searching Strategy Algorithm

Search selection process

After the search process was done, the collected literatures then were selected. First, the selection was begun by screening of the titles and abstracts. The title and abstracts of the literature were selected by excluding the literatures which were having inappropriate clinical question and the duplicated ones. Duplication here means the literatures with same or identical titles and the literatures included in the systematic review or meta-analysis which were already used in this study. The inclusion criteria consists of: any literature which had female subjects who underwent both vaginal or abdominal hysterectomy procedure along with vaginal vault prolapse prevention procedure; any systematic review and meta-analysis; and all were published in the recent 5 years. Meanwhile, the exclusion criteria was literatures which were using languages other than English and having incompatible outcomes with this literature. The complete literature selection process were as shown as in Figure 1.

Critical Review

From the literature selection process, three literatures were collected to be critically reviewed. Those three articles were cohort studies (2 retrospective cohorts and 1 prospective cohort). Critical review were performed by using critical review tool from University of Oxford Centre-for Evidence Based Medicine (CEBM) 2011.

RESULTS AND DISCUSSION

Summary from all three articles chosen were shown in Table 3, meanwhile the critical review results of those literatures were shown in Table 4.

All three studies have level of evidence IV. This is due to the cohort model was used for therapeutic study, which would have achieved a higher level of evidence if they were performed with a randomized controlled trial as a study design. In terms of validity, the three studies did not perform randomization because of the inapplicable study design. Studies by Schiavi et al.[7] and Niblock et al.[8] used retrospective cohort design meanwhile the study by Pal et al.[9] only had one trial group. In their studies, Schiavi et al.[7] and Niblock et al.[8] used two groups with same characteristics which have been proven not to differ significantly by a series of statistical calculation. All three studies have a loss to follow-up rate or drop-out rate less than 20%. The studies by Schiavi et al.[7] and Pal et al.[9] did not use intention-to-treat analysis. Both studies excluded the loss to follow-up participants and did not consider the lost participants as having any event.

In terms of importance, the study performed by Schiavi et al.[7] shows lower percentage in post hysterectomy vaginal vault prolapse occurences in both groups; the group underwent modified McCall culdoplasty (1%) and the group underwent Shull suspension (0.5%). The two procedures also successfully made an improvement in quality of life and sexual function during follow-up period that were significantly different between pre-procedure and post-procedure, proven by POP-Q, TVL, P-QoL, ICIQ-UI-SF, PISQ-12, FSFI, and FSDS scores. Both procedures did not show any significant difference regarding prevention efficacy, quality of life improvement, or perioperative complication. However, Shull procedure is proven better in terms of sexual function. Along with Schiavi et al.[7], the study by Niblock et al.[8] also showed a low percentage in vaginal vault prolapse occurrence following McCall culdoplasty procedure (0%). Otherwise, in USP procedure, vaginal vault prolapse occurrence rate following hysterectomy were higher (16.4%). There is no significant difference between the two procedures in terms of perioperative complications. Although, there is a significant difference in hospitalization period in which the hospitalization period for USP procedure is shorter. In contrast with the two studies beforehand, the study by Pal et al.[9] only assessed ULS procedure. The rate of vaginal vault prolapse occurrences following ULS procedure is 8.3%.

From the three critically reviewed studies, all of them have weak level of evidences to be considered as a base of evidence. This is due to the retrospective cohort designs used by the studies which did not perform any randomization and blinding so that they are susceptible to bias. Furthermore, all the three studies did not publish the sample calculation so that the number of samples cannot be stated adequate. The strength of the study performed by Schiavi8 is the adequate follow-up period, with a mean of follow-up period 8.9 years and a minimal of 5 years. However, the team which was in charge of data collection was the same team as the one that performed surgeries, thus there was a potential observer and data bias.

In addition, one of the sexual function scoring tools was translated from Italian to English and has not been validated yet. Another strength of this study is that both participant groups were having same characteristics which have been confirmed before the study had started. Unfortunately, in the assessment of the same character-istics, the information about distribution of the prolapse stage found in the participants was not included, nor the distribution of anterior or posterior vaginal wall prolapses which was found in some participants.

Table 3. Articles' Characteristics[7,8,9]

Literature (year), country	Study Design	Sample Characteristics	Intervention	Outcomes	Results
Schiavi et al. (2018), Italy[7]	Cohort	Women with mean age 59.13±8.14 (McCall) and 60.46±7.83 (Shull) who experienced uterine prolapse (hysterocele) ≥ 3rd stage (with or without anterior or posterior compartment prolapse). There is no significant difference between characteristics of the two groups. A total of 200 subjects underwent McCall procedure, meanwhile a total of 214 subjects underwent Shull procedure.	Both groups received vaginal vault prolapse prevention procedure as an intervention during hysterectomy, whereas one group underwent modified McCall culdoplasty procedure and the other group underwent Shull suspension procedure. Median of follow-up period is 8.9 years with a minimal limit of 5 years.	Primary outcome in the form of efficacy and safety assessment of both procedures in preventing post hysterectomy vaginal vault prolapse and compares the two procedures. Secondary outcome in the form of long term effects of the procedures to quality of life and sexual function which were assessed using POP-Q*, TVL†, P-QoL‡, ICIQ-UI-SF§, PISQ-12‖, FSFI¶, dan FSDS**.	Vaginal vault prolapse occurs in 1% women (McCall) dan 0.5% women (Shull). There is no significant difference in safety of both procedures (amount of blood loss, intraoperative complications, ureteral/bowel/ bladder injuries, hemoperitoneum and abscess). 85.5% women (McCall) and 92.4% women (Shull) felt better. A decrease in POP-Q ($p<0.001$) in both groups were found without any differences between them. TVL were lower in both groups ($p<0.001$) with bigger decrease was found in McCall group. P-QoL dan ICIQ-UI-SF were increased in both groups ($p<0.001$) without any differences between the two groups. PISQ-12, FSFI, dan FSDS were increased in both groups ($p>0.001$) with a difference between the two groups, whereas Shull group gave better results.
Niblock et al. (2017), Ireland[8]	Cohort	Women with vaginal prolapse. Mean age of the women underwent McCall culdoplasty is 59 years, whilst mean age of the women underwent USP†† is 52.3 years. Some women who also had anterior or posterior vaginal prolapse were given an additional procedure (anterior/posterior colporrhaphy). There is no difference of characteristics between the two groups except age differences ($p<0.001$). The McCall group consists of 73 subjects, meanwhile the USP group consists of 70 subjects.	Both groups received intervention in the form of vaginal vault prolapse prevention where one group underwent McCall culdoplasty procedure during vaginal hysterectomy, whilst the other group underwent USP procedure during laparoscopic hysterectomy. Mean of follow-up period in McCall group is 36 months (5-84 months), while the mean of follow-up period in USG group is 41 months (7-71 months)	Primary outcomes of this study are assessments of the efficacy of both procedures in preventing vaginal vault prolapse occurrence and comparison between the two groups. Secondary outcomes of this study are the hospitalization time and perioperative complications.	0% of the McCall group and 16.4% of the USP group experienced vaginal vault prolapse post hysterectomy—statistically significant ($p<0.001$). Hospitalization time in USP group significantly shorter compared to McCall group ($p<0.001$). Other than that, there is no difference between both groups in terms of perioperative complications.
Pal et al. (2018), India[9]	Cohort	Women with stage III-IV uterovaginal prolapse (stages were determined using POP-Q). The total number of women participated in this study is 51 subjects.	There is only one group in this study. The group underwent modified extraperitoneal ULS procedure with the mean of follow-up period is 2.3 years.	Efficacy of the modified extraperitoneal ULS‡‡ procedure as a prevention of vaginal vault prolapse post vaginal hysterectomy	8.3% of the total participants experienced vaginal vault prolapse after the procedures, meanwhile about 91.6% participants did not experienced vaginal vault prolapse during the follow up period.

*POP-Q: Pelvic Organ Prolapse Quantification System; †TVL: Total Vaginal Length; ‡P-QoL: Prolapse Quality of Life Questionnaire; §ICIQ-UI-SF: The International Consultation on Incontinence Questionnaire-Urinary Incontinence Short From; ‖PISQ-12: The Pelvic Organ Prolapse/Urinary

Incontinence Sexual Questionnaire Short Form; ¶FSFI: The Female Sexual Function Index; **FSDS; The Female Sexual Distress Scale; ††USP: Uterosacral Plication; ‡‡ULS: Uterosacral Ligament Suspension.

Table 4. Articles' critical review[7,8,9]

			Validity						Importance	Applicability		
Author (tahun)	Level of Evidence	Number of Samples	Randomization	Same Group Characteristics	Same Intervention	Loss to follow-up (%)	Intention To-treat Analysis	Blinding	VVP (follow-up) Percentage	Differences Between Two Groups	Same Characteristics	Feasible
Schiavi et al. (2015)[7]	IV	414	-	+	+	2.8 %	-	-	1% (McCall) vs 0.5% (Shull) (mean 8.9 years)	(McCall vs Shull) P-QoL = 31.77 vs 30.94 (p=0.34) ICIQ-UI-SF = 5.32 vs 4.83 (p=0.09) TVL = 2.16 vs 0.87 cm (p<0.001) PISQ-12 = 36 vs 38 (p=0.003) FSFI = 29 vs 31 (p=0.04) FSDS = 8 vs 8 (p=0.24)	+	+
Niblock et al. (2017)[8]	IV	143	-	+	+	0%	n/a	-	0% (McCall) vs 16.4% (USP) (mean 36 months vs 41 months)	McCall vs USP Hospitalization time = 3.6 vs 1.8 (p<0.001)	+	+
Pal et al. (2018)[9]	IV	51	n/a	n/a	n/a	5.9 %	-	n/a	8.3% (ULS) (mean 2.3 years)	n/a	+	+

These facts resulted in hesitation regarding the similar characteristics between the two groups. Though was having several weaknesses, this study succeeded in showing the efficacy of McCall culdoplasty and Shull suspension methods in order to prevent a long term vaginal vault prolapse. Moreover, this study showed that both methods were safe other than significantly improving quality of life and sexual function following a hysterectomy due to prolapse.

In contrast to Schiavi et al.[7], the study performed Niblock et al.[8] had a shorter follow-up period, with a mean of follow-up was 36 months for McCall culdoplasty group and 41 months for laparoscopic USP group; whilst the shortest follow-up period is 5 months. The relatively short follow-up periods could be a source of bias due to the possible occurrence of vaginal vault prolapse in this period was still low. Also, the difference in follow-up periods between the two groups could be another source of bias in this study. Another weakness of this study is that there was no sample calculation and the similar characteristics between the two groups were still questioned. Even though, this study shows that the McCall culdoplasty procedure had a high efficacy in preventing a vaginal vault prolapse with a incidence rate of 0%. On the other hand, laparoscopic USP technique had a low efficacy in preventing a vaginal vault prolapse with an incidence rate of 16.4% with a mean follow-up period of 41 months.

In comparison with the two studies beforehand, the study perfomed by Pal et al.[9] has the weakest evidence; because it was a descriptive study and lack of comparison group. In addition, this study were held with a few participants without any calculation of the number of sample earlier. Follow-up time were relatively short, with a mean of 2.3 years. Even though, this study shows a rather good efficacy of ULS technique in preventing a vaginal vault prolapse with an incidence rate of 8.3%.

The main weakness of this EBCR is an unspecified clinical question, resulting in different comparison groups in each of the selected studies. Moreover, lack of the study that uses vaginal vault prolapse prevention as a primary prevention before the prolapse occurred leads to lack of complete information regarding potential of those procedures. Only few hysterectomies were done because of other causes beside the prolapse. Another

weakness is in the filtered studies, no studies have compared potency of the vaginal vault prolapse prevention procedures when they are performed during vaginal hysterectomy to their potency when it is performed during a abdominal one. Some studies show that the the risk of post-hysterectomy prolapse is higher in women who underwent vaginal than abdominal hysterectomy so there was a potency of higher efficacy in the prevention procedure that were done during abdominal hysterectomy than a vaginal one.[10,11,12]

The results obtained in this study shows that one of the recommended prevention procedures is McCall culdoplasty. This goes parallel with a study by Robinson et al.[6], which found that McCall culdoplasty is superior in preventing a vaginal vault prolapse compared to other procedures such as Moschowitz closure or laparoscopic USP. McCall culdoplasty were capable to prevent vaginal vault prolapse in 89.2% patients, 2 years after vaginal hysterectomy procedure. About 10% of rest experienced stage I vaginal vault prolapse that were unnecessary to be corrected by operative procedures. Also, McCall culdoplasty could restore sexual function and pleasure in 89.2% patients, 2 years after the procedure. Other than preventing vaginal vault prolapse, McCall culdoplasty could prevent enterocele formation for at least 3 years after the procedure.[13] The study shows that this procedure can also be performed in abdominal hysterectomy. Although, there need to be a standard definition regarding McCall culdoplasty procedure that can be performed, reminding that many studies made several modifications and variations in suture materials in performing this procedure.

CONCLUSION

Vaginal vault prolapse prevention which was performed in conjunction with hysterectomy procedure; such as McCall culdoplasty, Shull suspension, laparoscopic USP and ULS; were found to be effective in preventing vaginal vault prolapse occurrence in the future. Amongst the four methods, McCall culdoplasty and Shull suspension method was discovered to be having the highest efficacy. Besides its capability of preventing vaginal vault prolapse, those two methods also increase the quality of life and sexual function of the women who had experienced pelvic organ prolapse and underwent a hysterectomy procedure. Even though, the quality and number of the literatures supporting those findings is still limited that further studies with better quality are needed to promote vaginal vault prolapse prevention procedures in a clinical setting.

ACKNOWLEDGMENT

I would like to thank Alfa Putri Meutia, Ajeng Larasati, Galuh Anindya Tyagitha, and Raden Kusumadewi for helping me to complete this case report. Thank you for all the advice, ideas, moral support and patience in guiding me through this project.

REFERENCES

1. Cruikshank SH. Preventing posthysterectomy vaginal vault prolapse and enterocele during vaginal hysterectomy. Am J Obstet Gynecol. 1987; 156(6): 1433-40.
2. Uzoma A, Farag KA. Vaginal vault prolapse. Obstet Gynecol Int. 2009;ID 275621:1-9.
3. Dallenbach P, Kaelin-Gambirasio I, Jacob S, Dubuisson JB, Boulvain M. Incidence rate and risk factors for vaginal vault prolapse repair after hysterectomy. Int Urogynecol J. 2008;19:1623-9.
4. Robinson D, Thiagamoorthy G, Cardozo L. Post-hysterectomy vaginal vault prolapse. Maturitas. 2018;107:39-43.
5. Hobson PT, Boos K, Cardozo L. Management of vaginal vault prolapse. Br J Obstet Gynaecol. 1998;105:13-17.
6. Coolen AW et al. The treatment of post-hysterectomy vaginal vault prolapse: a systematic review and meta-analysis. Int Urogynecol J. 2017;28:1767-83.
7. Schiavi MC, Savone D, Mascio DD, Tucci CD, Perniola G, Zullo MA, et al. Long-term experience of vaginal vault prolapse prevention at hysterectomy time by modified McCall culdoplasty or Shull suspension: clinical, sexual and quality of life assessment after surgical intervention. J Obstet Gynaecol Res. 2015;41(7):1099-107.
8. Niblock K, Bailie E, McCracken G, Johnston K. Vaginal McCall culdoplasty vs laparoscopic uterosacral plication to prophylactically address vaginal vault prolapse. Gynecol Surg. 2017;14(3):1-6.
9. Pal M, Bandhyopadhyay S. Modified extraperitoneal uterosacral ligament suspension for prevention of vault prolapse after vaginal hysterectomy. Int Urogynecol J. 2019;30(4):633-637.
10. Hodgson B. AAGL practice guidelines on the prevention of apical prolapse at the time of benign hysterectomy. J Minim Invasive Gynecol. 2014;21(5):715-22.
11. Altman D, Falconer C, Cnattingius S, Granath F. Pelvic organ prolapse surgery following hysterectomy on benign indications. Am J Obstet Gynecol. 2008;198:572.

12. Blandon RE, Bharucha AE, Melton LJ, et al. Incidence of pelvic floor repair after hysterectomy: a population-based cohort study. Am J Obstet Gynecol. 2007;197:664.e1-7.

13. Cruikshank SH, Kovac SR. Randomized comparison of three surgical methods used at the time of vaginal hysterectomy to prevent posterior enterocele. Am J Obstet Gynecol. 1999;180:859-65.

CASE REPORT:

Maternal and perinatal outcomes of hyperthyroidsm in pregnancy at Dr. Cipto Mangunkusumo Hospital, Jakarta, period of January 2015 - December 2016

Fita Maulina*, M Adya F Dilmy, Ali Sungkar
Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Indonesia,
Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia

ABSTRACT

Objectives: To report maternal and perinatal outcomes of hyperthyroidsm in pregnancy.
Case Report: There were 3622 cases of delivering pregnant women during the period of the study. From this number, the prevalence of pregnant women with hyperthyroid was 0.2 %. We reported 9 cases of hyperthyroid in pregnancy. The number of pregnancy complication and outcome on pregnant women with hyperthyroidism were preterm labor (44%) and preeclampsia (22%), both were found in group of mother who did taking antihyperthyroid therapy. In those who did not take antihyperthyroid therapy 11% had spontaneous abortion and 11% had preterm delivery. Fetal complications were intrauterine growth restriction (11%) and intrauterine fetal death (23%), both of these complication were on the group who did not take antihyperthyroid. On the contrary, 44% babies were born with normal birthweight in group who took antihyperthyroid.
Conclusion: There were differences noted between the group that took adequate treatment and the group that did not take antihyperthyroid. The incidence of intrauterine growth restriction and intrauterine fetal death were high in group that did not took antihyperthyroid therapy but the incidence of preterm delivery as the maternal complication was high in group that did take the antihyperthyroid therapy.

Keywords: Hyperthyroid in pregnancy; maternal outcome; perinatal outcome

ABSTRAK

Tujuan: Untuk melaporkan kondisi ibu dan perinatal pada hipertiroidsm dalam kehamilan.
Laporan Kasus: Ada 3622 kasus ibu hamil yang melahirkan selama masa penelitian. Dari angka tersebut prevalensi ibu hamil dengan hipertiroid pada periode penelitian ini sebesar 0,2%. Kami melaporkan 9 kasus hipertiroid dalam kehamilan. Jumlah komplikasi kehamilan dan hasil akhir pada wanita hipertiroid adalah persalinan prematur (44%), preeklamsia (22%), keduanya berasal dari kelompok ibu yang melakukan terapi antihipertiroid, sebaliknya yang tidak menjalani terapi antihypertiroid sebanyak 11% mengalami. abortus spontan dan 11% kelahiran prematur. Komplikasi janin adalah hambatan pertumbuhan intrauterin (11%) dan kematian janin intrauterin (23%). Kedua komplikasi tersebut terjadi pada kelompok yang tidak menggunakan antihipertiroid. Sebanyak 44% bayi lahir dengan berat badan normal pada kelompok yang mengonsumsi antihipertiroid.
Simpulan: Ada perbedaan yang dicatat antara kelompok yang mendapat pengobatan adekuat dengan kelompok yang tidak menggunakan antihipertiroid. Kejadian hambatan pertumbuhan intrauterin dan kematian janin intrauterin tinggi pada kelompok yang tidak menggunakan terapi antihipertiroid tetapi kejadian persalinan prematur karena komplikasi maternal yang tinggi terjadi pada kelompok yang mendapat terapi antihipertiroid.

Kata kunci: Hipertiroid pada kehamilan; kondisi ibu; kondisi perinatal

***Correspondence:** Fita Maulina, Department of Obstetrics and Gynecology Faculty of Medicine University of Indonesia, General Hospital Cipto Mangunkusumo, Jakarta, Indonesia. Email: maulinafieta@gmail.com

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.36-40
● Maj Obs Gin. 2021;29:36-40 ● Received 10 Feb 2021 ● Revised 24 Mar 2021 ● Accepted 9 Apr 2021

INTRODUCTION

Clinical hyperthyroidism complicates 0.1%–0.3% of pregnancies.[1] The diagnosis of hyperthyroidism may be difficult during pregnancy because some of the symptoms can occur physiologically during this time.[1,4] Uncontrolled disease is associated with an increased risk of perinatal complications such as intrauterine growth restriction, premature rupture of membranes, stillbirth, pre-eclampsia, and spontaneous abortion.[2] The prevalence of undiagnosed hyperthyroidism in women is about 4.7/1000,[4] and 0.2% of UK women have been previously diagnosed and treated.[3] We present 9 cases of hyperthyroid in pregnancy in a general hospital with characteristic as can be seen in Table 1. All subjects had provided their consent for publication of their cases.

CASE REPORT

Case I

Mrs. QA, a G2A1 25 year-old woman with 38 weeks of gestational age (wga). The fetus was singleton with dorsosuperior transverse lie, not in labor with Hashimoto thyroiditis on therapy and iron deficiency anemia (Hb 9.5 gr/dl). Thyroid disease was positive since the first pregnancy. She consumed PTU 3x/day, ceased since 2 weeks before admission. She had no clinical sign of hyperthyroid. The BMI was 27.5 (N), laboratory examinations revelead FT4 1.1 (N) and TSHs 0.7 (N). She had elective cesarean section (CS) with no pathological findings.

Case II

Mrs. M was a G3P2 of 28 years-old with inevitable abortion on 20 wga. She had twin pregnancy, both lived, and she had monochorionic monoamnion with hyper-thyroid not on therapy as well as chronic hypertension with controlled blood pressure. Her BMI was 28, laboratory examinations findings fT4/TSHs: 2,39/0,01 (H). She received expectant management, and with pathology of spontaneous abortion.

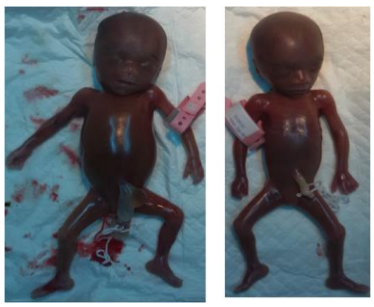


Figure 1. Babies born in Case II

Case III

Mrs. DR was a G4P3 of 39 years-old with no reassuring fetal status on 30 wga. The fetus was singleton, lived, with head presentation. She had PPROM for 6 hours, severe oligohydramnios, hyperthyroid on therapy since the previous three years, for which she received medication at another hospital with PTU 1 x 1 tab for 2 years, six months thereafter she received thyrozol 1 x 1 tab, and six months later, which was 6 months before admission, she received thyrozol 1x1/2 tablet. At about the same time she was checked for TSH and FT4, revealing TSH of 0.2 and fT4 of 1.4 with BMI of 27.6. Laboratory examination of the fetus revealed cord BGA : pH 7.209/pCO2 41.1/ pO2 21.1/O_2 saturation 30.3/BE (-10.1)/HCO_3 15.3/Total CO_2 17.8. Analysis of non-reassuring fetal status revealed fetal acidemia, and the management she received was emergency cesarean section and tubectomy pomeroy with pathology of preterm labor, low birth weight with congenital anomaly of oesophageal atresia and anal atresia.

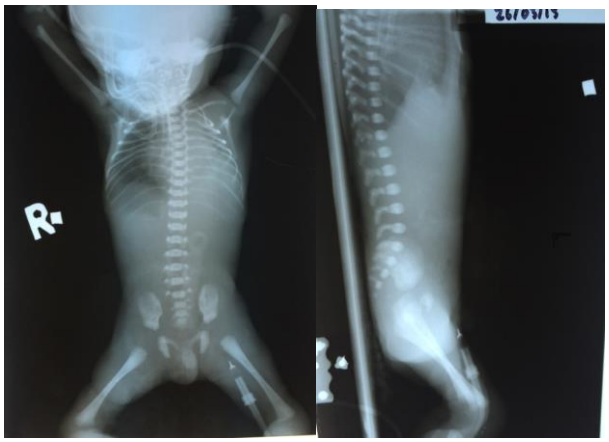


Figure 2. The baby born in Case III

Case IV

Mrs. EP, 30 years-old who was G3P0A2, had intrauterine infection on preterm labor on 26 wga. The fetus was singleton, lived with breech presentation. She had PPROM for 1 week, oligohidramnios (AFI 1.0), severe persistent asthma on attack, hiperthyroid on therapy, and chronic hypertension. Her BMI was 22.6 and laboratory results showed TSH of 0.010 and free T4 of 2.690. She had hyperthyroid, took tirozol 2 x per day (20 mg for morning dose and 10 mg for evening dose). She had vaginal delivery and the pathology was PPROM with normal birthweight.

Table 1. Hyperthyroid in pregnancy in a general hospital

No	Age	Obstetric stat	Diagnosis	Antithyroid Admission	Mode of delivery	Complication during Pregnancy	Baby outcome
1	25	G2A1 38 wga	Hashimoto thyroiditis	PTU 3x daily	C- section		3600 gr
2	28	G3P2 20 wga	Hyperthyroid	-		Spontaneous Abortion	300 gr and 350 gr
3	39	G4P3 30 wga	Hyperthyroid	Thyrozol 1x20mg	C- section	PPROM	1075 gr low birth weight
4	30	G3P0A2 26 wga	Hyperthyroid	Thyrozol 2x 20 mg	Vaginal delivery	PPROM	1010 gr low birth weight
5	24	G1 38 wga	Hyperthyroid	PTU 1x daily	Vaginal delivery	Preeclampsia	3000 gr
6	29	G2P1 28 wga	Grave disease	-	C- section	PPROM	1st Baby 1000 gr 2nd baby IUFD
7	37	G6P5 36 wga	Hyperhyroid	PTU 3x daily	Vaginal Delivery	Preeclampsia	3000 gram
8	26	G1 35 wga	Hyperthyroid	PTU 1x 100 mg	C- section	PROM	2000 gram
9	28	G2P1 25 wga	Grave disease	-	Vaginal delivery	Preterm Delivery	730 gr IUFD

Case V

Mrs. SM, aged 24 years, a G1 with 38 wga, had singleton living fetus with head presentation. She had diminished amniotic fluid (AFI 6.71), favourable cervix (PS 6), not in labor, preeclampsia with severe feature, and hyperthyroid on therapy. She was diagnosed as having hypertiroid since 2 years ago, for which she had received medication without knowing the name of the drug. During pregnancy, she received PTU 1 x 1 tab and routinely checked for hyperthyroid in another hospital. She had BMI of 24.2, laboratory results of free T4 of 1.920 and THS 0.01. She had vaginal delivery and the pathology was preeclampsia

Case VI

Mrs. L, a G2P1 aged 29 years with 28 wga. She had twin pregnancy, head-head presentation, TTTS Quinterro V (IUFD of second baby). She had olygo-hydramnios (AFI 2), periventricular leukomalacia, post lung maturation, Grave's disease, clinically euthyroid, and a previous cesarean section. She had hyperthyroid since 2013, controlled with PTU 1 x 100 mg per oral. Her BMI was 23.1, and laboratory examinations revealed FT4 1.06 and TSH 1.18. She had emergency c- section with pathology of IUFD and IUGR,

Case VII

Mrs. NK, a G6P5 of 37 years old, had preeclampsia with severe features on 38 weeks of gestational age.The fetus was living singleton with head presentation, not in labor. She had hyperthyroid on therapy, diagnosed since two years previously, treated with propanolol 1 x 10 mg and PTU 3 x 1 tab. At 8 month, she stopped the medication because she felt bored. During pregnancy she received PTU of 1 x 1 tab with BMI of 23.1. Laboratory examinations showed TSH <0.05 and fT4 3.1. She delivered with vaginal delivery and the pathology was preeclampsia. The baby was born with normal weight of 3000 grams.

Case VIII

Mrs. M, a G1 of 26 years old, had PROM on 35 weeks of gestational age. She had singleton living fetus with head presentation, small for gestational age. The fetus was suspected of IUGR. She had oligohydramnios (AFI 4), hyperthyroid on therapy, and microcytic hipo-chromic anaemia due to Iron deficiency (Hb: 9.7, Feritin: 10). The mother had the history of hyperthyroid since 2013 and routinely visited a certain hospital and had PTU 3 x 200 mg and dropped out from the therapy until one month before admission. She then continued her examination to another hospital and had PTU with lower dosage of 1 x 100 mg. The laboratory exam-ination results showed TSH/ FT4 of 0.04/ 0.97. She had vaginal delivery with PROM and the baby had IUGR.

Case IX

Mrs. R, a G2P1 aged 28 years-old of 25 wga. The fetus was singleton with IUFD and fetal hydrops. She had hyperthyroid due to graves disease. She had anemia microcytic hypochromic due to iron deficiency (Hb 8.2)

and since 2006 had been diagnosed with hyperthyroid by an internist from another town. She routinely consumed Tirozol 1 x 1, felt palpitation, tremor, hyperhydrosis, difficult of sleeping at that time, with light sensitivity and blurred vision. She stopped her medicine by herself in 2009 and did not go to check for her hyperthyroid condition because she felt no symptom at all. In 2013 she got routine examination at a hospital and continued her Tyrozol 1 x 1 due to high thyroid function test. Until she got her first pregnancy in 2015, she stopped the medicine until admission. At the admission, she did not feel any symptom about her illness except her mild palpitation and exophtalmos. She just obtained her PTU since 1 day before admission from another hospital. Her BMI was 26, laboratory examinations showed TSH/ FT4: 0.03/ 13. She had vaginal delivery and she gave birth to a preterm baby with IUFD.

DISCUSSION

Untreated overt hyperthyroidism are known to be associated with maternal and fetal complications. Common fetal complications of untreated maternal thyroid disease are low birth weight and a high frequency of fetal death. On the other hand, mothers with treated hypothyroidism may have an increased risk of large-for-gestational age (LGA) infants and also low-birth weight infants, infants with malformations and especially preterm delivery.[6] Overt hyperthyroidism might be associated with an increased prevalence of preeclampsia and pregnancy-induced hypertension. [6] Hyperthyroid condition in pregnant women also will affect to the delivered baby. Increase in preterm labor incidence (11-25%), stillbirth (8-15%) and decreasing baby's birthweight.

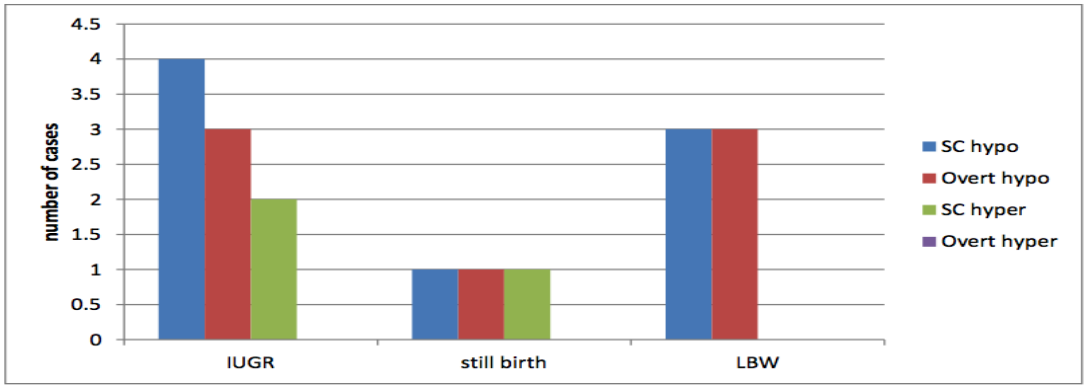


Figure 3. Incidence of fetal complication in 116 pregnant women with thyroid disorders.[4] Notes: Subclinical hypothyroidism: High serum TSH level with normal fT4, fT3 level,Overt hypothyroidism: High serum TSH level with fT4 and fT3 less than normal range, Subclinical hyperthyroidism: Low serum TSH level with normal fT3, fT4 level. Overt hyperthyroidism: Low serum TSH level with fT3 and fT4 more than normal range.

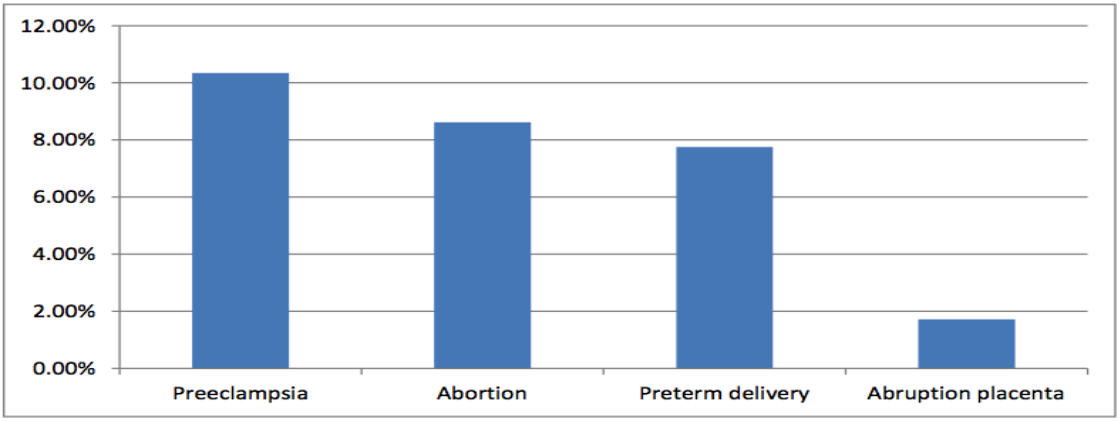


Figure 4. Incidence of maternal complication in pregnant women with thyroid disorders.[9]

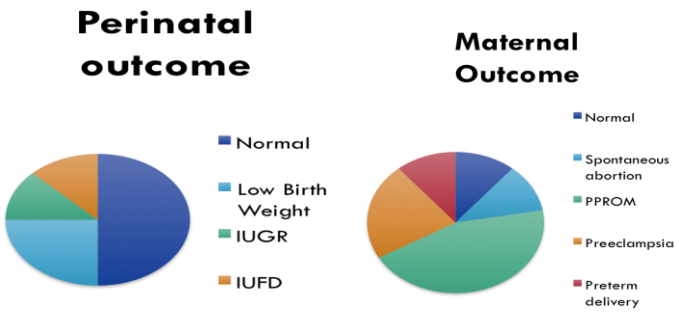


Figure 5. Outcomes of pregnancy complicated with hyperthyroidism in this case series

Changed in thyroid physiology is mainly to meet the increasing demand of maternal thyroid hormones, for the development of the foetus, mainly that of the Central Nervous System. As hCG is structurally similar to TSH, so the increase in hCG level in 1st trimester causes a transient increase in FT4 and therefore subsequent TSH suppression.[8]

The incidence of preeclampsia was also found to be significantly high in those with low TSH levels. The findings of the present study are in accordance with those of previous researchers. Other way round there are studies which have gone to show that women complicated with preeclampsia have high incidence of hypothyroidism that might correlate with the severity of preeclampsia.[8,10]

Even though most patients in this study were treated to controlled the disease with a satisfactory response, the fetal adverse outcomes were still consider. Pregnancy complicated with hyperthyroidism even in controlled status should prompt warrant close monitoring for fetal conditions, especially growth rate and well being.[5,11,12]

CONCLUSION

Treated maternal hyperthyroidism is not a risk factor for adverse perinatal outcome.

REFERENCES

1. Becks GP, Burrow GN. Thyroid disease and pregnancy. Med Clin North Am 1991;75(1):121
2. Rashid M, Rashid MH. Obstetric management of thyroid disease. Obstet Gynecol Surv. 2007;62 (10):680–8.
3. Mark H, Amin P, John HL. Hyperthyroidism and pregnancy. BMJ 2008;336:663-7.
4. Rama S, Kurmala TN, Shreen B, Vurani. Prevalence of thyroid disorder in pregnancy and pregnancy outcome. International Archives of Integrated Medicine. 2016;3(3).
5. Luewan S, Chakkabut P, Tongsong T. Outcomes of pregnancy complicated with hyperthyroidism: a cohort study. Arch Gynecol Obstet. 2011; 283:243–7.
6. Mannisto T. Maternal hyperthyroid in pregnancy. Effects on pregnancy, peri- and neonatal outcome and on later maternal health. University of Oulu. Oulu 2011
7. Begum F. Thyroid dysfunction and pregnancy outcome. IOSR Journal of Dental and Medical Sciences. 2016;15(9.II):7-10.
8. Brent GA. Maternal thyroid function: Interpretation of thyroid function tests in pregnancy. Clin Obstet Gynecol. 1997;40:3-15.
9. Pillar N, Levy A, Holcberg G, Sheiner E. Pregnancy and perinatal outcome in women with hyperthyroidism. International Journal of Gynecology and Obstetrics. 2010;108:61–4.
10. Harshvardhan L, Dariya SS, Sharma A, et al. Study of association of thyroid hormone in pre-eclampsia and normal pregnancy. J Assoc Physicians India. 2017;65(11):44-46.
11. Moleti M, Di Mauro M, Sturniolo G, et al. Hyperthyroidism in the pregnant woman: Maternal and fetal aspects. J Clin Transl Endocrinol. 2019;12;16:100190. Erratum in: J Clin Transl Endocrinol. 2020 Dec 17;23:100246.
12. Nguyen CT, Sasso EB, Barton L, et al. Graves' hyperthyroidism in pregnancy: a clinical review. Clin Diabetes Endocrinol. 2018;1;4:4.

CASE REPORT:

Acute Respiratory Distress Syndrome and septic shock in pregnant woman with COVID-19

Jesselyn Kristanti[1*], Fransiscus OH Prasetyadi[2]
[1]Emergency Department, Dr Ramelan Naval Hospital, Surabaya, Indonesia, [2]Obstetrics and Gynecology Department, Dr Ramelan Naval Hospital, Surabaya, Indonesia

ABSTRACT

Objectives: To prove that pregnancy do not worsen the clinical course of COVID-19 compared with nonpregnant individuals as found in the first case of COVID-19 pregnant woman died in our center.
Case Report: A 27-year-old female, G2P0A1 23/24 weeks without comorbidities, complaint of diarrhea and 4 days later got fever, cough, and dyspnea. She was referred to our hospital for further evaluation because of deterioration. SARS CoV-2 RT-PCR tested positive. Blood, sputum, and urine cultures tested negative. She was intubated and given LMWH. She was worsened rapidly despite being on intensive care for 3 days with last vital signs recorded: blood pressure 66/24 mmHg with vasopressors, heart rate 136 beats/minutes, temperature 41°C, oxygen saturation 62%, cardiac arrest and expired.
Conclusion: COVID-19 pregnant women need proper care so that they will not fall into conditions such as ARDS and septic shock. Close monitoring on clinical and laboratory course is recommended. We suggest clinicians to be aware so as rapid deterioration and death can be avoided.

Keywords: COVID-19; pregnant woman; ARDS; septic shock

ABSTRAK

Tujuan: Membuktikan bahwa kehamilan tidak memperburuk gejala klinis dari COVID-19 dibanding populasi tidak hamil seperti pada kasus pertama kematian ibu hamil dengan COVID-19 di sebuah rumah sakit.
Laporan Kasus: Wanita 27 tahun G2P0A1 usia kehamilan 23/24 minggu, tanpa komorbid dengan keluhan diare dan 4 hari kemudian mengeluh demam, batuk, dan sesak napas. Lalu dirujuk ke rumah sakit kami karena mengalami perburukan sehingga membutuhkan penanganan lebih lanjut. Hasil swab PCR SARS-CoV-2 positif. Kultur sputum, darah, dan urin tidak menunjukkan pertumbuhan kuman. Pasien terintubasi dan mendapatkan LMWH. Dalam perkembangannya selama 3 hari di ICU, pasien mengalami deteriorasi cepat dengan tanda vital terakhir tekanan darah 66/24 mmHg dengan vasopresor, nadi 136x/menit, suhu 41°C, saturasi oksigen 62%, henti jantung dan tidak tertolong.
Simpulan: Wanita hamil dengan COVID-19 membutuhkan penanganan yang tepat sehingga tidak jatuh pada kondisi seperti ARDS dan syok septik. Pemantauan secara ketat baik klinis maupun laboratorium berkala direkomendasikan. Penulis mengusulkan para klinisi mewaspadai hal tersebut sehingga potensi deteriorasi cepat dan kematian pada wanita hamil dengan COVID-19 dapat dihindari

Kata kunci: COVID-19; wanita hamil; ARDS; syok septik

***Correspondence:** Jesselyn Kristanti, Emergency Department, Dr Ramelan Naval Hospital, Surabaya, Indonesia.
E-mail: fjesselynkristanti@gmail.com

pISSN:0854-0381 ● eISSN: 2598-1013 ● doi: http://dx.doi.org/10.20473/mog.V29I12021.41-44
● Maj Obs Gin. 2021;29:41-44 ● Received 23 Feb 2021 ● Revised 2 Apr 2021 ● Accepted 16 Apr 2021

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a disease caused by SARS-CoV-2, a newly emergent coronavirus, was firstly identified in Wuhan, China, in December 2019.[1] Epidemiology and virologic studies suggest that transmission mainly occurs from symptomatic people to others by close contact through respiratory droplets, by direct contact with infected persons, or by contact with contaminated objects and surfaces.[2,3] Available data from multiple small series and case Pregnancy and childbirth, according to most studies, do not raise the risk of SARS-CoV-2 infection, do not exacerbate the clinical course of COVID-19 as compared to nonpregnant individuals of the same age, and most (>90 percent) infected mothers recover without giving birth.[4] In the medical literature, many maternal deaths due to cardio-pulmonary complications, including multiorgan failure, have been recorded.[5-7] Most of these women were generally healthy prior to the SARS-CoV-2 infection. This is the first death case of a pregnant woman with COVID-19 in our hospital, specifically a severe one with complications of acute respiratory distress syndrome (ARDS) and septic shock. A permission had been obtained to report this case.

CASE REPORT

This case study reported the circumstances surrounding a pregnant woman who contracted COVID-19 and died as a result of her illness.. We presented a case of a 27-year-old female in her second pregnancy at 23/24 weeks gestation with a history of miscarriage on her first pregnancy in October 2019. We did history taking with her husband, he stated that she has been admitted to the previous hospital for 1 week with chief complaint of diarrhea prior to admission, and four days after she was admitted she got additional complaints of fever, cough, and dyspnea and was moved to isolation ward. She did not have any history of hypertension, diabetes, obesity, alcohol use, drug use, or other significant comorbidities. She was referred to our hospital for further management and evaluation because of deterioration. Her RT-PCR swab for SARS-CoV-2 was positive; with blood, sputum, and urine cultures result tests are negative. Due to severe acute respiratory distress syndrome she was intubated and put under mechanical ventilation. She was given azithromycin 500 mg iv qd, chloroquine phosphate 500 mg po bid, oseltamivir 75 mg po bid, vitamin C 1 gram iv qd, other than that she was given low molecular weight heparin (enoxaparin 0.4 ml sc qd). She was worsened rapidly despite being on intensive care for 3 days with last vital signs recorded: blood pressure was 66/24 mmHg with vasopressors, heart rate was 136 beats/minute, temperature 41°C, oxygen saturation 62% on ventilator. Finally, due to this rapid deterioration, she was on cardiac arrest and expired following unsuccessful cardiopulmonary resuscitative efforts.

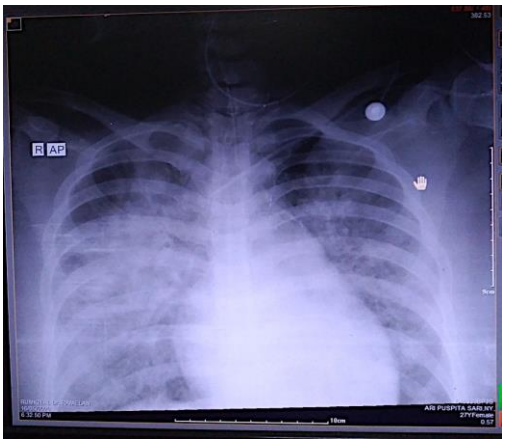


Figure 1. Patient's chest radiology

DISCUSSION

This patient first came with a chief complaint of gastrointestinal symptom (diarrhea) which has been reported in some medical literatures as a possible presenting complaint of COVID-19.[8,9] Since accumulated evidence supports SARS-CoV-2 transmission via feces, suspected COVID-19 patients with GI symptoms such as nausea, vomiting, and diarrhea should be seriously considered.[10] Four days later she was complaining of fever, cough, and shortness of breath which were the most emphasized symptoms of COVID-19.

Pregnancy and childbirth, according to available evidence from several small series and case reports, do not raise the risk of SARS-CoV-2 infection, do not exacerbate the clinical course of COVID-19 when compared to nonpregnant individuals of the same age, and most (>90 percent) infected mothers recover without giving birth. Older adults, especially those with comorbidities, are those demographically most affected by serious disease, and most pregnant women are younger than middle age; however, they may have comorbid conditions that increase their risk (eg, obesity, diabetes).[4]

It is known that some patients with severe COVID-19 have laboratory evidence of an exuberant inflammatory response (similar to cytokine release syndrome), which has been associated with critical and fatal illnesses.[4] It is unclear if pregnancy's normal immunologic changes

influence the occurrence and course of this response.[4] Symptomatic infection can range from mild to critical disease. As for this patient, based on WHO Interim Guidance on Clinical Management of COVID-19 which was published on 27 May 2020, from the COVID-19 disease severity, criteria of critical disease which is severe acute respiratory distress syndrome, sepsis and septic shock is obtained.[1]

Severely ill COVID-19 patients are often managed in the prone position in the ICU. While even a semi-prone position can be difficult to place a pregnant woman in the last half of pregnancy, some ICUs have applied this approach to pregnant women.[11] and so did in this patient.

This patient was given low molecular weight heparin (enoxaparin). We have learned that coagulopathy is common in patients with severe COVID-19, and both venous and arterial thromboembolism have been reported[5-7] so that per WHO recommendation a prophylaxis should been given.[1]

An antiviral agent, Remdesivir, is a treatment for COVID-19 which resulted in faster time to recovery.[12] Remdesivir is a novel nucleotide analogue that has activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro.[13] It was not given to this patient as the medication unfortunately is not yet available in our country.

Convalescent plasma which may possible in providing clinical benefit was not given because it is too, not yet available in our hospital by the time the patient was admitted. However, according to a recent randomized controlled trial, convalescent plasma therapy applied to standard treatment did not result in a statistically significant increase in time to clinical improvement within 28 days for patients with serious or life-threatening COVID-19, as compared to standard treatment alone.. Early termination of the experiment, which may have been underpowered to identify a clinically significant difference, has limited the interpretation.[14]

CONCLUSION

We report herein the first maternal death in our hospital due to COVID-19. Pregnant women with COVID-19 need proper care so that they will not fall into critical conditions such as ARDS and septic shock. Close monitoring on clinical and laboratory courses is recommended. We suggest clinicians that it is prudent to be aware of the potential of rapid deterioration and maternal death among pregnant women diagnosed with COVID-19 despite knowing that information about COVID-19 and its management including specific therapy is still evolving rapidly, and interim guidance by multiple organizations is constantly being updated and expanded.

ACKNOWLEDGMENT

We thank Dr Ramelan Naval Hospital staffs for their efforts to deal with COVID-19. We also thank the Almighty God for reasons too numerous to mention. We declare no competing interests.

REFERENCES

1. World Health Organization (WHO). Clinical Management of COVID-19 Interim Guidance 27 May 2020 [Internet]. 2020. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19
2. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med. 2020;172(9):577–82.
3. Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet [Internet]. 2020;395 (10223):514–23. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30154-9
4. Vincenzo B, Lockwood CJ, Barss VA. Coronavirus disease 2019 (COVID-19): Pregnancy issues [Internet]. 2020. Available from: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-pregnancy-issues?source=history_widget
5. Karami P, Naghavi M, Feyzi A, et al. Mortality of a pregnant patient diagnosed with COVID-19: A case report with clinical, radiological, and histopathological findings. Travel Med Infect Dis [Internet]. 2020;(March):101665. Available from: https://doi.org/10.1016/j.tmaid.2020.101665
6. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, et al. Maternal death due to COVID-19 disease. Am J Obstet Gynecol [Internet]. 2020; Available from: https://doi. org/10.1016/j.ajog.2020.04.030
7. Ahmed I, Azhar A, Eltaweel N, et al. First Covid-19 maternal mortality in the UK associated with thrombotic complications. Br J Haematol [Internet]. 2020;bjh.16849. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.16849

8. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virologi-cal characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut. 2020;1–8.
9. Wang D, Hu B, Hu C, et al. Clinical Character-istics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11) :1061–9.
10. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929–36.
11. Pacheco LD, Saad A. Ventilator management in critical illness. Crit Care Obstet. 2018;215–48.
12. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32445440
13. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269–71.
14. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. JAMA [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32492084

FORMULIR PESAN
MAJALAH OBSTETRI & GINEKOLOGI

Saya yang bertanda tangan di bawah ini

Nama Lengkap : .....

HP ..... E-mail .....

Alamat Rumah : .....

..... Kode Pos .....

Alamat Kantor : .....

..... Kode Pos .....

Telepon ..... Faks .....

Bermaksud untuk :

☐ Berlangganan MOG selama ..... tahun mulai edisi nomor ..... tahun ..... dengan mengirimkan biaya berlangganan sebesar Rp 300.000,00 per tahun

☐ Membeli MOG edisi .....

..... dan edisi .....

masing-masing sebanyak ..... eksemplar, @ Rp. 100.000,00

MOG dikirimkan ke*: ☐ Alamat Rumah ☐ Alamat Kantor

Mengenai biaya berlangganan dan/atau pembelian di atas, ditambah dengan ongkos kirim, atau mengenai informasi lainnya, dapat menghubungi:

Sekretariat Redaksi MOG
a.n. Priska Dwi Wahyurini
Departemen Obstetri dan Ginekologi
FKUA, RSUD Dr Soetomo, Jl. Prof. dr. Moestopo 6-8
Surabaya 60286. Telp. 031-5501185
E-mail: mog@journal.unair.ac.id

....., 20.....

Hormat Saya

*Pilih salah satu

(_____)

Nama Jelas


0854 0386

9 772598 101001