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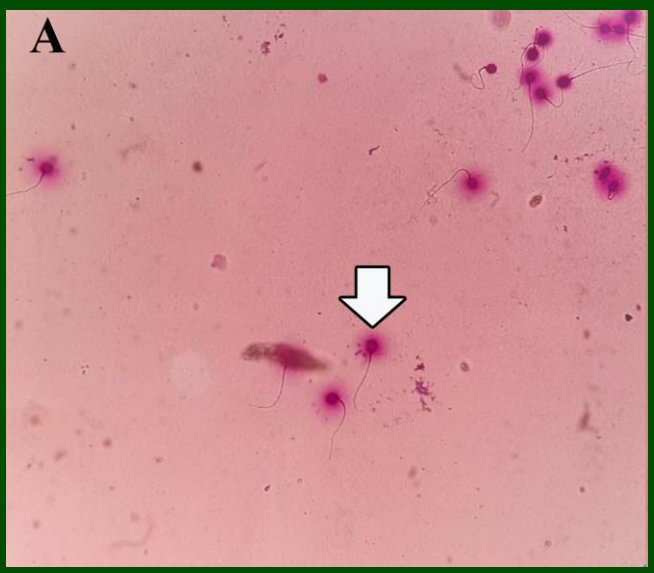

Sperm DNA fragmentation following Sperm Chromatin Dispersion (SCD) test. White arrow indicates sperm with fragmented DNA

Original Research

- Knowledge, education, and information affect chronic energy deficiency among pregnant mothers in the area of Public Health Center Balen, Bojonegoro, Indonesia
- The success rate of intrauterine insemination in sperm preparation swim-up method at room temperature compared to the incubator temperature
- A profile of Gestational Trophoblastic Neoplasia in a tertiary hospital in Surabaya, Indonesia
- The comparison of maternal stress level during pregnancy between two groups of pregnancy outcomes in the COVID-19 pandemic
- Abnormal Uterine Bleeding (AUB) at Haji Adam Malik General Hospital, Medan, North Sumatera, Indonesia
- Clinical profile of geriatric cervical cancer patients in a tertiary hospital in Surabaya, Indonesia
- Obstetric complications and delivery methods in Indonesia

Systematic Review

- Comparison of the potencies of ginger (*Zingiber officinale*) and fennel (*Foeniculum vulgare*) in ameliorating dysmenorrhea pain: A systematic review

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AUTHOR GUIDELINES

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

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Original research reports a substantial body of laboratory or clinical work, presenting the outcome of a large trial, case control, observational or retrospective study. The authors must confirm in the manuscript that they have ethical clearance for the conduct of the reported research. The procedure in the research should be in accordance with the **Declaration of Helsinki 2013**. The ethical clearance should be submitted along with the manuscript. The manuscript should be approximately 3500 words. Total number of tables and figures are limited, advisably not more than five, and references are minimally 20 from the last 10 years before the date of submission. The text consists of **Abstract, Introduction, Materials and Methods, Results and Discussion, Conclusion,** and **Disclosures**. The Disclosures consist of **Acknowledgment, Conflict of Interest, Funding, and Authors Contribution**.

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

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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

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Proceeding book

Offline proceeding

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Online proceeding

Muller S, editor. Proceedings of the 10th international conference on head-driven phrase structure grammar [Internet]; 2003 Jul 18-20; East Lansing (MI). Stanford (CA): CSLI Publications; 2003 [cited 2017 Nov 16]. Available from: http://web.stanford.edu/group/ csli publicationsSta/cslipublications/HPSG/2003/toc.shtml

Thesis/dissertation

Offline thesis/dissertation

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

Online thesis/dissertation

Pahl KM. Preventing anxiety and promoting social and emotional strength in early childhood: an investigation of risk factors [dissertation on the Internet]. St Lucia, Qld: University of Queensland; 2009 [cited 2017 Nov

22]. Available from: https://espace.library.uq.edu.au/view/UQ:178027

3. Website

With author

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

No author

The family impact of Attention Deficit Hyperactivity Disorder (ADHD) [Internet]. 2009 Nov 1 [updated 2010 Jan 1; cited 2010 Apr 8]. Available from:http://www.virtualmedical centre.com.au/healthandlifestyle.asp?sid=192&title=The-Family-Impact-of-Attention-Deficit-Hyperactivity-Disorder-%28ADHD%29page=2

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.

- should be placed outside full stops and commas
- the citation number can be place next to the author name where emphasis is place on the author eg. Smith[2]
- When multiple references are cited at a given place in the text, use a hyphen to join the first and last numbers that are inclusive. Use commas (without spaces) to separate non-inclusive numbers in a multiple citation e.g. ([2,3,4,5,7,10]) is abbreviated to ([2-5,7,10]).
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For example:

Moir and Jessel maintain "that the sexes are interchangeable".[1]
Numerous studies[20-22] have.....
Smith's research .....[21]
Smith and Jones'[22] research .....

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

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

ORIGINAL RESEARCH

Knowledge, education, and information affect chronic energy deficiency among pregnant mothers in the area of Public Health Center Balen, Bojonegoro, Indonesia

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Chronic Energy Deficiency
Knowledge
Education
Informative Support
Instrument Support
Maternal Health

ABSTRACT

Objective: To analyze the effect of knowledge, education and information on the incidence of chronic energy deficiency (CED) in pregnant women at Balen Health Center, Bojonegoro Regency, Indonesia.

Materials and Methods: This research was a correlational analytic study with a cross-sectional approach. The sample of this study were several pregnant women at Public Health Center Balen, Bojonegoro Regency, Indonesia. There were 122 respondents who were recruited with simple random sampling. The independent variables were the predisposing factors, comprising age, number of children, education background, mother's occupational status and knowledge; the enabling factors of the prenatal class participation, and the reinforcing factors of the family support. The dependent variable was the occurrence of CED. Data collection was carried out using questionnaire and secondary data (maternal cohort). Data were processed by editing, scoring, coding, and tabulating. Data analysis used multiple logistic regression with a significance level of 0.05.

Results: The most dominant factor influencing the occurrence of CED was the reinforcing factors of informative support with an Exp value (B) 3.918 and the instrument support with an Exp value (B) value of 3.450. The following factor that influenced the CED incidence was the predisposing factor of knowledge with an Exp value (B) of 2.677, the enabling factor of the prenatal class participation with an Exp value (B) of 1.793, and finally the predisposing factor of education with Exp value (B) of 0.176.

Conclusion: In Balen Health Center Bojonegoro, Indonesia, the predisposing factors significantly affecting Chronic Energy Deficiency in pregnant women were knowledge and education level, while the enabling factors were availability of health facilities and prenatal class participation, and the reinforcing factors were informative support and instrument support.

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Highlights:

1. One of the most common maternal health problems is the Chronic Energy Deficiency (CED) in pregnancy.
2. Factors that lead to CED incidence were analyzed to be able to provide adequate precautions.
3. It was found that knowledge, education, and information are factors that affect chronic energy deficiency among pregnant mothers.

INTRODUCTION

Maternal mortality rate is one of the key indicators of public health status. It refers to the number of maternal deaths due pregnancy complications relative to the total number of births. Maternal mortality is a major health problem in many countries, including Indonesia. Chronic Energy Deficiency (CED) is one of the most common maternal health problems in Indonesia. It is common among pregnant women who suffer from chronic food shortages and various health problems. A large number of pregnant women are still suffering from nutritional disorders, especially malnutrition, CED and nutritional anemia. Upper Arm Circumference (UAC) is a type of anthropometric measurement used to assess the risk of CED in women of childbearing age, which include adolescents, pregnant women, breastfeeding mothers and couples of reproductive age (EFA). UAC threshold in women of productive age with a risk of CED is 23.5 cm. If the circumference is less than 23.5 cm, a woman is regarded as having CED.[1]

CED is one of the health problems in the world, especially in developing countries. CED occurs when the intake of energy, protein, or even both is not sufficient for the body's needs. CED affects many women of childbearing age of 15-45 years. CED can also affect pregnant women who have risk factors for CED.[2]

The nutritional status of a mother prior to or during pregnancy plays a critical role in the outcome of conception. Adequate nutrition is essential for the healthy development of the fetus without congenital abnormalities. Conversely, poor maternal nutrition can result in low birth weight and congenital abnormalities.[3] Genetic and chromosomal disorders can also contribute to the occurrence of congenital abnormalities, with parental genetic abnormalities posing a greater risk.[4] Pregnant women with poor nutritional status are at risk of developing CED, a condition characterized by inadequate energy and protein intake due to insufficient consumption of staple foods, imbalanced meal arrangements, and impaired nutrient metabolism.[5] Multigravida, or women who have been pregnant and delivered a term baby, must prioritize their health and maintain proper nutrition before, during, and after pregnancy.[6] Education level is also an important determinant of nutritional status, as individuals with higher education are more likely to possess better knowledge and information regarding nutrition. Thus, optimal maternal nutrition and health before, during, and after pregnancy are critical for the prevention of adverse outcomes in fetal development.[7]

According to the Ministry of Health, Republic of Indonesia, in 2016 the proportion of pregnant women aged 15-49 years with UAC < 23.5 cm or at risk of CED in Indonesia was 24.2%. The lowest proportion was in Bali of 10.1% and the highest was in East Nusa Tenggara of 45.5%. As for the province of East Java, the prevalence was 29.8%. The number of pregnant women with CED in Bojonegoro Regency, East Java, in a report from 2017 was 10.06% and in 2018 it was 10.74%. The Health Office of Bojonegoro Regency reported that people with CED at Public Health Center Balen, Bojonegoro District in 2017 were as many as 122 or 13.09%, while in 2018 there were 154 people or 16.33%. There was an increase in the prevalence of pregnant women with CED at the health center from 2017 to 2018 by 3.24%.

CED can arise from an imbalance between energy intake and expenditure. This imbalance may be attributed to seasonal or chronic food unavailability, uneven distribution of food within the household, and the strenuous workload experienced by expectant mothers. Furthermore, the nutritional status of the mother plays a significant role in the occurrence of CED. Specifically, young maternal age (below 20 years), short intervals between pregnancies (less than 2 years), frequent pregnancies, and advanced maternal age (over 35 years) increase the likelihood of CED. CED in pregnant women has dire consequences not only on fetal growth, birth weight, and the growth of infants and children but also extends to the next generation. This cycle of poor nutritional status can perpetuate from infancy, toddlerhood, adolescence, and future mothers as the next generation. The maternal effects of CED include infectious diseases, obstructed labor, maternal mortality, low birth weight, and neonatal deaths.

In order to decrease the likelihood of low birth weight (LBW) deliveries, it is imperative to enhance the nutritional state of mothers with CED prior to conception. Preconception care should focus on achieving a healthy weight and ensuring adequate nutritional intake for optimal maternal and fetal health. It is crucial to emphasize the importance of proper nutritional intake during pregnancy.[3] To overcome CED in pregnant women, interventions such as education, information dissemination, and communication regarding CED and its influencing factors, as well as strategies for overcoming it, are necessary. These efforts should include recommendations for supplementary feeding and iron supplementation during pregnancy.[8]

In pregnant women, CED typically arises due to inadequate energy intake that existed prior to pregnancy. This is because the energy requirements for pregnant women are greater than those of non-pregnant

women. The factors contributing to CED can be classified as direct or indirect causes. Direct causes include insufficient dietary intake and infections. Indirect causes encompass various obstacles to nutrient utilization, poor nutritional status, low body weight, socioeconomic disadvantage, inadequate knowledge and education regarding nutrition, limited food availability, poor hygiene conditions, high parity, early pregnancy, low income, uneven distribution and trade, poor diet, and inadequate administration of iron tablets.[9]

The aim of this study was to analyze the effect of knowledge, education and information on CED incidence among pregnant women at Public Health Center Balen, Bojonegoro Regency, East Java, Indonesia. The effect of each variables on CED incidence among pregnant women in the health center were also elaborated as the specific purpose of this study.

MATERIALS AND METHODS

This was an observational cross-sectional analytic research using quantitative approach. The population was all pregnant women in the working area of Public Health Center at Balen, Bojonegoro District, East Java, Indonesia, up to August 2020 as many as 645 people. The sample in this study was some pregnant women in the area of Public Health Center Balen, Bojonegoro, in 2020 as many as 122 people. They were recruited using simple random sampling. Data retrieval was performed using questionnaire. This research had received a proper ethical certificate with number No. EA/326/KEPK-Poltekkes_Sby/V/2020.

RESULTS AND DISCUSSION

This study observed the predisposing factors of CED incidence, which included age, number of children, education level, mother's working Status, and knowledge, the enabling factors of the availability of health facilities and the prenatal class participation, as well as the reinforcing factors that comprised of the family support.

General description of the respondents

The distribution of the data is described in Table 1. The most dominant factor influencing CED incidence was the reinforcing factors, consisting of the informative support with an Exp (B) value=3.918 and instrument support with an Exp (B) value=3.450. The following factor that influenced CED incidence was the predisposing factors of knowledge) with Exp (B) value=2.677, the enabling factors of the prenatal class participation with Exp (B) value=1.793, and the last was the predisposing factors of education with Exp (B) value=.176.

Table 1. Distribution of predisposing factors (age, number of children, education level, mother's working status, knowledge) at the area of Public Health Center Balen.

Variables	Categories	F	Percentage
Age	< 20 - > 35 y.o.	25	20.5%
	≥ 20 - ≤ 35 y.o.	97	79.5%
	Total	122	100%
Number of children	0-1	92	75.4%
	≥ 2	30	24.6%
	Total	122	100 %
Educational background	Elementary school	47	38.5%
	High School	56	45.9%
	College	19	25.6%
	Total	122	100%
Occupational Status	Unemployed	87	71.3%
	Employed	35	28.7%
	Total	122	100%
Knowledge	Low	19	15.6%
	Average	44	36.1%
	Good	59	48.4%
	Total	122	100%

Table 2. Distribution of enabling factors based on class participation of the pregnant women in the area of Public Health Center Balen.

Variable	Categories	F	Percentage
Prenatal class participation	Never	27	22.1%
	Sometimes	43	35.2%
	Always	52	42.6%
	Total	122	100%

Table 3. Distribution of reinforcing factors based on family support in prenatal class participation among pregnant women at the area of Public Health Center Balen.

Variables	Categories	F	%
Information support	Unsupporting	48	39.3%
	Supporting	74	60.7%
	Total	122	100%
Instrumental support	Unsupporting		37.7%
	Supporting	76	62.3%
	Total	122	100%
Emotional support	Unsupporting	67	54.9%
	Supporting	55	45.1%
	Total	122	100%
Evaluation support	Unsupporting	63	51.6%
	Supporting	59	48.4%
	Total	122	100%

Presdisposing factors

This study showed that most of the respondents aged 20-35 years, comprising 97 people (79.5%). Most of the respondents had 0-1 children as many as 92 people

Table 4. Distribution of respondents with chronic energy deficiency in the area of Public Health Center Balen.

Variables	Categories	F	Percentages
CED	CED	24	19.7%
	Non CED	98	80.3%
	Total	122	100%

Table 5. The results of the influence of the predisposing factor variables (age, number of children, education level, mother's working status, knowledge), enabling factors (participation in prenatal class), reinforcing and factors (family support) on incidence of CED among pregnant women in the working area of the Public Health Center Balen in 2020.

Variables	Regression						Notes
	Regres-sion Coeffi-cient (B)	S.E	Wald	dF	Sig.	Exp (B)	
Age	.543	.719	.571	1	.450	1.722	Not significant
Number of children	1.047	.750	1.949	1	.163	2.849	Not significant
Educational background	-1.736	.468	13.751	1	.000	.176	Significant
Occupational status	.194	.622	.098	1	.755	1.215	Not significant
Knowledge	.985	.424	5.404	1	.020	2.677	Significant
Prenatal class	.584	.294	3.953	1	.047	1.793	Significant
Information support	1.365	.635	4.618	1	.032	3.918	Significant
Instrumental support	1.238	.518	5.723	1	.017	3.450	Significant
Emotional support	.425	.629	.457	1	.499	1.530	Not significant
Evaluation support	-.617	.643	.921	1	.337	.540	Not significant

Table 6. Dominant factors that influenced CED incidence in pregnant women in the working area of Public Health Center Balen in 2020.

Sub-Variables	Sig (p)	Exp (B)	Notes
Information support	.032	3.918	Significant
Instrumental support	.017	3.450	Significant
Knowledge	.020	2.677	Significant
Prenatal class	.047	1.793	Significant
Educational background	.000	.176	Significant

(75.4%), most of the respondents' education was high school, comprising 56 people with secondary education (45.9%), most of the respondents' occupational status, 87 people (71.3%). The presdisposing factors (age, number of children, education background, mother's occupational status, and knowledge), which had an influence on CED incidence in pregnant women, after being cross-tabulated and analyzed using multiple logistic regression test with SPSS with a significance value of 0.05, revealed that the level of education resulted in p value of 0.000 (< 0.05) and knowledge resulted in p value of 0.020 (< 0.05), underscoring the influence of the level of education and knowledge of pregnant women on CED incidence in pregnant women.

The knowledge that women possess plays a crucial role in their decision-making and subsequent behavior, particularly with regards to providing adequate nutrition to their infants during pregnancy. This is particularly important during periods of cravings, during which the mother may be reluctant to consume nutrient-rich foods due to feelings of nausea, leading to a preference for foods with a fresh and sour taste. However, with adequate knowledge, mothers are more likely to meet their own and their baby's nutritional requirements even during such conditions.[10] These findings align with a previous study conducted by Handayani and Budianingrum (2011), who investigated the factors influencing chronic energy deficiency (CED) in pregnant women at a public health center in Wedi, Klaten, Indonesia.[11] The researchers hypothesized that CED incidence could be attributed to a low level of knowledge among respondents who had not consulted health workers or lacked access to information about CED.[12]

Enabling factors

This study showed that most of the respondents always took prenatal class. They were as many as 52 people (42.6%). As many as 27 pregnant women who had never participated in prenatal class, 17 (37.0%) were not

CED mothers and of 43 pregnant women who sometimes participated in prenatal class, 37 86.0%) were not CED mothers. Among 52 pregnant women who always participated in prenatal class, 44 people (84.6%) were not CED mothers. After cross-tabulation and data analysis using multiple logistic regression test with significance value of 0.05 using SPSS, the obtained p=value was 0.047 (<0.05), showing the effect of prenatal class on CED incidence in pregnant women.

Reinforcing factors

This study showed that most of the families provided informative support to pregnant women, as many as 74 people (60.7%). Most of the families provided instrumental support to pregnant women, as many as 76 people (62.3%), but most did not provide emotional support, as many as 67 people (54.9%), and most did not provide assessment support to the pregnant women, as many as 63 people (51.6%).

Cross-tabulation and data analysis using multiple logistic regression test with a significance value of 0.05 with SPSS, revealed that informative support had p value of 0.032 (<0.05) and instrument support had p value of 0.017 (<0.05), indicating the influence of informative and instrument support on CED incidence in pregnant women.

Effect of predisposing factors on CED incidence

The results of logistic regression analysis showed that knowledge and level of education had a significant influence on CED incidence in pregnant women. Predisposing factors of age, number of children and working status of the mother did not have a significant effect on CED incidence in pregnant women. Presdisposing factors are factors that facilitate or predispose to the occurrence of a person's behavior, including knowledge, attitudes, beliefs and cultural values, perceptions, some individual characteristics such as age, gender, level of education and occupation.

Knowledge

Knowledge had a significant influence on CED incidence in pregnant women. Most of the respondents had knowledge in good category, which means that pregnant women who have good knowledge about nutrition in pregnancy are less likely to experience CED. Knowledge is the result of human sensing, or the result of someone knowing about objects through their senses. Knowledge is very important for the formation of a person's actions that are applied in the form of behavior.[13] Knowledge can be interpreted as actionable information or information that can be followed up and can be used as a basis for action, for making decisions and for taking certain directions or strategies.[14] Factors that influence knowledge include age, educational background, experience, and occupation. Age affects the perception and mindset of a person. The higher the level of maturity and strength of an individual, the more mature the individual in thinking or working. In terms of public trust, trust is given to more mature individuals will be more trusted than someone not mature enough. At middle age (31-49 years), individuals will play a more active role in the society and social life and make more preparations for the success of the efforts for old age adaptation. In addition, middle-aged people will spend more time reading.[15]

The results of this study were in accordance with research conducted by Hilda et al. (2022) regarding the relationship between knowledge and attitudes with CED incidence in pregnant women. They found that there was a relationship between knowledge and CED incidence.[16] The results of this study were also in accordance the results from a study by Rika et al. (2021) on the relationship between knowledge about nutrition and CED in pregnancy.[17] Aulia et al. (2020) in their study on the relationship between knowledge of nutrition, food availability and intake with CED incidence also found a significant relationship between those variables.[18]

In this research, it was identified that a subset of pregnant women exhibits suboptimal knowledge about nutrition during pregnancy. Insufficient understanding of pregnancy nutrition by expectant mothers can negatively impact their dietary intake, which is crucial for supporting maternal and fetal growth and development. Maternal knowledge of pregnancy nutrition plays a significant role in ensuring appropriate intake of essential nutrients and energy required during pregnancy. Pregnant women with higher knowledge of nutrition are better equipped to comprehend the increased energy and nutrient requirements associated with pregnancy, and subsequently select nutrient-dense food options. Adequate nutrition during pregnancy is critical to prevent adverse maternal and fetal outcomes. Suboptimal dietary intake during pregnancy has been associated with lower infant birth weight, and an increased incidence of maternal complications. Therefore, promoting maternal knowledge about optimal nutrition during pregnancy is an important strategy to support maternal and fetal health.

Education

Education has a significant influence on CED incidence in pregnant women. Most of the respondents had education in the middle category, which means that

pregnant women who had a fairly good education about nutrition in pregnancy were less likely to experience CED.

The higher the education, the easier it is for an individual to receive information, so the more knowledge the individual may have, and vice versa.[15] Lack of education will hinder the development of a person's attitude towards newly introduced values, including on nutrition during pregnancy. Education as a process of personal formation is defined as a systematic and systemic activity directed to the formation of the personality of the students. Educational factors affect the diet of pregnant women. Individuals with higher education levels are expected to have better knowledge or information about nutrition so that they can meet their nutritional intake. The results of this study were in accordance to those from a study by Anggraeni et al. (2016) on CED incidence at a public health center in Yogyakarta which found relationship between education and CED incidence in pregnant women.

Education can predict the occurrence of CED with an Exp (B) value of 29.83.[19] In addition, the results in this study were also supported by a previous study by Mijayanti et al. (2020), who investigated factors of CED in pregnant women in Sukoharjo, Indonesia. This study found a relationship between education factors and CED in pregnant women. [20]

The level of education is a significant determinant of an individual's understanding of health and pregnancy-related concerns, subsequently influencing maternal behavior regarding pregnancy care and nutrition. Education has a crucial role in modifying individuals' attitudes and behaviors towards healthy lifestyles. Higher levels of education are associated with better comprehension and uptake of health-related information. Inadequate nutrition and poor dietary habits can negatively impact an individual's nutritional status and increase their risk of malnutrition, particularly protein-energy malnutrition (PEM). Inadequate intake of energy and other essential food components can result in malnourishment and other associated consequences.

Age

Age did not have a significant effect on CED incidence in pregnant women. Most of the respondents aged 20-35 years, which means that pregnant women were of healthy reproductive age. Delivering a baby at a young or too old age results in lower quality of the child and will also harm the health of the mother. The best age is more than 20 years and less than 35 years, so it is expected that the nutritional status of the pregnant women will be better.[8] In this study, it was found that the age of pregnant women was not related to CED incidence. This was because the age of the respondents was mostly at the age of 20-35 years which was the best ages for women to get pregnant so that there was no relationship between age and CED incidence in this study. This finding was in line with that of Novitasari et al. (2019) who found no significant relationship between age and CED incidence.[21]

In this study, there were also pregnant women who experienced chronic lack of energy at an unhealthy reproductive age, which was of less than 20 years and more than 35 years. Pregnancy at this age is still acceptable as long as the condition of the woman's body and health, including nutrition, are in good condition. After the age of 35, some women are classified as having high-risk pregnancies. At this age, maternal and infant mortality rates have increased.

Number of children

The number of children did not have a significant effect on CED incidence in pregnant women. Most respondents had children in the 0-1 category, which means that the pregnant women tended to experience CED.

Parity (number of children) is a woman's condition related to the number of children born. Parity is also one of the factors that affect the nutritional status of pregnant women. Parity is a woman's condition related to the number of children born. Parity is a factor that greatly influences the outcome of conception.[22] This study was in line with a study conducted by Novitasari et al. (2019) who found no significant relationship between parity and CED. [21]

This study revealed that pregnant women who experienced CED had typically given birth to only one child or were currently pregnant with their first child. This observation is attributable to the fact that mothers with limited prior pregnancy experience may be less aware of the importance of nutrient intake during pregnancy, thus increasing the risk of developing various health complications, including anemia and mal-nutrition.

Mothers' occupational status

Mothers' occupational status did not have a significant effect on CED incidence in pregnant women. Most of the respondents had an unemployed status, which means that those pregnant women tended to experience chronic lack of energy. Work is an act or doing something that is done to earn a living in order to live.[23] The amount of

the family's income, the cost of the food itself, and the degree of management of the family resources are among the factors that affect the family's ability to purchase food. Families with low incomes are probably less able to provide for their food needs, particularly for their bodies' nutritional requirements. Diet can be influenced by income status. The most crucial element in influencing the quality and quantity of food is income. The quality of food increases along with income, thus the more money one has, the more of the money will be spent on fruit, vegetables, and a variety of other foods.[22]

The reason why some respondents had a poor economy was because they did not help their husbands acquire extra sources of income, which left their family's income dependent solely on their husbands' income. Their perspective was affected by their lack of knowledge, and as a result, they lacked the motivation to start their own businesses. They simply settled down to be housewives and waited for their husbands to give them money to spend.

Effect of enabling factors on CED incidence

The results of this study showed that there was a significant relationship between the enabling factor of participation in prenatal class on CED incidence. Most of the respondents always participated the prenatal class so they had improved their knowledge about pregnancy and about nutrition in pregnancy, preventing them from CED. In prenatal class, pregnant women will learn together, discuss and share experiences about maternal and child health in a comprehensive and systematic manner that can be carried out on a scheduled and continuous basis.[24] The general purposes of the class were to improve knowledge, change attitudes and behavior of the mothers to understand about pregnancy, body changes and complaints during pregnancy, pregnancy care, childbirth, postpartum care, postnatal family planning, newborn care, local myths/beliefs/ customs, infectious diseases and birth certificates.

The results of this study were in accordance with those of Agustiningsih (2018) who studied effectiveness of the classroom learning program for pregnant women on nutrition knowledge, anemia status, CED and LBW. The study found significant difference in UAC between pregnant women who participated the class and those who did not.[25]

In this study, pregnant women with CED mostly never participated in prenatal class. The impact that will arise from conducting health education activities on behavior change takes a long time, but if the behavior is successfully adopted by individuals or the community, then it will be persistent. It will last a long time, maybe even in a lifetime. Education is a form of intervention aimed at changing behavior to become conducive to health.

Effect of reinforcing factors on CED incidence

The results of logistic regression analysis showed that reinforcing factors of informative support and instrument support had a significant effect on CED incidence in pregnant women, while the reinforcing factors of emotional support and assessment support did not have a significant effect on CED incidence. Reinforcing factors are the consequences of actions that determine whether the perpetrator receives positive (or negative) feedback and is socially supported after the feedback has occurred. Reinforcing factors thus include social support, peer influence, and advice and feedback by health care providers. Reinforcing factors also include the physical consequences of behavior, which can be separated from the social context.

Information support

In this study, information support had a significant influence on CED incidence in pregnant women. Most of the respondents received informative support from their families. Family support is a process that occurs throughout life, the nature and type of support vary at each stage of the life cycle. However, in all stages of life, all family social support enables the family to function with various intelligences and senses. As a result this improves family health and adaptation. The family functions as a collector and disseminator of information about the world.[26] Family support is an attitude, action and acceptance of the family towards family members. Family support is a reinforcing factor in the formation of health behavior. The results of this study were in line with those of Juwita (2018), who studied relationship between counseling and family support to the compliance of pregnant women consuming Fe tablets,[27] and those of Novitasari et al (2019) which both found significant relationship between family support and CED incidence.[21]

Husband's support plays an important role in providing information about participating classes for pregnant women. Paying attention to the nutritional intake needed by pregnant women is a real form of care and responsibility of the husband in the wife's pregnancy, because the husband is the closest family member and can be trusted to provide support to the wife. Support is important for a pregnant wife as she is seeking for information regarding the potential risks of CED due to inadequate nutrient intake during pregnancy to prevent

adverse consequences such as persistent fatigue, fetal miscarriage, and low infant birth weight.

Instrumental support

Instrumental support has a significant effect on CED incidence in pregnant women. Most of the respondents received instrumental support from their families. Family is a source of practical and concrete help. The results of this study were in line with those by Novitasari et al. (2019) who found significant relationship between family support and CED incidence.[21] Mothers require instrumental support from their family or spouse during pregnancy, including assistance with attending healthcare check-ups and prenatal classes. This support facilitates mothers' access to health education, enhancing their knowledge of various aspects of pregnancy, including nutrition.

Emotional support

Emotional support does not have a significant effect on CED incidence in pregnant women. Most of the respondents did not get emotional support from their families. Family is a safe and peaceful place for rest and recovery and helps control emotions.[26] The finding in this study confirmed that of Sari (2020) who found that husband's support had no relationship with CED incidence in pregnant women.[28] The provision of emotional support by family members is a crucial determinant of pregnant women's participation in prenatal classes and adherence to recommended nutritional intake. Husbands or families may act as motivators, positively influencing the behavioral changes of pregnant women. To reduce physical stress, pregnant women require their husbands' support, providing emotional security and lending a listening ear. Encouragement from family members promotes healthy pregnancies and dietary practices.

Evaluation support

Evaluation support does not have a significant effect on CED incidence in pregnant women. Most of the respondents did not receive assessment support from their families. Evaluation support of the family acts as a feedback guide, guiding and mediating problem solving and as a source and validator.[26] This study also found results as those of Sari (2020) that there was no relationship with CED incidence in pregnant women.[28]

During prenatal classes, family assessment support plays a pivotal role in ensuring pregnant women receive necessary support. Family members, particularly the spouse, act as an encouraging and guiding system, reassuring the pregnant woman of their willingness to provide assistance whenever necessary. This support system acknowledges and values the family's current situation, emphasizing the importance of supportive measures in promoting positive outcomes.

CONCLUSION

In Health Center Balen, Bojonegoro, Indonesia, among the predisposing factors, which included age, number of children, education level, mother's occupational status, and knowledge, the factors that had significant effect on CED incidence in pregnant women were knowledge and education level. The enabling factors of availability of health facilities and participation in prenatal class had significant effect on CED incidence in pregnant women, while among the family support, which included informative, instrumental, emotional, and evaluation supports, those that had significant effect on CED incidence were informative and instrument supports.

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ORIGINAL RESEARCH

The success rate of intrauterine insemination in sperm preparation swim-up method at room temperature compared to the incubator temperature

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ABSTRACT

Objective: This study aimed to determine the effect of temperature during sperm preparation on total sperm motile count (TMSC), sperm motility, sperm morphology, DNA fragmentation index (DFI), and pregnancy rate.

Materials and Methods: A quasi-experimental laboratory study with pre- and post-test control group was conducted at Sekar Fertility Clinic, Dr. Moewardi General Hospital, Surakarta, Indonesia. A total of 20 sperm samples from infertile patients were prepared using the swim-up method at 27°C (group 1) and 37°C (group 2). TMSC, motility, morphology, and DFI examinations were performed. In addition, IUI was performed to confirm pregnancy rate. Sperm DNA fragmentation was determined using Sperm Chromatin Dispersion/SpermFunc DNAf test. Sperm DNA fragmentation was characterized by a halo <30% of the volume of the sperm head.

Results: Group 1 had mean TMSC of 13.77 ± 9.30, while group 2 had 14.82 ± 8.82; p=0.218. Group 1 had a motility value 82.25+12.77 and group 2 had 82.55 ± 11.69; p=0.968. The morphological value for group 1 was 11.25 ± 5.15 and group 2 was 11.6 ± 5.34; p=0.626. The mean DFI for group 1 was 17.79 ± 10.88 and group 2 was 18.18 ± 12.95; p=0.765. Pregnancy rate in group 1 was 10% and group 2 was 20%; p=1.000.

Conclusion: There were no significant differences in TMSC, sperm motility, sperm morphology, DFI, and pregnancy rate in sperm preparation using the swim-up method at 27°C and 37°C.

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Highlights:

1. There were no significant differences in TMSC, sperm motility, sperm morphology, and DFI in sperm preparation using the swim-up method at 27°C and 37°C. However, this study provided an overview of the average improvement of DFI at 27°C compared to 37°C.
2. There was no significant difference in the pregnancy rate of IUI in sperm preparation using the swim-up method at 27°C and 37°C.

INTRODUCTION

Malefactors' infertility accounts for half of all infertility cases. Infertility affects 15% of 48.5 million couples globally, and 50% is caused by male factors with a range of 20% to 70%. The leading cause of male infertility is sperm abnormalities, including oligo-zoospermia (low sperm count), asthenozoospermia (poor sperm motility), and teratozoospermia (abnormal sperm morphology).[1–3] Treatment options for male infertility are assisted reproductive technology (ART), including intrauterine insemination (IUI), in vitro fertilization (IVF), and intracytoplasmic sperm injection (ICSI). IUI is the most preferred choice because of the easy method and simple equipment.[4,5] However, the live birth rate in pregnancies with IUI is lower (7.7%) than in the IVF/ICSI program (19.8%). Sperm quality is also affected by sperm preparation technique, preparation temperature, preparation time interval, and preparation medium. It is an essential factor in the success of IUI.[6,7] Low levels of sperm DNA fragmentation during IUI increases pregnancy after IUI.[8]

Incubation at room temperature (23°C) for 24 hour had significantly higher progressive motility and normal morphology. In addition, a decrease in the levels of acrosome reactions, apoptosis, and death of spermatozoa at room temperature reduces the level of DNA fragmentation. On the other hand, incubation at 37°C for 4 hours increased vacuoles in the sperm head.[9] Each 5°C lower temperature was significantly associated with 1.94 × 10^6/ml, 7.12 × 10^6, 0.77%, 0.81%, 6.48 × 10^6, and 5.87 × 10^6 decreases in sperm concentration, total sperm count, total motility, progressive motility, TMSC, and progressively motile sperm count, respectively.[10] Based on those results, a research was conducted to study the effect of differences in temperature of sperm preparation using the swim-up method on total sperm motile count (TMSC), sperm motility, sperm morphology, DFI, and pregnancy rate.

MATERIALS AND METHODS

Sample preparation

A quasi-experimental laboratory test with pre and post-test control group designs was conducted at the Sekar Fertility Clinic, Dr. Moewardi General Hospital, Surakarta, Indonesia. Twenty sperm samples from infertility patients were prepared using the swim-up method at 27°C (group 1) and 37°C (group 2). Sampling used purposive sampling techniques using inclusion and exclusion criteria. The inclusion criteria were as follows: 1) Sperm comes from male infertility patients who a team of fertility doctors had decided to undergo the IUI program, 2) Ejaculate was removed after the patients' abstinence from sexuality for 2-7 days, 3) The volume of ejaculate semen was at least 2 ml, TMSC ≥5 x 10^6 and abnormal sperm morphology <4%. The patients were excluded from the study if they were unable to remove the ejaculate fluid on the day of sampling. Sperm preparation using swim-up method was performed according to WHO guidelines in 2010, where semen undergoes complete liquefaction for 15-60 minutes at incubator temperature of 37°C before processing. Furthermore, the samples were taken as much as 1 ml on each tube and transferred in a cone-shaped centrifugal tube sterilely. At the top of the liquid, the semen was coated with a 2 ml sperm rinse®, then the tube was placed at an angle of 45° and incubated for 60 minutes at a temperature of 23°C and 37°C. Sperm with good quality will actively move out towards the culture media and in aspiration. Sperm that swim farthest have the probability of being sperm with normal motility and morphology.[11]

Total motile sperm count calculation

All samples were divided into 1 ml for sperm preparation at temperatures of 27°C and 37°C. Sperm concentration was calculated using the Makler Chamber (Sefi, Israel). Sperm concentration was obtained by counting the total sperm in 10 boxes in the Makler chamber. The result obtained was the number of spermatozoa per unit volume of semen in milliliters (10^6). The results of TMSC were obtained by multiplying the parameters of semen in the form of volume, and concentration, by the proportion of motile sperm that was progressively divided by 100%.[12]

Sperm motility

Spermatozoa motility is divided into progressive, non-progressive, and immotile. The state in which the spermatozoa move actively, move straight or in large circular motions, and the speed is well measured based on WHO criteria (2010). Sperm motility in semen should be assessed as soon as possible after the sample is thawed (preferably at 30 minutes, maximum within 1 hour after ejaculation) to limit the effects of dehydration, changes in pH, and temperature. The semen sample was mixed evenly. Semen samples were prepared in wet preparations at a depth of 20 μm. The sample was allowed to float for 60 seconds. The slide was checked with contrast optics at 200x or 400x magnification. The assessment was carried out on at least 200 spermatozoa in one field of view and the value of motility. Normal sperm progressive motility value was 40%.[1]

DNA fragmentation index

DNA fragmentation index assessment used SpermFunc® DNAf (Fertitech, Canada) and followed sperm chromatin dispersion test technology. Semen samples were diluted using normal salts to reach a final concentration of 5-10x10^6. Next, a diluted sample was placed on a pre-coated slide and dipped in solution A at 20-28°C for seven minutes. The pre-coated slide was lowered and dried at room temperature, then dipped again in solution B and incubated for 25 minutes at a temperature of 20-28°C. Then, the pre-coated slide was washed with distilled water, 70% ethanol, 90% ethanol, and 100% ethanol for 2 minutes. The pre-coated slide had to be perfectly dry, then 15-20 drops of Wright color over the pre-coated slide was applied and then 30-40 drops Wright buffer solution was given slowly. After 15 minutes, the slide was rinsed with water and dried at room temperature. Observation of 500 spermatozoa under a microscope with 400x magnification was performed and sperm with DNA fragmentation was counted. Normal DNA was recognized to be at least 33.3% of halo formation in the head of the sperm. DFI was obtained by comparing the amount of DNA fragmentation with the total observed sperm count and multiplied by 100%. The average sperm percentage usually has DFI <30%.[13]

Sperm preparation using the swim-up method

Sperm preparation used the swim-up method based on World Health Organization (WHO) protocols. As much as 1 ml of the semen sample was added with a supplemented medium of 1.2 ml on a sterile tube and incubated at 37°C for 45 minutes with an oblique tube position of 45°. Sperm samples were collected with centrifugation of 1500 rpm for 5 minutes with the Thermo Scientific Heraeus Labofuge® 300. The samples were put into storage boxes with sterile techniques to avoid direct light exposure. Incubation was carried out a maximum of 1 hour after ejaculation.[7] Next, the sperm sample was divided into two parts. The first part was stored in a temperature incubator of 27°C and the second part at 37°C, each incubated for 20 minutes before insemination.

Intra Uterine Insemination (IUI)

The IUI step was done to see the pregnancy rate. At the time of IUI, the subject was randomized by the generation of numbers. IUI was performed after the sperm preparation was completed and the female partner of the subject was prepared (all less than 15 minutes). The sperm was inseminated using a Gynaetics catheter by an Obstetrics-Gynaecology specialist. The patients were rested in a lying position for 15-20 minutes after insemination. The use of IUI is recommended when TMSC values range from 3x10^6-19x10^6 motile sperm.[14]

Pregnancy

Sixteen days after insemination, β-HCG was taken. The outcome was categorized as pregnant if the β-HCG level was >5 mIU/ml.

Table 1. Characteristic of research participants

Characteristic	Frequency	Percentage (%)
Age (years)		
<30	6	30
≥30	14	70
Infertility period (years)		
<2	4	20
≥2	16	80
BMI (kg/m^2)		
Underweight	1	5
Normal	7	35
Overweight/Obesity	12	60
Body height (cm)		
<165	1	5
≥165	19	95
Bodyweight (kg)		
<70	8	40
≥70	12	60
Smoking		
Non-smoker	12	60
Smoker	8	40

Std. Dev: Standard deviation; BMI: Body mass index.

Statistical analysis

Normal distribution was tested using Kolmogorov Smirnov. Data were generally distributed if α >0.0 and customarily distributed, presented by mean and standard deviation, and tested using a T-test to sample pairs. The data that were not normally distributed were presented by median and analyzed using Wilcoxon. Categorical data were analyzed by Fischer's Exact test. Data were analyzed using SPSS 23.

Ethics considerations

The institutional review board approved by the Dr. Moewardi General Hospital, Surakarta, Indonesia (IRB No. 1.045/VIII/HREC/2022). The informed consent was submitted by all participants when they had enrolled in this present study.

RESULTS AND DISCUSSION

The participant's characteristics are shown in Table 1. The age of the study participants was mostly ≥30 years as much as 70%, and they experienced infertility ≥2 years since they married as much as 80%. The BMI of overweight/obesity was as much as 60%, height was mostly ≥165 cm in as much as 95%, and weight ≥70 as much as 60%. Most of the participants (60%) were non-smokers.

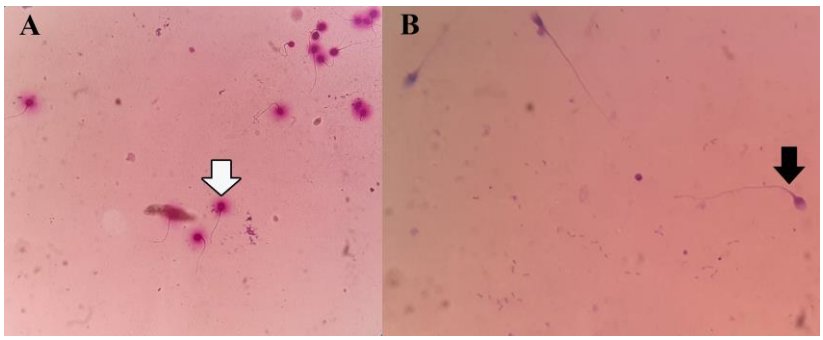

Figure. 1. Sperm DNA fragmentation following Sperm Chromatin Dispersion (SCD) test. (A) The white arrow indicates sperm with fragmented DNA. (B) The black arrow showed sperm with normal morphology.

Table 2. Effect of swim-up temperature on concentration, TMSC, motility, normal morphology, and DNA fragmentation index

Parameters	N	Mean ± Std. Dev	p
Concentration (million/mL)			
Before swim-up	20	66.25 ± 41.67	
After swim-up at 27°C	20	19.05 ± 14.33	0.797
After swim-up at 37°C	20	19.97 ± 13.06	
TMSC ($x10^6$)			
Before swim-up	20	90.16 ± 46.90	
After swim-up at 27°C	20	13.77 ± 9.30	0.218
After swim-up at 37°C	20	14.82 ± 8.82	
Motility (%)			
Before swim-up	20	60.10 ± 18.07	
After swim-up at 27°C	20	82.25 ± 12.77	0.968
After swim-up at 37°C	20	82.55 ± 11.69	
Normal morphology (%)			
Before swim-up	20	7.15 ± 3.07	
After swim-up at 27°C	20	11.25 ± 5.15	0.626
After swim-up at 37°C	20	11.60 ± 5.34	
DFI (%)			
Before swim-up	20	22.69 ± 11.39	
After swim-up at 27°C	20	17.79 ± 10.88	0.765
After swim-up at 37°C	20	18.18 ± 12.95	

TMSC: Total sperm motile count; DFI: DNA fragmentation index;
Std. Dev: Standard deviation

Swim-up at either 27°C or 37°C reduced the number of TMSC and DFI but increased motility compared to pre-swim-up. However, those changes were not statistically significant ($p>0.05$). P-value for each parameter were 0.218, 0.968, 0.626, and 0.765 respectively. This indicated that temperature during swim-up did not affect sperm quality. Table 3 shows that the pregnancy rate in 27°C was 1 (10%) and 37°C was 2 (20%). There were no significant results between IUI at a temperature of 27°C and 37°C ($p=1.000$). Most of the subjects were ≥30 years old.

A decrease in reproductive capacity is associated with age, gonadotropin levels increase, testosterone levels decrease, Leydig cell count, Sertoli cells, and germ cells decrease with age.[15]

Table 3. IUI and pregnancy outcome

IUI	Pregnancy				p
	Negative		Positive		
	n	%	n	%	
Sperm 27°C	9	90	1	10	1.000
Sperm 37°C	8	80	2	20	

IUI: Intrauterine insemination

BMI also affects infertility, in particular by altering the physical structure and molecules of gametes in the testes and sperm.[16] Obesity may cause sperm morphological abnormalities in the form of head abnormalities.[17] In

addition, overweight in men can cause endocrine disorders associated with decreased sex hormone binding globulins and decreased total testosterone levels.[18] The content of cigarettes such as nicotine, cadmium, lead, and benzopyrene negatively affects the integrity of DNA.[19] Cigarettes contain high levels of reactive oxygen species (ROS) (superoxide anions, hydrogen peroxide, and hydroxyl radicals). ROS is produced mainly in seminal fluids, increasing leukocyte levels and causing oxidation stress that leads to sperm DNA damage.[20]

The study showed significant differences between the sperm before and after preparation. Sperm preparation was capable of removing immotile sperm and immature cells.[21] The results showed that the highest DFI occurred in the sperm of the pretest group that had not undergone sperm preparation. Sperm preparation at 27°C had a lower DFI when compared to sperm preparation at 37°C, but showed no significant statistical results. These results were in line with previous research that DFI values increased in processed samples at 37°C compared to room temperature, although the difference was not statistically significant.[22]

This study showed the results that sperm preparation increases motility and morphological levels. Sperm motility and morphology results at 27°C lower than 37°C. This did not confirm the results of the study by Thijssen et al., who reported that sperm quality is better incubated at room temperature (23°C) when compared to 35°C. In addition, the sperm morphology also decreased significantly at 35°C incubation.[7]

Consistent with previous studies, this study showed a pregnancy rate of 15%. In those studies, mean pregnancy rate after IUI treatment was 10-20.5% The pregnancy rate in our study was based on chemical pregnancy, and the result was not statistically significant. Several factors in female and male partners influence the pregnancy rate in ART programs. In females, the increase in clinical pregnancy is affected by age, body mass index, FSH levels, estradiol levels, pre-ovulation follicles, and endometrial thickness. Males are affected by TMSC values and the ratio of sperm to progressive motility.[23,24]

CONCLUSION

There were no significant differences in TMSC, sperm motility, sperm morphology, DFI, and pregnancy rate in sperm preparation using the swim-up method at room temperature (27°C) and body temperature of 37°C. It is necessary to conduct studies with larger sample size, considering the ovary stimulation method, the number of follicles obtained, and observing the outcome until further clinical pregnancy.

DISCLOSURES

Acknowledgment

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Conflict of interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: EM, RKD, AMT, AZJ. Data curation: EM, RKD, AMT, AZJ. Formal analysis: EM, URB, MP, LS, MS. Funding acquisition: EM, URB, TP, AAR. Investigation: AL, D, AAR, CH. Methodology: MP, TP, AL, D, CH. Project administration: LS, MS. Resources: EM, URB, RKD, AMT, AZJ. Software: EM, AAR. Supervision: TP, AL, CH. Validation: EM, URB, MP, TP, AAR. Visualization: D, RKD, AMT, AZJ. Writing – original draft: EM. Writing – review & editing: all authors.

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ORIGINAL RESEARCH

A profile of Gestational Trophoblastic Neoplasia in a tertiary hospital in Surabaya, Indonesia

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ABSTRACT

Objective: Gestational Trophoblastic Neoplasia (GTN) is a pregnancy-related malignancy due to abnormal proliferation of trophoblastic tissue. This study aimed to identify the characteristics of patients with GTN to help diagnose cases of GTN earlier and provide better treatment.

Materials and Methods: This was a descriptive retrospective study on medical records of patients with GTN in Dr. Soetomo General Academic Hospital Surabaya, Indonesia, during the period of January 2018 to December 2020 with a total sampling technique. There were 41 patients with GTN included as study subjects.

Results: Forty-one cases of GTN met the inclusion criteria out of the fifty medical records collected. The majority of patients aged 21 – 30 years old (34%) and had parity status without data (42%). Regarding the clinical profile based on prognostic factors, the predominant patients (71%) also had no data about the time interval between the end of the last pregnancy and the first time diagnosed by GTN, Those with more than 100,000 mIU/ml of beta-hCG levels were 32%, and those without metastases were 41.5%. Most patients belonged to the low-risk group (49%) and received chemotherapy (71%) with the MTX LD regimen (69%).

Conclusion: GTN occurred predominantly in reproductive women that belonged to the low-risk group. Furthermore, chemotherapy is one of the chosen therapy for those patients.

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Highlights:

1. This study aimed to identify the characteristics of Gestational Trophoblastic Neoplasia (GTN).
2. GTN is chemosensitive, but without appropriate therapy and follow-up, GTN will develop into complications and fatalities.

INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is classified as a gestational trophoblastic disease (GTD). GTN is due to the abnormal proliferation of placental trophoblastic tissue and is associated with pregnancy. The features of GTN lesions depend on the genotype and phenotype of the trophoblastic tissue involved, including invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT).[1] GTN does not have exact statistics because the incidence of events is considered rare. Epidemiologically, according to Lurain,[2] GTN affects more women in Asia than in America or Europe. In Europe and North America, choriocarcinoma affects about 1 in 40,000 pregnancies, while in Southeast Asia and Japan, choriocarcinoma has a higher incidence rate of 9.2 and 3.3 per 40,000 pregnancies.

There are various risk factors for GTN, ie. endogenous estrogen, extreme reproductive age, multiparity, certain gestational age, history of spontaneous abortion, high beta carotene diet, high fat diet, ABO blood type, environmental pollution/toxins, ethnicity, smoking, alcohol consumption, socioeconomic status, and other risk factors.[2] More than 50% of patients with GTN show no clinical manifestations, but currently, stable or even elevated serum levels of human chorionic gonadotropin (hCG) in pregnant women or a history of previous pregnancy can be used as a tumour marker to confirm the diagnosis, monitor the effects of chemotherapy, and evaluate the presence of recurrences.[3] Goldstein and Berkowitz[4] explained that this malignant tumour is highly sensitive to chemotherapy and has a cure rate of more than 90%. The cure rate for GTN is indeed high, but all risk factors must be evaluated immediately after someone is diagnosed or suspected of GTN because GTN can invade, metastasize, and cause death if left untreated.

This study was conducted to identify several risk factors and clinical profiles experienced by GTN patients. The elaboration of these points will show how to handle it properly and also educate society regarding this matter.

MATERIALS AND METHODS

This was a descriptive retrospective study described the characteristics of GTN patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia for the period January 2018 – December 2020. This study was conducted at the POSA (*Poli Onkologi Satu Atap*/Integrated Oncology Clinic) with data sources from patients' medical records. The population in this study were all GTN patients at Dr. Soetomo Hospital for the period of January 2018 – December 2020. The sample in this study were patients with a diagnosis of GTN who met the inclusion criteria, ie. those with complete and unduplicated medical record data. The flow of this research was started with planning the theme, preparing proposals, then collecting, processing and analyzing data and preparing research reports. The results of data analysis in the form of GTN patient profiles are in the form of percentages and presented in tables. This research had received Ethical Eligibility Number: 0607/LOE/301.4.2/IX/2021.

RESULTS AND DISCUSSION

From the medical records of GTN patients at POSA Dr. Soetomo General Academic Hospital for the January 2018 – December 2020 period, 41 patients met the inclusion criteria. The results of the 41 sample study (Table 1) showed that most of the patients was in the age group of 21-30 years (34%), followed by ages 31-40 years (32%), >40 years (24%), and ≤20 years (10%). Based on parity status, there were more multiparous patients (34%) than nulliparas (24%). However, 17 (42%) of 41 patients had insufficient data on this subject. Another characteristic was the time interval between the end of the last pregnancy and the time the patient was first diagnosed with GTN. A total of 29 patients (71%) showed no data, 8 patients (19%) had an interval of fewer than 4 months, 2 patients with 4 - 6 months interval and 2 patients with >12 months.

In patients whose beta-hCG levels were known, 13 (32%) patients had the highest beta-hCG levels >100,000 mIU/ml, followed by 12 (29%) patients with beta-hCG levels <1000 mIU/ml, then 8 (24%) patients with beta-hCG levels of 10,000 - 100,000 mIU/ml. For the last, 6 (15%) patients had beta-hCG levels of 1000 - 10,000 mIU/ml. Patients who experienced metastases were 15 (36.5%) patients, then patients who did not experience metastases were more than those who experienced metastases, comprising 17 (41.5%) patients. Meanwhile, 9 (22%) other patients had no data. The most metastases were lung metastases, which were experienced by 10 (66.5%) patients out of all patients with metastases. Regarding single metastases in the vagina or brain, each patient did not have a single metastasis in these locations. Based on WHO and FIGO prognostic factor assessment scores. Most of the patients, consisting of 20 (49%) patients, were low-risk patients, 16 (39%) were high-risk patients, and 5 other patients had no data.

According to the therapy for GTN (Table 2), chemotherapy was the mainstay of management in GTN patients, provided to 29 (71%) cases, while surgery or

hysterectomy was only in 1 (2.5%) patient. In addition, there was no data on combination therapy between chemotherapy and hysterectomy (7%), combination therapy of chemotherapy and external radiation (2.5%) and the remaining 7 (17%) patients. Of the patients receiving chemotherapy, methotrexate (MTX) was the regimen given to most patients (69%). Then the others were MTX–EMACO in 2 patients (7%), MTX–EMACO – EP EMA in 1 patient (3%), EMACO in 4 patients (14%), and finally EMACO – EP EMA in 1 patient (7%).

The age of GTN patients in this study was mostly (34%) in the 21 - 31-year-old group which was also in line with the opinion expressed by Li et al.[5] that GTN is more experienced by reproductive age. The study by Raudina, Hidayat, and Rachmayati[6] showed that 57 (64.8%) of 88 patients aged less than 40 years old. In addition, referring to Katke's[7] study in Mumbai, it was stated that 17 out of 23 (73.4%) GTN patients aged 20-30 years. Then, a study in India showed that patients in the age range of 20-30 years were 89.6%.[8] In Denpasar, Indonesia, Azizi, Mahendra, and Widiyanti[9] conducted a study with the results explaining that 45.5% of GTN patients (5 out of 11 cases) were 21-30 years old. However, there are studies showing that age does not have a significant relationship with the patient's risk of experiencing malignancy in post-molar pregnancies.[10]

Table 1. Distribution of characteristics of GTN patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in 2018 – 2020

No.	Characteristics	Total	(%)
1.	Age		
	≤20	4	10%
	21 – 30	14	34%
	31 – 40	13	32%
	> 40	10	24%
	Total	41	100%
2.	Parity		
	Nuliparous	10	24%
	Multiparous	14	34%
	No data	17	42%
	Total	41	100%
3.	Time interval*		
	< 4 months	8	19%
	4 - 6 months	2	5%
	7 - 12 months	-	-
	> 12 months	2	5%
	No data	29	71%
	Total	41	100%
4.	β-hCG		
	< 1000 mIU/ml	12	29%
	1000 – 10,000 mIU/ml	6	15%
	10,000 – 100,000 mIU/ml	8	24%
	> 100,000 mIU/ml	13	32%
	Total	41	100%
5.	Metastasis		
a.	Metastasis (+)	15	36,5%
	1 site		
	Vagina	-	-
	Liver	1	6,7%
	Lung	10	66,5%
	Brain	-	-
	Vertebrae	1	6,7%
	>1 sites		
	Vagina and lung	1	6,7%
	Liver and lung	1	6,7%
	Lung and brain	1	6,7%
b.	Metastasis (–)	17	41,5%
c.	No data	9	22%
	Total	41	100%
6.	GTN type		
	Low risk GTN (≤ 6)	20	49%
	High risk GTN (≥ 7)	16	39%
	No data	5	12%
	Total	41	100%

Table 2. Distribution of the therapy of GTN patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia in 2018 – 2020

No.	Therapy	Total	(%)
1.	Chemotherapy	29	71%
	MTX LD	20	69%
	MTX LD – EMACO	2	7%
	MTX – EMACO – EP EMA	1	3%
	EMACO	4	14%
	EMACO – EP EMA	1	7%
2.	Histerectomy	1	2,5%
3.	Chemotherapy and histerectomy	4	7%
4.	Chemotherapy and external radiation	1	2,5%
5.	No data	7	17%
	Total	41	100%

In one study, the highest cases of GTN patients were from the primigravida or nullipara group, comprising 115 (37.7%) patients out of 235 patients.[11] Meanwhile, Orr et al.[12] considered that parity was not significantly related to GTN risk. Although in this study the parity status of GTN patients did not have enough data, 42% did not have data, other results showed that multiparous women were the dominant group, consisting of 14 (34%) patients compared to 24% nulliparous women. A case-control study of molar pregnancies that develop into a choriocarcinoma, a type of GTN, shows that multiparous women have a relatively greater risk. However, the association was significant only for women with more than 5 births.[13]

This study presented inadequate data regarding the time interval between the end of the patient's last pregnancy and the first diagnosis of GTN and receiving therapy. Of the 41 patients, 29 patients had no data and the other 12 patients showed results that were dominated by intervals <4 months, comprising 8 patients (19%), then 4-6 months, and >12 months. In a study in Bandung, Indonesia, 37 (58.7%) hydatidiform mole patients who had an interval of fewer than 4 months between the end of the last pregnancy and the first time they were diagnosed with GTN and received therapy had a greater risk of developing an invasive mole or GTN.[6]

β-hCG is the most used tumour marker for the diagnosis of GTN because it is more sensitive than other imaging techniques. The amount of beta-hCG produced by the chorionic tissue corresponds to the volume of this tumour. Since histopathology is not mandatory for diagnosing GTN, FIGO has prepared criteria for this diagnosis.[14] Patients with β-hCG levels >100,000 mIU/ml in this study were predominant, consisting of 12 patients (29%). These results were supported by research by Angelina and Hartono[15] that most GTN patients were in the group with β-hCG levels of 100,000 – 1,000,000 mIU/ml, comprising 26 patients (63%) of a total of 41 patients. In addition, a study commensurate with this study was conducted by Azizi, Mahendra, and Widiyanti[9] showing that 4 patients (36.4%) out of 11 patients had β-hCG levels >100,000 mIU/ml. In contrast to this study, Jagtap et al.[8], mentioned most gestational trophoblastic diseases show β-hCG levels between 50,000 – 100,000 mIU/ml. Then, the lowest β-hCG level of 65,340 mIU/ml was observed in PSTT cases.

The results of a total of 41 GTN patients, 17 patients (41.5%) did not experience metastases, then 15 patients (36.5%) had metastases, and 9 patients (22%) had no data. Most patients had lung metastases, covering 10 patients (66.5%) of the total who had metastases. Many studies support this research, such as the study of Hemida et al.[16] in 2020, 71.4% of low-risk patients did not experience metastases, then 16.1% of low-risk patients had metastases, and the remaining 12.5% were high-risk patients. Twenty-five of them had metastases (22.3%), with 20 patients dominated by lung metastases. A previous study conducted by Hemida et al.[17] in 2011 also showed that the most metastatic locations in GTN patients were in the lungs, which was 62.5%. Other cases that did not experience metastases were 33 (71.7%) cases out of a total of 46 cases. Meanwhile, most cases of metastases were in the lungs as many as 10 cases 76.9%.[18]

One study grouped patients diagnosed with GTN according to FIGO prognostic factors and found that 63.6% were categorized as low-risk GTN and 36.4% as high-risk GTN.[6] The study by Sita-Lumsden et al.[19] in London, based on the results of the FIGO prognostic assessment, 579 (94%) patients were in the low-risk category and only 39 (4%) patients were in the high-risk category. Likewise in this study, 49% of GTN had low risk, 39% had high risk, and the remaining 12% had no data. The results of this grouping were in line with the characteristics of metastases that have been discussed earlier in those patients who predominantly did not have metastases so the prognostic score of these patients was lower than those who have metastases.

This study showed the highest results, 29 patients (71%) were given chemotherapy. The results of this study confirmed studies which stated that 72.7% of GTD patients received methotrexate chemotherapy to treat their GTD.[9] Hussain et al.[20] also considered that chemotherapy could be a good option for low-risk GTN patients, especially in developing countries. Li et al.[5] thought that GTN is one of the most curable malignancies with monitoring of serum hCG and effective combination therapy of chemotherapy with other procedures such as surgery so that the cure rate reaches 90% even for extensive metastases.

Due to the limitations of this study, such as very limited medical record data and the inavailability of complete data regarding the studied variables, some dominant characteristics were found as having no data. In addition, the research variables also did not vary so they were not regarded as the risk factors for GTN.

CONCLUSION

This study describes many characteristics about the risk factor of GTN. Predominantly, the patients of GTN aged 21–30 years (34%) and had parity status without data (42%). Regarding the clinical profile based on prognostic factors, the predominant patients (71%) also had no data about the time interval between the end of the last pregnancy and the first time diagnosed by GTN, with more than 100,000 mIU/ml of beta-hCG levels (32%), and had no metastases (41.5%). Most patients belonged to the low-risk group (49%) and received chemotherapy (71%) with the MTX LD regimen (69%). Further studies using various variables and longer time are needed to accurately identify the characteristics of GTN.

DISCLOSURES

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Conflict of interest

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Author contribution

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

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ORIGINAL RESEARCH

The comparison of maternal stress level during pregnancy between two groups of pregnancy outcomes in the COVID-19 pandemic

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ABSTRACT

Objective: This study analyzed the comparison of maternal stress levels during pregnancy between two groups of pregnancy outcomes in the COVID-19 pandemic at Koja Regional General Hospital, North Jakarta, Indonesia.
Materials and Methods: A hospital-based analytic observational study conducted with a case-control approach, involving mothers giving birth in March-August 2022, aged 20–35, without disease histories such as hypertension, anemia, gestational diabetes mellitus, and tuberculosis. Two groups in this study had matched inclusion criteria, consisting of 24 respondents with adverse pregnancy outcomes in the case group and 34 respondents with good pregnancy outcomes in the control group. The sampling method used total population technique. Data were obtained from medical record and modification of Depression Anxiety Stress Scale (DASS42) questionnaire. Analysis of confounding variables used different tests and bivariate analysis using the Mann-Whitney test.
Results: Respondent characteristics had no difference (p >0.05). Respondent distribution with normal levels in the control group (70.6%) was higher than in the case group (45.8%). The result of Mann-Whitney test was no different in maternal stress levels during pregnancy between the case and control groups with pregnancy outcomes in COVID-19 pandemic (p=0.102).
Conclusion: Most maternal stress levels during pregnancy were in the normal category. There was no difference in maternal stress level during pregnancy between both groups in COVID-19 pandemic at Koja Regional General Hospital, North Jakarta, Indonesia.

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Highlights:

1. Maternal stress level during pregnancy in the COVID-19 pandemic had normal category.
2. There was no difference of maternal stress level during pregnancy between good and adverse pregnancy outcomes in the COVID-19 pandemic.
3. Other factors can influence maternal stress level during pregnancy in the COVID-19 pandemic.

INTRODUCTION

Maternal stress during pregnancy refers to the unbalance condition that pregnant women feel when faced with demands and worries.[1] Pregnancy makes women have different stressors such as physical change, less empowerment, job condition, relation with her spouse, and mood change.[2] Stress could happen when pregnant women feel that demand has proven more than their ability to receive. Around 78% of women have moderate stress during pregnancy, while 6% have severe stress.[3] A previous study showed that 54% of the mothers who had stress during pregnancy finally had preterm birth, while the percentage of all mothers with preterm bith was 23%.[4] The term birth occurs between 37 and 42 weeks, while preterm birth is defined as delivery before 37 weeks gestation age.[5] A meta-analysis study by Lima et al.[6] to 1,382 women have shown that mothers with stress during pregnancy had 1.68 more risk of having a baby with low birth weight (LBW) than mothers without stress. The normal birth weight for a baby is between 2500–4000 grams. If the birth weight is less than 2500 grams, it is referred as LBW. This condition may result from preterm birth, intrauterine growth restriction (IUGR), or both.[7,8]

Stress during pregnancy may be affected by COVID-19 pandemic.[9] Pregnant women may have psychological problems during the pandemic due to limited health facility access, lack of social support, and feeling worried about their health if infected with COVID-19.[10] Other factors that affect maternal stress are economic crisis and media exposure (pers, radio, television). It increases anxiety and depression symptoms in pregnant women due to COVID-19 pandemic.[11]

A study by Gruebner et al.[12] has shown the risk of mental health problems in urban areas is higher than in rural areas. Jakarta occupies the ninth position as the most stressful city in the world.[13] The prevalence of mental and emotional problems in Jakarta was 10.1%, while depression was 5.9%, while the prevalence increase from 2013 was 5.7%. The result also showed that North Jakarta becomes one of the top three cities in Jakarta region with higher mental health problems of 12.95% for mental and emotional problems, and 7.14% for depression prevalence.[14–16]

Those data only showed the prevalence of mental health problems in general society. Data on stress for pregnant women were still difficult to find, especially during the COVID-19 pandemic. Those previous studies were conducted in other countries, while in Indonesia studies exploring the effect of stress on pregnancy outcome remains limited. Moreover, another research only analyzed the impact of stress on one of the outcomes. Therefore, this study aimed to analyze the comparison of maternal stress levels during pregnancy between two groups of pregnancy outcomes in the COVID-19 pandemic.

MATERIALS AND METHODS

A study using observational analytic design with case-control approach was conducted at Koja Regional General Hospital, North Jakarta, Indonesia. The population, consisted of the case group (adverse outcomes) were all mothers with preterm birth and or LBW baby, while the control group (good outcomes) was all mothers with term birth and normal birth weight baby. Both groups underwent matching process with inclusion criteria, ie. giving birth between March–August 2022, aged 20–35, without history or pregnancy complications such as hypertension, pre-eclampsia, anemia, gestational diabetes mellitus, and tuberculosis. Respondents who refused to join this study were excluded. The total respondents were 58 mothers, 24 respondents in the case group and 34 respondents in the control group.

The sampling method used a total population technique. Data were related to pregnancy outcomes and respondents phone number obtained from the medical record. The general data of the respondents were obtained from the questionnaire. Data for assessing maternal stress levels during pregnancy used a modified questionnaire from Depression Anxiety Stress Scale 42 (DASS42). The questionnaire was already used before in a study by Tambunan[17] at Deli Serdang District, North Sumatera, Indonesia. The original DASS42 questionnaire consists of 42 statements to rate depression, anxiety, and stress levels in the general population. The modification of this questionnaire has 14 statements for assessing maternal stress levels during pregnancy in the COVID-19 pandemic. The evaluation scoring is 0 for none or never, 1 for sometimes, 2 for often, and 3 for almost every time. Furthermore, the evaluation indicators of stress levels depend on the score of the sum result in each statement that is normal (0–14), mild (15–18), moderate (19–25), severe (26–33), and very severe (≥34).

Data collection used an online form called Zoho Survey. The first page of the form displays information about the research procedure, purpose, and benefit. Respondents also signed an informed consent on their readiness to join this study. On the next page, respondents filled out the online form that consisted of biodata and DASS42 questionnaire. Data analysis used Statistical Program for Social Science (SPSS) application version 25. The comparative difference test

was used for the confounding variables between control and case groups, while the Mann-Whitney test was used for bivariate analysis. This study had received ethical approval through the Health Research Ethics Committee of the Faculty of Medicine Universitas Airlangga (No. 89/EC/KEPK/FKUA/2022).

RESULTS AND DISCUSSION

The general data distribution of respondents, percentage, and the comparative difference test are shown in Table 1. The results of the comparartive difference test showed no difference in the general data of the respondents between case and control groups. Table 2 shows that most maternal stress levels during pregnancy are in the normal category. Although the percentage of mild-level and moderate-level in the case group was higher than in the control group, the results of the Mann-Whitney test showed no difference between maternal stress during pregnancy with pregnancy outcomes in both groups (p=0.102). The systematic review study of Lima et al.[6] revealed no significant difference between the case and control groups with preterm birth. It was different from the result of a case-control study by Nurahmawati[18] which found an influence of maternal stress levels on LBW. This study stated that chronic stress during pregnancy without good stress management increased the risk of LBW as it decreased blood flow and inhibited fetal growth. Release of corticotropin-releasing hormone (CRH) by the placenta can affect gestational duration which is a risk for preterm birth. It is not just hormones, Saleha et al.[19] and Primawati et al.[20] stated that maternal stress levels during pregnancy have influenced by other factors such as job, parity, social economic factors, social support, and environment. There is a significant association between maternal jobs and stress levels during pregnancy.[21] Stress can arise in working mothers with a job that requires complete thought.[22]

Table 1. The general data distribution of the respondents

Data	Case		Control		P value
	f	%	f	%	
Job					
Housewife	20	83.3	29	85.3	
Employee	2	8.3	3	8.8	0.235[a]
Seller	0	0	2	5.9	
Other	2	8.3	0	0	
Education					
No/not yet graduated	1	4.2	0	0	
Elementary school	2	8.3	4	11.8	
Junior high school	3	12.5	7	20.6	0.534[b]
Senior high school	13	54.2	18	52.9	
University	5	20.8	5	14.7	
Household income					
Low	2	8.3	6	17.6	
Middle	15	62.5	17	50.0	0.958[b]
High	6	25.0	6	17.6	
Very high	1	4.2	5	14.7	
Smoking/alcohol					
Yes	0	0	2	5.9	0.632[a]
No	24	100	32	94.1	
BMI					
< 18.5	2	8.3	6	17.6	
18.5 – 24.9	16	66.7	20	58.8	0.072[c]
25 – 29.9	4	16.7	7	20.6	
≥ 30	2	8.3	1	2.9	
Gestational interval					
Risky	6	25	13	38.2	
Not risky	8	33.3	13	38.2	0.607[c]
-	10	41.7	8	23.5	
Parity					
Primipara	10	41.7	8	23.5	
Multipara	14	58.3	26	76.5	0.145[b]
Grand multipara	0	0	0	0	
Total respondents	24	100	34	100	

Chi-square[a], Mann Whitney[b], Independent sample t-test[c]

Table 2. Analysis of the comparison of maternal stress levels during pregnancy between two groups of pregnancy outcomes in during COVID-19 pandemic at Koja Regional General Hospital, North Jakarta, Indonesia.

Stress Level	Pregnancy Outcomes				Total		P value
	Good[a]		Adverse[b]				
	F	%	f	%	f	%	
Normal	24	70.6	11	45.8	35	60.3	
Mild	3	8.8	6	25	9	15.5	
Moderate	7	20.6	7	29.2	14	24.1	0.102
Severe	0	0	0	0	0	0	
Very severe	0	0	0	0	0	0	
Total	34	100	24	100	58	100	

The control group (all mothers with term birth and normal birth weight baby)[a], The case group (all mothers with preterm birth and or LBW baby)[b]

Most respondents in each group were housewives with the risk of having severe stress levels less than other job types. A study by Nasution[23] revealed an association between parity and stress level in pregnant women, where a mother with first pregnancy tends to have higher stress levels than multipara. The result is in line with respondent characteristics that are dominated by multipara. Stable social economics condition can decrease maternal stress levels because of higher affordability of health facilities where mothers are able to ensure their physical and psychological health.[24]

Most of the women in this study had middle household incomes which have not become a trigger for severe stress than women with low household incomes. Other factors like social and environment support also have a role in providing calm and comfort feelings that affect stress levels for pregnant women. Form of support like information or emotional support can be provided by family and friends.[25,26]

Most respondents in both groups had normal stress levels. Declining stress levels during pregnancy could happen through a positive coping strategy.[27,28] Coping strategy refers to an effort made by the pregnant women in response to stressors, so it can minimize negative affect.[29] A simple coping strategy such as a healthy diet and doing a hobby can decrease stress levels.[30] Moreover, coping strategies such as active and problem-focused coping aim to resolve stressors and prevent adverse pregnancy outcomes instead of maladaptive coping like avoidance as passive action and ineffective.[31]

Normal stress levels dominated in the case group refer to the possibility of other factors that influence preterm birth and LBW. Table 1 shows that almost all respondents in the case group (94.1%) are not smokers and alcohol consumers. Even though the mother is not a smoker, another study found an association between a passive-smoker mother with preterm birth and LBW.[32,33] Furthermore, although most respondents' BMI before pregnancy was in normal category, incidents of preterm birth and LBW also depend on nutrition status and weight gain during pregnancy.[34,35] The COVID-19 pandemic also had impact on the decline of antenatal care visits that raised adverse events for the mother and the fetus.[36] This is because mothers were afraid of being caught as having contacted with COVID-19, there were recommendations to postpone pregnancy checks, and the lack of personal protective equipment.[37]

However, this study approach could have had recall bias. Recall bias is a form of information bias that occurs when the respondents forget about data related to exposure.[38] Respondents cannot remember their experience accurately and there is possibility of changing or removing the detail. The accuracy in remembering some experiences also depends on the effect of the incident.[39] In this case, respondents could have forgotten or did not have capability to accurately remember stress exposure during the COVID-19 pandemic. This possibility can happen especially in the case group with adverse pregnancy outcomes. Those experiences could have made the mothers prefer to remove sad memories about their pregnancy and the baby's condition at birth.

This study design had also tried to minimize those effects by using just the last six months' birth period. The time range from the end of pregnancy to the filling the questionnaire was not too long and the stress exposure experienced during the COVID-19 pandemic could still have been well remembered. The process of collecting primary data was also preceded by explaining that there were no right or wrong answers in filling out the questionnaire and the answers could affect the research result so that respondents can be more honest in filling out the questionnaire. The strength of our study was that it included two types of pregnancy outcomes and also analyzed a comparison of maternal stress levels during the COVID-19 pandemic.

CONCLUSION

Most maternal stress levels during pregnancy in the COVID-19 pandemic were still in normal category in both case and control groups. There was no difference in stress levels during pregnancy between mothers with good and adverse pregnancy outcomes within the period of the COVID-19 pandemic at Koja Regional General Hospital, North Jakarta, Indonesia. Further studies need to explore other factors that influence pregnancy outcomes in both the mothers and the babies during the COVID-19 pandemic.

DISCLOSURES

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Author contribution

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

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ORIGINAL RESEARCH

Abnormal Uterine Bleeding (AUB) at Haji Adam Malik General Hospital, Medan, North Sumatera, Indonesia

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ABSTRACT

Objective: This study identified the incidence of Abnormal Uterine Bleeding (AUB) at Haji Adam Malik General Hospital, Medan, Indonesia, in 2020-2021.
Materials and Methods: This was a descriptive study with a cross-sectional design. Sampling was taken using total sampling and using retrospective data in the form of medical records with a diagnosis of AUB at Haji Adam Malik General Hospital Medan in 2020–2021.
Results: There were 197 cases of AUB, with the highest distribution in the age group of 41–50 years with 84 people (42.6%). The most cases of AUB with an obese BMI were 91 people (46.2%), married status as many as 176 people (89.3%), had the last education level of senior high school as many as 99 people (50.3%), 144 people (73.1%) got their first menstruation when they were >12 years old, 80 people (40.6%) had multiparity, 90 people (45.7%) received medical therapy. Based on the PALM-COEIN classification, the most AUB cases were AUB-L with 99 people (50.3%). Based on the classification of AUB-L locations, most locations were submucosa with 38.6%.
Conclusion: AUB-L cases were still the most common cases at Haji Adam Malik General Hospital, Medan, Indonesia, in 2020–2021.

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Highlights:

1. Leiomyoma is still the most common case in women aged 41–50 years.
2. Women who have an obese BMI are the main risk factor for abnormal uterine bleeding, so it is urged for women to maintain an ideal weight because it can be bad for health.

INTRODUCTION

Abnormal Uterine Bleeding (AUB) is one of the most common gynecological conditions in women of reproductive age. AUB is described as menstrual complaints in regularity, frequency, duration, and volume that occurs outside pregnancy.[1] Acute AUB can be interpreted as heavy bleeding that requires quick treatment to prevent blood loss.[2] The International Federation of Gynecology and Obstetrics (FIGO) divides AUB's causes into nine main categories according to the acronym PALM-COEIN: polyps,

adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified. In general, the PALM group is a structural component that can be measured visually by imaging and/or histopathology techniques, while the COEIN group is a non-structural component which means it cannot be measured by imaging or histopathology techniques.[3]

The incidence of leiomyoma is estimated to occur in 70%–80% of women aged 50 years and older. Leiomyoma is also known as uterine myoma and uterine fibroids. Leiomyoma is a benign tumor in myometrial muscle cells and connective tissue.[4] Generally, women with leiomyoma are asymptomatic. However, about 30% of them will show severe symptoms, including AUB, pelvic pain, back pain, constipation, frequent urination, and infertility.[5]

AUB is a problem that women often experience around the world. AUB is not a disease but a symptom that is a marker of a problem in the female reproductive organs. The research conducted at Prof. Dr. R.D. Kandou Hospital, Manado, Indonesia, obtained 62 AUB cases. The incidence of AUB by age is highest at the age of 41–50 years (33.87%). The incidence of AUB is based on BMI. Most of them occur in overweight individuals, which is 6 cases (30%). According to the PALM-COEIN classification, most cases of AUB were in AUB-L, with 8 cases (40%). The incidence of AUB was found in 8 patients (30.76%) who underwent a histo-pathological examination and 18 other patients (69.24%) who did not perform such examination. Based on the treatment, AUB incidence was found in patients with medicaments, dilation, and curettage treatment. The last treatment was the predominant one of 9 cases (34.62%).[6]

Haji Adam Malik General Hospital is a place for education, research, and health services and is a referral center for the North Sumatra region and its surroundings, so this can be a reflection on public health conditions, especially women's gynecological health in North Sumatra. Research linked to the characteristics, therapies, and types of AUB actions is still minimally carried out. This research was expected to be a reference that adds insight for both women and healthcare providers so that they can find out about and deal with AUB incidence earlier. A preliminary survey that was conducted at Haji Adam Malik General Hospital from 2020 to 2021 found that there were 224 patients diagnosed with AUB, and based on the AUB etiological classification, most cases of leiomyoma were obtained. In addition, leiomyoma was the second most common gynecological tumor in Indonesia after cervical cancer. Therefore, the aim of this study was to investigate the incidence of abnormal uterine bleeding (AUB) based on age, BMI, marital status, education level, menarche age, parity, etiology, therapy, and type of action at Haji Adam Malik General Hospital, Medan, Indonesia.

MATERIALS AND METHODS

This research was a descriptive study with a cross-sectional design to determine the characteristics and management of Abnormal Uterine Bleeding (AUB) events in Haji Adam Malik General Hospital. This study used retrospective data in the form of medical records. The research sample was selected using total sampling method, where the sample was a medical record diagnosed with AUB at Haji Adam Malik General Hospital for the period January 1, 2020–December 31, 2021, which met the inclusion criteria, ie. patients with complete and legible medical records that included variables to be studied such as age, BMI, marital status, education level, menarche age, parity, PALM-COEIN classification, therapy, and type of action. This study has obtained ethical approval with the number of ethical clearance 160/UN5.2.1.1.2.6/ SPB/2022.

RESULTS AND DISCUSSION

The number of cases of abnormal uterine bleeding at Haji Adam Malik General Hospital in 2020–2021 was 224, and those that met the inclusion criteria were 197. Twenty-seven cases fell under the exclusion criteria, such as multiple diagnoses (pregnancy, HIV, uterine prolapse, heart disease, liver disease, etc.) and incomplete medical records (interpretation of ultrasound test results, menstrual history, pregnancy history, BMI, etc.).

Women with AUB aged 41–50 years had the highest percentage (42.6%), and an obese BMI (46.2%). The majority of AUB patients had married (89.3%), had the last education level of senior high school (50.3%), had their first menstruation when they were >12 years old (73.1%), and the most parity was found in women with multiparity (40.6%).

The increasing prevalence of AUB in the age group of 41–50 years may be due to the fact that when women approach menopause, there will be a decrease in the number of ovarian follicles and an increase in resistance to gonadotropin stimulation, which can lead to a decrease in estradiol levels so that the endometrium cannot maintain its normal growth.[7] The occurrence of a high prevalence of leiomyoma at the age of 35-50 years is due to estrogen levels decreasing before menarche and increasing during reproductive age.[8] The American

College of Obstetricians and Gynecologists (ACOG) recommends that women over the age of 35 who have abnormal uterine bleeding perform an endometrial examination by biopsy. This is because a woman's risk of developing endometrial cancer is increasing along with age. The overall incidence of cancer was 10.2 cases per 100,000 in women aged 19–39 years, and in women aged 40–49 years the incidence of endometrial carcinoma was 36.5 cases per 100,000.[9]

Table 1. Characteristics distribution of women with AUB at Haji Adam Malik General Hospital

Characteristics	n	%
Age		
< 20 years old	6	3
21-30 years old	25	12.7
31-40 years old	50	25.4
41-50 years old	84	42.6
51-60 years old	23	11.7
> 60 years old	9	4.6
BMI		
Underweight	9	4.6
Normoweight	66	33.5
Overweight	31	15.7
Obesity	91	46.2
Marital status		
Married	176	89.3
Unmarried	21	10.7
Education level		
Unschooled	3	1.5
Elementary school	32	16.2
Junior high school	35	17.8
Senior high school	99	50.3
College Student	28	14.2
Menarche Age		
≤ 12 years old	53	26.9
> 12 years old	144	73.1
Parity		
Nulliparity	76	38.6
Primiparity	24	12.2
Multiparity	80	40.6
Grandemultiparity	17	8.6

A high level of education can support patient awareness and encourage them to undergo examinations and treatment at health facilities,[10] and it is also related to knowledge about the reproductive system, the menstrual cycle, early diagnosis, and better management of AUB.[11]

A study conducted by Anupamaresh et al.[12] found a significant relationship between BMI with endometrial hyperplasia and malignancy. High estrogen levels in the blood due to peripheral aromatization of subcutaneous fats cause hormonal imbalances in the blood, causing a higher rate of endometrial proliferation without being counteracted by progesterone. This can lead to the appearance of AUB complaints due to the formation of a fragile and easily bloody endometrial layer. This can also increase the risk of malignancy in obese menopausal patients.[13] Women who are at high risk of hyperplasia or malignancy, over 45 years old, obese, or have Polycystic Ovarian Syndrome (PCOS), failed in treatment, or have persistent bleeding are recommended to have a biopsy or endometrial tissue sampling as a first-stage examination.[14]

A study by Barrett et al.[15] found differences in ovarian function concerning parity and the time of the last birth. The study mentioned that the follicular phase in multiparity women lasted one day longer than in nullipara women. If estrogen levels decrease, there will be no excessive endometrial hyperproliferation, which can result in AUB. A continued decrease in ovarian function after childbirth and a reduction in exposure to free estradiol can reduce the risk of malignancy that can lead to AUB. Increased ovarian steroid levels coincide with the increase in the time of the last birth, so it can be assumed that a multiparity state can reduce the risk of AUB incidence.

Table 2. Characteristics distribution of women with AUB by PALM-COEIN classification

Diagnosis	n	%
AUB-P	2	1
AUB-A	7	3.6
AUB-L	99	50.3
AUB-M	86	43.7
AUB-C	0	0
AUB-O	0	0
AUB-E	1	0.5
AUB-I	0	0
AUB-N	2	1

Based on the PALM-COEIN classification, the highest proportion of AUB incidence at Haji Adam Malik General Hospital was caused by the PALM (structural) group (98.5%), mostly AUB-L cases (50.3%) and AUB-M (43.7%). A study conducted by Rifki et al.[16] at Prof. Dr. R.D. Kandou Hospital, Manado, Indonesia for the period of January 2013–December 2014 showed the same results, in which the majority of AUB patients were AUB-L (56.86%),

The high number of AUB-L and AUB-M cases at Haji Adam Malik General Hospital was likely because the patients were generally referred from regional hospitals. Haji Adam Malik General Hospital is a class A general hospital and serves as a referral center for the North Sumatra region and its surroundings, along with the

development of the medical profession because there are more and more obstetrics and gynecology specialists in the area who play a role in early diagnosis of cases of both AUB and malignancy, so that referrals are made to more competent health facilities when screening patients in regional hospitals.[13]

Table 3. Characteristics distribution of women with AUB-L by location classification.

Location Classification	n	%
Subserous	11	25
Intramural	16	36.4
Submucous	17	38.6

Based on this study, it was found that out of 99 cases of leiomyoma at Haji Adam Malik General Hospital, only 44 of them had a location interpretation determined from ultrasound, MRI, or hysteroscopy examinations. The majority of AUB-L patients had the highest percentage in the submucosa (38.6%). Research conducted by Tochie et al.[17] in Cameroon showed similar results and found that the majority of leiomyoma locations were submucosal (89.4%).

A study conducted at RS Tentara Tingkat II dr. Soepraoen Malang showed the same results and obtained the most locations in the submucosal (46.3%). This happens because the submucosal AUB-L is generally located below the endometrium and protrudes into the uterine cavity, so it most often shows complaints of bleeding disorders when compared to other types of leiomyomas that are larger in size and do not show complaints of bleeding.[18]

Table 4. Characteristics distribution of women with AUB by therapy and type of action

Therapy and type of action	n	%
Medicaments	90	45.7
Curettage dilatation	7	3.6
Myomectomy	20	10.2
Hysterectomy	80	40.6

In this study, the highest percentage of AUB patients received medicaments therapy (45.7%) and hysterectomy (40.6%). This was related to first-line management for AUB with medicaments such as iron supplements, combination of oral contraceptives (COCs), progesterone, nonsteroidal anti-inflammatory drugs, antifibrinolytics, desmopressin, and GnRH analogs that can provide hemodynamic stability, improve anemia, and maintain the normal menstrual cycle.[1] However, if medicaments therapy fails or there are pathologies in the uterus such as large uterine fibroids, endometrial hyperplasia, and carcinoma, then surgery is an option, such as polypectomy, hysteroscopy, endometrial resection and ablation, myomectomy, uterine artery embolization, and hysterectomy.[19] Hysterectomy is the most common surgical procedure performed in gynecology. Although it is invasive, it was the definitive therapy for heavy menstrual bleeding.[20] In addition, this procedure is permanent, so it is only indicated for women who do not need fertility in the future. It requires a longer recovery time and a higher rate of postoperative complications compared to endometrial resection and ablation.[19]

CONCLUSION

The majority of patients with AUB at Haji Adam Malik General Hospital, Medan, Indonesia in 2020–2021 were those who have the following characteristics: aged 41–50 years, had an obese BMI, married status, had the last education level of senior high school, had their first menstruation when they were >12 years old, multiparous, and received medicaments therapy. Based on the PALM-COEIN classification, the most AUB cases was AUB-L. Based on the classification of AUB-L locations, most locations were submucosa. Therefore, it is urged for women who are >40 years old to be able to maintain their ideal weight because this is the main risk factor for AUB. This research is expected to be a reference for future research as well as for healthcare providers to fill in complete medical records because this is important to display a comprehensive prevalence of AUB.

DISCLOSURES

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Conflict of interest

The authors declare no conflict of interest

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Author Contribution

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

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ORIGINAL RESEARCH

Clinical profile of geriatric cervical cancer patients in a tertiary hospital in Surabaya, Indonesia

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ABSTRACT

Objective: To identify the distribution of age, histopathology type, clinical stage, treatment type, parity, first complaint, and referral origin of geriatric cervical cancer patients at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Materials and Methods: This study was a retrospective study observing data from medical records and presented the data descriptively. The medical records were taken from Oncology Outpatient Clinic in Dr. Soetomo Hospital, from 2020-2021, covering geriatric patients aged more than 55 years old. The data were screened and processed.

Results: At Dr. Soetomo Hospital, in 2020-2021 there were 228 cervical cancer patients. From 176 patient data that met the inclusion criteria, the average age was 65.38 ± 4.86 years, with 4 types of histopathology dominated by squamous cell carcinoma (82.39%), adenocarcinoma (11.93%), adenoquamous (3.41%) and others (4%), divided into 8 clinical stages and dominated by stages IIIB (77.27%), IIB (15.9%), IVB (2.84%), IIIA and IB had same number (1.14%), 1A (0.57%) and no cases of IIA were found. The treatments were dominated by chemotherapy (86.36%), radiation therapy (7.38%), no treatment (3.41%), hysterectomy (1.7%), while for conization and palliative therapy each in 1 case (0.57%). Most experienced 3 parity (29.5%), followed by 4 parity (17.61%), >5 (13.07%), 5 (10.23%), 1 (6.82%) and no parity (2.27%). The three first complaints were. vaginal bleeding (82.38%), vaginal discharge (46.02%), and pain (82.38%), and the patients were dominated by referrals from Java Island other than Surabaya City (78.40%), outside Surabaya in Java Island as many as 36 referrals (20.45%) and outside Java Island 2 referrals (1.14%).

Conclusion: There were 176 geriatric patients with cervical cancer at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in the 2020-2021 period, dominated by age 56-65 years, the histopathology type of squamous cell carcinoma, stage IIIB patients, most received therapy was chemotherapy, most were multiparous with 3 parities, the majority experienced complaints of vaginal bleeding when diagnosed with cervical cancer, and were dominated by referrals from Java Island outside Surabaya.

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Highlights:

1. Squamous cell carcinoma majorly covered in histopathologic of the records, while adenosquamous followed second.
2. Most of the subjects were referral patients to Dr. Soetomo General Academic Hospital. They were mostly originated from Java outside Surabaya.

INTRODUCTION

Cervical cancer (CC) is known as gynecologist malignant, occurs often in women, caused mainly by human papillomavirus (HPV) type 16 and 18. The infection will trigger the transformation of c epithelial cells in the cervix, leading to pre-cancer lesions and gradually developing to cancer.[1]

According to World Health Organization (WHO) in 2022, cervical cancer has become the second leading cancer for women living in developing countries. There are approximately 540,000 new cases in 2018 alone and about 311,000 women died of cervical cancer during that year.[2] Aligned with the stated data from WHO, according to United Nations Programme on HIV and AIDS (UNAIDS), about 500,000 women suffer from cervical cancer each year, and half of the number passed away.[2]

Based on data served by *Himpunan Obstetri Ginekologi Indonesia* (HOGI) in 2017, 70-80% of the patients with cervical cancer in Indonesia were mostly geriatric. Therefore, early detection to see the possibilities of manifestation in the cervix is needed. The widely used screening method is a pap smear to retrieve the abnormality of the cervix, covering normal smear data, inflammation process, LSIL, HSIL, in situ, or invasive carcinoma. When the test result shows an abnormality, it could be concluded that there are changes in cells around the cervix.[3]

Despite efforts to combat cervical cancer, it remains a significant global health problem with high mortality rates. In light of the data mentioned above, it is imperative to study the current trends and clinical profiles of cervical cancer patients, particularly geriatric patients, in one of Indonesia's largest General Academic Hospitals, the Dr. Soetomo General Academic Hospital, in Surabaya, Indonesia. This study aimed to describe the distribution of the clinical profile of geriatric patients with cervical cancer in Dr. Soetomo General Academic Hospital during 2020-2021.

MATERIALS AND METHODS

This study used medical records as the main source of data. Here we extracted patients' age, histopathology, clinical staging, management, parity information, clinical manifestations, and patient's referral origin. Excluded medical records contained patients with incomplete variables needed. The research was conducted at Integrated Oncology Outpatient Clinic at Dr. Soetomo General Academic Hospital from 2020-2021. Data were processed using Microsoft Excel, went through editing, and coding, and were processed by SPSS software, cleaning. The results of this study will be presented in the form of distribution tables. This study has been approved by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya with the document number 1011/108/4/X/2021.

RESULTS AND DISCUSSION

Sample as many as 228 medical records were obtained. From 228 medical records, 52 were excluded due to incomplete data. Patients' ages were more than 55 when they were first diagnosed. The patients were divided into two categories of age, 56-65 years old and older than 65 years old.

Table 1. Age distribution of cervical cancer in geriatric patients at Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021.

Age Categories	Frequencies	Percentage
56-65	108	61.36%
>65	68	38.64%
Total	176	

Patients aged 56-65 years were the majority of the subjects with a total of 108 cases (61.36%) (Table 1). The research subjects in this study were elderly, persons aged more than or equal to 55 years. In this study, the majority aged 56-65 years (61.36%) with an average age of cervical cancer patients at Dr. Soetomo General Academic Hospital, Surabaya was 65.38 ± 4.86 years old (SD 4.86356). The age range of the subjects was 56-65 years, so all subjects had experienced menopause. Menopause itself does not affect the risk of cervical cancer.[4] However, it has been recognized that the older the age, the less capable the immune system, resulting in an increase of infection.[5] In addition, the CDC (2012) also reported that oncogenic HPV is related to cervical cancer and the incidence rate of this cancer increases after the age of 50 years.

Cervical cancer can develop in women of all ages, but generally develops in women aged 35-55 years with a varied peak age of incidence in each population.[6] The results of this study showed that the highest incidence of cervical cancer was found in the age group of 56-65 years, comprising 108 patients (61.36%). This was different from several other studies, as reported by Putri et al. (2019) and Pratiwi et al. (2022), that the majority of cervical cancer patients aged 41-50 years.[7,8] Whereas, a research in Jambi was dominated by ages 46-55 years,[9] and 41-50 years in Bali.[10] However, the results of this study were in line with a study in India that the

majority of cervical cancer patients were found at the age of more than 60 years (38.4%), followed by ages 50-59 years (31.2%).[6] The difference in the age of cervical cancer may be caused by several factors. One of which is the time when the patient is screened for cervical cancer. The earlier the patient is screened for cervical cancer after marriage, the earlier the cervical cancer can be detected. Another factor is due to the country's economic progress, and the age of having sexual activity for the first time.[10]

Table 2. Histopathology distribution of cervical cancer in geriatric patients in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021.

Etiology	Frequency	Percentage
Adenocarcinoma	21	11.93%
Squamous cell carcinoma	145	82.39%
Adenosquamous	6	3.41%
Others	4	2.27%
Total	176	

Table 2 shows that the histopathology distribution of geriatric patients with cervical cancer in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021 is dominated by squamous cell carcinoma (82.39%), followed by adenocarcinoma cases in 21 patients (11.93%), adenosquamous in six patients (3.41%) and others in four patients (2.27%).

Histopathological examination can be defined as a microscopic examination of a tissue to determine the course or level of disease.[11,12] In the context of cervical cancer, histopathological examination is the reference standard used by many clinicians and health institutions to diagnose cervical neoplasms. In addition, the determination of treatment for cervical cancer patients (inpatient or outpatient) can also depend on the results of histopathological examination.[12]

Among cervical cancer patients at Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021, from various histopathological types, invasive, non-keratinizing squamous cell carcinoma was found as the most common histopathological type. Squamous cell carcinoma, or is a cancer that develops from squamous epithelial cells. This type of epithelial cells is found in various parts of the body, including the surface of the skin, the surface of hollow organs, the surface of the respiratory organs, digestion, and also the genital organs. Therefore, squamous cell carcinoma may show different manifestations according to where it occurs.[11]

Based on its morphology, squamous cell carcinoma can be divided into keratinizing, non-keratinizing, and non-keratinizing types with maturation. Microscopically, the keratinizing type of squamous cell carcinoma appears as infiltrative nests with desmoplastic formations in the dominant stroma, while the non-keratinizing type usually appears as large nests with lots of mitotic formation, necrosis, and little reaction in the stroma. Clinically, the non-keratinizing type of squamous cell carcinoma is more likely to be associated with human papilloma virus (HPV) infection than the keratinizing type. In some cases, a tumor structure with both keratinizing and non-keratinizing characteristics is found. Such tumor cases are usually referred to as the hybrid type or non-keratinizing type with maturation. This type is also usually associated with HPV infection, but is less frequently detected than purely non-keratinizing tumors.[13]

The results of this study were consistent with the results of a previous study by Rasjidi (2009) which stated that the most common histopathological type of cervical cancer was squamous cell carcinoma (85%), followed by adenocarcinoma (10%), and the remaining 5% were other types.[14] such as adenosquamous, clear cell, small cell, verucous, etc. Another study by Kaseka et al (2022) showed that squamous cell carcinoma is the most dominant malignant histopathological type in the cervical cancer patient population.[15]

The clinical stage classification distribution of geriatric cervical cancer patients in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021, showed that the majority was IIIB stage as many as 136 cases (77.27%), followed by stage IIB of 28 cases (15.9%) (Table 3).

Cervical cancer stage indicates the severity of cervical cancer based on its size and distribution at the time of diagnosis according to the results of clinical examination. The stages of cervical cancer according to the Federation of Gynecology and Obstetrics (FIGO) consist stage I (1A, 1A1, 1A2, 1B, 1B1, 1B2), stage II (IIA and II B), stage III (IIIA and IIIB), and stage IV (IV A and IVB). In stage I, the carcinoma is still confined to the uterus, stage II has involved the vagina but does not involve the lower 1/3 of the vagina, stage III has extension to the pelvic wall and has involved the lower 1/3 of the vagina, and stage IV has extended beyond the reproductive organs. Meanwhile, the pre-invasive or in situ cancer stage is referred to as stage 0.[16]

In this study, it was found that the majority of cervical cancer patients at Dr. Soetomo Hospital for the 2020-2021 period was at stage IIIB (77.27%). This result was in line with many other studies where stage IIIB was the most commonly found type of cervical cancer

stage.[8,17,18] However, in contrast to the results of Sharma's study, the results showed that most cervical cancer patients were in stage IIB (32.5%), followed by stage IIIB.[6]

Table 3. Clinical stage distribution of cervical cancer in geriatric patients in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021.

Clinical stages	Frequency	Percentage (%)
IA	1	0.57%
IB	2	1.14%
IIA	0	0
IIB	28	15.9
IIIA	2	1.14
IIIB	136	77.27
IVA	2	1.14
IVB	5	2.84

This study showed that the majority of cervical cancer patients at Dr. Soetomo General Academic Hospital was in an advanced stage of IIIB. This is because cervical cancer at an early stage does not yet cause specific clinical symptoms or complaints and in general the patients come for treatment after the symptoms or complaints arose. Symptoms that occur in the early stages are generally vaginal discharge which is often ignored by the the patients, whereas in later stages there is pain in the lower abdomen and vaginal bleeding which disturbs the patients.[9] In addition, the level of knowledge is also a risk for cervical cancer. Research on cervical cancer at Dr. Soetomo General Academic Hospital, Surabaya in 2014 showed that 85% did not receive cervical cancer education.[19] It has been reported that there is a significant relationship between the level of knowledge and the stage of cervical cancer.[20,21] Thus, the low level of knowledge about cervical cancer can be a cause of delay in diagnosis in patients which can then affect the prognosis. In addition, low socioeconomic status can also be a risk factor.[21]

Table 4. Management distribution of cervical cancer in geriatric patients in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021

Etiology Classification	Frequency	Percentage (%)
Histerectomy	3	1.7
Chemotherapy	152	86.26
Conization	1	0.57
Palliative	1	0.57
Radiation	13	7.38
Receive no therapy	6	3.41
Total	176	

Majority of treatment received by the patient was chemotherapy which covered 86.25% of the total cases or 152 out of 176 cases, followed by radiation in 13 cases (7.38%), no therapy cases were found as many as 6 cases (3.41%), while histerectomy history was found in 3 medical records (1,7%). Palliative and conization were recorded each in 1 case (0.57%).

The treatment modalities for cervical cancer vary depending on the clinical stage of the patient. Based on the results of this study which showed that the majority of cervical cancer patients were in stage IIIB, the management was in the form of chemoradiation or radiation. In addition, if a patient with stage IIIB is accompanied by CKD, the form of treatment is nephrostomy/hemodialysis if needed, and chemo-radiation with a non-cisplatin regimen or radiation.[22]

There are various types of cervical cancer therapy options, both surgical and non-surgical. In this study, there were 5 types of therapy received by cervical cancer patients at Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021, ie. hysterectomy, chemotherapy, conization, radiation, and palliative therapy.

Conization, also known as cold knife conization, is a surgical method of treating cervical cancer. Conization uses a scalpel to remove malignant tissue from the cervix and cervical canal of the uterus. In some cases, all cancerous tissue can be removed using this conization method. This procedure is performed under general anaesthesia.[22]

Hysterectomy is a surgical procedure to remove the entire uterus. When performed on cervical cancer patients, hysterectomy usually also removes other structures around the uterus. There are several types of hysterectomy, including total hysterectomy, the removal of the uterus and cervix; radical hysterectomy, removal of the uterus, cervix, part of the vagina, and the ligaments and surrounding tissue; and modified radical hysterectomy, removal of the uterus, cervix, upper part of the vagina, ligaments, and other tissues around it.[22]

Radiation therapy for cervical cancer patients usually uses high-energy x-ray waves to stop the growth of cancer cells. This therapy damages the DNA of malignant cells to prevent them from spreading to other locations. There are several types of radiation therapy, including external radiation, which is the use of machines outside the body to shoot radiation to areas of the body affected by cancer, and internal radiation, which is the use of facilities such as needles, seeds, wires, or catheters to give radiation right near location of the cancer lesion.[22]

Chemotherapy is a pharmacological therapy that aims to stop the growth of cancer cells, either by killing cancer cells directly or stopping their proliferation. Some of the drugs used in cervical cancer chemotherapy are cisplatin, carboplatin, gemcitabine, phosphamide, irinotecan, paclitaxel, topotecan, and vinorelbine. These drugs can also be used as combination therapy.[22]

Palliative therapy is a type of therapy that focuses on improving the quality of life of patients and their families. This therapy is a common therapy given to patients with terminal conditions. This therapy does not focus on healing the patient's illness, but focuses on the identification and management of pain, as well as physical, psychosocial and spiritual management aimed at alleviating the burden on patients and their families. The basic concept of palliative therapy is to provide humane dignity to patients in the final phases of their lives.

Although radiotherapy is one of the main therapies used to treat patients with advanced cervical cancer, based on the data, it was found that there were limitations in the use of radiotherapy for the treatment of advanced cervical cancer at Dr. Soetomo Hospital, Surabaya.

Table 5. Parity status distribution of cervical cancer in geriatric patients in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021.

Parity	Frequency	Percentage (%)
0	4	2.27
1	12	6.82
2	36	20.45
3	52	29.55
4	31	17.61
5	18	10.23
>5	23	13.07

Data on the distribution of parity status shows that majority of the patients with 3 partus history were in 52 cases (29.55%), followed by 2 partus history in 36 cases, and 4 partus history in 31 cases.

Parity is a term used to describe the number of times a woman successfully gives birth at term, whether born alive or not. This term must be distinguished from gravidity, which means the number of pregnancies a woman has gone through, whether the birth was successful or not.[23] Parity and gravidity are usually asked when clinicians perform obstetric history on pregnant women.[24] Women who have never had a pregnancy before 20 weeks are called nulliparas or para 0, women with a parity score of 1 are called primiparas, while women with a parity score of more than 1 are called multiparas.[25]

In this study, 97.7% of cervical cancer patients in Dr. Soetomo General Academic Hospital, Surabaya in 2021-2022 had parity score of 1 or more, which means that most of the research subjects had given birth to term before. This was in line with research by Tekalegn et al (2022) which stated that high parity is related to the incidence of cervical cancer. The study found that women with high parity are twice as likely to experience cervical cancer.[26] A study at Dr. Moewardi Hospital, Surakarta, Indonesia, also found a relationship between parity numbers (especially above 3) and the incidence of cervical cancer.[27]

From a number of previous studies, there are several explanations about the relationship between parity and cervical cancer. Parity can be seen as a reflection of a woman's sexual activity. The higher the parity number, the more often a woman gives birth, and this can be seen as an illustration of higher sexual activity. In addition, there are also hormonal influences on the incidence of cervical cancer. Blood concentrations of the hormones progesterone and estrogen are known to increase during pregnancy and reach a peak in the last weeks of pregnancy. Increased level of this hormone is believed to be related to changes in the transformation zone or the boundary between the squamous and columnar epithelium in the cervix. Squamous cell metaplasia is also known to increase in the third trimester of pregnancy.[26]

Table 6. Clinical manifestations of cervical cancer in geriatric patients in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021.

Variables	Frequency	Percentage (%)
Bleeding per vaginam		
Yes	145	82.38
No	31	17.62
Discharge		
Yes	81	46.02
No	95	53.98
Pain		
Yes	81	46.02
No	95	53.98

The clinical manifestation of geriatric patients with cervical cancer in Dr. Soetomo General Academic Hospital from 2020-2021 showed that most of the patients came with bleeding per vagina (82.38%). The distribution of patients with and without discharge was almost even, with more patients without discharge (52.98%). Patients with pain and without pain were also almost even (46.02% vs 52.98%) (Table 6).

Patients with cervical cancer are often asymptomatic in the early stages, and only have symptoms when the

stage has increased. Some of the symptoms that often occur in patients with cervical cancer are vaginal bleeding, especially after sexual intercourse, the presence of discharge from the vagina or vaginal discharge with characteristics of liquid, mucoid, purulent or foul-smelling. In a more severe course of cancer, symptoms can include pain that radiates from the back and pelvis towards the lower extremities.[28]

In cervical cancer patients at Dr. Soetomo General Academic Hospital, Surabaya for the 2020-2021 period, the majority of patients (82.38%) experienced complaints of vaginal bleeding. The same results were obtained from a study in Mangalore City, India, which found vaginal bleeding as the most frequent complaint or clinical manifestation in cervical cancer patients.[6] In contrast to the results of research by Kumar in 2020, the results showed vaginal bleeding experienced by patients as much as 28.40% of the total number of cases.[29] Similar findings were also found in a study in Jambi in 2022 majority of the patients' complaints were vaginal bleeding, as much as 58.9%.[9]

Vaginal bleeding is bleeding that occurs outside of normal menstrual periods. The incidence rate of vaginal bleeding in cervical cancer varies from 0.7% to 100%.[30] In addition, vaginal bleeding is also one of the causes of death in cervical cancer, as much as 6%. Vaginal bleeding can occur acutely or chronically. Acute vaginal bleeding is a secondary symptom due to tumor growth which causes angiogenesis, local tumor invasion to systemic effects of the body due to side effects of cancer treatment itself. Treatment for vaginal bleeding can be done through anticoagulants and nonsteroidal anti-inflammatory drugs (NSAIDs).[30]

In geriatric cervical cancer patients at Dr. Soetomo General Academic Hospital for the 2020-2021 period, it was found that 46.02% of the patients experienced vaginal discharge. The majority of the medical record data obtained was that there was no vaginal discharge in 95 cases (53.98%). For patients with complaints of vaginal discharge, there were 81 cases (46.02%). The results in the Mangalore city study showed statistics of 33.5% of patients experiencing vaginal discharge. Quite different results were obtained in Naufaldi's study that the vaginal discharge was reraly found as a symptom that was present only in 3.6% of the total cases.[9]

Leucorrhoea is one of the abnormal symptoms of cervical cancer because cervical cancer usually does not have clinical symptoms that are complained of at an early stage. When several symptoms appear, it indicates that it has already been in a more advanced stage.

Data found that 53.98% of patients without pain complaints in cervical cancer patients at Dr. Soetomo General Academic Hospital, Surabaya for the 2020-2021 period and 46.02% had complaints of pain. In a study in Mangalore City, India, data found that 33% of the total cases experienced pain.[6] Similar results were also found in Naufaldi's study, with a percentage of 37.5% of patients experiencing pain.[9]

According to Schmidt, pain in cancer is caused by the interaction between cancer cells and the surrounding sensory nerves, different from inflammation or neuropathy mechanisms.[31] Chronic pain is found more in female patients who are taking medication. In addition, chronic pain is found in women in the abdomen and pelvis, twelve months after undergoing radiotherapy.[32]

Out of all patients recorded in this study, majority of the cases, as many as 138 (78.40%) patients were referred to Surabaya to be treated, followed by 36 patients originated from Surabaya, and 2 (1.14%) patients originated from outside the island of Java.

Dr. Soetomo General Academic Hospital is the main and largest referral hospital in Eastern Indonesia. Dr. Soetomo Hospital has an Integrated Oncology Clinic (POSA) which consists of an oncology outpatient unit and a traditional medicine outpatient unit. The subjects of this study were cervical cancer patients who underwent outpatient care at the Obstetric Oncology Outpatient Clinic at the POSA.

Table 7. Origin distribution of cervical cancer in geriatric patients in Dr. Soetomo General Academic Hospital, Surabaya in 2020-2021.

Origin	Frequency	Percentage (%)
Surabaya	36	20.45
Java outside	138	78.40
Surabaya		
Outside Java	2	1.14
Total	176	

Based on Minister of Health Regulation No. 1 of 2012 concerning Referral System for Individual Health Services Article 3, the health service referral system is the implementation of health services that regulates the delegation of tasks and responsibilities for health services reciprocally both vertically and horizontally.[33] This referral system is mandatory for patients, whether they are participants in health insurance or social health insurance and health service providers or not. Referral patients have been given a previous referral letter that has been approved by the patient and/the patient's family, to the referral hospital so that communication is created between the referrer and the referral recipient.

This referral is only given if the patient requires specialist health services and the primary health facility appointed to serve the participant is unable to provide health services according to the participant's needs due to limited facilities, services, and/or staff.

Most of the reasons why patients are referred to Dr. Soetomo General Academic Hospital, Surabaya is due to limited facilities at the primary service level. With such limited facilities and infrastructure, a screening or early detection program can be carried out with the VIA test.[16] However, patients will require higher-level diagnostic measures, such as biopsy and anatomical histopathological examination to determine the stage. In addition, cervical cancer patients are generally treated in the form of chemotherapy, radiation, and in some cases surgery is required. Therefore, most cervical cancer patients need to be referred to higher health facilities, such as Dr. Soetomo General Academic Hospital, Surabaya, to obtain the health services needed by patients with adequate facilities.

CONCLUSION

There were 176 cervical cancer patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, in 2020-2021 period. The patients were dominated by patients aged 56-65 years. The most common type of histopathological anatomy found in the cervical cancer patients was invasive, non-keratinizing squamous cell carcinoma. The majority of cervical cancer patients at Dr. Soetomo General Academic Hospital was at stage IIIB cancer patient. Chemotherapy was the most widely used type of treatment for cervical cancer patients. Most of the cervical cancer patients at Dr. Soetomo General Academic Hospital were multipara, with the highest number of parities being three parities. The majority of the patients experienced complaints of vaginal bleeding when diagnosed with cervical cancer, but did not experience complaints of pain or vaginal discharge. The cervical cancer patients in the hospital were dominated by patients who came from Java outside Surabaya.

DISCLOSURES

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Conflict of interest

The author declared that there is no conflict of interest.

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Author Contribution

The authors contribution are as followed: ND drafting and revising the manuscript, acquisition of data, analysis of the data. BA: revising the manuscript, study concept or design, interpreting the data responsibility for conduct of research. BU: revising the manuscript, analysis of the data. NK: revising the manuscript, analysis of the data.

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ORIGINAL RESEARCH

Obstetric complications and delivery methods in Indonesia

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ABSTRACT

Objective: This study aimed to determine the delivery methods, indications and any associations between delivery methods and obstetric complications in Indonesia in 2018.

Materials and Methods: This study analyzed data from the Basic Health Research (Riskesdas) 2018. The population and sample were married eligible women of 10 – 54 years old who had children, as many as 78,737 mothers. The variable taken in this study was the problems/complications during pregnancy as the independent variable, and the methods of delivery as the dependent variable. Chi-square test was used for comparison purposes. Logistic regression was run to relationship between complications and delivery methods.

Results: Delivery indications were complications during the delivery process (23.23%), premature rupture of membranes (5.07%), obstructed labor (3.37%), transverse fetus (3.09%), bleeding (2.36%), and other complications (3.98%). Methods of delivery were expected delivery (81.45%), cesarean section (17.64%), and with other procedures (0.90%).

Conclusion: Complications of labor correlate significantly with the methods of cesarean section. The cesarean section still dominated among other delivery modes, and there are still many mothers who did not have complications or no medical indications but choosing cesarean section delivery.

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Highlights:

1. Nearly a quarter of pregnant women experience pregnancy complications during the delivery process.
2. Caesarean section delivery is dominant among other methods, and 8.4% of mothers do not have any complications but choosing cesarean section delivery.

INTRODUCTION

Pregnant mothers are hoped to have a healthy and smooth pregnancy, with no problems/complications that will impact their delivery process.[1] Pregnancy is a period that is vulnerable to health status, health conditions before pregnancy also affect pregnancy, such as a history of hypertension, diabetes, and anemia. These conditions must be controlled first so there will be no more significant risk during pregnancy. A high-risk pregnancy is associated with many problems that

can affect marital well-being as well as maternal and fetal health.[2,3]

Delivery can by vaginal (standard), some medical assistants/procedures or surgically (cesarean section). Those methods should be based on the condition if the mother and the fetus during delivery. The vaginal delivery method is a delivery that can be done generally without any special procedures/treatments from medical staff. Vaginal delivery with procedures means delivery where the condition of the mother and the fetus requires special treatment from medical personnel using several tools or drugs such as vacuum, forceps, induction, etc. Cesarean section is a particular procedure when there is abdominal surgery by an expert doctor if vaginal delivery cannot be conducted[4] because it is expected to endanger the mother and the fetus.[5] Epidemiological data around the world and in Indonesia regarding complications of pregnancy and delivery methods are very limited. In Indonesia, almost 30 percent of births do not have complications during labor, while other births have one or more complications. The most dominant labor complications are prolonged labor (40.6%) and rupture of membranes (19%).[6] Meanwhile the number of deliveries by cesarean section in most countries in the world is very high, including in Indonesia (17.64%)[7] and in France (20.2%).[8]

Caesarean section is caused by maternal factors, fetal factors or both.[9] Some mothers think that giving birth by caesarean section will be safer and more comfortable for both the mother and the baby. This is related to the mother's knowledge about pregnancy and delivery methods.[10] Advances of technology and science, as well as medical devices, have provided alternatives for delivery process. However, this procedure is not justified considering that childbirth is a natural process if there are no complications or if there is no medical indication to caesarean section.[11] Sometimes, mothers prefer to choose it even though they can actually choose normal delivery. As a result, caesarean section delivery rate has increased significantly in most countries, either in low, middle, or high income countries. Based on these conditions, it is necessary to review the indications and method of delivery and the relationship between complications and mode of delivery in Indonesia.

MATERIALS AND METHODS

The data were based on a survey in Basic Health Research (Riskesdas) 2018. The population and sample in this article were eligible married women between the age of 10 – 54 years who met the inclusion and exclusion criteria. The inclusion criteria in this study were women aged 10 – 54 who had given birth and included as the sample of Basic Health Research 2018. The exclusion criteria were the ones with incomplete data. The sample was taken using multistage stage cluster sampling method with census block as the cluster collected 78,737 samples (NIHRD, 2018).

The variables were delivery complications as the independent variables and methods of delivery as the dependent variables. Delivery complications included the transverse fetus, bleeding, seizure, premature rupture of membranes, extended delivery, umbilical cord loop, placenta previa, retained placenta, and hypertension, while the delivery methods included standard delivery, cesarean section, vacuum, forceps, induction, and others.

The data analyzed used the licensed software full term (SPSS) version 21 owned by Health Research and Development Center, Magelang, Indonesia. After data screening, descriptive analysis was conducted by cross-tabulation between pregnancy complications and delivery methods. Chi-square tests were used for comparison purposes. Logistic regression was run to relationship between complications and delivery methods. This study obtained ethical approval from the Indonesian Health Research and Development Ethics Committee Number LB.02.01/2/KE.380/2018. All parents declared their participation in a signed consent form.

RESULTS AND DISCUSSION

Table 1 shows that almost a quarter of the respondents experienced labor complications. The percentage distribution of the frequency of delivery complications, ie. the premature rupture of membranes, extended delivery, and the transverse fetus, was higher than the others. Table 1 also shows that 17.64% of respondents gave birth via cesarean section. This high cesarean rate has exceeded the maximum limit of the WHO standard. Other studies reinforce the statement that the population rate of the cesarean section above 10-15 per cent is hardly justified from a medical perspective.

Table 2 shows the cross-tabulation of labor complication indications for the delivery method. The cause of the high rate of cesarean section is a several labor complications: placenta previa, transverse fetus and hypertension. For these three labor complications the section can still be carried out generally based on data from research results that have been conducted in several countries.

Table 1. Distribution frequency of delivery complications and delivery methods in Indonesia 2018 (N=78.737)

Variables	Frequency, *n* (%)	
	Yes	No
Delivery complications		
Transverse fetus	2.432 (3.09)	76.305 (96.91)
Bleeding	1.858 (3.09)	76.879 (97.64)
Seizure	101 (0.13)	78.636 (99.87)
Premature rupture of membranes	3.989 (5.07)	74.748 (94.93)
Long delivery	2.656 (3.37)	76.081 (96.63)
Umbilical cord loop	1.666 (2.12)	77.071 (97.88)
Placenta previa	433 (0.55)	78.304 (99.45)
Retained placenta	453 (0.58)	78.284 (99.42)
Hypertension	1.567 (1.99)	77.170 (98.01)
Other	3.132 (3.98)	75.605 (96.02)
No issues	60.450 (76.77)	18.287 (23.23)
Delivery Methods		
Normal	64.134 (81.45)	14.603 (18.55)
Cesarean section	13.891 (17.64)	64.846 (82.36)
Vacuum	534 (0.68)	78.203 (99.32)
Forceps	53 (0.07)	78.684 (99.93)
Induction	70 (0.09)	78.667 (99.91)
Other	55 (0.07)	78.682 (99.93)

Table 2. Crosstabulation of the indications of the delivery problems/complications towards the choice of delivery methods in Indonesia 2018

Labor complication	Delivery method, *n* (%)						Total
	Normal	Cesarean section	Vacuum	Forceps	Induction	Others	
Transverse fetus	689 (28.33)	1.735 (71.34)	5 (0.21)	1 (0.04)	0 (0.00)	2 (0.08)	2.432 (100.00)
Bleeding	1.524 (82.02)	310 (16.68)	23 (1.24)	1 (0.05)	0 (0.00)	0 (0.00)	1.858 (100.00)
Seizure	50 (49.50)	48 (47.52)	3 (2.97)	0 (0.00)	0 (0.00)	0 (0.00)	101 (100.00)
Premature rupture of membranes	2.131 (53.42)	1.750 (43.87)	84 (2.11)	1 (0.02)	9 (0.23)	14 (0.35)	3.989 (100.00)
Long delivery	1.210 (45.56)	1.251 (47.10)	163 (6.14)	4 (0.15)	21 (0.79)	7 (0.26)	2.656 (100.00)
Umbilical cord loop	1.203 (72.21)	448 (26.89)	14 (0.84)	0 (0.00)	1 (0.06)	0 (0.00)	1.666 (100.00)
Placenta previa	75 (17.32)	355 (81.99)	3 (0.90)	0 (0.00)	0 (0.00)	0 (0.00)	433 (100.00)
Retained placenta	438 (96.69)	8 (1.77)	1 (0.22)	0 (0.00)	6 (1.32)	0 (0.00)	453 (100.00)
Hypertension	712 (45.44)	821 (52.39)	26 (1.66)	3 (0.19)	2 (0.13)	3 (0.19)	1.567 (100.00)
Others	945 (30.17)	2.085 (66.57)	73 (2.33)	7 (0.22)	16 (0.51)	6 (0.19)	3.132 (100.00)
No issues	55.157 (91.24)	5.080 (8.40)	139 (0.23)	36 (0.06)	15 (0.02)	23 (0.04)	60.450 (100.00)

Pregnant women hope that their pregnancy will be smooth and healthy until the birth process and hope that the position of the fetus is normal with head presentation. However, sometimes an abnormal fetal position, such as a transverse fetus, occurs. This makes problem in the delivery process, causing labor complications if assisted improperly.[12] Studies have shown that fetal position with pure breech presentation can still be born normally.[13] Table 2 show that 28.33% of women gave birth normally and 71.31% of fetal transverse were born with caesarean section or other procedures. Studies showed that normal delivery can still be attempted or by procedures to reduce the number of deliveries by caesarean section. Table 3 shows the relationship between labor complications and delivery method. Transverse fetal position is significantly related to the mode of delivery by cesarean section approximately 24 times. A study in Australia showed similar findings where there was an increase in the cesarean delivery rate which was mainly due to a more significant number of breech presentations.[14] Table 3 shows relationship between several labor complications and delivery methods. Close relationship was found in placenta previa, transverse fetus and hypertension, followed by other cases.

Delivery bleeding still indicates how high maternal mortality, especially postpartum bleeding, is in Indonesia. Some efforts have been made by the Health Ministry to manage and improve the treatment of postpartum bleeding.[15] This study showed that 82.0% of mothers underwent standard delivery and 16.68% were by cesarean section, meaning that mothers with labor bleeding can still be attempted to deliver typically. Table 3 shows that bleeding has the potential for delivery with cesarean section approximately two times.

Table 3. The relationship between labor complications and delivery methods in Indonesia in 2018

Labor complication	Delivery method, *n* (%)		OR (95% CI)	*p*-value
	Vaginal	Cesarean section		
Transverse fetus	697 (28.66)	1.735 (71.34)	24.74 (22.49-27.22)	<0.001
Bleeding	1.548 (83.32)	310 (16.68)	2.28 (2.01-2.59)	<0.001
Seizure	53 (52.48)	48 (47.52)	6.33 (4.35-9.21)	<0.001
Premature rupture of membranes	2.239 (56.13)	1.750 (43.87)	8.56 (7.94-9.22)	<0.001
Long delivery	1.405 (52.90)	1.251 (47.10)	9.23 (8.47-10.05)	<0.001
Umbilical cord loop	1.218 (73.11)	448 (26.89)	3.48 (3.08-3.93)	<0.001
Placenta previa	78 (18.01)	355 (81.99)	47.56 (36.46-62.04)	<0.001
Retained placenta	445 (98.23)	8 (1.77)	0.33 (0.19-0.56)	<0.001
Hypertension	746 (47.61)	821 (52.39)	10.85 (9.75-12.08)	<0.001
Other	1.047 (33.43)	2.085 (66.57)	22.78 (20.93-24.80)	<0.001
No issues	55.370 (91.60)	5.080 (8.40)	0.10 (0.99-0.11)	<0.001

CI: confidence interval; OR: odds ratio

Premature Rupture of Membranes (PROM) is one of the delivery complications. Previous studies showed that PROM is related to the delivery method of cesarean section.[16,17] This study elaborates that the methods of delivery can be done in a balance between standard delivery and cesarean section, and PROM has the potential to deliver approximately eight times with cesarean section. The cause of PROM is yet to be identified, but it is related to age, gemeli, parity, anaemia, preterm, infection, working mother, and pregnancy interval.[18]

Long delivery correlates with less than usual uterus contractions. Contraction becomes less frequent, and strength of control also reduces.[19] Another study showed that long delivery does not correlate with a delivery method of cesarean section.[17] However, in this study there was little difference in the delivery method, 47.10% by cesarean section and 52.90% by standard delivery (Table 3). Table 3 also shows that respondents delivered with cesarean section were nine times higher.

The umbilical cord loop and placenta previa are two different cases, but the umbilical cord loop is related to placenta previa. In the case of an umbilical cord loop with the right and left winding, most cases occur in the proper umbilical cord winding. However, both have risks towards the limit of intrauterine growth and fetal death.[20] Standard delivery can mostly make the umbilical cord loop in the distinctive delivery handling process. However, if the placenta previa has closed most of the birth path, it will be challenging to hold a standard delivery. This study showed that 73.11% of mothers with umbilical cord loops are giving birth with standard delivery, while among mothers with placenta previa, only 18.01% had a standard delivery. Table 3 shows the association of placenta previa with the method of delivery about 47 times for cesarean section.

Some labor problems in this study showed how a mother and health staff can decide which delivery method is done with various problems. Table 1 describes that 60,450 (76.77%) mothers have no delivery problem. In contrast, less than one-fifth (23.23%) of pregnant mothers are indicated to have the issues. Health staff, especially midwives and obstetric doctors, will undoubtedly focus on the mothers with the issues so they can pass the process well without complications. The result of the previous study elaborated that this delivery problem implies the delivery methods which inflict mothers' and fathers' anxiety.[21,22] The mother's anxiety about the delivery problem cannot be avoided and must be faced with a mature mind. Besides, it was the awareness of the mothers who had issues in delivery that there was still 8.40% of them choosing cesarean section. It can be reviewed how caesarean section delivery becomes an option for mothers who may undergo standard delivery.

In labor process in Indonesia and worldwide, caesarean section tends to increase as shown by ecological evidence. It is considered one of the most effective interventions to save both mother and fetus. Although it has been a trend, the percentage of cesarean section delivery is 10% higher than the population level. It is not automatically related to reduction of maternal and fetal mortality rate.[11] The options of cesarean section delivery must be considered well and it is applied when there is an apparent benefit as shown by medical indication. Other reasons are not allowed. Surgical procedures' high cost and risk/complications must be examined.[11] Robson's classification could help identify possibilities for decreasing cesarean section rates.[23] Cesarean section surgery can effectively prevent maternal mortality and morbidity when the reason is justified medically. However, no evidence showed benefit of cesarean section delivery methods to women not suitable for the procedure. Even the risk will

increase with limited access to the more comprehensive service.

Cesarean section delivery is categorized as a high-risk surgery with some possibilities of having complications such as postoperative bleeding, sepsis, bladder injury, ureteric injury, bowel injury, postoperative ileus, or Ogilvie syndrome.[24] The more severe impacts, especially to the mother's health and consequences to physical health and social-economic, will be suffered by mothers with middle and low economic levels. The result of the study using in-depth interviews shows that women are unlikely to obtain precise information about the short-term and long term complication and indications of cesarean section. It is related to the hospital facilities and infrastructure and the referral management process. Local hospitals with less equipment are different compared to referral hospitals.

The results showed that some factors affected cesarean section delivery, such as the maternal characteristics, maternal and fetal health status, delivery problems, parity, and ANC records. All of these factors increased the chance of cesarean section delivery.[25-28] Another study also indicated that more women request cesarean-section delivery for medically unacceptable reasons.[29] Cesarean section without any indication will have harmful impacts on maternal health in both the short and long term sequelae. Before deciding to have a cesarean section to decrease the number of cesarean section delivery, interventions can be in the form of induction, partograph, or vacuum/forceps birth. As observers of maternal health, the government, the public, and the media must work together to reduce the suffering of mothers due to the high number of cesarean sections.[30,31]

Inaccurate information on cesarean section from media about advances in science and technology in handling cesarean section delivery process and socio-cultural and medicolegal that are not conveyed completely have caused mothers choosing wrong delivery method. Intraoperative and postoperative risks of cesarean section must be considered, along with complications that could potentially affect subsequent pregnancies. Cesarean section should only be performed when it benefits the mother.[29] The lack of quality of the information received by mothers during ANC may need to be reviewed and conveyed clearly, a procedure that should have been taken during the preventive period.[32]

Several issues raise questions about the increase in cesarean sections, including changes in pregnancy management, the availability of delivery services, and the expectations of patients or healthcare providers. In low-income countries such as Bangladesh, the rate of cesarean section in private facilities is very high at 73%.[5] The high cost of cesarean section delivery, especially for mothers with low economic status, can negatively affect health and socioeconomic status.[4] The probability of a woman using cesarean method varies according to each individual's characteristics, history of pregnancy, and childbirth. A study in Iran showed that women who received prenatal care from obstetricians had about 2.3 times more, and with the increased number of ultrasounds, the odds of cesarean section augmented by 25%.[33] Based on the 2017 IDHS data analysis, the use of the cesarean section method in childbirth was not only based on the presence or absence of medical indications, but many other factors ha played a role in the selection of this method.[34,35]

Cesarean section rate in Indonesia, according to 2018 Basic Health Research results, was 17.6%, This rate has passed the maximum limit of the WHO standard. Other studies corroborate the statement that population rates of the cesarean section of above 10-15% are hardly justified from a medical perspective, and it must have impact on maternal, newborn, and infant morbidity and mortality.[11,36] A study conducted by Suryati in 2013 showed that the average characteristics of mothers living in cities, low education and poor people, and not at high-risk age were factors associated with cesarean section.[37]

In recent years, observers of maternal health, the government, and the WHO have expressed concern about the increasing number of births through cesarean section and the potential negative consequences for maternal and infant health, and the need to review indications of whether or not cesarean section can be performed.[11,38]

CONCLUSION

Labor complications have significant correlation with cesarean section. The method of cesarian section remains predominant among other delivery modes. Even many mothers who do not have complications or with no medical indications have chosen to give birth using cesarean section delivery.

DISCLOSURES

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Conflict of interest

The authors declared no conflict of interest in this study. Additionally, this article does not have comprehensive ethical issues, such as plagiarism, implied consent, theft, data creation and, or falsification, duplicate publication or requests, and redundancy.

Author Contribution

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

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SYSTEMATIC REVIEW

Comparison of the potencies of ginger (*Zingiber officinale*) and fennel (*Foeniculum vulgare*) in ameliorating dysmenorrhea pain: A systematic review

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ABSTRACT

Objective: We aimed to compare the effect of ginger and fennel herbs treatment in reducing dysmenorrhea pain intensity.
Materials and Methods: We used a systematic review method employing the PRISMA chart. PubMed, Science Direct, Scopus, and EBSCO were searched which resulted in 418 compatible literature. Among the studies found, 13 works of literature that met the PICO inclusion criteria were included in this study. The study subjects involved women aged 15 to 25 years old who experienced dysmenorrhea, had normal or high BMI levels, consumed or did not consume oral contraceptive pills (OCP), and had normal menstrual cycles.
Results: The results presented significant decreases in pain intensity in 11 studies, while the two others have shown otherwise. The two studies, with insignificant results, failed to determine the optimum dose to produce the desired analgesic effects.
Conclusion: The administration of herbal ginger is considered more effective in reducing the intensity of dysmenorrhea pain.

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Highlights

1. Dysmenorrhea pain could be reduced through various non-pharmacological treatments, including administration of ginger (*Zingiber officinale*) and Fennel (*Foeniculum vulgare*) which had been shown to significantly reduce the dysmenorrhea pain intensity.
2. The dysmenorrhea pain intensity reduction due to the administration of the natural herbs was not as significant as compared to the ibuprofen or mefenamic acid administration.

INTRODUCTION

The most notable change in puberty is menstruation. Menstruation frequently causes pain or tenderness in the lower abdomen that extends to the waist, lower back, and thighs, known as dysmenorrhea.[1] Dysmenorrhea is a gynecological problem commonly experienced by women during adolescence and adulthood.[2] Dysmenorrhea occurs through the imbalance of the low progesterone hormone and high prostaglandins (PGF2 and PGE2) in the luteinized endometrium. Prostaglandin levels increase, with a PGF2 predomination, triggering uterine hyperactivity, which amplifies the nerve terminal sensitization to prostaglandins and endoperoxides.[3] In addition to uterine hyperactivity, uterine ischemia emerges during menstruation, causing hypertonus and excessive vasoconstriction in the myometrium. Thus, dysmenorrhea occurred.[4]

Dysmenorrhea is quite common in Indonesia, with 60 to 70% of women suffering from this condition. Based on the etiology, dysmenorrhea comprises primary and secondary dysmenorrhea. Primary dysmenorrhea is generated merely by uterine hypercontractions without the presence of any gynecological disorders. On the other hand, secondary dysmenorrhea is more likely to be pathologically originated by abnormalities in the uterus and other reproductive organs.[3] Primary dysmenorrhea has a higher incidence rate than secondary dysmenorrhea, comprising 54.89% of all dysmenorrhea incidence. Dysmenorrhea has significant influences on adolescents' quality of life and social activities due to the pain and the sequels, such as headaches, weakness, vomiting, and seizures.[5]

Treatment of dysmenorrhea has been done through pharmacological and non-pharmacological treatment. Pharmacological agents, including analgesics, hormonal contraceptives, and non-steroidal anti-inflammatory drugs (NSAIDs), such as mefenamic acid, are commonly prescribed.[6] However, prolonged use of NSAIDs can give rise to disturbances in metabolism and the digestive system, as well as the emergence of allergic reactions and organ damage. Therefore, non-pharmacological therapy has been considered a better approach to dysmenorrhea with a much lower adverse effect than NSAIDs.[7] Non-pharmacological treatments, including herbal substances, acupuncture, aromatherapy, heat therapy, and physiotherapies, such as stretching, muscle relaxation, and exercise, could be applied for dysmenorrhea. Herbal products and phytopharmaceuticals have been extensively implemented in Indonesia. Treatments using herbal substances are considered effective in reducing dysmenorrhea pain.[8] In this systematic review, we observe the potency of ginger (*Zingiber officinale*) and fennel (*Foeniculum vulgare*) in reducing dysmenorrhea pain. Ginger (*Zingiber officinale*) contains gingerols, free fatty acids, proteins, and carbohydrates, which have anti-inflammatory and analgesic effects, while fennel (*Foeniculum vulgare*) contains phytoestrogens (fenchone, estragole, and trans-anethole), which have antispasmodic effects against the PGE2 and oxytocin-induced uterus hypercontraction.[9]

Non-pharmacological therapy is considered to have minimal side effects compared to therapy using NSAID drugs. Herbal therapy also does not cause dependence on sufferers, so it is considered more effective and a more economical treatment solution. In consideration of the high prevalence of dysmenorrhea among young women, along with its burden on their career, education, economy, and overall quality of life, this study aims to compare the efficacy of ginger and fennel in relieving and reducing dysmenorrhea pain. This study compared two herbal plants to assess their effectiveness against dysmenorrhea and so far no studies have discussed or compared the effectiveness of ginger and fennel together. This study compared two herbal plants to assess their effectiveness against dysmenorrhea and so far no studies have discussed or compared the effectiveness of ginger and fennel together.This study can be a reference for further research to discuss the effects of the two herbs in depth.

MATERIALS AND METHODS

We conducted a systematic review using secondary data to determine the potential of ginger (*Zingiber officinale*) and fennel (*Foeniculum vulgare*) in reducing dysmenorrhea pain intensity. The PRISMA checklist and flow diagram were employed in searching, selecting, and adjusting the found literature according to the PICO, inclusion, and exclusion criteria.[11]

We searched through four databases, including PubMed, Scopus, Science Direct, and EBSCO, for studies exploring the potencies of ginger (*Zingiber officinale*) or fennel (*Foeniculum vulgare*) in reducing the dysmenorrhea pain intensity. Quasi-experimental, randomized control trials (RCT), and case-control studies were selected. The keywords used in the search were ("Dysmenorrhea" OR "Menstrual Pain" OR "Painful Menstruation" OR "Cramping" OR "Period Pain" OR "Primary Dysmenorrhea") AND ("*Zingiber officinale*" OR "Zingiber" OR "Ginger") AND ("*Foeniculum vulgare*" OR "fennel").

Table 1. PICO Table

Population (P)	Women with dysmenorrhea (menstruation pain)
Intervention (I)	Administration of ginger (*Zingiber officinale*) or fennel (*Foeniculum vulgare*)
Comparison (C)	No intervention
Outcome (O)	Decrease in dysmenorrhea pain intensity via VAS and NRS measurement

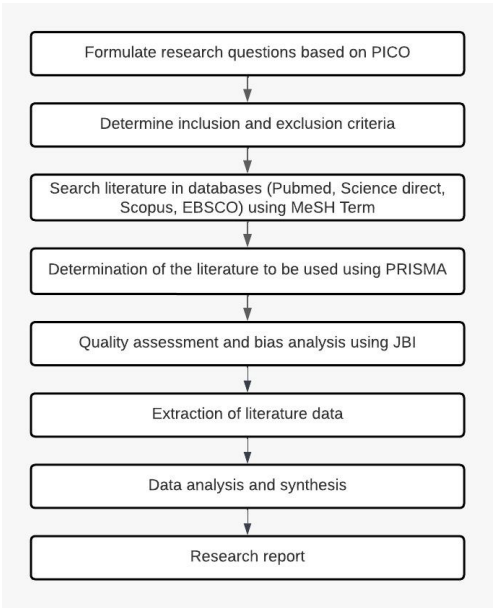

Figure 1. The systematic review workflow

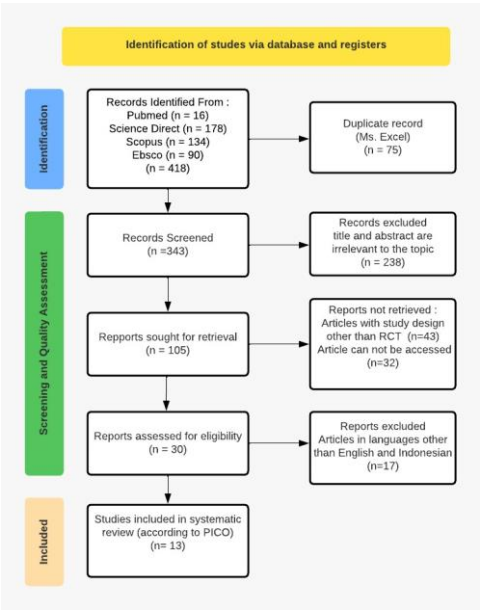

Figure 2. The PRISMA flow diagram

The systematic workflow of this study is shown in Figure 1. Details of the literature search, screening, and selection are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 2). We compared the dysmenorrhea pain intensity pre- and post-administration of ginger and fennel.

RESULTS AND DISCUSSION

From the literature search, we obtained 13 studies matching the PICO and the inclusion criteria. Two independent reviewers carried out the articles' assessment. The RCT articles were assessed using the RCT questionnaire. The risk of bias in each article was appraised using the Joana Briggs Institute (JBI) Critical Appraisal Tool. We present the risk analysis assessment in Table 3.

The study subjects' age ranged from 13 to 25 years old. The demographic characteristics of the study subjects represented an educational background of high school diploma or higher degree of education, except for the Sultan et al. (2021) and Kashefi et al. (2013) study which had a high school diploma as their highest degree of education.[12,13]

Dysmenorrheal patients in this study predominantly had menarche at the age of 12 to 13 years, except in the Nasehi et al. (2013) study at 16.1 ± 1.7 years, with respondents' mean age of 21.8 ± 2.5 years,[14] and in the Ghodsi et al. (2014) study at 14.7 years for the intervention group and 14.4 years for the control group. Overall there were no significant differences in mean age, menarche age, and dysmenorrhea initiation between the intervention and the control groups. The mean menstrual cycle duration of the study subjects is 28 days.[6] The characteristics and intensity of dysmenorrhea pain among the study subjects are relatively diverse, ranging from mild, to moderate, to severe dysmenorrhea.

Not all articles presented the body mass index (BMI) of the study subjects. Most of the study subjects had a normal BMI average, except for the Abadi et al. (2020) study with a BMI average of 26.83 ± 12.34 kg/m^2 for the intervention group.[14] Jenabi et al. (2013) reported a BMI average of 21.33 ± 1.3 kg/m^2, Shirvani et al. (2015) 21.65 ± 3.08 kg/m^2, Adib et al. (2018) 22.06 ±

3.37 kg/m^2, and Pakniat et al. (2019) 21.62 ± 3.15 kg/m^2.[16-18]

In Adib et al. (2018) study, the pre-intervention dysmenorrhea pain intensity of the ginger (*Zingiber officinale*) group was 7.60 ± 1.84, which decreased to 2.97 ± 2.69 in 48 hours post-intervention.[19] These findings indicate a significant reduction in pain intensity following the ginger treatment. At a one-time observation, no significant difference was shown between the ginger and the control group ($p > 0.05$). However, the difference became significant ($p < 0.001$) in multiple times observations. In Jenabi et al. (2013) study, the pain intensity decreased significantly in the group receiving ginger at a 500 mg dose three times a day for three days, with the average pain intensity decreasing from 7.08 ± 1.02 to 4.81 ± 1.20. Jenabi et al. (2013) study also reported that the nausea symptoms in the ginger group improved by 82% compared to the control group.[17]

A study by Kashefi et al. (2013) showed that ginger and zinc sulfate had similar therapeutic effects in lowering pain intensity and could only show maximum effect for two months. The pain intensity mean was reduced from 7.97 ± 1.4 to 3.08 ± 1.52 in the ginger group, and 8.01 ± 1.12 to 3.12 ± 1.2 in the zinc sulfate group.[13] The study of Shirvani et al. (2015), which compared ginger and mefenamic acid, found that ginger only lowered the pain intensity in the first and second months of the observed cycle, therefore there was no significant difference between the ginger and the mefenamic acid interventions. Nonetheless, ginger was only administered in low doses in that study.[18]

Rahnama et al. (2012) reported that the dysmenorrhea duration was significantly shorter in the ginger group.[20] Pakniat et al. (2019) found that the maximum decrease in dysmenorrheal pain intensity was observed in the ginger group, with a significant decline in the first and second month of observations, from 7.08 ± 0.8 to 3, 72 ± 1.39 in the first month and to 3.20 ± 1.28 in the second month.[18] Sultan et al. (2021) also showed a significant decrease in pain intensity in the ginger group, with the pain intensity average reduced from 4.13 ± 0.63 to 2.10 ± 1.52. Ginger was considered more effective than peppermint in relieving menstrual pain and symptoms associated with primary dysmenorrhea. Sultan et al. (2021) also proved ginger's capability to maintain normal blood pressure.[12]

Abadi et al. (2020) study failed to illustrate the expected analgesic effect of ginger due to the incorrect dosing. No significant difference was found in the pain duration between the intervention and control groups. However, the pain duration was shorter during the second month for the ginger group compared to the other groups.[15] Shirvani et al. (2017) indicated that stretching exercises have a more significant effect in reducing pain duration than ginger administration in a two-month observation. However, the overall pain reduction was remained more advantageous in the ginger group and not the over-exercise therapy. Shirvani et al. (2017) study also reported a decrease in bleeding quantity and menstrual duration in the ginger group.[18]

In this review, ten studies explored ginger's impact on dysmenorrhea. Eight studies showed a significant reduction in pain intensity, while the remaining two were not. Thus, ginger could have substantial potential for dysmenorrhea pain relief, including reductions in pain intensity, duration, symptoms, and problems experienced by women with primary pain. Ginger is considered effective in the treatment of dysmenorrhea. The complex active compound contained in ginger could regulate prostaglandin excess and inhibit pro-inflammatory enzymatic processes. Based on these findings, ginger herbal therapy may produce better pain-relieving properties when combined with proper physical exercise.

Modares et al. (2006) found that fennel and mefenamic acid were equally effective in elevating pain and activity limitations in adolescent girls with primary dysmenorrhea.[21] 73% of the study subjects taking fennel extract reported a lowered pain intensity or even no pain at all. A study by Nasehi et al. (2013) showed that the average maximum pain intensity in the fennel and vitamin E combination group was lower than the ibuprofen group in observations at 1, 2, 3, 6, 12, 24, and 48 hours, and a significant difference was achieved in the first and second hours of observation ($p < 0.03$ and $p < 0.04$). The pain intensity average was 3.9 ± 2.6 at 1 hour following the treatment and further decreased to 1.2 ± 1.6 at 48 hours of observation. The study of Ghodsi et al. (2014) showed that the pain quality and quantity in dysmenorrheal women changed further after several months of daily fennel soft capsules consumption. In this study, three months of use of fennel capsules could elevate the pain drastically.[6] Among the studies observing fennel, only three studies met the inclusion criteria. Fennel (*Foeniculum vulgare*) has the potential as a dysmenorrhea pain reliever. However, it was often found that the differences between the fennel herbal therapy and standard drugs were not quite significant. Fennel could help lower dysmenorrhea pain intensity with regular use. The combination of fennel and vitamin E intervention should be evaluated in more in-depth research in future studies to produce a maximum therapeutic effect compared to a single intervention only.

Table 2. Studies on the characteristics of fennel (*Foeniculum vulgare*) and ginger (*Zingiber officinale*) in a review

Author, Year Study Design	Study Characteristics	Sample Size		Treatment Method		Outcome Indicator	Research Result	Side Effect	Cycle Observation
		I	C	I	C				
Modaress *et al*., 2006 RCT	120 high school students in Kerman City with 1-year history of regular menstruation; no history of epilepsy, GI disturbance, or other diseases; and had dysmenorrhea begins 1-3 months after menarche	60	60	30 drops of fennel extract at the beginning of menstruation, then every 6 hours for 3 days of menstruation	250 mg of mefenamic acid every 6 hours for 3 days	Multidimensional verbal evaluation, including analgesic dosing, activity limitation, need for rest	80% of the fennel group vs 73% of the mefenamic group experienced a reduction in pain, 80% vs 62% reduced activity limitations, and 83% vs 71% did not need rest.	No report	2 menstruation cycle
Nasehi M, *et al*., 2013 Quasi double-blind experiment	68 Tabriz students with a history of primary dysmenorrhea; regular menstruation in the last 3 months; and no history of gynecological disease or allergy to NSAIDs	34	34	No description	No description	VAS	Fennel extract/vitamin E group showed a significant decrease in maximum pain intensity compared to the ibuprofen group at 1-2 hours	No report	No report
Ghodsi Z, *et al*., 2014 Clinical trial	80 female students in Toyserkan, Iran, suffer from primary dysmenorrhea	40	38	1 soft capsule of 30 mg fennel every 4 hours for 3 days before until day 5 of menstruation	No description	VAS McGill Pain Questionnaire VASA	The severity of pain and nausea decreased significantly in the existing group after 1-3 months	No report	3 month
Ozgoli *et al*., 2009 Double-blind comparative clinical trial	150 boarding students in Iran with primary dysmenorrhea; aged above 18 years old; and BMI between 19 to 36 kg/m^2	50	100	250 mg capsules of powdered ginger rhizome, 4 times a day for 3 days from the beginning of menstruation	250 mg mefenamic acid or 400 mg ibuprofen capsule 4 times a day	Multidimensional verbal score, including illness severity, 5-point scale pain relief, and treatment satisfaction	Ginger is as effective as mefenamic acid and ibuprofen, with 80% efficiency	No side effect	1 menstruation cycle
Rahnama *et al*., 2012 RCT	120 boarding students in Iran with moderate or severe primary dysmenorrhea; aged above 18 years old; BMI between 19 to 25 kg/m^2; and no previous OCP use	56	46	500 mg of ginger root powder capsules 3 times a day for a month on the first month 500 mg of ginger root powder capsules 3 times a day for only the first 3 days of menstruation on the second month	Placebo 3 times a day for a month on the first month Placebo 3 times a day only the first 3 days of menstruation on the second month	Multidimensional verbal score VAS	Pain severity significantly lowered with ginger compared to placebo for protocol one and protocol 2 Pain duration significantly lowered with ginger compared to placebo	GI side effects have been reported Heartburn in 5,1% of the ginger group Nausea in 8,7% of the placebo group	2 menstruation cycle
Kashefi, *et al*., 2014	High school students in Iran with moderate to severe primary dysmenorrhea; aged 15 to 18 years old; and no previous OCP, hormonal drugs, or analgesic use	47	45 placebo 54 zinc	250 mg of ginger powder capsule, 3 times a day for 4 days in two-cycles	Zinc and placebo 3 times a day for 4 days	VAS	The ginger and zinc groups experienced more symptom improvement compared to the placebo group for either cycle one or two.	Headache and heartburn	2 menstruation cycle
Shirvani, *et al*., 2015	Boarding students in Iran with primary or secondary dysmenorrhea; aged above 18 years old; no previous IUD or OCP use	61	61	250 mg of ginger powder capsule, four times a day until the pain relieves	250 mg of mefenamic acid, three days until the pain relieves	VAS Pain duration	The difference in the painseverity and duration between ginger and mefenamic acid are not significant.	No report	
Shirvani *et al*., 2017	Mild to severe primary dysmenorrhea	61	61	250 mg of ginger capsule	Physical exercise for 10 minutes 3	VAS	Pain reduction was significantly lower in the	No report	2 menstruation cycle

RCT					times per week		exercise group		
Adib *et al*., 2018 Crossover clinical trial	168 students in Iran; aged 18-26 years old, single; with primary dysmenorrhea in the first three days of menstruation; and had a regular menstruation	84	84	200 mg of ginger powder capsule	200 mg of Novafen capsule	VAS Verbal multidimensional score (MVRS)	Ginger and Novafen are effective in relieving pain, both of which show no significant difference	No report	2 menstruation cycle
Pakniat, *et al*., 2019 Single-blind clinical trial	Students aged 18-25 years old with mild to severe dysmenorrhea; regular menstruation cycle and duration, 21-35 days and 3-7 days	50	50	500 mg of ginger capsule	250 mg of mefenamic acid 2 times per day and 100 vitamin E capsules	VAS Pain duration	Ginger has a greater effect in reducing the severity of dysmenorrhea, as well as vitamin D and vitamin E	Nausea, vomiting, allergy, headache	2 menstruation cycle
Abadi, M.D, *et al*., 2020 Triple-blind RCT	210 students; aged 20-30 years old, single; with regular menstruation cycle, 21-35 days; and no menstruation clotting	70	70 valerian 70 placebo	250 mg of ginger every 8 hours in the first three days of menstruation	350 mg of valerian and 250 mg of sugar-containing-placebo	Pain duration	Dosage in the study did not produce an analgesic effect	No report	2 menstruation cycle
Sultan *et al*., 2021 RCT	150 teenagers with primary severe dysmenorrhea; aged 13-22 years old	50	50 peppermint 50 control	15 ginger capsules 250 mg in one month, 3 capsules per day in 5 days	15 placebo capsules 250 mg in one month, 3 capsules per day in 5 days	VAS	A significant pain and symptoms reduction in the ginger group	Associated with blood pressure, serum calcium, hemoglobin	No report
Jenabi, *et al*., 2013 Clinical trial	70 students in Iran with severe dysmenorrhea	35	35	3 ginger capsules 500 mg per day in 3 days	Placebo	VAS Likert scale	Significant VAS scores decrease in the ginger group	No report	1 menstruation cycle

Table 3. Bias quality assessment using JBI for ginger studies

Description: +: yes -: no ?: uncertain ×: can't be applied	Modares, 2006	Nasehi, 2013	Ghodsi, 2014	Ozgoli, 2009	Rahnama, 2012	Jenabi, 2013	Kahefi, 2014	Shirvani, 2015	Shirvani, 2017	Adib, 2018
Were clinical trial participants really randomized?	+	+	+	+	+	+	+	+	+	+
What is the classification of participants?	+	+	?	+	?	+	+	?	+	+
Is the nature of the groups the same?	+	+	+	+	+	+	+	+	+	+
Does the participant not know which group he is in?	+	+	?	+	?	?	+	?	+	+
Does the therapist not know what treatment they are giving?	+	+	?	?	?	?	+	?	?	+
Does the outcome rater not know which group they are assessing?	+	+	?	?	?	?	+	?	?	+
Did the groups get the same treatment as the ones being tested?	+	+	+	+	+	?	+	+	+	+
Was the follow-up done?	+	?	+	?	?	?	?	+	?	?
Were participants analyzed in their groups?	+	+	+	+	+	+	+	+	+	+
Is the measured output the same?	+	+	+	+	+	+	+	+	+	+
Is the output well measured?	+	+	+	+	+	+	+	+	+	+
Is good statistical analysis used?	+	+	+	+	+	+	+	+	+	+
Is the research design appropriate?	+	+	+	+	+	+	+	+	+	+

Table 4. Bias quality assessment using JBI for fennel studies

Description: +: yes -: no ?: uncertain ×: can't be applied	Pakniat, 2019	Abadi, M.D., 2020	Sultan, 2021
Were clinical trial participants really randomized?	+	+	+
What is the classification of participants?	+	+	+
Is the nature of the groups the same?	+	+	+
Does the participant not know which group he is in?	+	+	+
Does the therapist not know what treatment they are giving?	+	?	?
Does the outcome rater not know which group they are assessing?	?	?	?
Did the groups get the same treatment as the ones being tested?	+	+	+
Was the follow-up done?	?	?	?
Were participants analyzed in their groups?	+	+	+
Is the measured output the same?	+	+	+
Is the output well measured?	+	+	+
Is good statistical analysis used?	+	+	+
Is the research design appropriate?	+	+	+

CONCLUSION

The administration of ginger (*Zingiber officinale*) and fennel (*Foeniculum vulgare*) reduces the dysmenorrhea pain intensity. Both herbs have the same potential in reducing the intensity of dysmenorrhea. However, compared to fennel, ginger can reduce pain in a shorter time.

DISCLOSURES

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Conflict of interest

The authors declare there is no conflict of interest.

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Author Contribution

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