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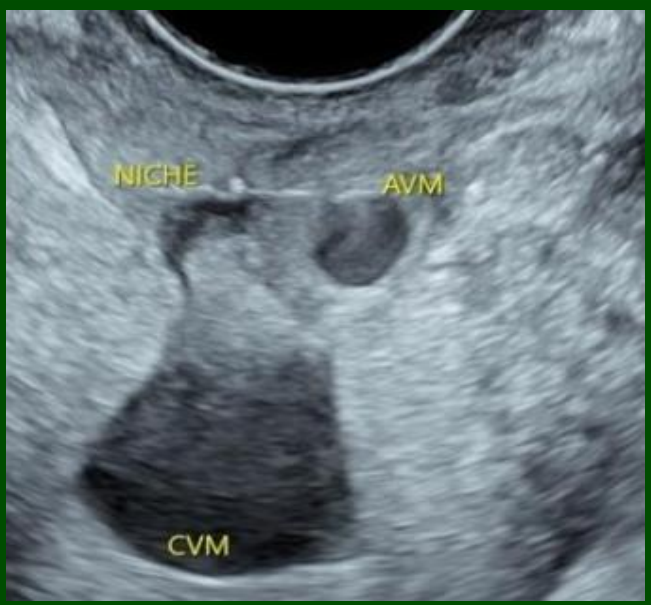

Color Doppler ultrasonography showing a hypervascularity in the uterus around surgical lesion, suggesting a uterine arterio-venous malformation.

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CONTENT

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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 series, review article, systematic review,** and **meta-analysis** that keep the readers informed of current issues, innovative thinking in obstetrics and gynecology. We welcome submissions that contribute to the advancement of knowledge 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. 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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Case series highlights important innovations with wide applicability or previously unpublished complications of new techniques or medications.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 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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Full text electronic 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

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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

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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

The prognostic role of mitosis index, stage and grade of endometrial cancer in Dr. Soetomo General Academic Hospital Surabaya, Indonesia, in 2018-2020

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Molecular prognostic factors;
Maternal health

ABSTRACT

Objective: This study aimed to analyze the correlation between the mitotic index and the stage and grade of endometrial cancer.

Materials and Methods: We collected pathology reports of endometrial cancer from the Pathology Laboratory at Dr. Soetomo General Hospital in Surabaya, Indonesia, covering cases diagnosed between 2018 and 2020. A total of 106 cases of endometrial cancer were included in this study. For each case, detailed records of the cancer stage, grade, and mitotic index were recorded. The mitotic index, an indicator of cell proliferation, was quantified, and its correlation with cancer stage and grade was assessed. To determine the strength and direction of these relationships, we performed a Spearman rank correlation statistical analysis for non-parametric data.

Results: Our findings indicated a significant positive correlation between the mitotic index and the stage of endometrial cancer. An increase in the mitotic index, reflecting a higher proliferation rate of cancer cells, was associated with a more advanced cancer stage, suggesting that the mitotic index could potentially serve as a prognostic marker for assessing tumor progression in endometrial cancer. However, our analysis revealed no significant correlation between the mitotic index and the histological grade of endometrial cancer, implying that the grade, which typically reflects the differentiation status and morphological characteristics of the tumor cells, is independent of the proliferation rate as measured by the mitotic index.

Conclusion: The mitotic index is positively correlated with the stage of endometrial cancer but does not show a correlation with the histological grade. These findings highlight the potential use of the mitotic index in staging endometrial cancer.

How to cite: Choviva FU, Sandhika W, Mulawardhana P. The prognostic role of mitosis index, stage and grade of endometrial cancer in Dr. Soetomo General Academic Hospital Surabaya, Indonesia, in 2018-2020. Majalah Obstetri & Ginekologi (Journal of Obstetrics & Gynecology Science). 2024;32(2):74-79. doi: 10.20473/mog.V32I22024.74-79.

Highlights:

1. Mitotic index and grade are prognostic factors for endometrial cancer, but both are independent.
2. Stage and mitotic index associated with cell proliferation affect the prognosis of endometrial cancer.

INTRODUCTION

Endometrial carcinoma is the sixth most common cancer, accounting for about 5% of all cancer cases in women. According to the World Health Organization, the global rate of cancer rates by 50%, reaching 15 million by 2020. Endometrial cancer is estimated to have 417,000 incidents and 97,000 deaths due to the disease worldwide.[1]

Endometrial carcinoma is generally thought to have a good prognosis, but more than 20% of women with endometrial cancer die from it.[2] Mortality is directly linked to poor prognostic factors that drive tumor recurrence.[3] Significant prognostic factors in endometrial cancer are the stage of cancer, the grade, and the mitosis index.[4,5] The grade and the stage are independent prognostic factors. High histopathological graduation and staging are associated with low long-term survival rates.[6] The mitosis index is used as a simple way to measure proliferation in the microscopic examination of endometrial cancer.[7] With a useful and simple method for analyzing cell proliferation so that it can analyze quickly.[8] In the uncontrolled proliferation of epithelial cells causing cancer development that affects the size of endometrial cancer, the size of endometrial cancer determines the clinical stage according to the TNM classification, which indicates the higher the tumor size, the higher the stage and the worse the prognosis. The degree of histological differentiation of cancer can help predict how fast the tumor growth rate is. In general, the slower the growth, the better the prognosis.[9] Proliferation also affects the growth rate of endometrial cancer tissue.[10] The growth rate of endometrial cancer can be predicted by determining the grade of the cancer. In general, the slower the growth, the better the prognosis.[11] This study aims to show whether there is a correlation between mitotic index with stage and grade of endometrial cancer. By a relatively simple method calculating the mitotic index, it is found that the prognosis can be established earlier and provide faster information for treatment recommendations and better future collection of outcome and survival data.[7,8,12]

MATERIALS AND METHODS

The method of this study is analytic observation with a cross-sectional study design. A sample of this study was taken from some endometrial cancer patients who did post-surgical staging and visited the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from January 2018 to December 2020, 106 patients have endometrial cancers. Patients had two primary or unclear primaries during this period, and no medical records were excluded. The samples were obtained by total population sampling. This observational analytical study reviews anatomic pathology results in Surabaya from 2018 to 2020. The staging, grade, and mitotic index variables were seen in medical records in each case. The result of the study was analyzed with the Spearman rank statistic formula to obtain a correlation between the variables. Health Research Ethics Committee, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia No. 1732/125/4/X/2022, approved this study ethically.

RESULTS AND DISCUSSION

One hundred and six patients were enrolled in this study. Most of the samples were aged women with endometrial cancer aged 45-65 (59.43%), and there were stage characteristics in endometrial cancer. Most 40 patients (37.74%) were in stage III, while 4 (3.77%) were in stage IV. Most endometrial cancer patients in Dr. Soetomo, General Hospital Surabaya have a grade III of 40 patients (37.73%), based on the characteristics of the degree of differentiation histology in endometrial cancer obtained. (Table 1).

Table 1. Patients' characteristics in this study

No.	Variables	Total	N (%)
1.	Age		
	<45 years old	12	11.32%
	45-60 years old	63	59.43%
	>60 years old	31	29.25%
	Total	106	100%
2.	Stage		
	I	37	34.91%
	II	25	23.58%
	III	40	37.74%
	IV	4	3.77%
	Total	106	100%
3.	Grade		
	I	32	30.19%
	II	34	32.08%
	III	40	37.73%
	Total	84	100%

This study revealed that most patients were diagnosed with endometrial cancer at 45-60 years old. At that age, the average woman experiences menopause. This result was under the previous research, which showed that age affects endometrial cancer. When a woman is over 46.5 years the risk of cancer increases with her menopausal age.[13] There are differences in the age of menopause in every country in the world due to differences in lifestyle, geographical, ethnic, and socioeconomic locations that affect the period of menopause.[14] Women with lower socioeconomic status experience significantly earlier menopause.[15] According to WHO 2022 and the Ministry of Health in Indonesia, the

menopause period age is 45-55 years after 12 consecutive rounds without menstruation naturally. No clear physiological or pathological exists without clinical intervention.[16] There is no definitive research on the cause of endometrial cancer being more frequent in menopausal women, but the hypothesis that women with older menopausal age have higher hormone levels and a long time of estrogen exposure before menopause has been suggested as an essential etiology in addition to that in menopausal women it occurs Progesterone deficiency associated with anovulatory cycles can also increase the risk of endometrial cancer.[13]

The study's results found that the stage and grade of endometrial cancer at the Dr. Soetomo general hospital are high, illustrating that the prognosis of endometrial cancer patients is poor. This can be influenced because, according to the profile of the Dr. Soetomo General Hospital, Surabaya, it is a type A hospital that is an eastern referral area. Hence, the patients treated are more varied, and many patients have degrees of histological differentiation and advanced stages. It can also be seen that Indonesia is a developing country. Most developing countries have low public health quality because public awareness about health is also every day. In Indonesia, the 2018 Riskesdas data states that only 20% of Indonesians care about health.[17] With inadequate public health awareness in Indonesia, patients come to health workers at an advanced level, making patients have a poor prognosis.

The characteristics of the mitosis index from the total sample of 106 obtained the minor data with the mitosis index two and the highest data for the mitosis index 55, with an average of 18.41 and a standard deviation of 10.599. The mitosis index has a high standard deviation because its value is higher than the average value, which suggests that the data of the mitotic index is highly variable, supported by the presence of mitotic index data from 2 to 55.

The various mitotic indices are due to the time of identification of mitotic indices limited to the cell cycle phase of tissue retrieval and the substantial variability of observers in their title because the area of one high-power field can vary up to 3-5-fold in different microscopy.[18] These factors allow subjectivity so that the data obtained has a varied mitotic index.

The lowest mitosis index is 2, found in patients with a grade II, whereas the mitotic index should not be found at grade II because it has a high level. The highest mitosis index of 55 was found in patients with a grade III, but a shallow mitotic index of 4, which should not be found in grade III (Table 2).

Table 2. Mitotic index versus grade of endometrial cancer.

No.		Min	Max	*Mean*	SD	Total
1.	Grade I	4	42	15.75	9.119	32
2.	Grade II	2	46	19.15	11.988	34
3.	Grade III	4	55	19.90	10.305	40

At the levels of grades I, II, and III, the standard deviation values are pretty high because they are higher than the average half-value, which indicates that at grade I, II, and III, the mitosis index values vary greatly, as demonstrated by the presence of the lowest and highest range of mitosis indexes of any very wide of grade.

The lowest mitosis index of 2 was found in patients with stage I. The highest mitotic index of 55 was found in stage III, but in stage III was the presence of a shallow mitosis index of 4, which should not be found in stage III because, at stage III, the spread of cancer has been widespread (table 3).

Tabel 3. Mitotic index versus stage of endometrial cancer.

No.		Min	Max	Mean	SD	Total
1.	Stage I	2	34	14,05	8,086	37
2.	Stage II	5	46	17,24	10,293	25
3.	Stage III	4	55	22,68	11,555	40
4	Stage IV	18	32	23,25	6,702	4

In stages, I, II, and III, the standard deviation values are pretty high because they are higher than the average half-value, which indicates that in stages II and III, the mitosis index values are highly variable, as demonstrated by the presence of the lowest and highest ranges of mitosis indexes in each very distant stage. In stage IV, there is a typical standard deviation compared to the average; the lower the standard deviation, the better because the sample is homogeneous, but this is due to the small number of samples.

In this study, we used the Spearman rank test to find the correlation between two variables. Based on the correlation between the mitosis index and the degree of histological differentiation of endometrial cancer obtained from the results of the analysis with a p-value of 0.076 ($p > 0.05$), it can be concluded that there is no relationship between the index of mitosis and the degree of histological differentiation of endometrial cancer. When the correlation between the mitosis index and the stage of endometrial cancer is obtained at $p > 0.001$ (p 0.05), it can be concluded that there is a relationship between mitosis and the stage of endometrial cancer. The correlation coefficient value of 0.370 indicates the turning of the relationship between the mitotic index and a weak stage, as well as obtaining a positive value

in the correlation coefficient so that the connection between the mitosis index and the stage of endometrial cancer is aligned. The higher the mitosis index, the higher the stage of endometrial cancer.

In this study, there was a correlation between the mitosis index and the stage of endometrial cancer at Dr. Soetomo General Academic Hospital, Surabaya, in 2018–2020. With fairly tight rotation values and the direction of the relationship, the higher the mitosis index, the greater the stage in endometrial cancer patients. TNM stage is classified according to tumor size, metastasis, and tumor spread tumor, which refers to the size and breadth of the primary tumor.[19] Tumor size and tumor growth induce angiogenesis. Angiogenesis is triggered due to uncontrolled proliferation.[20] The more cells proliferate, the larger the size of the tumor, so to measure cell growth by cell division, the activity of mitosis is defined. The mitotic index can measure it.[21] This study demonstrated a correlation between the mitosis index and cancer stage with directional correlations. In gynecological cancer such as breast cancer, the prognosis is greatly influenced by the proliferation of cancer cells seen from the histopathology results which are assessed based on the mitotic index.[22] In other cancers, it has also been shown that there is a correlation between the mitotic index and the stage of the bladder tumor, which is explained by a significant increase in the proliferative activity of tumor cells in proportion to the increase in the stage of the bladder tumor.[18] This is comparable to this study which found a correlation between mitotic index and stage.

The correlation between the mitosis index and the stage has a reasonably tight distortion due to the probability caused by the mitotic index, whose examination is limited to the cell cycle phase with significant observing variability in its identification. Since the area of one high-power field can vary up to 3–5 times in different microscopes, the mitosis index is a more reliable marker and can be used to assess proliferation.[18]

The grade assesses the cell morphology suspected as part of the tumor tissue based on the similarity of malignant cell shapes with the cells of origin.[23] The fewer glands formed, the greater the grade and the poorer the prognosis of endometrial cancer.[24] Lower gland formation and higher proliferation were expected to result in a higher mitosis index. However, this study found no link between the mitotic index and the grade. Histological degrees decrease the tumor growth rate, affecting the prognosis. The slower its growth, the better the forecast.[11] The mitosis index also affects the tumor growth rate in the presence of cell proliferation 10. The mitosis index is a significant prognostic indicator.[7] The grade has also been established as one of the prognostic factors.[4] This indicates that the mitosis index and the degree of histological differentiation equally affect the prognosis and tumor growth rate, but they are neither interrelated nor independent.

Mitosis has long been used as a simple way to measure proliferation in routine areas. This simple measurement method can practically save costs, time and workload. This method can be used as a practical tool in a developing countries, where this is not possible to perform 6 multiple repeat biopsies and the patient was often lost to follow-up.[8] This mitotic index is associated with the well-established prognostic parameters, that is, tumor grade and stage.[6] Thus, adding this marker to existing protocols can increase the objectivity and reliability of accurate diagnosis, patient management, and tumor progression compared with conventional grade and stage.[8]

At Dr. Soetomo General Hospital, some patients had a poor prognosis. This is an unusual thing to happen because, in general, endometrial cancer has a good prognosis due to symptoms that are typical of endometrial cancer. Limitations of research vary due to the subjectivity of the observers themselves. This affects the research results, which makes the relationship relatively weak.

CONCLUSION

These data demonstrate a correlation between the mitotic index and the stage of endometrial cancer and no correlation between the mitotic index and the grade of endometrial cancer. Increase. The mitosis index does not correlate with the grade, but there is a correlation between the mitotic index and endometrial cancer stage in the Dr. Soetomo General Hospital Surabaya in 2018–2020.

DISCLOSURES

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Conflict of interest

All authors do not have a 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

Body fat percentage and Body Mass Index in association with menstrual irregularities in young adults. A cross-sectional study

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ABSTRACT

Objective: Body fat percentage measures overall amount of fat as a proportion of total body weight. Basal metabolic index (BMI) is an unreliable predictor of body fat percentage as excess fat, lean, muscle, or bone density are indifferentiable. However, the relation between body fat percentage and BMI on menstrual characteristics are still unclear. The aim was to compare the correlations between body fat percentage and BMI towards menstrual characteristics.

Materials and Methods: A cross-sectional sample of 211 young adults was taken by means of cluster random sampling. Cross tabulations were performed between variables and Pearson's chi square value were observed. Multiple logistic regressions were performed to observe the odds ratio and 95% confidence interval.

Results: Body fat percentage was found to be associated with menstrual cycle (p=0.000) and menstrual bleeding period (p=0.000) but not daily pads usage, intermenstrual bleeding, and menstrual pains. Age was found not to correlate with any of the collected menstrual characteristic data. BMI was also found to be associated with menstrual cycle (p=0.008) and menstrual bleeding period (p=0.003). Further analysis showed that a one unit increase of body fat percentage was linearly correlated with increased of menstrual cycle by a factor of 1.109 days ($p < 0.01$) and a decreased of menstrual bleeding period by a factor of 0.887 days ($p < 0.01$).

Conclusion: Although both body fat percentage and BMI showed associations with menstrual cycle and menstrual bleeding period, only body fat percentage was linearly correlated with menstrual cycle and menstrual bleeding period.

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Highlights:

1. Body fat percentage and BMI were found to be associated with menstrual cycle and menstrual bleeding period.
2. The odds of having a prolonged menstrual cycle were increased by a factor of 1.109 with an increase of one unit of body fat percentage, while the odds of having a prolonged menstrual bleeding period was decreased by a factor 0.887 with an increase of one unit of body fat percentage.

INTRODUCTION

A study conducted among university students showed that BMI had the strongest correlation with body fat percentage when opposed to waist circumference, waist-to-height proportion, and body roundness index.[1] However, considering that BMI does not distinguish between fat mass and fat-free mass, the prevalence of obesity could be misrepresented. BMI is a poor indicator of personal fat mass as healthy people with a larger proportion of muscle might be mistakenly labeled as overweight. In a community study, women have a much higher fat mass relative to overall BMI than men.[2] There are several techniques for calculating the percentage of body fat, including magnetic resonance imaging (MRI), dual-energy X-ray absorptiometry (DXA), and air displacement plethysmography (ADP). However, their usage are extremely difficult in the typical clinical settings because to their massive cost, complexities, radiation hazard, and mobility due to size.[3,4]

By factoring in sex and age, the Clinica Universidad de Navarra-Body Adiposity Estimator (CUN-BAE) index is recommended as the best measure of body fat percentage. Using ADP as the gold standard in calculating body fat percentage, the study showed that the correlation between %BF derived from CUN-BAE formula was much more significant compared to %BF calculated from BMI and waist-to-height2 ratio.[5] Moreover, adipose accumulation has been demonstrated to be an effective predictor of mortality in overweight women and is known to result in a higher risk of acquiring obesity-related comorbidities, such as type 2 diabetes, cardiovascular disease and hormonal dysregulation.[6]

The menstrual cycle governs the fertile window during which conception happens. The fertility window is limited to six days every cycle which includes ovulation day and the five days prior.7 While ovum can only last up to 1 day in the female reproductive system, sperm can last up to 5 days. Since the menstrual cycle is the foundation for development of conception, menstrual cycle must be reviewed as a possible source of infertility. The precise effect of body fat percentage on menstrual cycles and menstrual bleeding has not yet been established, despite early research with limited sample numbers showing obesity connected with irregular menstrual cycles. Given the global growth in fat consumption and increasing obesity prevalence among reproductive women, the researchers found the need to establish the association between body fat percentage and menstrual irregularities.

MATERIALS AND METHODS

Ethics

The study was conducted in accordance with the accordance of the International Conference on Harmonization – Good Clinical Practice (ICH-GCP). Ethical clearance (208/UN14.2.2.VII.14/LT/2022) was obtain on February 2nd 2022 with protocol number 2022.01.1.0017 from Udayana Research Ethics Commission Unit. This study adopted a clustered random sampling method to select 211 participants from a public University in Indonesia between June 2022 and August 2022 as the respondents. Ten people from each class were selected randomly as participants.

Study design

The research was an analytical observational study using a cross-sectional method to find the relationship between body mass index and menstrual cycle irregularities. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used in this research.

Participants and study size

The minimum number of respondents needed is as shown below:

$$n = \frac{Z^2 p(1-p)N}{d^2(N-1) + Z^2 p(1-p)}$$

Therefore,

$$n = \frac{1{,}96^2(0.275)(1-0{,}275)(354)}{0{,}05^2(354-1) + 1{,}96^2(0.275)(1-0.275)} = 164.482 \sim 165 \text{ participants}$$

n: Minimum sample size
N: The number of approachable respondents
Z: Level of significance (1.96; 95% confidence interval)
p: Prevalence of overweight women (27.5%)
d: Limit of error or absolute precision (0.05)

The inclusion criteria were as follows: (1) Respondents had to consent to partake in the interview and show that they comprehended the research's topic, (2) Respondents are checked for their weight and height at the same point of time, and (3) Respondents have gone through puberty and were experiencing menstrual cycle. The exclusion criteria were as follows: (1) Respondents who changed their diet or exercise specifically in the past year, (2) Respondents who have been diagnosed with chronic or hormonal disorders affecting cycle regularity, (3) Respondents who have consumed any kind of hormonal birth control pills, and (4) Respondents who have been receiving medication for a condition for the past year.

Variables

The independent variable used in this study were BMI and body fat percentage. Body Mass Index is an index calculated based weight in kilograms divided by the square of height in meters obtained from the interview. The Asian Body Mass Index category was used to determine the appropriate group according to the BMI formula. BMI will be categorized into Underweight <18.5, Normal weight 18.5 – 22.9, and Overweight 22.9 - 29.9. The scale used was ordinal scale. Body fat percentage was calculated with CUN-BAE formula proposed by Gomez-Ambrosi et al.[8]

BF% = -44.988 + (0.503 × age) + (10.689 × sex) + (3.172 × BMI) - (0.026 × BMI2) + (0.181 × BMI × sex) - (0.02 × BMI × age)? (0.005 × BMI2 × sex) + (0.00021 × BMI2 × age)

Age was measured in years and sex was classified as men=0 and women=1. Body fat percentage was classified to Low fat percentage <25%, Normal body fat percentage 25% - 35%, and High body fat percentage >35%. The scale used was ordinal scale. Age was used as a control variable to normal hormonal change. The age of the respondent was calculated from the difference between the date of birth and the date of interview. Age was be categorized into <19 years, 19-20 years, and >20 years. The scale used was interval scale.

Dependent variables used were menstrual cycle and menstrual bleeding period. Menstrual cycle period is the distance of days between the menstrual cycle and the next cycle. The results of the answers are grouped as regular and irregular. Short menstrual cycle is indicated by a cycle of <21 days, the duration of normal menstrual cycle is 21 – 35 days, and longer duration of menstrual cycle is >35 days. The scale used was ordinal scale. Menstrual bleeding period is the number of days of active menstrual bleeding during menstruation. The results of the answers are grouped as regular and irregular. Regular results are indicated by menstrual duration of 3-7 days while irregular with menstrual duration <3 days or >7 days. Some potential confounding variables were nutritional intake, type of diet followed, physical activity, and stress.

Data measurement and bias

Height and weight were calculated in a consistent manner. Selection bias was prevented by using random sampling instead of non-random sampling, while measurement bias was avoided by Cronbach's Alpha reliability test. Cronbach's Alpha reliability test showed the data to be reliable with a value of 0.639 (>0.6).

Statistical methods

The mean, standard deviation (SD), and absolute frequencies (%) of the ordinal variables were used in a descriptive analysis to determine the characteristics of the individuals. In terms of quantitative variables, researchers used cross tabulation and Pearson chi square to assess the distribution correlations between age, BMI, and body fat percentage in relation to categories of menstrual cycle, menstrual bleeding, daily pads usage, intermenstrual bleeding, and menstrual pains. Researchers performed multivariate logistic regression adjusted for age, BMI, and body fat percentage. Researchers provided the odds ratio (Exp(B)), Wald chi square, estimate, and 95% confidence interval. This study used analytic models to examine the data, taking into account the numerous clusters and strata. The data were imported into Microsoft Excel, cleaned up, and coded before being exported to SPSS version 25 for analysis. A P value of less than 0.05 was used to determine the degree of significance.

RESULTS AND DISCUSSION

There were 211 participants in this study. The mean of weight, height, BMI, and body fat percentage were 55.50 (SD±9.49), 1.60 (SD±0.05), 21.75 (SD±3.39), and 33.16 (SD±6.61) respectively. The distribution of BMI category was 16.6% for BMI less than 18.5, 48.8% for BMI 18.5 – 22.9, and 34.6% for BMI more than 22.9. Similarly, 8.5% of participants had a body fat percentage of <25%, 55.9 % had a body fat percentage of 25-35%, and 35.5% had a body fat percentage of >35% (Table 1).

Table 1. Baseline characteristic of study population

	n (%)	Mean	SD	CI (95%)	
				Lower	Upper
Age		19.65	1.13	19.50	19.81
Menarche		12.07	1.23	11.90	12.24
Weight	211 (100)	55.50	9.49	54.21	1.60
Height		1.60	0.05	1.59	1.60
BMI		21.75	3.39	21.29	22.2
Underweight (<18.5)	35 (16.6)	17.34	1.01	-	-
Normal weight (18.5 – 22.9)	103 (48.8)	20.57	1.15	-	-
Overweight (>22.9)	73 (34.6)	25.53	3.92	-	-
Body fat percentage		33.16	6.61	32.26	34.06
Low fat %	18 (8.5)	22.34	2.40	-	-
Normal fat %	118 (55.9)	30.25	2.85	-	-
High fat %	75 (35.5)	40.32	3.96	-	-

The study collected menstrual characteristics which includes menstrual cycle, menstrual bleeding, daily pads usage, intermenstrual bleeding, and menstrual pains. Out of 211 participants, 12 women had menstrual cycle of less than 21 days (5.7%), 168 women had menstrual cycles of 21 – 35 days (79.6%), and 31 women had menstrual cycle of more than 35 days (14.7). In regards of menstrual bleeding period, 15 women experienced less than 3 days of menstrual bleeding per cycle (7.1%), 190 women experienced 3 – 7 days of menstrual bleeding per cycle (90.0), and 6 women experienced more than 7 days of menstrual bleeding per cycle (2.8%). Daily pads usage was used to estimate the amount of blood loss during menstrual bleeding period. Data showed that 23.2% of participants used 1 – 2 pads daily, 64.0% of participants used 3 – 4 pads daily, and 12.8% of participants used more than 4 pads daily. Intermenstrual bleeding was uncommon with a prevalence of 1.4% among participants. In terms of menstrual pains, 23.7% participants did not experience any form of pain during menstrual period. Out of all participants, 33.6% experienced menstrual pain at least once daily, 33.2% experienced menstrual pains at least twice daily, and 9.5% experienced menstrual pains more than twice daily (Table 2).

The Pearson' chi square test is a statistical analysis used to evaluate whether categorical variables are associated with each other in sets of ordinal/nominal attributes. Table 3 showed analytic cross tabulations between menstrual characteristics data compared with body fat percentage, BMI, and age. Both body fat percentage and BMI were found to have correlations only with irregularities in menstrual cycle ($p < 0.05$) and menstrual bleeding period ($p < 0.05$), but not daily pads usage, intermenstrual bleeding, and menstrual pains. Age was found not to correlate with any of the collected menstrual characteristic data, thus indicating that menstrual abnormalities development is not a normal physiological condition in early adulthood.

Table 2. Menstrual characteristic of study population

Menstrual characteristics	n (%)
Menstrual cycle	
< 21 days	12 (5.7)
21 – 35 days	168 (79.6)
> 35 days	31 (14.7)
Menstrual bleeding	
< 3 days	15 (7.1)
3 – 7 days	190 (90.0)
> 7 days	6 (2.8)
Daily pads usage	
1 – 2 pads	49 (23.2)
3 – 4 pads	135 (64.0)
> 4 pads	27 (12.8)
Intermenstrual bleeding	
Yes	3 (1.4)
No	208 (98.6)
Menstrual pains	
0	50 (23.7)
1	71 (33.6)
2	70 (33.2)
> 2	20 (9.5)

Table 3. Cross tabulation of body fat percentage, BMI, and age on menstrual characteristics

	Body fat percentage			Pearson Chi-Square	BMI			Pearson Chi-Square	Ages			Pearson Chi-Square	Total
	< 25% body fat percentage (%)	25 – 35 % body fat percentage (%)	> 35% body fat percentage (%)		Under-weight	Normal weight	Over-weight		< 19	19 – 20	> 20		
Menstrual cycle													
< 21 days	6 (50.0)	4 (33.3)	2 (16.2)	32.474 ***; p= 0.000	6 (50.0)	4 (33.3)	2 (16.7)	13.703 ***; p= 0.008	4 (33.3)	8 (66.7)	0 (0.0)	10.126; p= 0.052	12
21 – 35 days	12 (7.1)	99 (58.9)	57 (33.9)		27 (16.1)	85 (50.6)	56 (33.3)		37 (22.0)	92 (54.8)	39 (23.2)		168
> 35 days	0 (0.0)	15 (48.4)	16 (51.6)		2 (6.5)	14 (45.2)	15 (48.4)		2 (6.5)	17 (54.8)	12 (38.7)		31
Menstrual bleeding													
< 3 days	6 (40.0)	1 (6.7)	8 (53.3)	28.001 ***; p= 0.000	6 (40.0)	1 (6.7)	8 (53.3)	16.227 ***; p= 0.003	3 (20.0)	8 (53.3)	4 (26.7)	0.735; p= 0.947	15
3 – 7 days	12 (6.3)	114 (60.0)	64 (33.7)		27 (14.2)	101 (53.2)	62 (32.6)		38 (20.0)	106 (55.8)	46 (24.2)		190
> 7 days	0 (0.0)	3 (50.0)	3 (50.0)		2 (33.3)	1 (16.7)	3 (50.0)		2 (33.3)	3 (50.0)	1 (16.7)		6
Daily pads usage													
1 - 2	9 (18.4)	23 (46.9)	17 (34.7)	8.793; p= 0.066	14 (28.6)	18 (36.7)	17 (34.7)	8.285; p= 0.082	14 (28.6)	30 (61.2)	5 (10.2)	8.333; p= 0.080	49
3 - 4	7 (5.2)	81 (60.0)	47 (34.8)		17 (12.6)	73 (54.1)	45 (33.3)		24 (17.8)	71 (52.5)	40 (29.6)		135
> 4	2 (7.4)	14 (51.9)	11(40.7)		4 (14.8)	12 (44.4)	11 (40.7)		5 (18.5)	16 (59.3)	6 (22.2)		27
Intermenstrual bleeding													
Yes	0 (0.0)	1 (33.3)	2 (66.7)	1.367; p= 0.505	0 (0.0)	1 (33.3)	2 (66.7)	1.559; p= 0.459	0 (0.0)	2 (66.7)	1 (33.3)	0.795; p=6.72	3
No	18 (8.7)	117 (56.3)	73 (35.1)		35 (16.8)	102 (49.0)	71 (34.1)		43 (20.7)	115 (55.3)	50 (24.0)		208
Menstrual pains													
0	4 (8.0)	26 (52.0)	20 (40.0)	2.135; p= 0.907	10 (20.0)	21 (42.0)	19 (38.0)	1.973; p= 0.922	9 (18.0)	26 (52.0)	15 (30.0)	9.264; p= 0.159	50
1	6 (8.5)	39 (54.9)	26 (36.6)		10 (14.1)	35 (49.3)	26 (36.6)		14 (19.7)	37 (52.1)	20 (28.2)		71
2	5 (7.1)	42 (60.0)	23 (32.9)		12 (17.1)	36 (51.4)	22 (31.4)		19 (27.1)	38 (54.3)	13 (18.6)		70
> 2	3 (15.0)	11 (55.0)	6 (30.0)		3 (15.0)	11 (55.0)	6 (30.0)		1 (5.0)	16 (80.0)	3 (15.0)		20
Total													
	18 (8.5)	118 (55.9)	75 (35.5)		35 (16.6)	103 (48.8)	73 (34.6)		43 (20.4)	117 (55.5)	51 (24.2)		211

*p <0.05, **p <0.01, ***p<0.001

A parametric statistical test called the Wald chi squared test may determine whether a group of independent variables is considered to be significant for a model or not. The difference between the chi square and the walt chi square is the denominator: variances (Wald) vs means (Chi-square). In Wald chi squared test, body fat percentage showed linear correlations menstrual cycles (positive estimate), menstrual bleeding (negative estimate). No statistically significant linear correlation was found between BMI and any menstrual characteristics. Multiple logistic regression was conducted on numeric values of body fat percentage and BMI with menstrual characteristics. Multiple linear regression employs a straight line to evaluate the connection between a quantitative predictor variable and two or more independent variables. Exponentiating the coefficients yields odds ratios. The chances change for a unit increase in the predictor is predicted by Exp(B). The odds of having a prolonged menstrual cycle were increased by a factor of 1.109 with an increase of one unit of body fat percentage, while the odds of having a prolonged menstrual bleeding period was decreased by a factor 0.887 with an increase of one unit of body fat percentage (Table 4).

Table 4. Multivariate logistic regression of body fat percentage and BMI on menstrual characteristics

Variables		Wald Chi Square	Estimate	Exp(B)	CI (95%)	
					Lower	Upper
Menstrual Cycle	< 21 days	0.274	0.489	1.570	0.290	8.500
	21 – 35 days	29.503***	8.059***	214.695	30.932	1490.181
	> 35 days	-	-	-	-	-
Body fat percentage		11.241**	0.162**	1.109	1.052	1.169
BMI		0.410	0.265*	0.969	0.881	1.066
Menstrual Bleeding	< 3 days	11.951**	-20.081**	0.013	0.001	0.153
	3 – 7 days	2.485	-1.649	6.414	0.636	64.659
	> 7 days	-	-	-	-	-
Body fat percentage		12.026**	-0.410**	0.949	0.887	0.974
BMI		3.678	-0.752**	0.082	0.776	1.003
Daily pads usage	1 - 2	0.040	1.284	0.864	0.205	3.640
	3 - 4	14.985***	4.916***	19.981	4.386	91.024
	> 4	-	-	-	-	-
Body fat percentage		3.332	0.077	1.033	0.989	1.078
BMI		1.857	0.155	1.060	0.975	1.154
Intermenstrual bleeding	Yes	10.042**	-92.690	1.121E-5	0.724E-9	0.13
	No	-	-	-	-	-
Body fat percentage		5.061*	-1.835	0.826	0.700	0.976
BMI		5.418*	-3.176	0.726	0.554	0.951
Menstrual pains	0	9.752**	-1.902**	0.125	0.034	0.462
	1	0.852	-0.566	0.550	0.154	1.959
	2	4.230*	2.452**	3.941	1.067	14.562
	> 2	-	-	-	-	-
Body fat percentage		1.996	-0.024	0.973	0.937	1.011
		2.455	-0.052	0.943	0.876	1.015

*p <0.05, **p <0.01, ***p<0.001

An analytic cross tabulation was performed to observe the categorical distributions and correlations of variables. Our study found that Pearson chi squared showed significant correlation between both body fat percentage and BMI with menstrual cycle and menstrual bleeding period. Both body fat percentage and BMI did not show any correlation with any other menstrual characteristics. Moreover, the control variable age was found not to be correlated with any of the menstrual characteristic, showing menstrual irregularities not to be part of a normal physiological progression. Statistically, out of 31 participants who experienced a menstrual cycle of more than 35 days, 51.6% had a body fat percentage of more than 35% and 48.5% had an overweight BMI.

We further performed multiple linear regressions on both body fat percentage and BMI towards the menstrual characteristic to observe any linear association. The results showed that only body fat percentage was linearly significant towards menstrual cycle and menstrual bleeding period, and not BMI. We found that with an increase of 1% body fat percentage, the odds of having a prolonged menstrual cycle were increased by 1.109 times and the odds of having a prolonged menstrual bleeding period were decreased by 0.887 times. This suggested body fat percentage as one of the risk factors in developing menstrual cycle and menstrual bleeding period irregularities. These irregularities were caused by an imbalance in hormone levels which was characterized by a major increase in estrogen levels.

One of the most abundant androgen hormones was testosterone. Testosterone could be considered as a circulating pro-hormone and can be converted to 5a-dihydrotestosterone (DHT) with 5a-reductase types 1 and 2 enzymes, and to 17-beta-estradiol/estrogen with aromatase enzymes found in adipose tissue.[9] Fat tissue aromatized androgens to estrogen hormones. In the body, the aromatization process of androgens into estrogen occurred in the granulosa cells of fat tissue, so an increase in the amount of body fat tissue would cause an increase in the amount of estrogen hormone formed.[10] Eventually, it would disrupt the balance of reproductive hormones in the female body leading to menstrual irregularities. When fat mass increased showed by an increased body fat percentage, aromatase

expression and estrogen levels also increased.[11] The main hormone acting on the proliferation phase was estrogen. The length of the menstruation varies owing to differences in the duration of the proliferation phase.[12] As estrogen was the major hormone in proliferation phase, the duration changed in response to hormonal level imbalance. The increase in adipose tissue caused abnormalities in the hypothalamic-pituitary-gonadal system, resulting in an increase in available estrogen levels.[13,14] In healthy premenopausal women, estrogen was synthesized in the ovaries following the control of gonadotropin-releasing hormone from the pituitary.

Aromatization of the A ring of testosterone to produce estradiol in the human body was mediated by the P450 aromatase enzyme.[15-17] This process produced the hormone estrogen in large quantities.[18] When levels of 17-beta-estradiol increased, negative feedback occurs to the anterior pituitary to decrease the levels of FSH and LH produced.[19] The increased in estrogen produced negative feedback to the hypothalamus to decrease GnRH secretion and the pituitary to decrease FSH and LH secretion. Subsequently, it also indirectly reduced the levels of 17-beta-estradiol and progesterone produced by ovaries.[20] Inconsistency of sex hormones in the body caused menstrual cycles irregularities due to dysregulation of the Hypothalamic-Pituitary-Gonadal (HPG) axis.[21] The reduced natural production of sex hormones had an uneven impact on the distribution of sex hormones.

We hypothesized that the delay in reaching the critical level of FSH and progesterone due to estrogen imbalance caused shorter menstrual bleeding periods. This was indicated by the correlation between high body fat percentage and menstrual bleeding period of less than 3 days. Research conducted by Kafaei-Atrian et al found that the duration of bleeding had a significant relationship with body weight, and waist, hip and arm circumference.[22]

However, this study was not comparable with other studies of menstrual duration. Several studies have shown an increase in the period of menstrual bleeding for more than 7 days in respondents with an obese body mass index.[22,23] The difference in these findings could be caused by differences in the distribution of fat in the body. General indicators of obesity such as body fat mass, body fat percentage, and body mass index did not significantly affect menstrual disorders, but fat mass in the upper body and the ratio of hip to thigh fat in obese women had more influence on irregularity in menstrual duration.[22,24] Recent studies had shown a positive relationship between changes in menstrual status and the distribution of central obesity.[25] In addition to the quantity of body fat, the distribution of body fat also played an important role in reproductive health. Visceral fat was metabolically more active than subcutaneous fat, and played a greater role in obesity-related chronic diseases. The characteristics of the menstrual cycle could be affected by a higher amount of visceral fat.[26] Researchers suspected that there were several factors that could influence this, namely differences in the number of research samples, differences in external stress, differences in nutrition, and differences in fat distribution. This study could not definitively determine whether there were any other additional factors that might affect menstrual characteristics. However, this study supported body fat percentage as a risk factor of menstrual irregularities and that managing body weight would serve as an effective treatment approach.

Nevertheless, this study still has several shortcomings, such as not reviewing internal factors (genes, stress, and hormones) and external factors (diet, drugs, and exercise) apart from the body mass index and fat percentage of the respondents. Further research is also needed to control for some confounding variables with multivariate analysis.

CONCLUSION

This study found correlations between body fat percentage and BMI towards irregularities in menstrual cycle and menstrual bleeding period. However, only body fat percentage was found to be linearly correlated with both menstrual cycle and menstrual bleeding period. An increase in one unit body fat percentage led to an increase of prolonged menstrual cycle by a factor of 1.109 and a decrease of prolonged menstrual bleeding by a factor of 0.887. Based on the results of this study, the researchers encourage further large-scale clinical trial studies and raise awareness on the effects of high body fat percentage towards menstrual cycle irregularities.

DISCLOSURES

Acknowledgment

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

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Author Contribution

BGdL and GD analyzed and interpreted the patient data, performed examination and was a major contributor in writing the manuscript. The authors have read and approved the final manuscript.

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ORIGINAL RESEARCH

The influence of patriarchal cultural factors on pregnancy complications (antepartum hemorrhage) at Mitra Medika General Hospital, Bandar Klippa, Indonesia

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ABSTRACT

Objective: The objective of this study was to determine the influence of patriarchal culture on the occurrence of antepartum hemorrhage at Mitra Medika General Hospital.

Materials and Methods: This study employed an analytical observational design with a case-control approach. The sample for this study included pregnant women in their third trimester and mothers who had given birth within a maximum of 4 months from the time of the study at Mitra Medika General Hospital, Bandar Klippa, Indonesia. There were 90 respondents, comprising 30 case groups and 60 control groups. The sampling method for the case group used quota sampling, while the control group utilized accidental sampling. The research instrument utilized questionnaires and secondary data (antepartum hemorrhage diagnoses). Data analysis employed the chi-square test for bivariate analysis and multiple logistic regression for multivariate analysis, with a significance level of 0.05.

Results: There was a significant relationship between decision-making (p=0.030), family support (p=0.003), psychological domestic violence (p=0.024), and sexual domestic violence (p=0.039), no relationship with physical domestic violence (p=0.257) with the occurrence of antepartum hemorrhage. Multivariate analysis revealed that the family support variable was the most dominant risk factor with an Exp (B) value of 8.230 in causing antepartum hemorrhage.

Conclusion: The patriarchal cultural factors that significantly affect antepartum hemorrhage at Mitra Medika General Hospital, Bandar Klippa, Indonesia, are decision-making, family support, psychological domestic violence, and sexual domestic violence.

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Highlights:

1. Antepartum hemorrhage stands as one of the major contributors to maternal mortality globally.
2. Patriarchal culture is among the societal factors impacting maternal mortality rates.
3. Patriarchal cultural factors associated with antepartum hemorrhage are examined to establish effective preventive measures.

INTRODUCTION

Obstetric bleeding still contributes to 50% of the estimated 500,000 maternal deaths occurring worldwide each year, making it one of the leading causes of maternal mortality in underdeveloped countries. Antepartum and postpartum hemorrhages together account for approximately 27% of unexpected maternal deaths.[1] Obstetric emergencies known as antepartum bleeding are a major cause of maternal and neonatal morbidity and mortality.[2] According to the WHO, cases of antepartum bleeding, especially placenta previa, contribute to 15% to 20% of maternal deaths.[3] On average, 0.5% to 5% of all pregnancies are complicated by antepartum bleeding with sociodemo-graphic causes.[4]

The high incidence of antepartum bleeding is not devoid of indirect causes in the form of social determinants and behavior. Discussing the cultural aspects of society will closely relate to behavior. The patriarchal culture in Indonesia, where male dominance within households is prevalent, is one of the social cultures influencing maternal mortality. Within families, the decision-making authority often rests more with men than women. Decision-making is frequently delayed, leading to late seeking of medical care, and thus not receiving timely attention during pregnancy.[5] Decision-making regarding hospital referrals for pregnant women at high risk is predominantly dominated by husbands, accounting for 86.7%. This indicates that women lack choices or rights to make decisions about their own health in order to safeguard both themselves and their babies.[6]

In addition to placing men as the ultimate decision-makers, patriarchal culture also normalizes Domestic Violence (DV). There exists a stigma in society that husbands are “allowed” to be violent towards their wives if the wives do not follow their rules and commands.[7] Domestic violence is more likely to occur during pregnancy, with nearly a third of abused women being pregnant. Previous studies have indicated that domestic violence affects the health of pregnant women between 3% to 11% in developed countries and 3% to 66% in developing countries. Therefore, domestic violence is a significant risk factor for maternal health.[8] Domestic violence, including physical, psychological, and sexual violence, can lead to antepartum bleeding.[9]

Given the issue discussed above, where patriarchal culture plays a significant role as a contributor to increased risk of antepartum bleeding, there was s a need for research on the influence of patriarchal culture on antepartum bleeding at Mitra Medika General Hospital. The selection of this location was based on the consideration that it aligns with the identified problem.

MATERIALS AND METHODS

This study employed an analytical observational design with a case-control approach. The sample for this study consisted of pregnant women in their third trimester and women who had given birth within the last four months at Mitra Medika General Hospital in Bandar Klippa, Indonesia. The study involved a total of 90 participants, divided into 30 cases and 60 controls. Sampling for the case group was conducted using quota sampling, while the control group was sampled using the accidental method. The independent variables in this study included decision-making, family support, physical intimate partner violence (IPV), psychological IPV, and sexual IPV. The dependent variable was the antepartum bleeding. Research instruments included questionnaires and secondary data (diagnoses of antepartum bleeding). The software program used to analyze the data was IBM SPSS Statistic Version 26. Data analysis involved the use of the chi-square test for bivariate analysis and multiple logistic regression for multivariate analysis, with a significance level of 0.05. This research protocol had received approval from the Research and Ethics Committee of the Politeknik Kemenkes Medan, with protocol number 01.25-140/KEPK/POLTEKKES KEMENKES MEDAN 2023.

RESULTS AND DISCUSSION

This study involved 90 respondents in total. Overall, it was found that the highest education level among case group respondents was dominated by high school, while in the control group, it was college. The employment status of the majority of respondents indicated that they were unemployed. Among respondents with employ-ment status, in the case group, most were civil servants, while in the control group, most were teachers.

From the results of the homogeneity test, the characteristics of respondents who had homogeneous data distribution were education, employment status, and type of work. So, the characteristics of the respondents did not influence the results of subsequent data analysis.

Table 1. Distribution of respondent characteristics in the research at Mitra Medika General Hospital, Bandar Klippa, Indonesia

Characteristics	Groups				F	%	95% CI	
	Casse		Control					
	f	%	f	%			Low	Upper
Education								
College	13	43.3	28	46.7	41	45.6	34.4	54.4
Senior High School	16	53.3	21	35	37	41.1	31.1	52.2
Junior High School	1	3.3	11	18.3	12	12	6.7	22.2
Employment Status								
Employment	14	46.7	26	43.3	40	44	34.4	55.6
Non-Employment	16	53.3	34	56.7	50	55.6	44.4	65.6
Type of Work								
Housewife	16	53.3	34	56.7	50	55.6	45.6	65.6
Entrepreneur	3	10	8	13.3	11	12.2	5.6	20
Merchant	3	5	4	13.3	7	7.8	3.3	14.4
Government Employee	4	13.3	5	8.3	9	10	4.4	16.7
Teacher	3	10	10	16.7	13	14.4	6.7	22.2
Total	30	100	60	100	90	100		

Table 2. Homogeneity of respondent characteristics in the research at Mitra Medika General Hospital, Bandar Klippa, Indonesia.

Characteristic	Levene Statistic	df1	df2	p-values
Education	2.591	2	87	0.081
Employment Status	0.088	1	88	0.767
Type of Work	0.385	4	85	0.819

Table 3. The relationship between patriarchal culture factors and the occurrence of antepartum bleeding at Mitra Medika General Hospital, Bandar Klippa, Indonesia

Variables	Groups				p-values	OR (95% CI)
	Case		Control			
	f	%	f	%		
Decision-making						
Husband	22	73.3	28	46.7	0.030	3.143 (1.209 – 8.167)
Wife	8	26.7	32	53.3		
Family Support						
Inadequate	11	61.1	7	17.5	0.003	7.408 (2.122 – 25.864)
Good	7	38.9	33	82.5		
Total	18	100	40	100		
Adequate	12	63.2	20	37.7	0.100	2.829 (0.956 – 8.372)
Good	7	36.8	33	62.3		
Total	19	100	53	100		
Physical Domestic Violence						
Experienced	2	6.7	1	1.7	0.257	4.214 (0.367 – 48.459)
Not Experienced	28	93.3	59	98.3		
Psychological Domestic Violence					0.024	3.143 (1.256 – 7.867)
Experienced	16	53.3	16	26.7		
Not Experienced	14	46.7	44	73.3		
Sexual Domestic Violence						
Experienced	11	36.7	9	15	0.039	3.281 (1.175 – 9.157)
Not Experienced	19	63.3	51	85		

Table 4. Multivariate logistic regression modeling of patriarchal culture factors on the occurrence of antepartum bleeding at Mitra Medika General Hospital, Bandar Klippa, Indonesia

Variables	B	S.E.	Wald	df	*P value*	Exp. (B)	95% CI	
							Low	Upper
Decision-making	1.148	0.587	3.826	1	0.050	3.151	0.998	9.950
Family Support			9.424	2	0.009			
Family Support_Inadequate	2.108	0.696	9.162	1	0.002	8.230	2.102	32.221
Family Support_ Adequate	1.229	0.619	3.947	1	0.047	3.418	1.017	11.490
Psychological Domestic Violence	0.626	0.548	1.305	1	0.253	1.869	0.639	5.468
Sexual Domestic Violence	1.248	0.588	4.507	1	0.034	3.485	1.101	11.035
Constant	-2.923	0.684	18.250	1	0.000	0.054		
Omnibus Test: 0.000					Nagelkerke R Square: 0.324			

In the bivariate analysis, the factors significantly associated with antepartum bleeding were decision-making, family support, psychological domestic violence, and sexual domestic violence. The variable of physical domestic violence was not associated with antepartum bleeding. The prevalence of decision-making dominance in the case group was attributed to husbands, whereas in the control group, it was attributed to wives. The majority of family support in the case group was categorized as sufficient, while in the control group, most family support was rated as good. The highest prevalence of domestic violence was psychological violence, followed by sexual violence, and physical violence.

In the multivariate analysis, the variable of physical domestic violence was excluded from the model due to its p-value of >0.25. The variable of psychological domestic violence acted as a confounder, causing a change in the odds ratio (OR) of more than 10% in the decision-making variable. Therefore, the variable of psychological domestic violence was included in the final multivariate model. Based on the Exp.(B) or OR values, the factor mostly associated with antepartum bleeding was the insufficient family support (p=0.002; OR 8.230). The Nagelkerke R Square result of 0.324 indicates that the independent variables in the multivariate model can explain 32.4% of the occurrence of antepartum bleeding. This implied that 67.6% of other factors beyond the scope of this study influenced the occurrence of antepartum bleeding.

Calculation of probability of antepartum bleeding was based on the b values of significant factors in the final model. Thus, from the multivariate modeling analysis, the probability of antepartum occurrence was derived as in Table 5. Based on Table 5, it was found that the likelihood of pregnant mothers experiencing antepartum bleeding was 83% if they experienced all the risk factors. Conversely, if they did not experience all the risk factors, the probability of pregnant mothers experiencing antepartum bleeding was 5.09%.

Table 5. Probability of antepartum bleeding occurrence at Mitra Medika General Hospital, Bandar Klippa, Indonesia

Variables				Probability (%)
Decision-making by husband	Family Support		Experiencing sexual domestic violence	
	Inadequate	Adequate		
✓	✓	×	✓	83
✓	×	✓	✓	60.9
×	✓	×	✓	60.9
✓	✓	×	×	58.9
×	×	✓	✓	39
✓	×	×	✓	37.1
✓	×	✓	×	36.7
×	✓	×	×	29.7
×	×	×	✓	23.8
×	×	✓	×	15.5
✓	×	×	×	14.4
×	×	×	×	5.09

The influence of patriarchal culture on antepartum bleeding decision making

Very often, within household dynamics, a wife's role is positioned as a subject where all final decisions rest in the hands of the husband. This goes beyond just determining aspects related to healthcare; in other matters as well, the opinions of wives are frequently overlooked.[10] Decision-making is often based on various considerations, one of which is economic and financial status; however, it ultimately depends on the prevailing circumstances at the time the decision is made.[11]

Based on observations made in the field, it is evident that the extent of a husband's role in decision-making within the household is undeniably tied to the wife's employment status. Frequently, husbands prohibit their wives from pursuing careers, so much so that when a wife decides to use her husband's money to meet personal or family needs, she often needs to seek his permission first. This situation instills fear in women when deciding matters concerning household needs, healthcare services, and even pregnancy check-ups. This fear can lead to delayed intervention, becoming a boomerang for pregnant women. This is because women find it challenging to take the initiative to take action, which results in delayed medical treatment.

The absence of decision-making freedom for women within the family is a discriminatory act that has negative implications for mental and physical health. Discrimination has adverse effects on pregnant mothers, triggering psychological and physiological stress. Severe stress can stimulate the sympathetic nerves, subsequently increasing blood pressure gradually. In other words, the greater the stress, the higher the blood pressure, which can lead to antepartum bleeding.[12]

To prevent delays in the care of pregnant women due to male dominance in decision-making, efforts are needed to empower women in enhancing antenatal visits as an early detection approach for antepartum bleeding. An example is the "Devi's Strategy" a women empowerment program which involves women's groups using participatory learning and action cycles while employing a two-tier empowerment strategy — community and individual levels. The desired concept of women's empowerment includes their participation in decision-making, gentle negotiation, protection against all forms of discrimination, and active participation in their own health.[13]

Family support

In line with the research conducted by Paulina Lince Suwo (2020)[14], a well-functioning family role in caring for and nurturing pregnant mothers is strongly associated with preventing pregnancy complications. The findings of this research were consistent with those of Sunaringtyas' study (2023)[15], where the majority of family support provided to the respondents fell into the "insufficient" category, particularly in the case group. This was because respondents viewed prenatal check-ups as routine activities that pregnant women can independently manage. This incorrect perception of the respondents can influence family decisions regarding accompanying pregnant women, leading to less attention and absence of family support during prenatal check-ups.

Active family support during pregnancy benefits the physical and mental health of mothers, as well as the growth and development of the fetus. Support can manifest in the form of affection, trust in the pregnant mother, care, and active family involvement—all of which positively influence fetal growth, maternal physical and emotional health. Support provided can take the shape of attention, affection, trust in the pregnant mother, and tenderness.[16] Addressing this issue as early as possible is crucial, as pregnant mothers without emotional support from their families are more likely to experience stress, which increases the likelihood of complications occurring.

Physical domestic violence

The findings in this study was also in line with the findings of Martin-de-Las-Heras et al. (2019)[17] and Elkhateeb et al. (2021)[18], stating that physical violence is not associated with the occurrence of antepartum bleeding. Physical violence during pregnancy can be linked to high blood pressure, severe nausea, and even kidney and urinary tract infections. It can lead to vaginal bleeding, placental issues, premature rupture of membranes, and preterm delivery. According to Auger et al., (2022)[19] physical violence can increase the risk of antepartum bleeding, and the findings suggest that the physical violence experienced by mothers can be detrimental to both the mother and the fetus.

Physical violence is also associated with placental abruption, antenatal and postpartum bleeding, and cesarean section delivery. Women who experience physical violence during the third trimester may be especially vulnerable due to their protruding bellies and decreased uterine wall thickness, which provides less protection against blunt trauma.[20] Physical trauma to the abdomen can damage the placenta and lead to placental abruption and bleeding, which is an indication for a cesarean section.[19]

Psychological domestic violence

This study was in line with Martin-de-Las-Heras et al., (2019)[17] and Khatoon et al., (2021)[21] that psychological violence is associated with antepartum hemorrhage. Psychological violence during pregnancy can increase the risk of antepartum hemorrhage through psychosocial or physical stress, depression, anxiety, isolation, decreased social support, and low self-esteem.[22] Stress due to psychological violence during pregnancy can increase the activity of the hypothalamic-pituitary-adrenal (HPA) axis. Higher levels of HPA hormones, including corticotropin-releasing hormone (CRH), can restrict blood flow to the placenta, which can result in placental abruption.[23]

Pregnant women who experience psychological violence are twice as likely to not have prenatal examinations until the third trimester and significantly more likely to miss three or more prenatal visits. This is because psychological violence can intimidate and control access to health care, medication, nutrition, and financial resources, resulting in some women arriving late for prenatal visits.[24]

Sexual domestic violence

This study confirmed a research conducted by Auger et al., (2022)[19] and Gisladottir et al., (2016)[25] that there was a relationship between sexual violence and antepartum bleeding. Coercion in having sexual intercourse with pregnant women continuously will have a negative impact on the condition of the mother and fetus. Pregnant women who often have sexual intercourse (once a week or more) are at risk of antepartum bleeding because direct contact between the penis and the placenta can occur, which can interfere with the position of the placenta in the uterus. In addition, sexual violence also has an impact on the mental health of pregnant women. Forced sexual intercourse can put pressure on pregnant women, resulting in unsafe behavior in pregnant women that makes women tend to experience adverse pregnancy outcomes.

This research has several weaknesses, particularly related to the collection of primary data through questionnaires, which have intrinsic weaknesses such as the possibility of recall bias or sampling errors in remembering the information being asked. This is because there were research respondents taken over the past four months. There are limitations in the study regarding the domestic violence variable, the experiences of domestic violence experienced by respondents are observed both before and during the pregnancy period, so the possibility of violence received may originate from previous spouses or not in respondents who have been married more than once.

CONCLUSION

At Mitra Medika General Hospital, Bandar Klippa, Indonesia, the factors that significantly influence the incidence of antepartum bleeding are decision making, family support, psychological abuse, and sexual abuse. Meanwhile, the physical abuse variable has no significant relationship with the incidence of antepartum bleeding. The factor that is most related to the incidence of antepartum bleeding is family support.

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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SYSTEMATIC REVIEW

The role of vitamin D supplementation on levator ani muscle remodeling post-delivery

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ABSTRACT

Objective: Vitamin D is considered a crucial vitamin for the restoration of levator ani muscle strength. Therefore, this study aimed to evaluate the association between vitamin D and levator ani muscle remodeling in the post-delivery period.
Materials and Methods: The literature search was conducted across three electronic databases, namely PubMed, Google Scholar, and Springerlink. Our investigation yielded a total of 2613 studies, out of which 8 studies were found to meet the inclusion criteria and were subsequently included in our study. Among these, 4 studies specifically examined the impact of vitamin D micronutrient status on the levator ani/pelvic muscles during the post-delivery period.
Results: The mean maximum contraction strength of the levator ani muscles following the administration of vitamin D supplements was 26.77 ± 7.15 cmH2O. The analysis conducted utilizing a paired t-test yielded a p-value of less than 0.05, indicating statistical significance. Additionally, a coefficient correlation of 0.831 was observed, with a p-value also less than 0.05. The findings of this study indicate a noteworthy correlation between levels of vitamin D and the magnitude of levator ani muscle contractions, as evidenced by a statistically significant p-value of less than 0.05.
Conclusion: The administration of vitamin D supplements has been found to play a significant role in the remodeling of the levator ani muscle during the post-delivery period. This is evidenced by the observed increase in strength of the levator ani muscles following vitamin D supplementation.

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Highlights:

1. In pregnant women, vitamin D insufficiency may play a role in the development of post-delivery illness.
2. Vitamin D supplementation is significant in remodeling of post-delivery levator ani muscle.

INTRODUCTION

The levator ani muscle is made up of additional smooth muscle fibers as well as striated muscle fibers. It has a cone shape and is very complex.[1] The levator ani muscle is located on both sides of the lower pelvis and is very important for supporting and elevating the pelvic floor. This makes it easier for other pelvic structures to move. Because it works with the coccygeus muscle, the levator ani muscle is an important part of the pelvic floor muscles. The puborectalis, the pubococcygeus, and the iliococcygeus are the three separate muscles that make up this muscle. There are nerves that connect to most of these muscles that come from the inferior hypogastric plexus, the levator ani muscles, and the pudendal nerves.

According to Timoh et al.,[2] birth-related levator ani injuries seen on magnetic resonance images in affected women (Fig. 2) have been linked to a much higher risk of vaginal prolapse and a notable 40% drop in pelvic floor muscle strength. An instrumented speculum is a special tool that is often used to measure the isometric strength of the pelvic floor muscles. This tool can measure the highest voluntary force that is used to close the vaginal opening in the mid-sagittal plane. However, the measurement of the force that the vaginal muscles put out when they were at rest and the increase in the maximum strength of that force did not show a noticeable drop as people got older. This finding is surprising because it is common to see striated muscle lose 30 to 40 percent of its volume as a person ages.

A lot of research has been done on this and found that it explains why isometric muscle strength decreases and axial or appendicular striated muscle strength grows more slowly in healthy older adults.[3] If you hurt your levator ani muscle, your pelvic organs may fall out. Many women have experienced pelvic organ prolapse; a health problem that can make them feel less healthy overall. Pelvic organ prolapse may give rise to aberrations in the digestive system, sexual function, and bladder system, alongside psychological, social, and emotional strain that precipitates symptoms of depression, social withdrawal, and anxiety.

The accurate identification of a medical condition is crucial in order to administer appropriate and efficient therapeutic interventions. Levator ani muscle injuries are commonly misdiagnosed, and the therapeutic interventions typically involve limited vaginal repairs. Insufficient focus may be directed towards the dome, also known as the upper part of the vagina, or the descent of the uterus.[4,5]

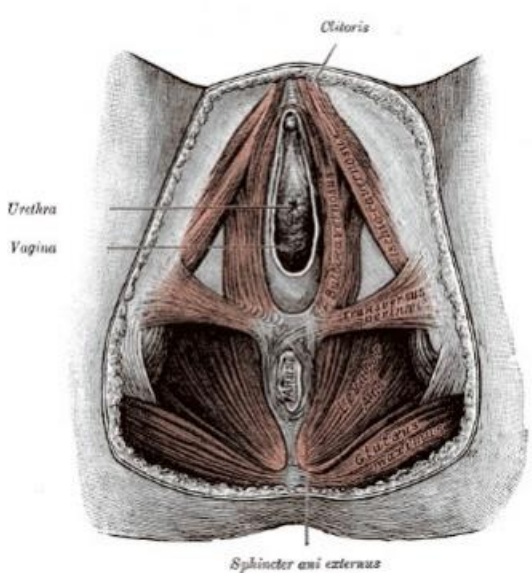

Figure 1. Female perineum, clitoris, urethra, vagina, sphincter ani externus, anus, gluteus maximus, levator ani, transversus perinea.[3]

There is a pressing necessity for the establishment of nutritional guidelines to prevent levator ani muscle injury. The baseline characteristics encompass the average daily energy and nutrient intakes expressed as a proportion of the recommended dietary allowances among women in the post-delivery period. The study revealed that the post-delivery diet exhibited sufficient intake levels (above 80% of the Recommended Dietary Allowance) for energy (82.6%), protein (80.6%), carbohydrates (99.5%), vitamin C (88.7%), vitamin B2 (95.1%), and vitamin B12 (170.8%). However, inadequate intake levels (below 35%) were observed for vitamin D (12.3%), iron (28.3%), and folate (33.8%).[6]

People think that vitamin D is very important for many organ systems. It is becoming more common for people to not get enough vitamin D. Several studies have shown that vitamin D deficiency is still common in Indonesia, as well as in Australia and the US. Lower levels of vitamin D in the blood have been linked to a loss of both tone and strength in skeletal muscles in previous research publications. Between 3 and 8 days after giving birth, the pelvic floor muscles tend to get weaker, but they get stronger again between 6 and 10 weeks after giving birth. Most people think that not getting enough vitamin D can cause both skeletal muscle mass and strength to decrease[7] show that when 1,25(OH)2 D3 interacts with the vitamin D receptor (VDR), it starts the process of transcribing proteins that help the body use calcium.

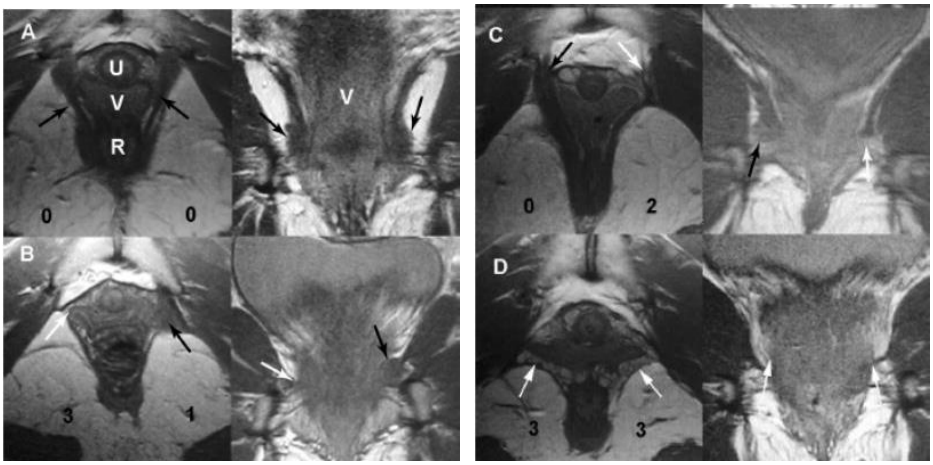

Figure 2. On axial and coronal magnetic resonance images, these examples show the different levels of damage to the levator ani pubovisceral muscle. A: A woman whose muscles are normal; B and D: Three women who each have a major disability; and C: Three women who each have a minor disability. The scores for each side are shown by the handicap scores on the left. There are black arrows that show where the muscle should be and white arrows that show where the muscle is damaged or should be. U stands for the urethra, V for the vaginal canal, and R for the rectum.

It has been shown that vitamin D can affect how strong and well skeletal muscles work. An important link exists between not getting enough vitamin D and having very weak muscles. The levator ani and coccygeus muscles are skeletal muscles that are an important part of the pelvic floor. Some people think that the amount of vitamin D in your body may have an effect on these muscles. Research has indicated that when consumed in suitable quantities, vitamin D has been observed to enhance the efficiency of skeletal muscle. The assessment of micronutrient requirements for the treatment of post-delivery levator ani muscle injury poses a significant challenge for healthcare professionals. Consequently, it is imperative to conduct a comparative analysis to determine the efficacy of different micronutrient interventions in addressing this condition. Therefore, this study aimed to evaluate the association between vitamin D and levator ani muscle remodeling in the post-delivery period.

MATERIALS AND METHODS

Search strategy

There was a search of the literature in three electronic databases: PubMed, Google Scholar, and Springerlink. Our research turned up a total of 2613 studies. Of these, 8 met the predetermined criteria for inclusion and were therefore added to our study. These 8 studies gave detailed information on 4 studies that looked at the micronutrient status of vitamin D and 4 studies that looked at the micronutrient status of collagen, specifically in the levator ani muscle and pelvic muscles after giving birth. Boolean operators "AND" and "OR" were used along with keywords that are related to the clinical questions to do the search. What was found was shown following the rules set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Article selection

The articles acquired through the search process will once again undergo elimination, this time based on the predetermined criteria for inclusion and exclusion. The search for this article employed specific inclusion criteria, namely the utilization of English/Indonesian language, the inclusion of quasi-experimental and observational studies, the examination of the percentage of micronutrient requirements for levator ani muscle repair, and the utilization of human subjects as research participants. Exclusion criteria encompassed interventional studies, studies lacking meta-analytic data, literature sources characterized by regular publication patterns, as well as data derived from reviews or abstracts. The reported results solely pertain to the standard deviation of score coloring, with no additional information provided. After applying the

predetermined inclusion and exclusion criteria, a total of 19 articles that were deemed relevant were acquired.

Eligibility criteria

The authors collectively engaged in a systematic process of summarizing and evaluating the available evidence by employing a standardized abstraction form. Prior to commencing the process of abstraction and review, the team will conduct tests on the screening and abstraction forms using a variety of articles. The screening and data collection forms will be subject to revision by the team.

Data synthesis

A quantitative synthesis was not conducted for four reasons. Significant variations exist in the operational definition of the condition under treatment across various studies, accompanied by a scarcity of interventions that span a broad spectrum. The present study aims to conduct a trial replication by employing similar interventions while utilizing distinct primary and secondary outcome measures.

Data Extraction

The data obtained from the identified publications encompassed various aspects, such as the study design and corresponding outcomes, the total number of patients involved, the duration of follow-up during the intervention, details regarding the intervention itself, the effectiveness of the intervention, and any additional comments provided. Tables are employed as a means to present data in a descriptive manner and subject it to analysis.

RESULTS AND DISCUSSION

A total of 2163 studies were identified through our search process. After applying the inclusion criteria, a final selection of 8 studies was included in our study. Figure 1 illustrates the flowchart representing the progression of literature through the grading process for the purpose of this review update.

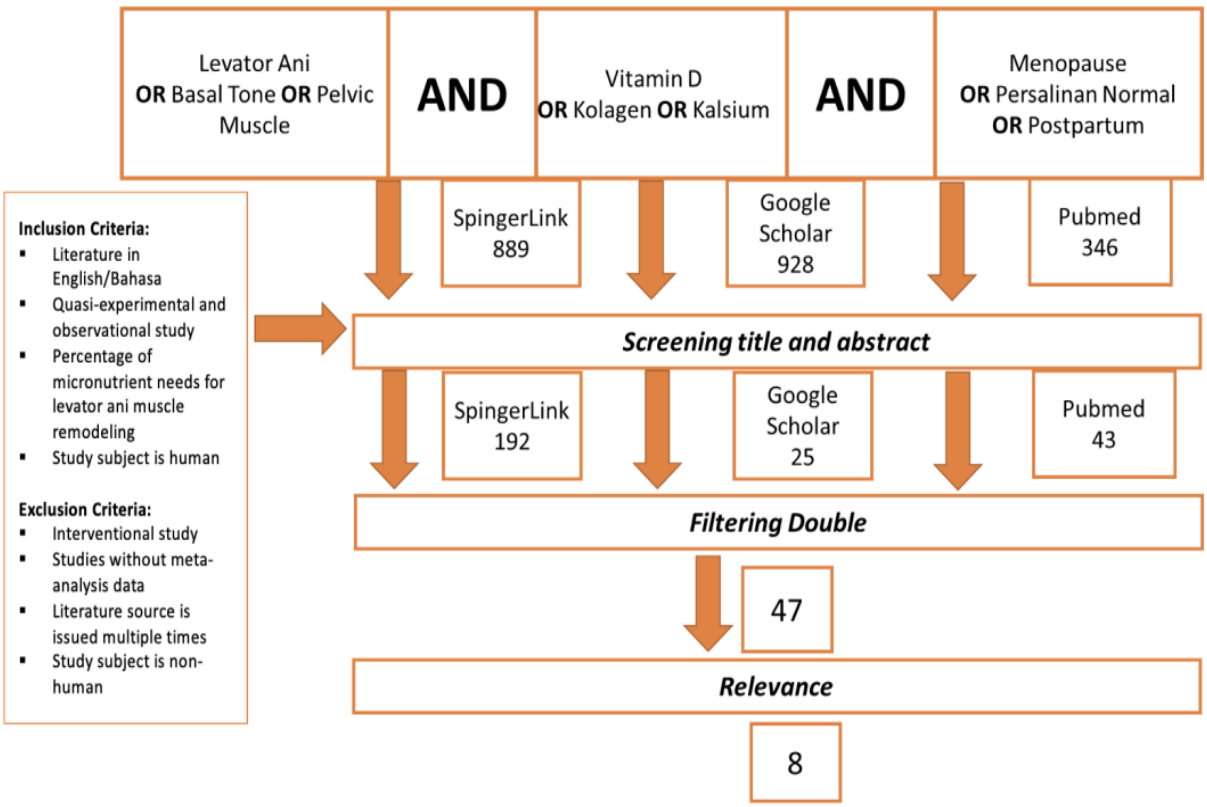

Figure 1. Flowchart of data filtering.

Effects of vitamin D on levator ani muscle remodeling

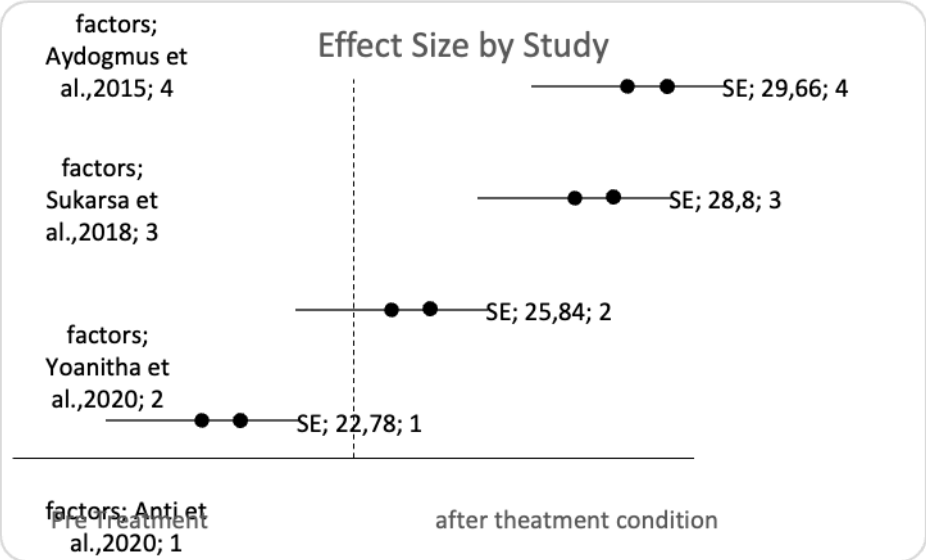

Figure 2. Forest plot effect of vitamin D on levator ani muscle strength.

Research conducted on both animals and humans has demonstrated that Vitamin D3 can enhance muscular strength and function in striated muscle. The clinical manifestation of weakened pelvic floor muscles may manifest as symptoms indicative of pelvic floor dysfunction. There is a notable correlation between the administration of Vitamin D supplementation and muscle, as evidenced by trials conducted by Aydogmus et al.,[8] (SMD = 29.66, 95% CI: 19.36; 39.96) in comparison to Sukarsa et al.[7] (SMD = 22.78, 95% CI: 18.88; 26.68) and Yoanitha et al.[9] (SMD = 25.84 95% CI: 18.73; 32.95), and The current study examined the average maximum pelvic floor muscle contraction strength after vitamin D3 supplementation. The measured value was 26.77 ± 7.15 cmH2O. The results were statistically significant because the paired t-test p-value was less than 0.05. They also had a 0.83 correlation coefficient. This suggests a link between vitamin D levels and levator ani muscle strength. Vitamin D levels and levator ani muscle contraction strength are statistically significant at 0.05 or higher. Vitamin D has many effects on striated muscle strength and function.[7,10]

Research indicates that vitamin D supplementation significantly reduces TGF-β3 levels. Vitamin D's antioxidant properties may cause this. These properties reduce reactive oxygen species (ROS), which inhibits MMP. However, Vitamin D increases cell structure-produced type I collagen, elastin, and fibronectin.[11–13] Vitamin D affects striated muscle genomically and non-genomically. Genomically, vitamin D controls gene transcription in striated muscle. By activating vitamin D receptors in muscle nuclear membranes. Muscle cells differentiate and multiply through the insulin growth factor (IGF) pathway after activation, resulting in hypertrophy. When 1,25(OH)D binds to membrane receptors, it has a nongenomic effect. Signal transmission activates the MAPK and PLC pathways. Calcium entry into cell structures is affected by these pathways.

Effect of collagen type I on pelvic muscles

A change (rs1800012) in the gene that codes for type I, alpha 1 collagen at the collagen binding site of Sp1 has been shown to change gene expression and the way transcription factors bind. A small link has been found between minor alleles and lower bone mineral density and a higher risk of breaking a bone in people with osteoporosis. What makes up the vaginal epithelium and endopelvic fascia? They are mostly made up of collagen type I, alpha 1. The gene and protein expression data in pelvic tissue from women with prolapse or stress incontinence who took part in a previous study are very different, showing that the data needs to be improved and refined even more.

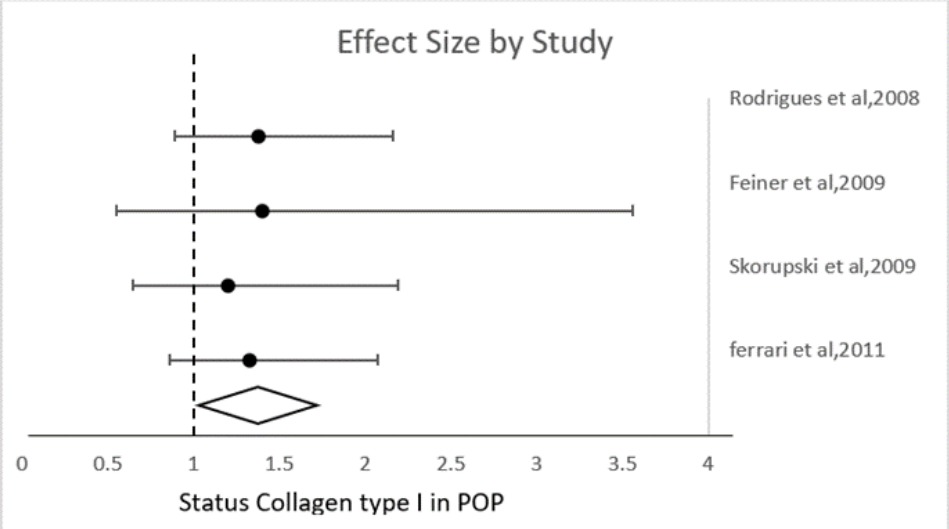

Figure 3. Forest plot status collagen type I in POP

Anatomical POP has been linked to the genetic variant rs1800012 in five different studies. These studies were done in Brazil, Israel, Poland, Italy, and Korea. Because all 30 people who took part in a study had the GG allele, they were not included in the statistical analysis. There was some disagreement between the last four studies, but not a lot. Their effect sizes were still statistically important (OR, 1.33; 95% CI, 1.02-1.73). We think that bias can't be ruled out completely because we don't know much about QC genotypes and the two samples may have been affected by population stratification. One sample is very different from Hardy-Weinberg equilibrium, which suggests a large amount of bias. But leaving out this study would not change the result. It was written by Cartwright et al.[14,15]

The study discovered a strong link between vitamin D levels and both the levator ani's basal tone and its maximum contractions. Some of the things that can change a person's vitamin D levels and pelvic floor muscles are their age, body mass index, race, vaginal delivery, diet, and time spent in the sun. Sukarsa et al.[7] found that women of childbearing age and pregnant women in their first trimester are more likely to have nutritional problems because of the way their bodies work during their periods and during pregnancy. Vitamin D deficiency can be fixed by making more vitamin D, which can be done through fortification, supplements, and other means. A study looked at 25 primiparas and 20 multiparas who had a spontaneous vaginal delivery between 36 and 42 weeks of pregnancy. The results were different for the same women 3–8 days after giving birth, 6–10 weeks after giving birth, and 9–15 months after giving birth. Pain during contractions and/or pressure inside the abdomen during the exam have both been linked to the chance of perimetric assessments being biased.[16–19] This study shows that taking extra vitamin D is important for remodeling the levator ani muscle after giving birth.

If you don't get enough vitamin D, the calcium balance in your pelvic floor muscles gets off, which makes them less effective and can cause problems with your pelvic floor. A small amount of vitamin D has been shown to improve the function of skeletal muscles. PFMT is meant to make the levator ani muscles stronger, which are very important for a woman's ability to control her bladder. This should be your first line of defense when dealing with SUI, OAB, UUI, or FI. Studies using random assignments have shown that strengthening the muscles in the pelvic floor can help reduce urinary incontinence by 54 to 75%. Low 25(OH)D levels may impair skeletal muscle function, which the urethra needs. The levator ani, extrinsic urethral, and external anal sphincters may work better with normal vitamin D levels. Thus, vitamin D levels may affect how well behavioral therapy helps PFMT women control urinary and fecal incontinence. More research is needed to determine how vitamin D affects the levator ani muscle and how vitamin D supplements and PFMT may treat pelvic floor symptoms.

The study's correlation analysis backs up the explanation that was put forward. Vitamin D and muscle strength have been looked at in a lot of different studies. Aydogmus et al. discovered a link between the strength of the levator ani muscle and the amount of vitamin D a woman had before giving birth. When women had enough vitamin D, their pelvic floor muscles were stronger after giving birth.[8] Low vitamin

D levels in the third trimester have been linked to pelvic floor muscles that aren't as strong after giving birth.[20–23] A study by Parker et al. looked at 394 women who said they had problems with their pelvic floor and found that not getting enough vitamin D was linked to more urinary incontinence and other colorectal symptoms that made their quality of life worse. In a study of 99 girls ages 12 to 14, Ward et al. found that vitamin D levels were linked to better measures of strength, speed, and vertical jump. Other studies have looked at what happens to muscle tissue when people take extra vitamin D. Teenage girls between the ages of 12 and 14 who took 150,000 IU of vitamin D supplements every three months for a year showed improvements in their strength, height, and efficiency when jumping, according to a study by Ward et al.[24–26]

Gabriel et al. did an in vitro study and found that the sacrouterine ligament in the neck may be able to hold up to 17 kg of weight before the hip gives way. The ECM is made up of elastin, collagen, and fibronectin. It is the main structure-supporting protein.[4,27] There is a special structure to the ligaments of a woman's genitalia because elastin and collagen can change shape during the reproductive stages of her life. The component goes back to its pre-pregnancy levels after giving birth, even though it rose a lot during pregnancy. POP is more likely in older women, multi-pregnant women, and vaginal birthers. Oxford Family Planning found that POP hospital admissions increased four times for women with one child, eight times for two children, and ten times for more than two children in a prospective study of 17,000 women.

New studies show that vitamin D deficiency increases POP risk. Vitamin D supports skin and heart connective tissues better than bone building and mineral density. Here, Skowronska et al.[10,19,28] explain the biomolecular processes that regulate vitamin D intake or exposure in POP. TGF-3 levels dropped significantly after vitamin D exposure. Due to its antioxidant properties, vitamin D reduces ROS and matrix metalloproteinase. Vitamin D boosts type I collagen, elastin, and fibronectin production. Grinnell also found that vitamin D grows fibroblast growth factor II, which makes elastin and collagen. Vitamin D makes it easier for skin and heart tissues to make collagen types I and II. Along with the transcription process, this way of copying is thought to be passed down from parent to child.[11,26–29]

Strength and limitation of the study

Strength of this study are there is specific micronutrient and specific vitamin D observed on this study. The limitation of this study is that there is wide gap of age of post-partum woman observed and there isn't exact measurement of levator ani muscle strength.

CONCLUSION

During pregnancy and childbirth, the levator ani muscles are under a lot of stress from both mechanical and neurological issues. However, there are other issues that come into play as well. Women who are pregnant and don't get enough vitamin D may have more problems after giving birth. Strength gains in the levator ani muscle after taking vitamin D3 supplements after giving birth show that vitamin D is an important part of muscle remodeling after giving birth.

DISCLOSURES

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Conflict of interest

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Author contribution

All of the authors worked on this study in some way, including planning, collecting and analysing data, writing, and getting permission to publish.

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SYSTEMATIC REVIEW

The use of N-acetylcysteine to prevent further progression of preeclampsia

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ABSTRACT

Objective: Preeclampsia is a prevalent disorder among pregnant women, characterized by hypertension and proteinuria, leading to serious complications. However, the precise pathophysiology of preeclampsia remains debated. Oxidative stress is believed to play a significant role in its development, and N-acetylcysteine (NAC) is known to influence this pathway. NAC aids in glutathione synthesis, a critical antioxidant, and acts as a free radical scavenger. This study aimed to examine the role of NAC in women with preeclampsia, focusing on its potential therapeutic benefits.

Materials and Methods: A comprehensive literature search was conducted using PubMed and ScienceDirect databases, yielding 17 articles from PubMed and 395 articles from ScienceDirect. Reviews were excluded, resulting in 12 articles from PubMed and 89 articles from ScienceDirect. After further screening, 5 articles were selected for review, including 2 human studies and 3 animal studies, to understand the impact of NAC on preeclampsia.

Results: Human studies indicated that NAC supplementation reduced the rate of preeclampsia among women at increased risk. Animal studies supported these findings, showing improvements in oxidative stress biomarkers, laboratory values, and blood pressure in models treated with NAC. NAC supplementation was associated with positive outcomes in managing oxidative stress, a key factor in the pathogenesis of preeclampsia.

Conclusion: NAC supplementation in women with preexisting preeclampsia has beneficial effects on oxidative stress biomarkers, laboratory values, and blood pressure. These highlight the potential of NAC as a therapeutic intervention for preeclampsia, particularly in women at high risk. However, no significant differences were observed in maternal complication rate between the NAC-treated group and the control group. Further research is needed to fully understand the clinical implications of NAC supplementation and its long-term safety and efficacy in managing preeclampsia.

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Highlights:

1. The generation of free radicals in the placenta leads to endothelial dysfunction, which contributes greatly in preeclampsia.
2. N-acetylcysteine have a role in the oxidative stress pathway, helping in glutathione synthesis and as a free radical scavenger.
3. N-acetylcysteine supplementation in women with preexisting preeclampsia had positive effects on oxidative stress biomarkers, laboratory values, and blood pressure.

INTRODUCTION

Preeclampsia is a very common disorder, associated with high numbers of both maternal and fetal morbidity and mortality.[1,2] The pathophysiology of preeclampsia remains in academic debate, but one such theory states that the generation of free radicals in the placenta leads to endothelial dysfunction, which contributes greatly in preeclampsia.[3] As such, the use of antioxidants became one such promising endeavor in combating pre-eclampsia.

Average fetal growth depends on the placental vascular function that is operating at its best. Nitric oxide (NO), a calming agent created from the endothelium, plays a significant role in regulating normal fetal placental blood flow because the placenta lacks autonomic innervation. The enzyme NO-synthase (NOS), stimulated by various substances (such as shear stress, serotonin, and bradykinin), produces NO in the endothelial cell. NO diffuses to the vascular smooth muscle cells, stimulating the guanylate cyclase to raise the amount of cyclic guanosine monophosphate (cGMP) inside the cells. The calcium channels then close, the intracellular calcium level drops, and the vessel wall relaxes.[4]

NAC have a role in the oxidative stress pathway, helping in glutathione synthesis and as a free radical scavenger.[5–8] N-acetylcysteine (NAC) transportation across the placenta indicates the potential for maternal NAC supplementation to reach the endothelium of the fetoplacental unit.[9–12] The mechanism of action of NAC involves increasing the intracellular levels of cysteine/glutathione biosynthesis (GSH) and functioning as an oxidant scavenger. The pharmacological effects of this substance encompass the restoration of cellular antioxidant capacity through the replenishment of glutathione levels depleted by free radicals and reactive oxygen species (ROS). Additionally, it inhibits neutrophil activity and the production of tumor necrosis factor (TNF).[13,14] In keeping with this reasoning, we speculate that administering NAC to the fetoplacental vascular bed may enhance endothelial function, particularly that mediated by the NO-pathway, in the placentas of preeclamptic women. This study aims to examine the role of NAC on women with preeclampsia.

MATERIALS AND METHODS

This systematic review aims to find the effectiveness of NAC in managing women with preeclampsia. This study is done according to PRISMA guidelines. Literature search was done using the PubMed and ScienceDirect database.

Search strategy

The keywords used in the search were "N-acetylcysteine" and "preeclampsia". The results following the search were reviewed by the reviewer to determine the eligibility of the study. The inclusion criteria in this study were studies published in English, about the effect of NAC on patients with preeclampsia or in animal model, and published from the year 2000 and forward, while the exclusion criteria were studies not published in English, in vitro, and in patients without preeclampsia.

Selection process

Using the PubMed and ScienceDirect database, 17 and 395 articles were obtained. Reviews were then excluded from both pooled articles, resulting in 12 articles from PubMed and 89 articles from ScienceDirect. Studies examining the effect of NAC in vivo and discussing other substances were excluded. After removing duplicates, a total of 6 articles were screened for eligibility. One study was excluded due to its study population were women without preexisting pre-eclampsia. A total of 5 articles, consisting of 2 human studies[6,15] and 3 animal studies.[16–18] were obtained and included in this systematic review. Article selection process is described in Figure 1.

Risk of bias assessment

Risk of bias assessment in animal studies were done using the SYRCLE's risk of bias tool, this tool examines selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[19] Cochrane risk of bias tool was used to assess human studies, examining selection bias, performance bias, attrition bias, detection bias, reporting bias, and other bias.[20]

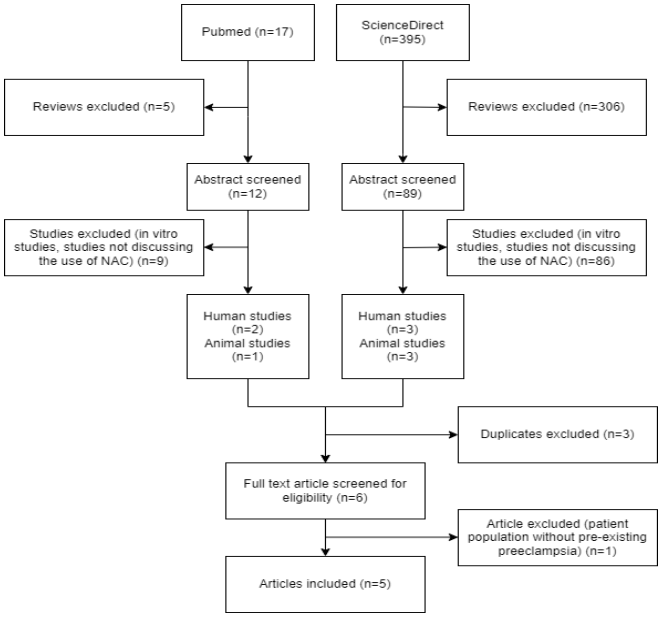

Figure 1. Article selection process

Table 2. Summary of human studies

Author	Year	Country	Dose	Other Interventions	Sample Size		Sample Characteristics	Result
					Intervention	Control		
Motawei, et al.	2016	Egypt	400 mg/day	Methyldopa 250 mg with calcium-channel blockers if hypertension remains uncontrolled, nutritional deficiency correstion therapy, and magnesium	50	50	Patients with pre-eclampsia	Significant increase in intervention group compared to control group in GPx, SOD, ALT, AST, serum creatinine, proteinuria, SBP, and DBP values in both 4 and 6 weeks post intervention. Significant improvement of birth weight and Apgar score (1 and 5 minuters). No significant difference found in MDA value and the rate of maternal complications.
Roes, et al.	2006	Netherlands	3 tablets of 600 mg/ hours until delivery	Antihypertensives, corticosteroids, and magnesium sulfate	19	19	Patients with early onset severe preeclampsia and/or HELLP syndrome between 25 and 33 weeks gestation, excluding those with twin pregnancy, predominantly Caucasian	Significantly less concentration of homocysteine in intervention group compared to control group. No significant difference in plasma thiol levels, treatment-to-delivery interval, gestational age at delivery, maternal complication, neonatal morbidity and morality, birth weight, and Apgar score at 5 minutes.

Table 3. Summary of animal studies

Author	Year	Country	Sample Characteristics	Dose	Result
Ayasolla, et al.	2006	USA	Sprague-Dawley rats with RUPP model	100 mg/kg every 12 hours, first dose given prior to RUPP procedure on day 15/22 of pregnancy	Significant decrease of GSH, GPx, and GR activity accompanied by decreasing Cu/ZnSOD expression in the RUPP group. Increased activity of MnSOD activity in the RUPP model. Changes were observed to be reversed with the administration of NAC.
Chang, et al.	2004	USA	Sprague-Dawley rats with RUPP model	100 mg/kg every 12 hours, first dose given prior to RUPP procedure on day 15/22 of pregnancy	Significant decrease in litter size, pup weight, and pup brain weight in the RUPP group, accompanied with significantly higher MAP. The changes were observed to be attenuated with the administration of NAC.
Chang, et al	2005	USA	Sprague-Dawley rats with RUPP model	100 mg/kg every 12 hours, first dose given prior to RUPP procedure on day 15/22 of pregnancy	Significant decrease in pup weigth and pup brain weight in the RUPP group, accompanied with significantly higher MAP. No significant difference found in litter size. The changes were observed to be significantly improved with the administration of NAC except for pup weight.

Table 4. Risk of bias of animal studies

Authors	Year	Selection Bias			Performance Bias		Detection Bias		Attrition Bias	Reporting Bias	Other
		Sequence Generation	Baseline Characteristics	Allocation Concealment	Random Housing	Blinding	Random Outcome Assessment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias
Ayasolla, et al.	2006										
Chang, et al.	2004										
Chang, et al.	2005										

Labels : Low risk; Some concerns; High risk

Table 5. Risk of bias of human studies

Authors	Year	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Incomplete Outcome Data (Attrition Bias)	Blinding of Outcome Assessment (Detection Bias)	Selective Reporting (Reporting Bias)	Other Bias
Motawei, et al.	2016							
Roes, et al.	2006							

Labels : Low Risk; Some Concerns; High Risk

RESULTS AND DISCUSSION

A total of 5 articles were included in this review, consisting of 2 human studies.[15,21] and 3 animal studies.[16,17,22–24]. The inclusion of studies based on animal models were done to supplement more data regarding the effect of NAC in preeclampsia due to there being few human based studies available. The risk of bias in animal-based studies are regarding the blinding of researchers and randomization which are not explicitly stated in the articles. The risk of bias in human based studies are the same in the study done by Motawei, et al, due to there being no explicit statement regarding blinding and randomization.[15]

The results of NAC administration in animal RUPP models, which were done by using a calibrated silver clip placed on the infrarenal aorta and the branches of the right and left ovarian arteries that supply the uterus, were favorable in the administration of NAC. The changes induced by the RUPP procedure were ameliorated by the administration of NAC.[16,17,22] Pup weight, pup brain weight, and MAP were found to be improved using NAC.[16,18] Regarding litter size, one study found there to be a significant difference.[18] and another study didn't find any difference.[16] The resulting measurement of oxidative stress biomarkers indicate a significant improvement in GSH, GPx, GR, and SOD activity in subjects that underwent the RUPP procedure and treated with NAC.[17] This opens the possibility of the potential of NAC to reduce oxidative stress and improve maternal outcomes.

Regarding the human studies, the study done by Motawei, et al. shown a significant improvement in laboratory values (ALT, AST, serum creatinine, proteinuria), improved SBP and DBP measurement, oxidative stress biomarkers (GPx and SOD), and maternal outcomes (birth weight and Apgar score both in 1 and 5 minutes).[15] These findings are conflicting with the study done by Roes, et al., which shown no significant improvement in maternal (birth weight and Apgar score at 5 minutes) and neonatal mortality and morbidity.[21] No significant prolongation of gestational age at delivery were found, indicating the lack of NAC's ability on stabilizing the process of ongoing preeclampsia, which should result in the prolongation of pregnancy. The level of homocysteine, a marker indicating the promotion of formation of ROS, were found to be significantly decreased in the treatment group.[21] The severity and the time of treatment were stated to influence the outcome produced by the study. The dose used in the study could also affect the results, since there is no information regarding the dosing, response time, and optimal duration of NAC administration in preeclampsia.

A study done by Rumiris, et al., shown that the supplementation of antioxidants results in a lower rate of preeclampsia in women with low antioxidant status. This study used plenty of different antioxidants combined, including NAC.[25] Both studies included in this review also didn't find any significant side effects resulting from the use of NAC, even in higher doses, as shown by the study done by Roes, et al. A study done by Chappell, et al and Fu, et al. found a reduction in

preeclampsia rate using antioxidants in women having increased risk of preeclampsia, defined by the study as having an abnormal doppler waveform in either uterine artery at 19-22 weeks' gestation or a history in the preceding pregnancy of preeclampsia necessitating delivery before 37 weeks gestation, eclampsia, or HELLP syndrome. This study, utilizing vitamin C and E, also found a significant reduction on the ratio of plasminogen-activator inhibitor 1 and 2, a marker of endothelial activation and placental dysfunction, suggesting an improvement in endothelial function.[4,26–28]

The limitations of this study are the lack of studies specifically researching the effects of NAC in preeclampsia, leading to our decision to supplement it with animal studies to increase the base of evidence. The dosing of NAC in human studies differ greatly, possibly affecting the benefits derived from NAC supplementation, as there is no prior reference or guidelines discussing the effective dose of NAC supplementation in preeclampsia. The results assessed by the studies also differ in the type of biomarkers measured and clinical outcomes.

Further studies could be done with more specific population regarding time of gestation, severity of preeclampsia, time to treatment, and dosing to further clarify the potential effects of NAC.

CONCLUSION

NAC supplementation in women with preexisting pre-eclampsia had positive effects on oxidative stress biomarkers, laboratory values, and blood pressure. No significant difference was found in the rate of maternal complications.

DISCLOSURES

Conflict of interest

There has 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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META-ANALYSIS

Maternal-related factors associated with development and improvement of peripartum cardiomyopathy and therapeutic outcomes of bromocriptine

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ABSTRACT

Objective: This study aimed to fill the significant knowledge gap regarding peripartum cardiomyopathy (PPCM), a heart failure phenotype linked to pregnancy. The main objectives were to explore the factors influencing the development and progression of PPCM and to assess the outcomes of bromocriptine.

Materials and Methods: Systematic search across PubMed, ScienceDirect, and Cochrane Library identified studies until December 2022. This study includes non-randomized prospective and retrospective studies, as well as relevant randomized controlled trials. Risk factors were compared between the recovered and non-recovered PPCM groups, and bromocriptine therapy outcomes were evaluated against standard heart failure treatment as the primary endpoint.

Results: The analysis included 24 observational studies and 1 randomized controlled trial involving 1,651 PPCM patients; 9 studies evaluating the outcomes of bromocriptine therapy. The most prevalent factors were caesarean delivery (proportion = 53%, 95% CI = 41%-66%) and anemia (proportion = 51%, 95% CI = 38%-65%). Non-recovered patients were younger (MD=-1.04 years old, 95%CI=-1.82-(-0.27), p=0.008) and predominantly black (RR=1.82, 95% CI = 1.43-2.31, p <0.001). Hypertensive disorders and primiparity were found less among non-recovered patients (RR=0.73, 95% CI = 0.60-0.88, p=0.001; RR=0.81, 95% CI = 0.66-0.99, p=0.04, respectively). Non-recovered patients also exhibited higher baseline serum creatinine levels, lower LVEF, larger left ventricular end-systolic diameter (LVESD), larger left ventricular end-diastolic diameter (LVEDD), and lower fractional shortening (all p-values <0.05). Furthermore, bromocriptine significantly reduced major adverse cardiac events (MACE), mortality, and increased LVEF (all p-values <0.05).

Conclusion: Younger maternal age, black race, absence of hypertension, and multiparity are associated with poorer prognosis for PPCM recovery. Bromocriptine therapy demonstrates superior benefits in reducing adverse events in PPCM.

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Highlights:

Younger age, black race, normotension, and multiparity indicate a poorer prognosis for peripartum cardiomyopathy recovery, while bromocriptine therapy reduces adverse events.

INTRODUCTION

Peripartum cardiomyopathy (PPCM) is an idiopathic cardiomyopathy occurs during pregnancy or in first few months after childbirth. PPCM is diagnosed when there is unexplained onset of heart failure with a reduced left ventricular ejection fraction (LVEF) below 45% in previously healthy women.[1] Incidence of PPCM varies globally and is estimated to be 1 in 1000 pregnancies.[2] In United States, over 40% of PPCM cases are observed in women of black race.[3,4] Interestingly, although anemia is a well-established contributor to the pathophysiology of chronic heart failure, its consistency as a risk factor for PPCM has not been established.[5] However, a cohort study reported that pregnant women with anemia were five times more likely to develop PPCM.[6] Other factors that have been suggested to contribute to development of PPCM, such as history of preeclampsia/eclampsia or other hypertensive disorders, and multiple gestation, have also shown inconsistent associations with PPCM.[7] Therefore, the factors associated with the development of PPCM remain unclear.

Despite the unclear understanding of the risk factors and pathophysiology, the prognosis of PPCM appears to be improving. This is supported by the Investigations of Pregnancy Associated Cardiomyopathy (IPAC) study, which reported a spontaneous recovery in 72% of patients, with only 13% experiencing persistent cardiomyopathy with an ejection fraction <35%.[8] The mortality rate of PPCM patients seems to be influenced by race/ethnicity and varies across geographical regions.[9] In contrast to previous studies citing mortality rates ranging from 2% to 10%, recent reports have shown a decrease in mortality to below 2%.[6,10] Recent research has revealed the involvement of the hormone prolactin in the pathogenesis of PPCM, suggesting that the inhibition of pituitary prolactin secretion through lactation cessation or the use of bromocriptine may be beneficial in PPCM treatment.[11] In a prospective observational study conducted in Germany, the use of bromocriptine demonstrated echocardiographic improvements compared to non-users.[12] However, it should be noted that bromocriptine has the side effect of suppressing lactation.[13] Since previous studies have reported spontaneous recovery of PPCM without the use of bromocriptine,[8,14–16] the administration of bromocriptine should be selective for patients who have a lower likelihood of recovery to balance the risks and benefits of this therapy.

Due to the substantial knowledge gap surrounding PPCM, systematic review and meta-analysis are necessary to provide a holistic assessment of various aspects, including risk factors, factors associated with recovery, and the outcomes of bromocriptine therapy. Such an analysis would contribute to the refinement of clinical management strategies for PPCM by providing robust evidence. The aims of study are to evaluate factors associated with development, recovery, and poor outcomes of PPCM and to assess outcomes of bromocriptine therapy.

MATERIALS AND METHODS

This meta-analysis strictly following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[17] The protocol was registered in international prospective register of systematic reviews (PROSPERO) under the registration code of CRD42023435415.

Search strategies

Comprehensive literature search conducted in MEDLINE (Medical Literature Analysis and Retrieval System Online) via PubMed, ScienceDirect, and the Cochrane Library. The search was performed from the beginning of the databases until December 2022, without any language restrictions. The following search string was used: ((Peripartum Cardiomyopathy) OR (PPCM)) AND ((Recovery) OR (Bromocriptine) OR (Prolactin)). Five authors (I.G.B.M.A.P, G.N.P.J, I.B.S.W, F.D, I.W.A.S.P) oversaw the entire process, from conducting the literature search to data extraction and bias assessment. Any discrepancies or uncertainties regarding study eligibility were thoughtfully resolved through consensus, involving an additional author (R.S.M) in the decision-making process.

Study selection

Identified studies were initially screened based on title and abstract. Studies met the criteria were included in this analysis. Population of study consists of all patients diagnosed with PPCM defined as signs and symptoms of left ventricular systolic dysfunction occurring towards the end of pregnancy or in the months following delivery, without the possibility of another identified cause of heart failure. Inclusion criteria for this study encompassed non-randomized two-arm prospective studies, two-arm retrospective studies, and randomized controlled trials. We excluded studies falling into the following categories: experimental animal models/basic science, review/meta-analysis, secondary research papers, case reports, and case series, as well as those involving duplicate populations. The search strategy included both Medical Subject Headings (MeSH) terms and relevant free-text keywords pertinent to the subject of inquiry. From the initial pool of 2,233 retrieved manuscripts, a total of 25 met the predefined inclusion criteria, as delineated in the PRISMA flowchart (Figure 1).

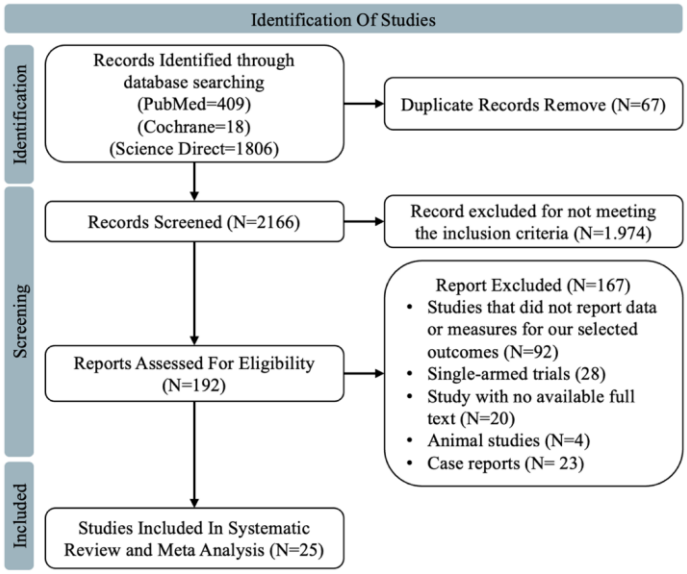

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Data extraction

A systematic data extraction process was carried out to assemble comprehensive demographic, baseline characteristics, and outcome-related data derived from the studies included in the analysis. Data extraction was conducted independently by five researchers (I.G.B.M.A.P, G.N.P.J, I.B.S.W, J.C.S, B.G.D.L). Standard forms were utilized to extract the relevant information. The extracted data included the baseline characteristics and demographic patients in each study, such as study design, sample size, definition of PPCM, number of patients who recovered from PPCM, criteria for recovery, number of patients treated with bromocriptine, dosage of bromocriptine, follow-up duration, mean age, and other key variables. The research aimed to evaluate factors associated with development, recovery, and poor outcomes of PPCM and to assess outcomes of bromocriptine therapy. Thus, the data for analysis focused primarily on the specified outcomes of interest. These outcomes included factors related to the recovery of PPCM, such as hypertensive disorders, preeclampsia/eclampsia, primiparity, multiple gestations, caesarean delivery, gestational diabetes, race/ethnicity, baseline New York Heart Association (NYHA) functional class >3, baseline age, baseline serum creatinine, baseline C-reactive protein (CRP), baseline prolactin, baseline LVEF, baseline left ventricular end-systolic diameter (LVESD) baseline left ventricular end-diastolic diameter (LVEDD), baseline fractional shortening (FS), and baseline brain natriuretic peptide (BNP). Outcomes of bromocriptine therapy included major adverse cardiac events (MACE), mortality, PPCM recovery, and change in LVEF.

Quality and risk-of-bias assessment

Following data extraction, the systematic quality assessment of the included studies was independently performed by the five reviewers. Newcastle-Ottawa Scale (NOS) were performed for assessing the quality of observational studies, which comprises eight items categorized into three domains. Based on the total score, if the score ranged from 7 to 9 was classifies as good, score ranged from 4 to 6 as moderate and otherwise as poor, and the Cochrane Risk of Bias tool (RoB) were used for randomized controlled trial (RCT) studies,[18,19] which evaluated the possible risk of bias in various domains. The judgments for each domain were categorized as "low risk," "unclear," or "high risk" of bias.

Outcome measurement

This meta-analysis encompasses three primary outcomes, namely the proportion of baseline risk factors among PPCM patients, the differences in baseline characteristics of PPCM patients who achieved recovery and those who did not, and the outcomes of bromocriptine therapy. We conducted a comparative analysis of each risk factor between recovered and non-recovered PPCM patients, as well as a comparison of the outcomes between bromocriptine and standard heart failure (HF) treatment, which served as the endpoint of our study. Data synthesis and Analysis Quality Assessment Review Manager Software (RevMan 5.4.1) was utilized for conducting the analysis. Continuous data were presented as mean difference (MD) with standard error, along with 95% confidence intervals.

Dichotomous outcomes were expressed as percentages and totals. Inconsistency among studies was assessed using the I-square test (I2) and the P-value of the x2 test.[20] The overall proportion of risk factors for PPCM development was analyzed using a random-effects model of proportional meta-analysis through RStudio (version 4.1.3).

RESULTS AND DISCUSSION

Study selection and study characteristics

Study selection process is summarized in the PRISMA flow diagram shown in Figure 1. The initial search yielded 2,223 studies, and after removing duplicates, 2,166 studies were independently screened by five researchers. A total of 192 potentially relevant studies underwent full-text review. Ultimately, this meta-analysis included 25 studies with 1,651 PPCM patients.[12,14–16,21–41] Among these studies, only one was a RCT.[28] The characteristics of included studies, including methodology, endpoints, and demographic data, are presented in Table 1. Of the total population, 703 patients recovered from PPCM, while 948 patients did not. Regarding the definition of PPCM, which has been explained above. There were variations in the criteria for recovery, considering clinical improvement and an increase in ejection fraction. Only seven studies administered bromocriptine therapy, with daily doses ranging from 2.5 to 5 mg.[12,16,28,29,32,39,41] The follow-up duration for patients varied from 6 to 45 months.

Table 1. Baseline summary of study characteristics

No	Study ID, Year	Country	Study Design	Sample Size	Recovery Patients	Recovery Criteria	Bromocriptine Use	Bromocriptine Dosage
1	Amos, 2006	USA	Cohort Retrospective, Single Center	49	27	Recovery of LV function was defined as an improvement in absolute EF of 50%.	NA	NA
2	Azibani, 2020	South Africa and Germany	Cohort Prospective, Multi Center	151	105	Gain of 10% in LVEF and, LVEF ≥35% at 6 months of follow-up; full left ventricular recovery was defined as LVEF ≥50% at 6 months of follow-up.	97	NA
3	Biteker, 2018	Turkey	Cohort Prospective, Single Center	52	30	Resolution of heart failure symptoms or signs and normalization of LVEF (ejection fraction >50 %)	15	2.5 mg b.i.d for 2 weeks, followed by 2.5 mg o.d for 6 weeks.
4	Blauwet, 2014	South Africa	Cohort Prospective, Single Center	176	30	LVEF ≥55% at 6 months.	NA	NA
5	Duran, 2007	Turkey	Cohort Retrospective, Single Center	33	8	NYHA FC I (New York Heart Association Functional Class) and LVEF above 50%.	NA	NA
6	Ekizler, 2019	Turkey	Cohort Retrospective, Single Center	64	29	Presence of LV ejection fraction (LV EF) >45%.	NA	NA
7	Ersbøll, 2017	Denmark	Cohort Retrospective, Single Center	61	32	LVEF ≥55% after 12 months or at last available follow-up before 12 months	NA	NA
8	Fett, 2005	Haiti	Cohort Prospective, Single Center	98	26	LVEF of 50% or higher, a LVFS of 30% or higher, and NYHA class I, with or without continuation of medications related to HF.	NA	NA
9	Goland, 2011	USA	Cohort Retrospective, Multi Center	187	115	LVEF ≥50% at ≥6 months after the diagnosis.	NA	NA
10	Gürkan, 2017	Turkey	Cohort Retrospective, Single Center	40	19	LV ejection fraction (EF) >45%	NA	NA
11	Haghikia, 2013	Germany	Cohort Prospective, Single Center	115	45	Reaching an LVEF of 55 % and NYHA class I to II.	64	2.5-5mg o.d. for 4 weeks

12	Hilfiker-Kleiner, 2017 (a)	Germany	Randomized Multicenter Clinical Trial	63	NA	NA	31	2.5 mg b.i.d. for the first 2 weeks and 2.5 mg o.d. for another 6 weeks
13	Hilfiker-Kleiner, 2017 (b)	South Africa, Germany, Scotland	Cohort Prospective, Multi Center	34	18	LVEF ≥50% were classified as fully recovered	21	2.5-5mg o.d. (For four weeks)
14	Hoevelmann, 2018	South Africa	Cohort Prospective, Single Center	66	21	LVEF ≥50% was regarded as a full recovery of LV function	19	NA
15	Hoevelmann, 2021	South Africa	Cohort Prospective, Single Center	35	18	LVEDD <55 mm and LVEF ≥ 50% within the 12-month follow-up period	NA	NA
16	Kurbanov, 2020	Republic of Uzbekistan	Cohort Retrospective, Single Center	43	18	Full recovery of LV function (LVEF >55%) and significant regression of CHF symptoms	21	2.5 mg b.i.d for 2 weeks, followed by a decrease to 2.5 mg per day for another 2 weeks
17	Li, 2015	China	Cohort Retrospective, Single Center	71	40	Presence of LVEF >50%	NA	NA
18	Liang, 2020	China	Cohort Retrospective, Single Center	21	10	LVEF ≥50% over at least 6 months' follow-up.	NA	NA
19	Mahowald, 2019	USA	Cohort Retrospective, Single Center	59	22	LVEF ≥55% at the conclusion of follow-up	2	NA
20	Modi, 2009	USA	Cohort Retrospective, Single Center	44	14	LV function recovery as the presence of LVEF of 50% or higher at any follow-up visit after the diagnosis	NA	NA
21	Perveen, 2016	Pakistan	Cohort Prospective, Single Center	22	14	Resolution of HF symptoms and signs and normalization of left ventricular systolic function (LVSF) (EF >50%) and persistent left ventricular dysfunction (PLVD) (EF<50%) at 6 months postpartum.	NA	NA
22	Prasad, 2014	India	Cohort Prospective, Single Center	16	13	LVEF of 50%, LV fractional shortening of 30% or higher and NYHA functional class I with or without continuation of medication related to heart failure.	NA	NA
23	Safirstein, 2012	USA	Cohort Prospective, Single Center	55	43	LVEF ≥50% at the conclusion of follow-up	NA	NA
24	Silwa, 2010	South Africa	Cohort Prospective, Single Center	20	16	NYHA functional class III/IV, or LVEF 35% at 6 months as death, NYHA functional class III/IV, or LVEF 35% at 6 months as previously described.	10	2.5 b.i.d for 2 weeks followed by 2.5 mg daily for 6 weeks in addition to standard heart failure therapy.
25	Tremblay, 2019	Canada	Cohort Prospective, Multi Center	76	NA	NA	8	2.5 mg b.i.d for 2 weeks followed by 2.5 mg daily for 6 weeks

Table 2. Risk of bias assessment of observational studies included in the meta-analysis according to the Newcastle-Ottawa Scale

No	Author, years	Selection			Comparability		Outcome			Overall score	Quality of study
		Representative-ness exposed cohort	Selection of non-exposed cohort	Ascer-tainment of exposure	Outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assess-ment of outcome	Enough follow up time	Adequacy of follow up of cohorts		
1	Amos, 2006	*	*	*	*	**	*	*	*	9	Good
2	Azibani, 2020	*	*		*	*	*	*	*	7	Good
3	Biteker, 2018	*	*		*	*	*	*	*	7	Good
4	Blauwet, 2014	*	*	*	*	*	*	*	*	8	Good
5	Duran, 2007	*	*	*		*	*	*	*	7	Good
6	Ekizler, 2019	*	*	*	*	**	*	*	*	9	Good
7	Ersbøll, 2017	*	*	*	*	**	*	*	*	9	Good
8	Fett, 2005	*	*	*	*	*	*	*	*	8	Good
9	Goland, 2011	*		*	*	*	*	*	*	7	Good
10	Gürkan, 2017	*	*	*	*	*	*	*	*	8	Good
11	Haghikia, 2013	*	*		*	*	*	*	*	7	Good
12	Hilfiker-Kleiner, 2017 (b)	*		*	*	**	*	*	*	8	Good
13	Hoevelmann, 2018	*	*		*	*	*	*	*	7	Good
14	Hoevelmann, 2021	*	*		*	**	*	*	*	8	Good
15	Kurbanov, 2020	*	*	*		**	*	*	*	8	Good
16	Li, 2015	*	*	*	*	**	*	*	*	9	Good
17	Liang, 2020	*	*	*	*	*	*	*	*	8	Good
18	Mahowald, 2019	*	*		*	*	*	*	*	7	Good
19	Modi, 2009	*	*	*	*	*	*	*	*	8	Good
20	Perveen, 2016	*	*		*	**	*	*	*	8	Good
21	Prasad, 2014	*	*		*	**	*	*	*	8	Good
22	Safirstein, 2012	*	*	*	*	**	*	*	*	9	Good
23	Silwa, 2010	*	*	*	*	**	*	*	*	9	Good
24	Tremblay, 2019	*	*	*	*	*	*	*	*	8	Good

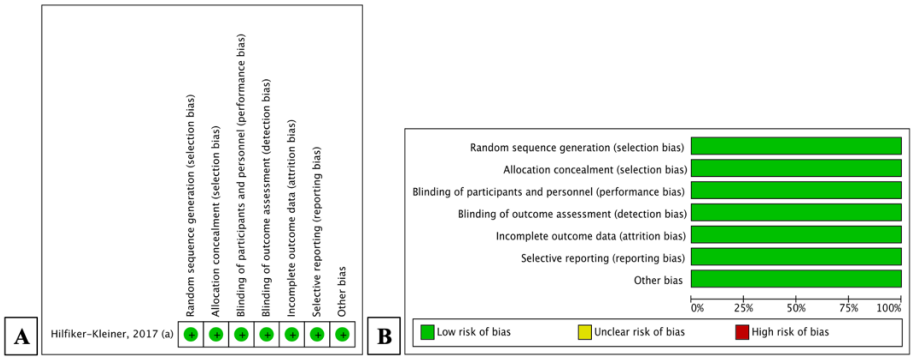

Figure 2. Quality assessment of RCT. (A) Risk of potential bias of individual RCT studies. (B) Risk of bias summary of all RCT studies. RCT: Randomized controlled trial.

Risk-of-bias of included studies

Regarding the quality assessment of the studies using the Cochrane RoB tool, it was observed that 1studies exhibited a low risk of bias, as presented in Figure 2. The quality of included observational studies were all deemed 'Good' with NOS values ranging from 7 to 9. However, two studies did not include elaboration regarding the selection of non-exposed cohort, 9 studies did not include ascertainment of exposure, and 2 studies did not evaluate presence of the outcome at start of study, as presented in Table 2.

Synthesis of results

Proportion of risk factors of PPCM

Figure 3 presents the ten risk factors for PPCM discussed in this study, including smoking habits, history of preeclampsia/eclampsia, hypertension disorder, caesarean delivery, gestational diabetes,

anemia during pregnancy, multiple gestations, primiparity, age >30 years, and race/ethnicity. The risk factor with the highest proportion was a history of caesarean delivery (Proportion = 53%, 95%CI = 41%-66%), followed by anemia during pregnancy as the second highest and age >30 years as the third highest (Proportion = 51%, 95%CI = 38%-65%, and Proportion = 45%, 95%CI = 33%-57%, respectively). On the other hand, the risk factor with the lowest proportion was a history of gestational diabetes (Proportion = 6%, 95%CI = 9%-12%). Meanwhile, the proportions for a history of hypertension disorder and preeclampsia/eclampsia were (Proportion = 32%, 95%CI = 22%-41%, and Proportion = 24%, 95%CI = 15%-34%, respectively).

Maternal factors associated with recovery of PPCM

In terms of the factors associated with recovery from PPCM, the comparison was made between the recovered and non-recovered groups. It was found that African descent/Black race population is associated with an increased risk of non-recovery (RR= 1.82, [1.43-2.31], p <0.001) as shown in Figure 4. Conversely, primiparity (Figure 6) and hypertension (Figure 5) is associated with a decreased risk of non-recovery (RR= 0.81, [0.66–0.99], p=0.04 and RR= 0.73, [0.60–0.88], p=0.001). Additionally, Figure 5 shows that significantly younger age is correlated with an increased risk of non-recovery (MD= -1.04, [-1.82-(-0.27), p= 0.008). Although no significant associations were observed for other parameters, Figure 5 presents a trend towards an increased risk of non-recovery was observed in patients with a history of preeclampsia/eclampsia (RR=1.01) baseline NYHA >3 (RR= 1.08) (all p-values >0.05), and gestational diabetes (RR= 1.71) as presented in Figure 4.

In the comparison of baseline laboratory examinations and echocardiography parameters between the recovered and non-recovered groups, it was found that non-recovered PPCM patients had higher baseline values of serum creatinine (MD= 8.93, [3.67–14.19], p= 0.001), LVEDD (MD= 4.70, [3.70–5.70], p <0.001), and LVESD (MD= 5.29, [3.90-6.67], p <0.001) all shown in Figure 7. Additionally, non-recovered PPCM patients had lower baseline values of LVEF (Figure 7) and FS (Figure 8) (MD= -6.81, [-7.66-(-5.97)], p <0.001 and MD= -4.13, [-5.12-(-3.14)], p <0.001, respectively).

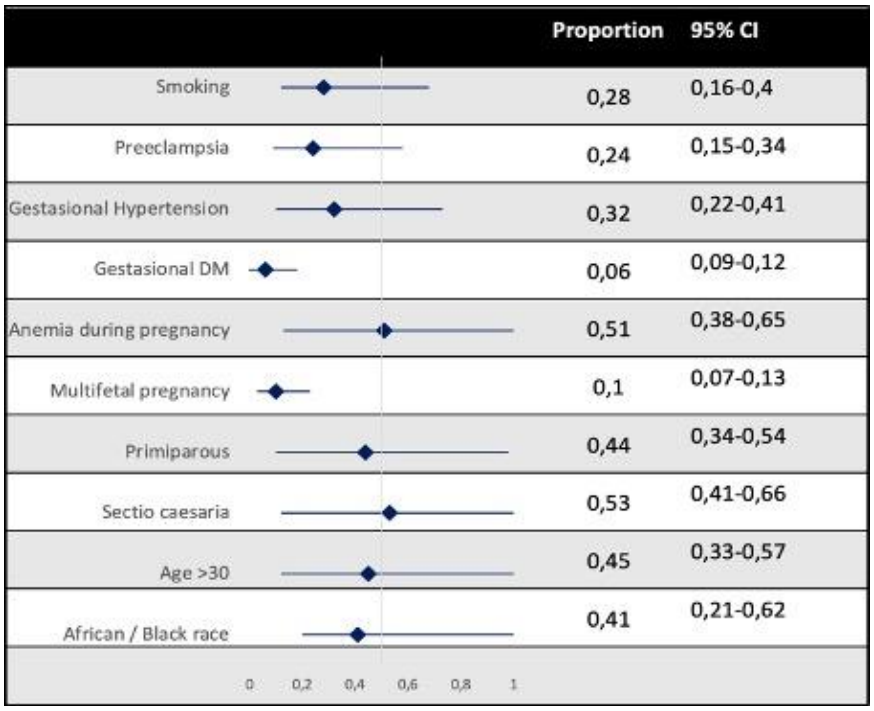

Figure 3. Single-arm forest plot for proportion of risk factors of PPCM

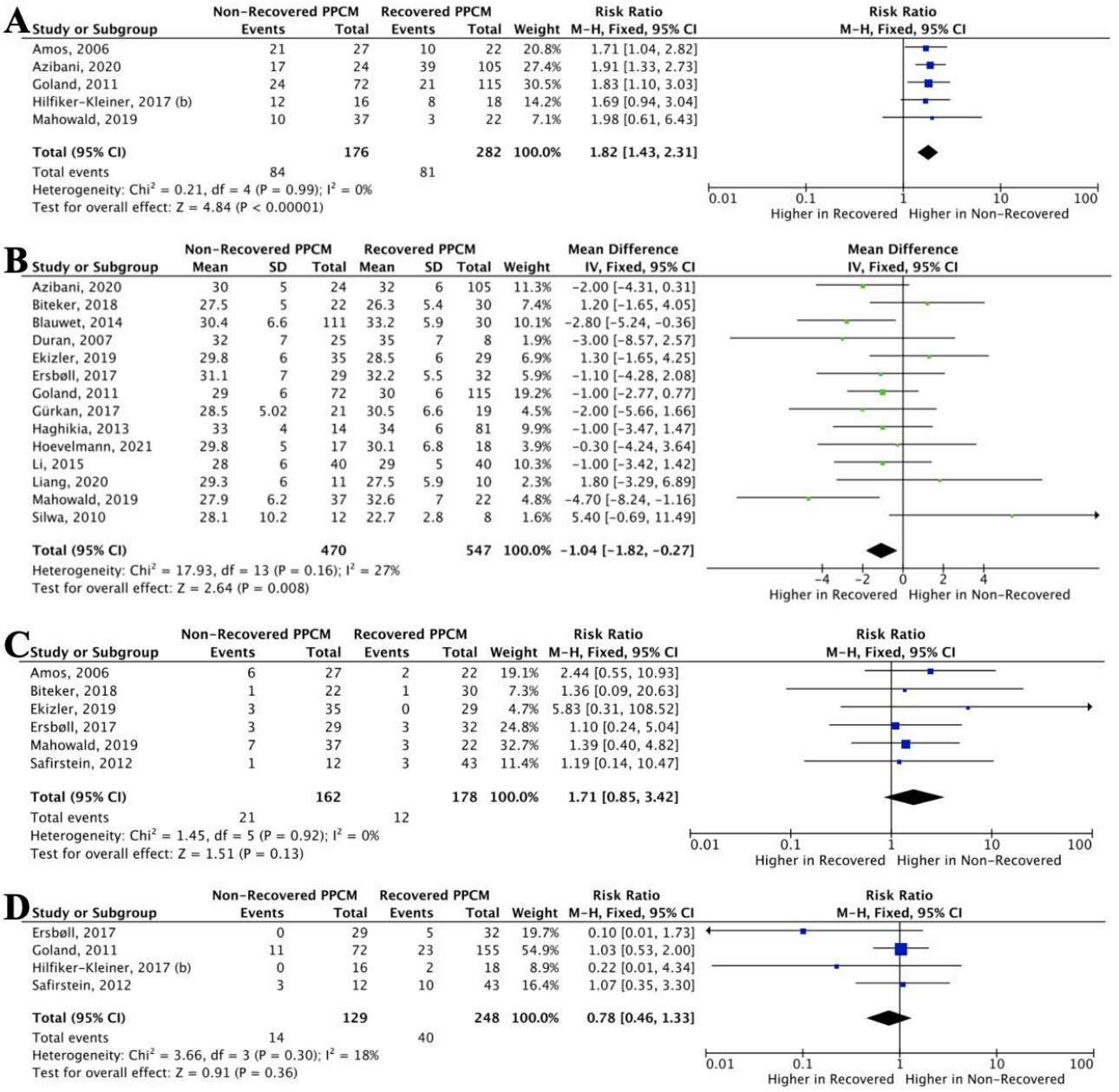

Figure 4. Forest plot of maternal factors associated with recovery PPCM. (A) Risk ratio of African ethnicity or black race. Test for overall effect: Z= 4.84 (p <0.001). heterogeneity: I2 = 0%. (B) Risk ratio off baseline age. Test for overall effect: Z= 2.64 (p=0.008). heterogeneity: I2 = 27%. (C) Risk ratio off history of gestational diabetes. Test for overall effect: Z= 1.51 (p=0.13). heterogeneity: I2 = 0%. (D) Risk ratio off multiple gestation. Test for overall effect: Z= 0.91 (p=0.36). heterogeneity: I2 = 18%.

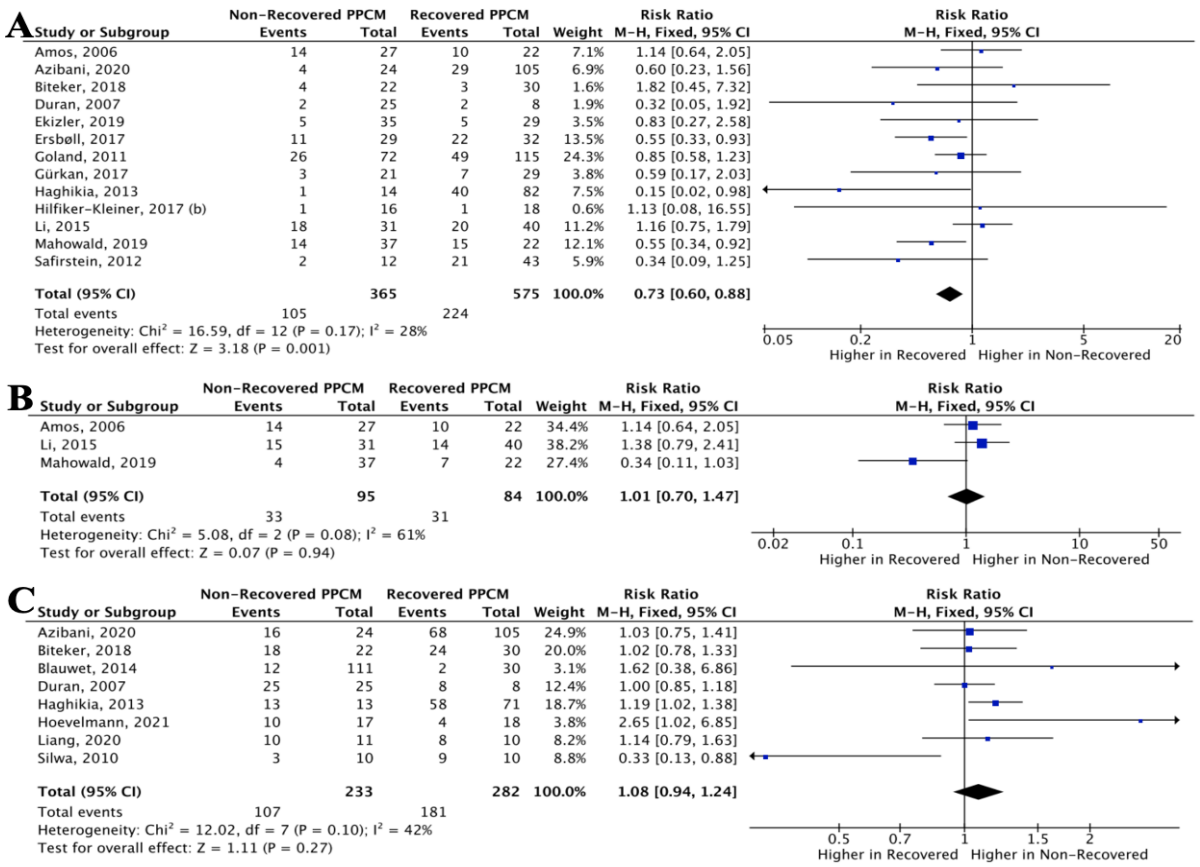

Figure 5. Forest plot of maternal factors associated with recovery PPCM. (A) Risk ratio of hypertension disorder. Test for overall effect: Z= 3.18 (p=0.001). heterogeneity: I2 = 28%. (B) Risk ratio off history of preeclampsia or eclampsia. Test for overall effect: Z= 0.07 (p=0.94). heterogeneity: I2 = 61%. (C) Risk ratio off baseline NYHA $\geq$ 3. Test for overall effect: Z= 1.11 (p=0.27). heterogeneity: I2 = 42%. NYHA: New York Heart Association

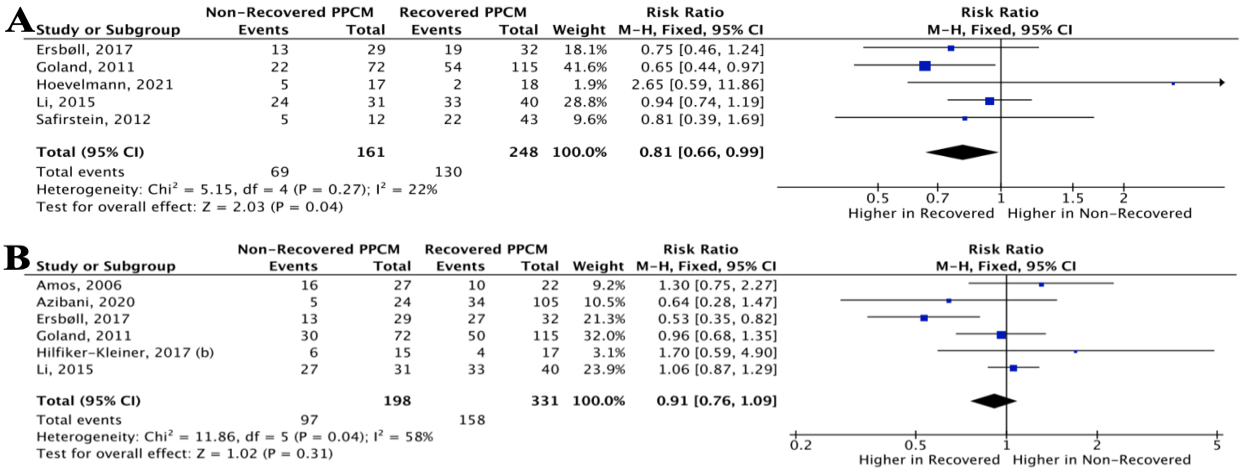

Figure 6. Forest plot of maternal factors associated with recovery PPCM. (A) Risk ratio of primiparity. Test for overall effect: Z= 2.03 (p=0.004). heterogeneity: I2 = 22%. (B) Risk ratio off history of caesarean delivery. Test for overall effect: Z= 1.02 (p=0.31). heterogeneity: I2 = 58%.

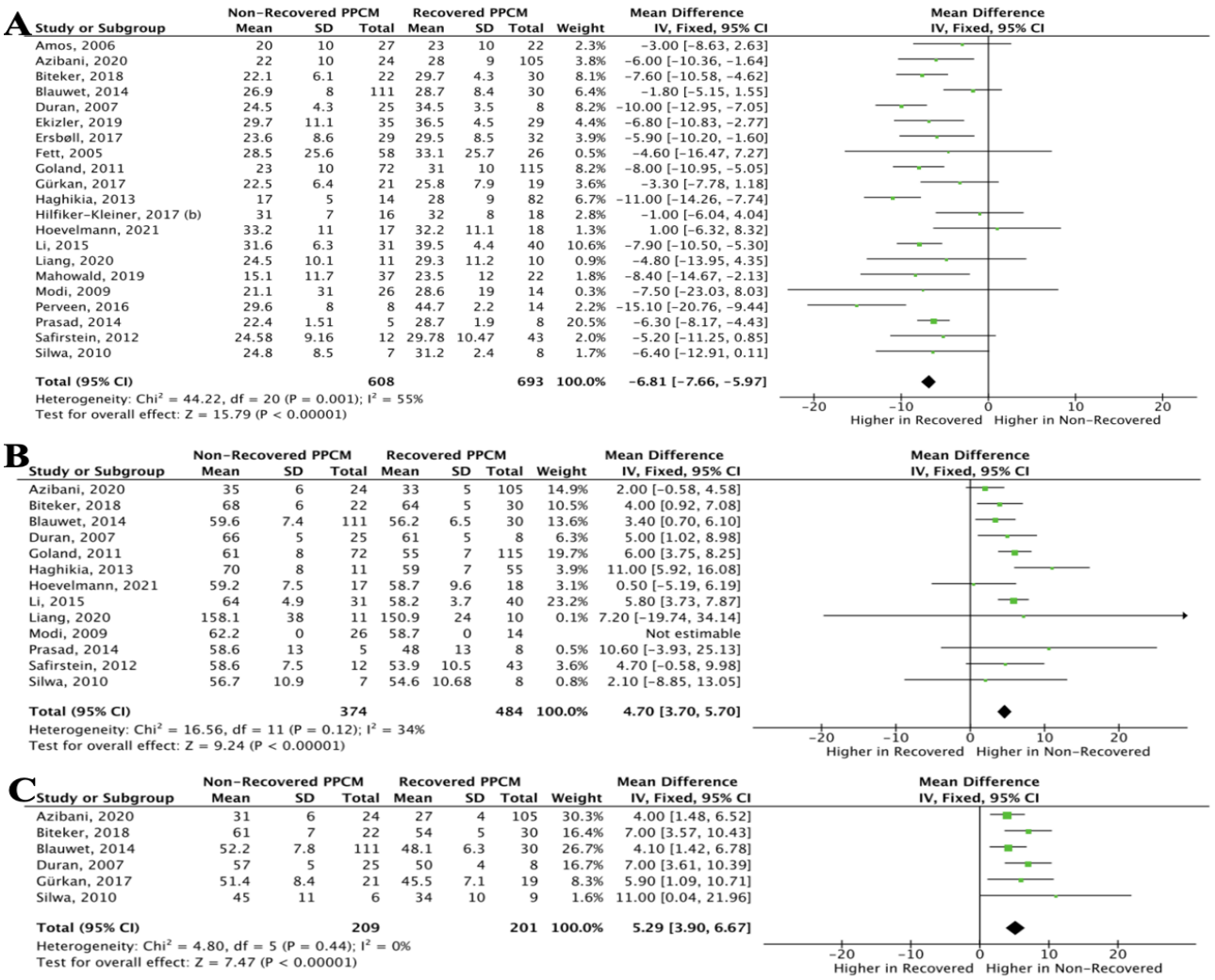

Figure 7. Forest plot of maternal factors associated with recovery PPCM. (A) Mean difference of baseline LVEF. Test for overall effect: Z= 15.79 (p <0.001). heterogeneity: I2 = 55%. (B) Mean difference of baseline LVEDD. Test for overall effect: Z= 9.24 (p <0.001). heterogeneity: I2 = 34%. (C) Mean difference of baseline LVESD. Test for overall effect: Z= 7.47 (p <0.001). heterogeneity: I2 = 0%.

Bromocriptine therapy outcomes

The use of bromocriptine in PPCM patients yielded favorable outcomes (Figure 9), as evidenced by a significant reduction in the risk of non-recovered PPCM (RR= 0.70, [0.55-0.90], p= 0.005), MACE (RR= 0.38, [0.22-0.65], p= 0.0004), and all-cause mortality (RR= 0.32, [0.15-0.66], p= 0.002). Furthermore, a significant increase in LVEF was observed in the group receiving bromocriptine therapy (MD=5.52, [1.48-9.57], p=0.007).

This study included twenty-four observational studies and one RCT. The key findings of this study revealed that the highest proportion of risk factors for PPCM was a history of caesarean delivery and anemia during pregnancy, while a history of gestational diabetes was the least commonly encountered risk factor in PPCM patients. As expected, African/Black ethnicity increased the risk of non-recovery in PPCM patients, whereas primiparity decreased the risk of non-recovery. Interestingly, a history of hypertension disorder was found to decrease risk of non-recovery in PPCM.

Thus far, pathogenesis of PPCM remains a subject of controversy, with various theories proposed encompassing genetic influences, nutritional deficiencies, hemodynamic responses to pregnancy, inflammatory processes, and heightened oxidative stress.[1,16,26] Noteworthy risk factors implicated in PPCM develop-

ment include maternal age exceeding 30 years, African/Black ethnicity, multiple gestations, as well as a history of preeclampsia and hypertension.[7] Remarkably, PPCM patients exhibit a higher rate of recovery compared to other forms of heart failure characterized by reduced LVEF, typically manifesting within the initial 3-6 months postpartum.[42]

Caesarean delivery emerges as the highest proportionate risk factor in this study, likely attributable to the escalating global incidence of this procedure. The World Health Organization (WHO) reports the current rate of caesarean delivery to be 1 in 5 of all childbirths, with projections indicating a continued upward trend in

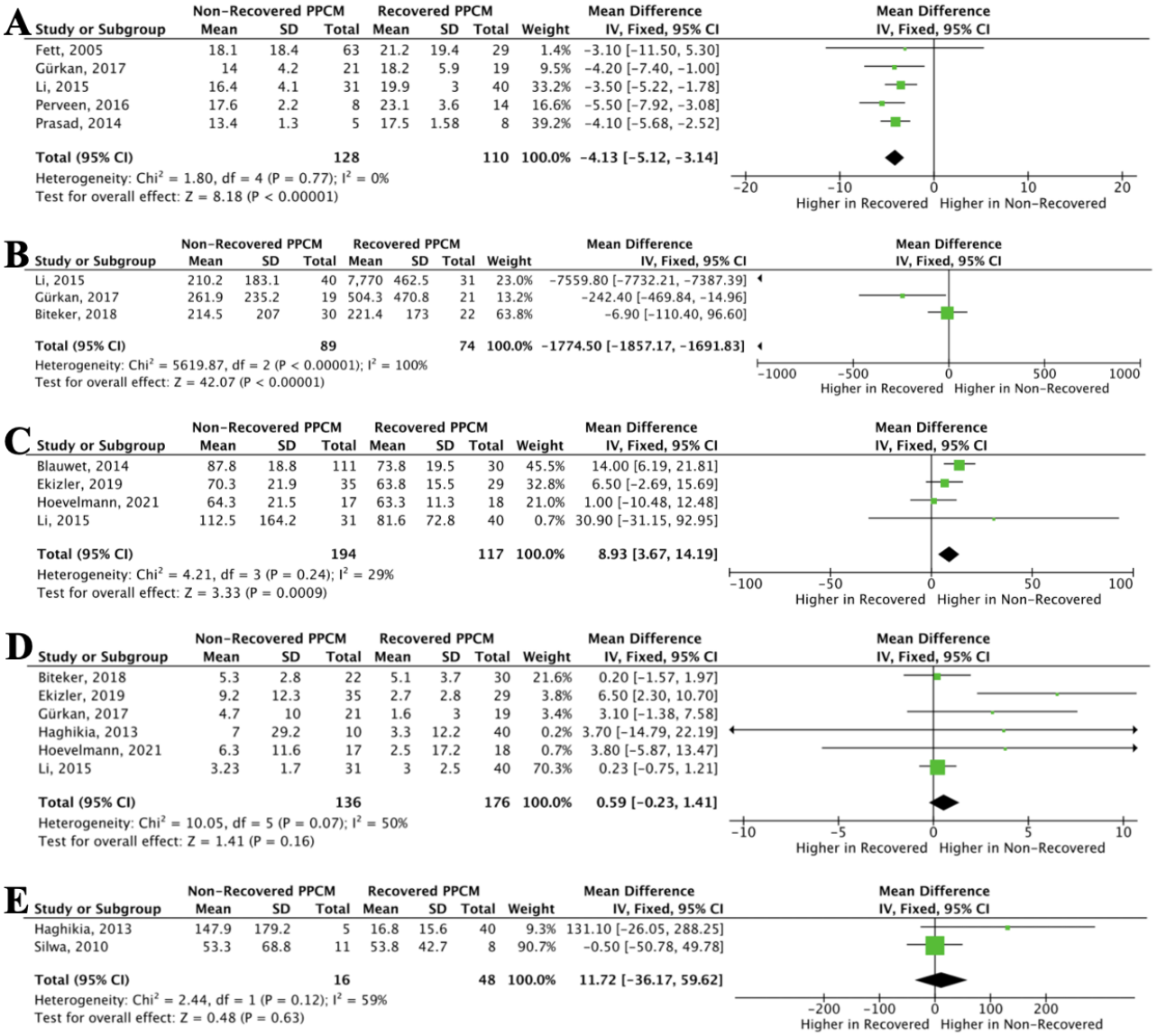

Figure 8. Forest plot of maternal factors associated with recovery PPCM. (A) Mean difference of baseline FS. Test for overall effect: Z= 8.18 (p <0.001). heterogeneity: I2 = 0%. (B) Mean difference of baseline BNP. Test for overall effect: Z= 42.07 (p <0.001). heterogeneity: I2 = 100%. (C) Mean difference of baseline creatinine serum. Test for overall effect: Z= 3.33 (p=0.0009). heterogeneity: I2 = 29%. (D) Mean difference of baseline CRP. Test for overall effect: Z= 1.41 (p=0.16). heterogeneity: I2 = 50%. (E) Mean difference of baseline prolactin. Test for overall effect: Z= 0.48 (p=0.63). heterogeneity: I2 = 59%. CRP: C-reactive protein.

the coming decades.[43] Furthermore, the heightened incidence of PPCM following caesarean delivery may be attributed to immunological reactions triggered by this surgical intervention, involving a higher degree of cellular interaction between the mother and the baby.[12] In addition to caesarean delivery, anemia during pregnancy also presents as a significant risk factor with a proportion exceeding 50%. The underlying mechanism behind this association lies in the increased heart rate and stroke volume observed in cases of anemia, leading to cardiac remodeling characterized by left ventricular hypertrophy and dilation as a compensatory response to the augmented cardiac workload.[44]

The findings of this study reveal that individuals of African/black ethnicity are at an increased risk of non-recovery in PPCM cases. The reasons underlying the disparity in recovery outcomes between black women and white women remain unclear and may be influenced by genetic factors or lower social and economic conditions.[45] Another contributing factor is that black patients are more likely to exhibit eccentric hypertrophy compared to concentric hypertrophy, which is associated with inflammation, cardiomyocyte death, and replacement fibrosis. Consequently, the difference in recovery rates may be attributed to a greater extent of cardiac tissue loss and replacement fibrosis among individuals of African/black ethnicity.[22]

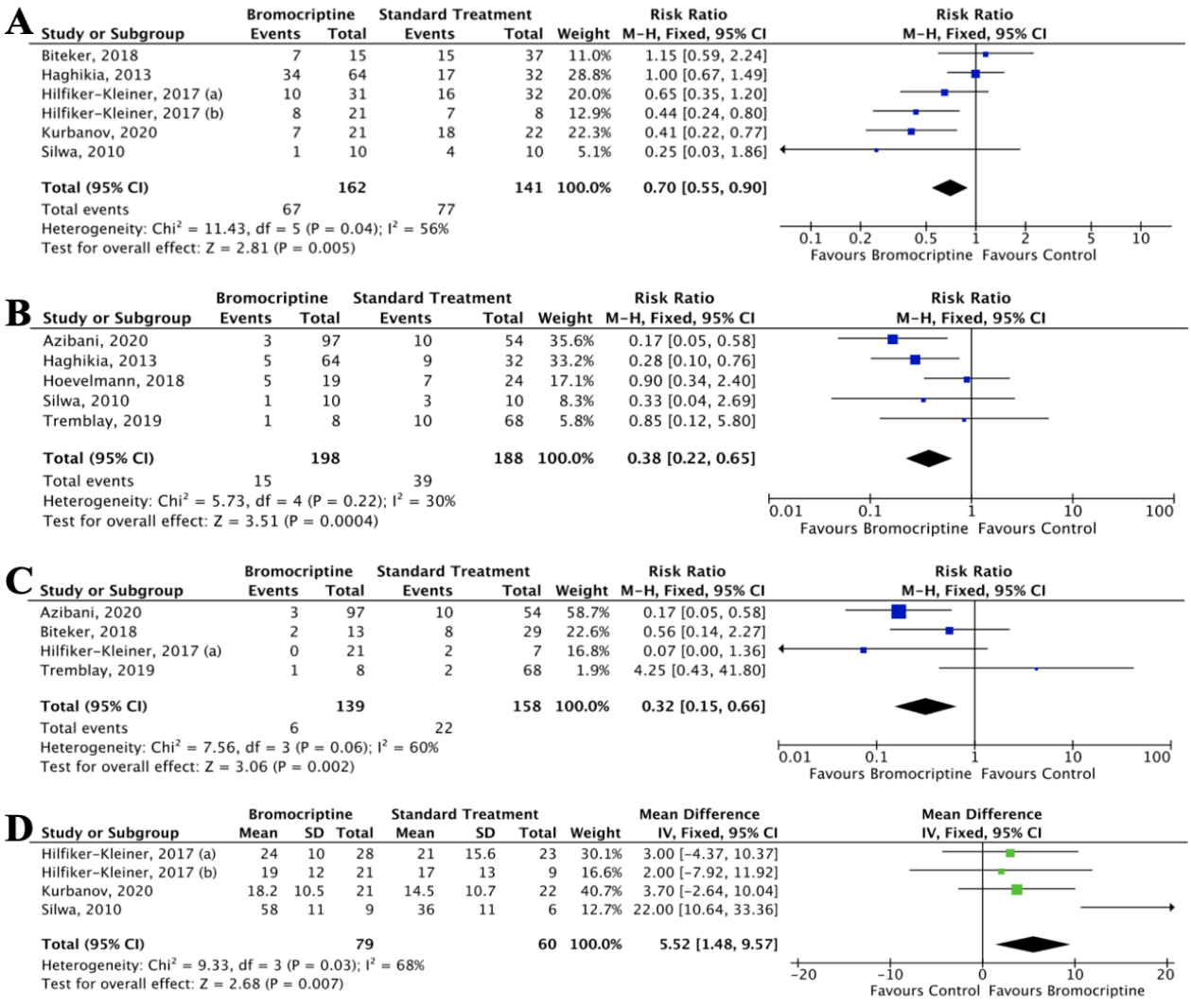

Figure 9. Forest plot of outcome of bromocriptine therapy. (A) Risk ratio of PPCM recovery. Test for overall effect: Z= 2.81 (p=0.005). heterogeneity: I2 = 56%. (B) Risk ratio off major adverse cardiac outcome. Test for overall effect: Z= 3.51 (p=0.0004). heterogeneity: I2 = 30%. (C) Risk ratio off all-cause mortality. Test for overall effect: Z= 3.06 (p=0.002). heterogeneity: I2 = 60%. (D) Mean difference of change value of LVEF. Test for overall effect: Z= 2.68 (p=0.007). heterogeneity: I2 = 68%.

On the contrary, hypertension disorder actually increases the risk of recovery in PPCM patients, and the early administration of beta-blockers is suspected to play a role in this condition.[25] Furthermore, this study found that being over the age of 30 increases the risk of recovery in PPCM patients. To date, age has rarely been reported as a factor influencing recovery in PPCM patients, as the theories supporting this claim are still unclear. However, it is possible that a more severe immune response in younger individuals leads to more extensive myocardial damage in PPCM patients.[15]

The observed significance of echocardiography parameters in relation to non-recovery in this study is not unexpected, as it aligns with the underlying pathophysiological mechanisms. The deteriorated values of LVEF, FS, LVESD, and LVEDD reflect the extent of cardiac remodeling in the studied population, indicative of more advanced disease progression.[46] These findings suggest that this particular population may require an extended duration to achieve favorable improvements in LVEF. Moreover, the correlation between increased LVEDD and major adverse cardiac events identified in follow-up echocardiography of other heart failure conditions further supports the clinical relevance of these parameters.[47] Despite optimal medical therapy, the presence of persistently high LVESD as independent predictor of ongoing LVEF impairment in context of transitioning from heart failure with reduced ejection fraction (HFrEF) to heart failure with improved ejection fraction (HFimpEF), underscores the prognostic value of echocardiographic assessments in assessing disease progression and response to treatment. These insights shed light on the intricate interplay between cardiac structural alterations and functional recovery in heart failure patients.[48]

The utilization of bromocriptine as an adjunct therapy in this study demonstrated superior outcomes compared to those receiving standard HF therapy alone. Bromocriptine is known to suppress prolactin secretion and prevent cardiac myocyte apoptosis. One of the underlying mechanisms of PPCM involves an increased oxidative stress leading to the activation of cathepsin D, which subsequently cleaves prolactin into a 16 kDa anti-angiogenic and pro-apoptotic form. This form is believed to induce endothelial inflammation, disrupt cardiomyocyte metabolism, and impair myocardial contractility, ultimately contributing to the development of PPCM. Therefore, the use of bromocriptine emerges as a potential treatment modality in PPCM patients, as it can counteract these pathological processes. By targeting the prolactin-related cascade, bromocriptine holds promise in mitigating the progression of PPCM and improving patient outcomes.[40]

Strengths and limitations

In our study, we conducted a comprehensive analysis involving echocardiography and laboratory parameters in PPCM patients. Additionally, in order to circumvent the detrimental impact of breastfeeding restriction on newborns, we included factors associated with non-recovery with the outcomes of bromocriptine therapy, enabling a more selective selection of suitable patients for the administration of bromocriptine. However, our study also has inherent limitations. Limitations of our study include the absence of separate analysis based on study types, as there was only one RCT included. Furthermore, there were limited number of studies regarding certain outcomes, resulting in lower statistical power. There was also no long-term analysis of the side effects of bromocriptine on patients or newborns. Furthermore, dosage variations among the included studies hinder the determination of the optimal dosage for PPCM therapy.

CONCLUSION

The study revealed significant associations between particular demographic and clinical factors and the prognosis of PPCM. Younger age at pregnancy, absence of hypertension, black race/ethnicity, and multiparity are key determinants to indicate a less favorable prognosis for recovery from PPCM. Additionally, bromocriptine therapy demonstrates notable benefits in mitigating adverse events in PPCM patients. By identifying the proportion of risk factors associated with the development of PPCM, it is hoped that primary prevention, such as avoiding anemia, considering alternatives to general anesthesia, limiting excessive fluid infusion in pregnant women, as well as increasing awareness through tighter monitoring in groups with unavoidable risk factors is crucial. The results of this meta-analysis, which discovered factors linked to recovery and assessed the validity of bromocriptine outcomes, can serve as a guide in identifying patients requiring bromocriptine therapy and, with the results of the discovery of factors associated with recovery and validity of bromocriptine outcomes, this meta-analysis can be used as a consideration to sort out which patients need bromocriptine treatment therapy and populations that can pursue regular heart failure therapy without bromocriptine. This consideration is important due to the potential side effects of bromocriptine, including restrictions on breast milk production, which may be detrimental to the growth and development of infants. To further understand the underlying mechanisms and strengthen therapeutic approaches, future research should concentrate on verifying and expanding upon these findings.

DISCLOSURES

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Conflict of interest

The authors report 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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REVIEW ARTICLE

The promise and challenges of Artificial Intelligence-Large Language Models (AI-LLMs) in obstetrics and gynecology

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ABSTRACT

The introduction of Artificial Intelligence through Large Language Models (AI-LLM) into medicine holds great promise for improving patient care and medical education, especially in obstetrics and gynecology. AI-LLM can significantly improve diagnostic accuracy and treatment efficiency by utilizing large medical databases, which is especially useful for dealing with rare diseases that are difficult to document or understand by human practitioners alone. In addition, AI-LLM can provide informed patient care recommendations by analyzing large amounts of data and providing insights based on unique patient profiles, with the added benefit of being accessible 24/7 via the internet. This constant availability ensures that patients receive prompt information and assistance as needed.

In the field of education, AI-LLMs enhance the learning experience by incorporating interactive simulations into the curriculum, improving medical students' and professionals' practical knowledge. They also ensure that educational materials are always up-to-date reflecting the most recent research and worldwide medical standards. This access latest information from global resources helps to bridge the educational gap, making advanced knowledge more accessible to learners regardless of their geographic location.

However, the introduction of AI-LLMs is not without challenges. Ethical issues, such as data privacy and the risk of overreliance on technology, must be addressed. Effective management of these concerns necessitates collaboration among medical professionals, technological experts, academics, hospital committees, and representatives of patients. This multidisciplinary teamwork is vital for upholding ethical norms and preserving patient dignity and respect. AI-LLMs can considerably improve both patient care and medical education in obstetrics and gynecology provided they are appropriately balanced with innovation and ethics.

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Highlights:

1. The article highlights how Artificial Intelligence with Large Language Models (AI-LLMs) greatly improves diagnosis and treatment personalization in obstetrics & gynecology, and also enhances medical education through interactive simulations and up-to-date learning materials.
2. The article also discusses the ethical issues linked to AI, emphasizing the need for cooperation among different stakeholders to use AI responsibly in medicine, focusing on protecting data privacy and minimizing reliance on technology.

INTRODUCTION

In modern medicine, the use of technology, particularly artificial intelligence (AI), has grown dramatically in recent decades. AI in the form of Large Language Models (LLMs) such as ChatGPT, Gemini, and Copilot has demonstrated significant promise in supporting the healthcare sector, including patient care and medical education.[1-3] The study and application of AI-LLMs in medicine provide numerous benefits while also posing problems for practitioners and educational institutions.

AI-LLM has gained popularity among the general public due to its ability to provide answers that closely resemble the expertise of a trained doctor or healthcare professional. This capability significantly improves the accessibility and reliability of medical information. One important advantage of AI-LLMs is their 24/7 internet connectivity, which allows them to meet human needs globally, regardless of time or location. Whereas the "Google doctor" phenomenon of the previous decade was considered quite limited and tended to contradict doctors' decisions, AI-LLM has gone a step further with improved quality and accuracy of the answers generated. As such, AI-LLM has the potential to play an important role in healthcare, especially two key aspects that require careful utilization and management: patient care and medical education. By effectively utilizing AI-LLM, healthcare providers can offer more accurate diagnoses and personalized treatment plans, while enhancing the educational experience for medical students and professionals, ensuring they have access to the latest knowledge and training tools.

THE ROLE OF AI IN OBSTETRICS & GYNECOLOGY PATIENT CARE

In the context of general patient care, AI-LLM can be utilized to improve the quality of diagnosis and the efficiency of the treatment.[4,5] One of the most promising features is the use of AI-LLM to support diagnosis systems. By accessing vast medical databases and up-to-date information on diseases, AI-LLM can provide fast and accurate diagnosis recommendations to doctors. This is especially helpful in identifying rare and complex diseases that medical practitioners may not often encounter.

Meanwhile, AI-LLM can also be used for treatment personalization.[6] By integrating individual patient data, such as medical history, genetics, and environmental factors, AI-LLM can assist doctors in designing treatment plans that are better suited to each patient's specific needs. This technology opens up opportunities for more focused and result-oriented care, which can ultimately improve patient health outcomes.

A recent study revealed that ChatGPT is a powerful tool that has the potential to enhance obstetric patient care.[7,8] Similar to the previous study, the same AI-LLM is able to correctly answer questions in obstetric gynecology up to 90%.[9] Another study reports that ChatGPT has the potential to serve as a valuable aid for healthcare professionals in refining differential diagnoses.[10] and advise the general public on maternity preparedness information.[11] Interestingly, AI-LLM also plays a role in the development of patient monitoring systems. For example, AI-based systems can provide analysis of laboratory results, and translate doctor's notes including recommending personalized health.[12] If this is applied in the scope of obstetrician-gynecology patients, it will help the doctor's task in managing patients more comprehensively and effectively. This not only improves patient adherence to treatment plans but also helps in proactive patient health management.

Our study results also show the amazing ability of ChatGPT, Gemini, and Copilot to provide adjuvant therapy recommendations for endometrial cancer.[13] Although there are significant differences in the recommendation of therapies based on location, the expertise of each AI-LLM is convincing in addressing the complex issue of endometrial cancer. It is certainly not impossible in the future for AI to help doctors with CTG and ultrasound interpretation.

Furthermore, our search on PubMed (May 6th, 2024) also yielded 40 works of literature in 2 years (2023-2024) using the search words "ChatGPT" and "obstetric". This phenomenon will continue to grow every day and become a hot trend. Around the same time, Google launched Med-Gemini aimed at improving the quality of healthcare through better diagnosis, more efficient research discovery, wider access to information, and overall advancements in the use of AI in the medical field.[14] This shows the interest of researchers and clinicians in involving AI-LLM as a tool for diagnosis, patient management as well as evaluation in improving better patient care. As a concise and comprehensive overview, the promising opportunities of the role of AI-LLM in the field of obstetric gynecology are set out in the following illustration (Figure 1).

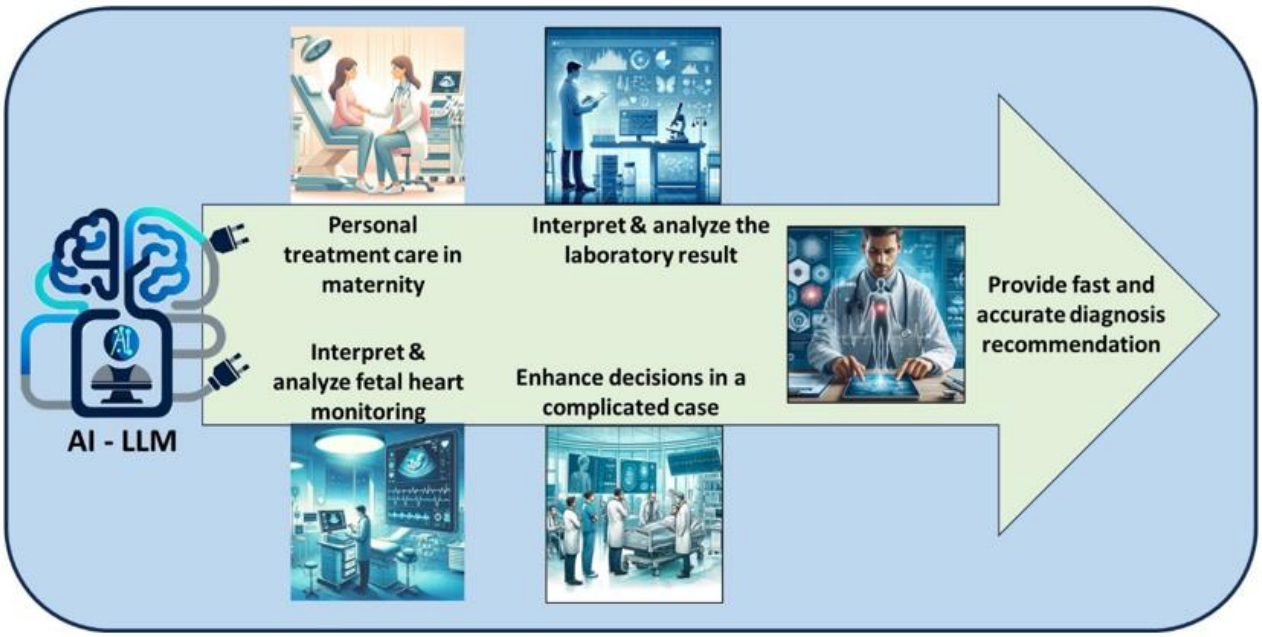

Figure 1. The role of AI-LLM in obstetric gynecology. There are at least 5 areas where performance can be improved. There is a huge opportunity for AI-LLM in its role in gynecologic obstetric services in the future.

AI ROLES IN MEDICAL EDUCATION

In terms of medical education, AI-LLM offers the potential to transform the way medical education is delivered and acquired. AI-LLM can be integrated into medical curricula to provide realistic and interactive simulations, helping medical students learn diagnosis and treatment in a risk-free environment.[15,16] These simulators allow medical students to practice diagnosis and treatment in a safe setting, considerably increasing their practical abilities without jeopardizing actual patients. For example, AI-LLMs can provide virtual patient situations in which students can practice communication skills, medical decision-making, and clinical interactions. These scenarios can simulate a wide range of medical situations and patient responses, giving students a varied and complete teaching experience.

Furthermore, AI-LLM can also be a valuable tool in the ongoing training of doctors and healthcare workers. With the ability to update current information, AI-LLM can provide educational materials that are always up-to-date and relevant to the latest developments in medicine. In terms of enhancing practical ability, AI-LLM provides features where students can repeatedly practice clinical procedures and skills, leading to mastery in the pursuit of competencies. For example, AI-LLM can guide students through the diagnostic process, interpret test results, and suggest possible treatment plans. This hands-on approach helps students gain confidence in their clinical abilities before they face actual patients. This is especially important in the rapidly changing medical world, where up-to-date knowledge is essential for effective medical practice.

In addition, AI-LLM is able to adjust to the pace and learning style of each learner. By providing personalized feedback and adjusting the complexity of the simulation based on the student's progress, AI-LLM ensures that every student can optimize their educational journey. This personalized approach is especially beneficial for students who may need more time to understand certain concepts or who excel in certain areas and need advanced challenges.

AI-LLM can also facilitate access to learning resources. Students and healthcare professionals from under-resourced regions can gain access to world-class educational materials that may not be available in their location. This helps reduce disparities in the quality of medical education between regions and countries, and in turn improves healthcare standards globally.

SOME OTHER POTENTIALS OF AI IN MEDICAL EDUCATION

AI-LLM is not only beneficial for medical students but also serves as a valuable resource for the continuous

education of practicing doctors and healthcare workers. The medical field is characterized by rapid advancements, and staying updated with the latest research and treatment guidelines is crucial for effective practice. It can provide up-to-date educational materials that reflect the latest developments in medicine, ensuring that healthcare professionals have access to current and relevant information.

For instance, AI-LLM can assist in continuing medical education (CME) by offering modules on new treatment protocols, emerging diseases, and advancements in medical technology. This ongoing training helps healthcare professionals maintain their competence and stay informed about innovations that can improve patient care. Additionally, AI-LLM can facilitate the completion of mandatory CME credits required for maintaining medical licensure, making the process more efficient and accessible.

In under-resourced regions, where access to advanced medical training and resources is limited, AI-LLM can provide world-class educational materials and simulations. This accessibility helps bridge the gap between different regions and ensures that medical students and professionals worldwide receive consistent and high-standard education.[17] By making these resources available online, AI-LLM enables learners from remote and underprivileged areas to access the same training as those in well-equipped institutions. This not only improves the quality of medical education globally but also contributes to better healthcare standards. As a result, disparities in medical education and healthcare delivery can be reduced, leading to more equitable health outcomes.

AI-LLM's capability to offer personalized learning experiences is another transformative aspect of its integration into medical education. Each student has unique learning needs and preferences, and AI-LLM can tailor educational content to suit these individual requirements.[18] By analyzing a student's performance and learning patterns, AI-LLM can recommend specific modules, adjust the difficulty level of simulations, and provide targeted feedback. This level of personalization ensures that students remain engaged and motivated throughout their educational journey. It also helps identify areas where a student may need additional support, allowing for timely intervention and remediation. Personalized learning experiences facilitated by AI-LLM lead to more effective education and better preparation for real-world clinical practice.

AI-LLM also ensures that learners as well as practitioners have real-time access to the most recent medical data. Given the quick pace of medical breakthroughs, it is critical to stay up to date on new research findings, clinical guidelines, and therapeutic improvements. AI-LLM can give learners and practitioners quick access to up-to-date publications and evidence-based procedures, keeping them on the cutting edge of medical knowledge. This real-time access is especially useful in healthcare settings, where timely information might influence patient outcomes. For example, a doctor confronting a complex case can swiftly use AI-LLM to obtain the most recent and relevant information, allowing for more accurate and effective decision-making. This integration of AI-LLM into daily practice ensures that healthcare providers can deliver the best possible care based on the latest evidence.

CHALLENGES AND ETHICAL CONSIDERATIONS

While AI-LLM technology has many advantages, it also poses substantial problems and ethical concerns that must not be neglected. One of the most important challenges is data privacy and security.[19] Health data is among the most sensitive sorts of information, and using AI to manage such data requires extraordinary vigilance to minimize breaches of patient privacy. Ensuring that patient data remains secret and secure is critical, and any breaches might have major ramifications for both patients and healthcare professionals.

Another major concern is the risk of over-reliance on technology. Clinical skills and medical decision-making necessitate substantial training, experience, and the nuanced understanding that comes with hands-on practice.[20] AI, while powerful, cannot completely replace the skill and judgment of educated medical practitioners. The use of technological technologies should not lessen the importance of interpersonal skills and clinical knowledge among healthcare providers. Instead, AI should be considered as a compliment to human capabilities, rather than a replacement for them.

As a result, while AI-LLM has the potential to improve healthcare, its adoption should be approached with caution. Protecting data privacy and security, as well as maintaining the primacy of human clinical expertise, is crucial to ensuring that AI benefits are realized without violating ethical standards.

Another obstacle to be aware of is AI-LLM's flaws and misinterpretations, which can manifest as hallucinations, fabrications, and even faults in supplying reference sources.[21,22] As a result, human doctors and health specialists are required and capable of validating

AI-LLM results. Furthermore, this advanced technology must be regulated by giving suitable commands or prompts based on human needs.

Finally, AI-LLM integration in patient care and medical education offers many exciting possibilities to improve efficiency and effectiveness in both fields. However, there must be ongoing efforts to address the challenges and ensure that these technologies are used ethically and responsibly. There are at least 5 representative stakeholders who must collaborate to come up with an agreement that will be followed up by policymakers. The 5 representatives are expert doctors, AI and technology experts, academics, hospital leaders, and patient representatives.

STEPS TO PUT AI-LLM IN ITS PROPER PLACE

Here is a concept for putting the AI-LLM in the proper seat to improve patient care and medical education (Fig 2). The concept comprises of five technical moves for placing the AI-LLM in the appropriate position.

AI-LLM can serve as a clinical assistant and case manager, seamlessly linked to the clinical system. In this role, it can manage patient data, schedule appointments, and provide reminders for follow-up care. By automating administrative tasks, AI-LLM allows healthcare providers to focus more on direct patient care. Additionally, it can analyze patient records and identify trends or anomalies, facilitating early intervention and personalized care plans.[23] This proactive approach enhances patient outcomes by ensuring timely and accurate responses to evolving health conditions.

Additionally, AI-LLM can function as a diagnostic tool, improving the efficiency and accuracy of medical diagnoses. By processing vast amounts of clinical data, AI-LLM can identify patterns and correlations that might be missed by human practitioners.[24] For example, it can analyze medical images, lab results, and patient histories to suggest potential diagnoses and recommend further tests. This capability not only supports healthcare providers in making informed decisions but also helps in reducing diagnostic errors. The integration of AI-LLM into diagnostic processes can lead to faster, more precise identification of medical conditions, ultimately enhancing patient care.

Moreover, chatbots can aid in developing treatment strategies based on current evidence and patient preferences. By continuously reviewing the latest medical research and clinical guidelines, AI-LLM ensures that treatment plans are up-to-date and aligned with best practices. It can also incorporate patient-specific factors, such as genetics, lifestyle, and preferences, to tailor treatment plans. This personalized approach not only improves the effectiveness of treatments but also enhances patient satisfaction by involving them in their care decisions. AI-LLM's ability to synthesize complex data into actionable insights supports clinicians in making well-informed treatment choices.

Meanwhile, incorporating AI-LLM into medical education and training programs can revolutionize how healthcare professionals are trained. AI-LLM can simulate challenging clinical scenarios in a safe and controlled environment, allowing students to practice and hone their skills. It can provide instant feedback and adapt to each student's learning pace and style, identifying areas that require additional attention. Furthermore, AI-LLM ensures that students and faculty have rapid access to the latest journals, case studies, and research findings, keeping them informed about advancements in medical science. This dynamic and interactive learning model fosters a deeper understanding of complex medical concepts and prepares students for real-world clinical challenges.

Ethical and security issues are critical considerations in the integration of AI-LLM into healthcare. Ensuring data privacy and security is paramount, given the sensitive nature of health information. A consensus among various stakeholders, including healthcare providers, policymakers, and technology experts, is necessary to establish robust guidelines and regulations. Ethics training should be incorporated into medical curricula to educate future healthcare professionals about the importance of data security and patient confidentiality. This training will equip them with the knowledge and skills to navigate ethical dilemmas and ensure compliance with data protection regulations.

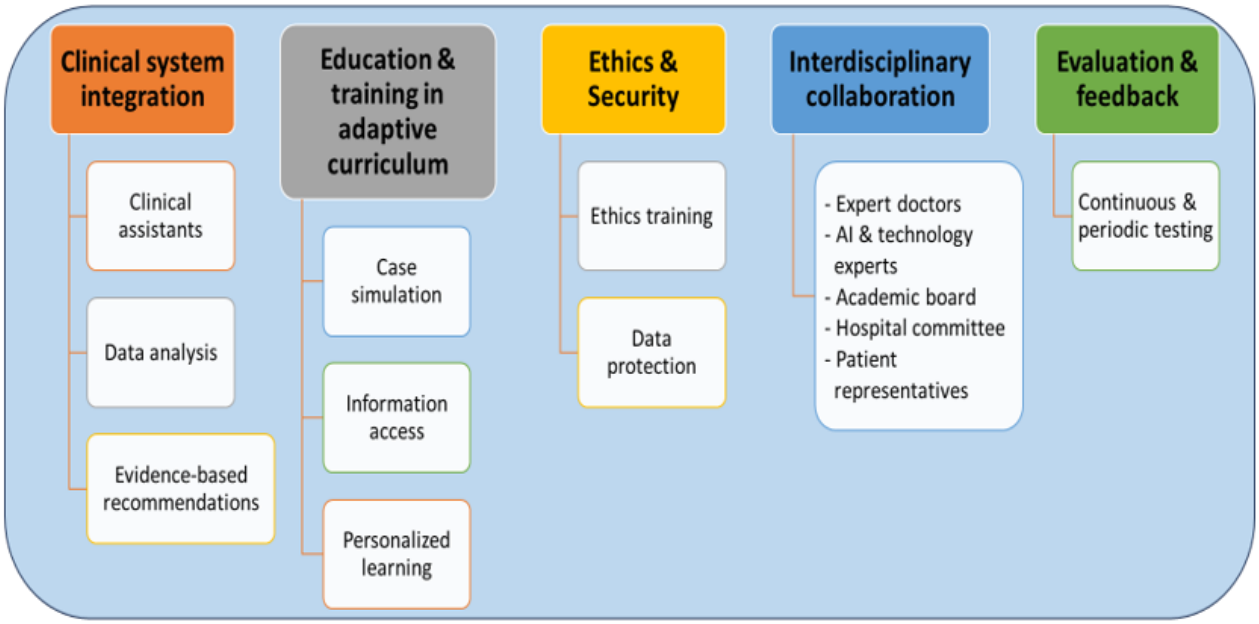

Figure 2. Strategies for utilizing AI-LLM in healthcare services and medical education

This requires interdisciplinary collaboration among several disciplines with the same vision and mission of developing AI in medicine ethically and successfully. As a last phase, evaluation and feedback should be provided through ongoing and regular examinations. This type of evaluation will ensure that the quality of service and education remains high, as well as provide an opportunity for introspection and innovation to bring about new and better things. Hopefully, by implementing these five measures, AI-LLM can considerably improve the quality of patient care and medical education.

CONCLUSION

The use of AI through Large Language Models (AI-LLMs) in healthcare and medical education is proven to be quite effective. AI-LLMs improve diagnostic accuracy and therapy customization, especially in obstetrics and gynecology, and contribute to holistic patient care. They also transform medical training by creating dynamic, simulation-based learning environments that keep instructional content up-to-date and accessible around the world. However, key concerns like as data protection, technology dependence, and the necessity for precise AI performance must be addressed by joint regulation and ongoing oversight. AI-LLMs, when properly managed, have the potential to greatly improve both patient care quality and medical education standards around the world.

DISCLOSURES

Acknowledgments

During the preparation of this work the authors used Open AI ChatGPT-4.0 in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Conflict of Interest

The authors have no conflict of interest.

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Author contribution

This manuscript was conceived, written, and revised by KEG and MT. All authors have read and approved the manuscript.

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CASE REPORT

Left hemiparesis due to space-occupying lesion in pregnancy

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Pregnancy
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ABSTRACT

Objective: The objective of this study was to present the findings from cases of space-occupying lesions (SOL) that were diagnosed late in pregnancy. This case report aimed to highlight the importance of considering space-occupying lesions as a differential diagnosis in instances of hemiparesis during pregnancy, thereby raising clinical awareness and improving diagnostic accuracy.

Case Report: A female patient aged 30 years 34 weeks pregnant came with complaints of slurred speech since 3 months before entering the hospital accompanied by weakness in the left limbs since 3 months before admission. The patient felt weak and fell in the bathroom 2 times, at the office and at home. The patient had a history of taking aspilet for 1.5 months due to a misdiagnosis as a stroke in a Type B hospital and stopped when she came to the obstetric emergency room at a Type A Hospital for the first time. Cardiothoracograph examination shows a picture of a silent baby. Computed Tomography (CT) Scan examination showed a picture of hydrocephalus.

Conclusion: To date, it has not been proven that pregnancy triggers brain tumors. However, increased blood supply to the brain during pregnancy may lead to tumor growth. This is also evident in this case where there is an increase in maternal blood volume and subsequent cerebral blood flow, causing an increase in the size of the SOL. On the other hand, there is no evident that brain tumors directly harm the fetus, though fetal hypoxia may occur indirectly due to maternal respiratory failure.

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Highlights:

1. Present a case report detailing the diagnosis and management of a space-occupying lesion identified late in pregnancy.
2. Current studies consistently indicate that the optimal period for tumor removal during pregnancy is the second trimester, balancing maternal and fetal outcomes. This case report contributes to the existing literature by providing a practical reference for managing space-occupying lesions in accordance with the latest evidence.

INTRODUCTION

There are several differential diagnoses of hemiparesis such as hemorrhagic stroke, ischemic stroke and space occupying lesion (SOL). As many as 12.2 from 100.000 pregnancies have ischemic and hemorrhagic strokes. An incidence of 30 per 100,000 pregnancies, or three times the rate in non-pregnant females aged 15 to 44 years, was found in a systematic review and meta-analysis of 11 studies on stroke in pregnancy published between 1990 and January 2017. Hemorrhagic stroke during pregnancy has a fatality rate of 13.9% compared to ischemic stroke during pregnancy, which is 3.4%. Intracranial hemorrhage is the leading cause of maternal stroke death, and residual impairment is higher in hemorrhagic stroke (50%) than ischemic stroke (33%) episodes in pregnancy.[1,2]

There is a significant increase in brain tumor prevalence during pregnancy. However, there are no precise prevalence statistics available. Pituitary tumors, meningiomas, gliomas, and breast cancer metastases are the most common tumors. Women experience meningiomas at a rate that is around twice as high as men's. Specifically, intracranial meningiomas are twice as common and intraspinal meningiomas nine times as common in females. Meningiomas also appear to be influenced by sex hormones, as these tumors develop more quickly during pregnancy and during the luteal phase of the menstrual cycle. Pituitary tumors are more common in women, especially during the child-bearing years, and make up around 15% of all primary intracranial neoplasms. The female preponderance of these tumors is due to the increased frequency of prolactinomas in women in the second and third decades. Women account for 78% of all prolactinomas and are affected four times more frequently than men.[3]

Intracranial space occupying lesion (SOL) is a substantial physical lesion within the intracranial space that can cause progressive neurological disorders. Intracranial SOL can be in the form of cerebral contusions, hematomas, infarctions, abscesses, and tumors that grow in the intracranial space. SOL in the intracranial space can increase intracranial pressure. Symptoms or clinical manifestations of SOL arise based on the site of predilection. Hemiparesis that arises as a manifestation of SOL which occupies cranial space is related to the corticospinal tract which allows the right cerebral hemisphere to innervate most of the functions of the left side of the body and vice versa.[4,5]

SOL during pregnancy poses a number of difficulties for neurosurgeons, obstetricians, and anesthesiologists, including difficulties in diagnosing the condition and difficulties in perioperative management since it necessitates careful planning to balance mother and fetal well-being. This requires modifying neuroanesthesia and obstetric practices which often have competing clinical goals of achieving optimal safety for the mother and fetus.[6]

The aim of this study was to report the findings of cases of space occupying lesions that were "late to be diagnosed" in pregnancy so that this case report was expected to provide benefits in the form of awareness not to forget to include space occupying lesions as one of the differential diagnoses if hemiparesis is found during pregnancy. Apart from that, the benefits of this research also include a literature review which discusses how to manage cases of space occupying lesions that arise during pregnancy, consisting of treatment options for the first trimester, second trimester and also third trimester of pregnancy.

This study also strengthened the evidence that installing a VP shunt in patients can improve the patient's clinical condition. As has been recognized, installing a VP shunt is to reduce the intracranial pressure. The shunt allows some fluid to drain from the brain to a different part of the body. By reducing some of the symptoms it may make the patient feel better.

CASE REPORT

The patient was a referral from a type B hospital, 30 years old with G1P0A0 34 weeks pregnancy, came to the obstetric emergency room at a type A hospital on April 8 2023 and complained of a left hemiparesis which began with a tingling sensation 3 months before admission to the hospital. The patient also complained of slurred speech and blurry vision. All these complaints had never been felt by patients before. The patient's family also never had complaints. The patient had regular sleep patterns, patients did not have history of smoking or drinking alcohol and taking any long-term medication/drugs. The patient had a history of taking aspilet for 1.5 months due to a misdiagnosis as a stroke at the type B hospital and stopped when she came to the obstetric emergency room at the type A hospital for the first time. The patient had a history of falling twice, namely in the patient's home bathroom and also in the patient's office bathroom. Based on the results of the physical examination, the patient appeared mildly ill with sound consciousness. On motor examination, the patient experienced decreased muscle tone and decreased motor function in the left limb. After the CTG examination, there was a picture of a silent baby so this could not be assessed.

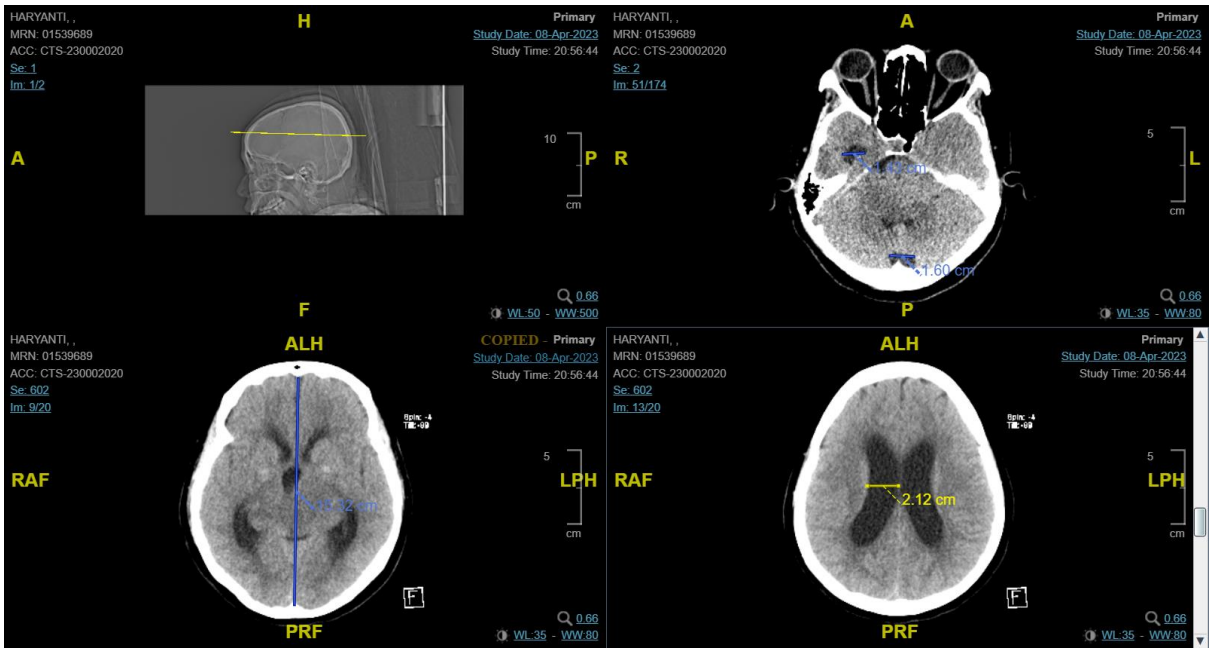

Figure 1. Computed tomography scan results taken on April 8th 2023.

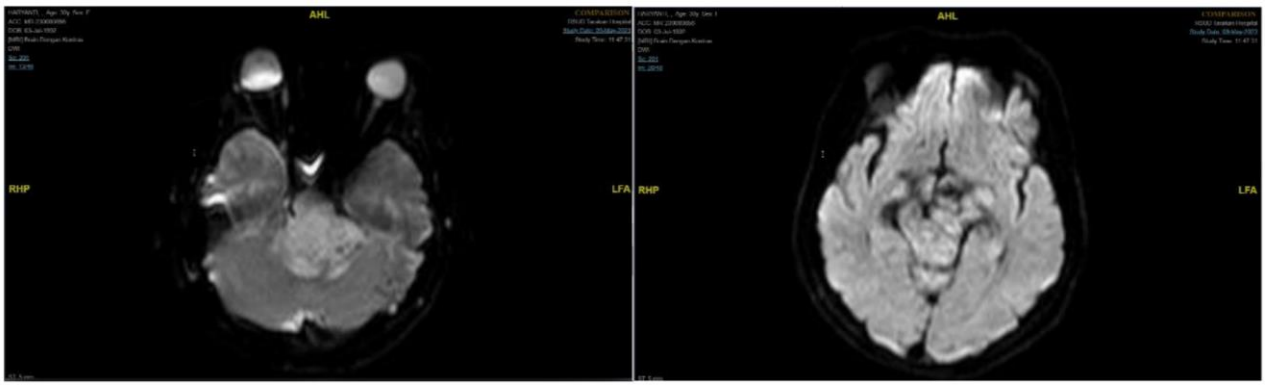

Figure 2. Magnetic resonance imaging results taken on May 9, 2023.

CT scan investigation showed that there was a picture of hydrocephalus in the patient. The results of the CT scan showed that there was SOL in the anterior fossa of the right hemisphere, a mild shift to the left, and widening of the midline structure.

MRI showed that there was an hyperintensive lesion in the left CPA region that presses the III ventricle and the bilateral lateral ventricle. Both the orbits, the paranasal sinuses, and the mastoids did not seem to differ. The bones seemed crumbling.

However, CT scan cannot accurately diagnose lesions in the posterior fossa and spine, and also has a lower resolution than magnetic resonance imaging (MRI). The MRI to this patient was challenging because it was performed after delivery, so that there were safety precautions for both the mother and the baby, in addition to higher cost than the CT scan.

The differential diagnosis of this patient was hemorrhagic stroke and infarction stroke. As might be predicted, the area of the brain injured by an insult determined the symptoms of a stroke. It is possible to experience speech and vision problems, numbness, and

also weakness. Furthermore, alterations in mental state can indicate hemorrhagic as well as ischemic infarctions. Although there are not many strokes among women of childbearing age generally, pregnant women and those who have recently given birth are more vulnerable because of a variety of factors that affect the body's coagulation and circulatory hemodynamics.

The patient underwent a caesarean section operation and then a VP shunt was placed for the indication and prevent worst obstructive hydrocephalus. After the action was taken, the hemiparesis complaints reduced and postoperatively it was continued with the installation of a ventilator for indications of respiratory failure and physiotherapy rehabilitation was carried out by the patient with walking exercises. Recommend-ations for foods high in protein and vitamins such as egg whites, free-range chicken, vegetables and fruit were also carried out. On April 17, 2023, the patient was able to walk yet still staggering and was allowed to go home. On April 28 2023 the left hemiparesis had improved but there was still mild hemiparesis and tingling in the patient's left upper leg and left lower leg. Speech articulation sounds less clear.

DISCUSSION

During pregnancy, the hormone human chorionic gonadotropin is produced which can increase the levels of vascular endothelial growth factor (VEGF) which functions as a factor for the formation of new blood vessels in the fetus. During pregnancy, an increase in VEGF is associated with an increase in blood supply to various organs of the body, one of which is the brain. According to research conducted by Yust-Kazt et al, there is an increase in blood volume in the mother. This then increases the blood supply to the brain and can increase the size of brain tumors. Until now, it has not been proven that pregnancy can cause brain tumors. However, there is evidence that there is an increase in the size of brain tumors in pregnancy due to the increased blood supply to the brain, and vice versa. At this time, it has not been proven that brain tumors can cause harm to the fetus. The mechanism that may occur is indirect fetal deterioration, the mechanism of respiratory failure which causes fetal hypoxia.[7-9]

The most common brain tumor in the cerebellopontine angle (CPA) is the vestibular schwannoma, which accounts for 75-85% of brain tumors. In pregnancy, the incidence of this tumor is 2.0-3.2 per 100,000 women. The CPA is a triangular space in the posterior cranial fossa that borders the tentorium superiorly, the brainstem posteromedially, and the posterolateral portion of the temporal bone. These tumors mostly occur at the age of 40-60 years. Other tumors that can grow in CPA are meningioma, epidermoid, lipoma, arachnoid cyst, glomus tumor, and choroid plexus tumor. Although the exact cause of these tumors is not yet known, one theory links the presence of these tumors with the addition of the progesterone receptor.[10,11]

It is yet unknown what causes faster tumor growth during pregnancy. There are two dominant theories, though. First, the expansion of blood vessels during pregnancy as a result of the increased blood volume causes an increase in tumor size. Second, progesterone and estrogen receptors' direct hormonal effects on the body's receptors mediate tumor growth. The levels of estrogen receptor expression and patient age, sex, or tumor size were not clearly correlated in a study of 16 vestibular schwannoma specimens conducted by Brown et al. Nevertheless, it was concluded that antiestrogen therapy might prove to be an effective treatment option given that it has been linked to decreased proliferation and increased apoptosis.[12,13]

The left hemiparesis in the patient in this case was suspected by the presence of suspected vestibular schwannoma SOL in the left cerebral hemisphere which then inhibited the corticospinal tract so that it could inhibit motor control which could then result in left hemiparesis of the body. On the CT scan imaging, an isodense image was found on the left CPA which then pressed the IV ventricle and lateral ventricles. On MRI there was a hyperintense solid mass in the CPA region of the left cerebral hemisphere. The presence of SOL can cause pressure on the lateral ventricles and bilateral IV ventricles which can give a picture of hydrocephalus in the brain. The patient underwent a VP shunt.

When a vestibular schwannoma is detected or becomes worse during pregnancy, there may be competing risks and advantages for both the mother and the fetus. The best course of action for both mother and fetus is close monitoring, followed by delivery and tumor removal. The second-best course of action is to give birth to the child (if it is sufficiently late in the third trimester), then quickly remove the tumor. The possibility of increasing intracranial pressure during phase 2 of vaginal birth makes cesarean delivery the recommended option. Several authors have reported cases of spontaneous vaginal delivery before tumor resection, but the risks remain uncertain.[11,14-16]

Due to the effects of general anesthesia, undergoing surgery in the first trimester poses the fetus with the greatest risk, because it will cause contraction of the womb. Therefore, the chance of spontaneous abortion is significantly decreased if surgery can be scheduled until

after the first trimester. If mass effect causes obstructive hydrocephalus, a VP shunt can be implanted to delay primary surgery until late in the pregnancy. A VP shunt enables sustained cerebrospinal fluid (CSF) drainage and requires far less time during anesthesia and surgery than tumor excision does. Despite best efforts, surgical resection during pregnancy is sometimes necessary.[11,17,18]

If a tumor needs to be removed when a woman is pregnant, the second trimester is the optimum period for both the mother and the fetus because general anesthesia surgery is safer at this time for both of them. A VP shunt can be implanted to postpone tumor excision until after delivery if hydrocephalus is present. Primary resection, however, should be strongly considered if it is early in the second trimester and there is concern that the patient may need tumor removal while pregnant.[11,17-20]

Women are mostly at risk from surgery during the last trimester of pregnancy. This risk is likely due to hemodilution, decreased functional residual respiratory capacity, increased oxygen consumption which predisposes to hypoxemia, and swelling of the airway capillary veins. If obstructive hydrocephalus is present, a VP shunt may be placed to delay tumor resection until after delivery. The risk to the mother and fetus is lower if the tumor is removed surgically after the baby is delivered if it is discovered too late in the pregnancy. Appropriate therapy is critical when there is a large symptomatic tumor associated with elevated intracranial pressure and hydrocephalus. According to a case report in Scotland, a large acoustic neuroma was successfully removed during the third trimester without endangering the woman or fetus. The optimal strategy is CSF drainage prior to emergency cesarean delivery, immediately followed by tumor resection. To allow for the recovery of hemodynamic stability, resection might be postponed for a few days to a week. However, a case report in India described a case where a cesarean delivery was followed immediately by surgical resection, and both mother and baby recovered smoothly.[11]

The strength of this study is with the report findings of a case of “late diagnosed” space occupying lesion in pregnancy makes us aware and increases our awareness of hemiparesis complaints so that we can include space occupying lesion as one of the differential diagnoses, and this case report provides literature of the management of patients with space occupying lesion during pregnancy. The limitation of this study was, as this was a case report, it did not study the risk factors for space occupying lesion in pregnancy and it did not study whether pregnancy can trigger space occupying lesion.

CONCLUSION

The left hemiparesis in the patient was suspected by the presence of SOL in the left cerebral hemisphere which then blocked the corticospinal tract so that it inhibits motor control which resulted in weakness in left body movements. On CT Scan imaging it is not clear where the lesion is in the cerebral hemispheres, but the location of the lesion can be estimated, namely in the primary motor cortex and primary somatosensory cortex. It was also suspected that SOL in the patient also pressed the facial nerve (CN VII), which innervates the majority of the face. Lesions to these cranial nerves can cause symptoms like Bell's Palsy. Until now, it has not been proven that pregnancy can trigger a brain tumor. However, there is evidence that there is an increase in the size of brain tumors in pregnancy due to increased blood supply to the brain. Evidence that SOL can affect pregnancy was supported by an increase in blood volume in the mother's body followed by an increase in blood supply to the brain, causing an increase in tumor size. Likewise, it is currently not proven that brain tumors can cause harm to the fetus. The mechanism that may occur is indirect fetal deterioration, namely the mechanism of respiratory failure which causes fetal hypoxia.

DISCLOSURES

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Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this case report.

Patient consent for publication

Written informed consent for the case to be published (including CT scan results images, MRI results images, case history, and data) was obtained from the patient for publication of this case report.

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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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CASE REPORT

Evaluation and diagnostic approach in patient with Perrault Syndrome

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ABSTRACT

Objective: A multidisciplinary team, which included a reproductive endocrinologist and an otolaryngologist, identified Perrault Syndrome in a patient with secondary amenorrhea and bilateral sensorineural hearing loss.

Case Report: A 16-year-old female presented to the obstetrics and gynecology clinic at a type B hospital with primary amenorrhea for one year. Menarche occurred at age 13, followed by regular menstrual cycles for two years, after which menstruation gradually ceased. She denied dysmenorrhea, constipation, leukorrhea, genital pruritus, growth retardation, and weight loss. The patient expressed concern about potential future infertility. At age 9, she was diagnosed with a viral infection by an ENT specialist due to bilateral hearing loss, leading to emotional disturbances. There was no history of prior medication, family illness, or chronic infections. Born at term via spontaneous vaginal delivery, the patient weighed 3,000 grams. Laboratory tests revealed normal T3 (1.51 ng/dl), FT4 (1.16 ng/dl), prolactin (18.25 ng/ml), estrogen (11 pg/ml), and progesterone (0.1 pg/ml) levels, but elevated FSH (66.46 mIU/ml) and LH (29.97 mIU/ml) levels. Symptomatic treatment included bone conduction hearing aids and estrogen replacement therapy.

Conclusion: Perrault Syndrome, a rare hereditary condition, manifests as sensorineural hearing loss (SNHL) and ovarian dysfunction, including primary ovarian insufficiency (POI) and gonadal dysgenesis, in individuals with a 46, XX karyotype. Molecular diagnosis remains challenging. Consultation with a pediatric endocrinologist can guide cyclic estrogen and progesterone therapy to induce withdrawal bleeding in adolescents with amenorrhea. Women at risk of ovarian failure should consider donor eggs or oocyte cryopreservation. Avoiding aminoglycosides and excessive noise is crucial for managing hearing loss.

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Highlights:

1. The rare hereditary condition Perrault Syndrome is characterized by sensorineural hearing loss (SNHL) and ovarian dysfunction
2. Cyclic estrogens and progesterone may be given to adolescents with amenorrhea to induce withdrawal bleeding and mimic the menstrual cycle.

INTRODUCTION

Perrault syndrome is a rare autosomal recessive genetic disease, which reported worldwide about 40 families approximately with a 2:1 female-to-male ratio. There are two types of Perrault syndrome.[1] People with type 1 Perrault Syndrome characterized with symptoms of progressive sensorineural hearing loss, ovarian dysfunction, which usually begins at birth or in early childhood, and ovarian insufficiency in women with karyotype 46, XX, manifests as primary and secondary amenorrhea.[1] Additional neurologic symptoms and muscle or renal indications are present in type 2.[1]

Genetics are believed to be one of the factors causing ovarian dysfunction and hair cells abnormalities. One of eight causative genetic genes named LARS2, has biallelic mutations that support the diagnosis. LARS2 encodes mitochondrial amino acid protein, which is required in the cytoplasm and mitochondria for the translation of nuclear and mitochondrial encoded genes.[1,2]

Age of hearing loss onset and ovarian dysfunction can change depending on the frequency of delayed puberty in females with sensorineural hearing loss. Congenital hearing loss can start at birth or develop in infancy. Primary amenorrhea and primary ovarian insufficiency are two examples of ovarian dysfunction. In the literature, a diagnosis is made at a median age of 22.[2] Hearing impairment (mean age at diagnosis seven years) was noted in all but one reported case.[2,3] A multidisciplinary team with a reproductive endocrinologist and otolaryngologist is needed to prepare for puberty, mimicking the menstrual cycle and maintaining healthy bones.

The purpose of this case report was to provide an overview of Perrault syndrome because it is an uncommon genetic disorder with little existing literature. This case report highlighted the possibility that adolescents who have secondary amenorrhea may have genetic issues and explained how the family may be informed and what treatments are available.

CASE REPORT

A 16-year-old female came to the obstetrics and gynecology clinic at a type B hospital with the main complaint of not having her period since one year ago. The patient first menstruated at the age of 13 years, then for two years, the patient experienced regular menstruation every month, but in the last year, the patient felt that her menstruation had decreased until it stopped. Complaints of abdominal pain during menstruation were denied. Other complaints, such as difficulty defecating, vaginal discharge, genital itch, stunted growth, and weight loss, were rejected by the patient. The patient also worried about not being able to get pregnant in the future other than this problem.

According to the patient's mother, at the age of 9 years, the patient was brought to the ENT doctor because hearing in both ears felt reduced and was diagnosed by the doctor as a disease caused by a virus. The patient could not hear using both her ears, and emotional changes occurred because of the patient's reduced hearing. There was no history of previous drug use, family illness, and chronic infections. The patient is the second of two children, born when the patient's mother was 20 years old through spontaneous vaginal delivery without complications at term, with a birth weight of 3,000 grams.

Laboratory results showed normal Triiodothyronine (T3) levels (1.51 ng/dl), free thyroxine (FT4) levels (1.16 ng/dl), prolactin (18.25 ng/ml), estrogen (11 pg/mL), and progesterone test (0.1pg/mL). However, there was an increase in follicle-stimulating hormone (FSH) levels (66.46 mIU/mL) and luteinizing hormone (LH) levels (29.97 mIU/mL). Symptomatic treatments were given, such as bone hearing aids and estrogen replacement therapy.

DISCUSSION

Sensorineural hearing loss (SNHL) and ovarian dysfunction are hallmarks of a rare autosomal recessive genetic disorder known as Perrault Syndrome.[2,3,4] SNHL is bilateral and can be severe in the congenital stage or mild in early childhood. Hearing loss can get worse over time, even if it started in infancy. Ovarian dysfunction includes primary ovarian insufficiency (POI) and gonadal dysgenesis, characterized by absence or dysplasia of the gonads and manifests as primary and secondary amenorrhea.[2,3] There are two types; type I is Perrault Syndrome, which is static without neurological disease. At the same time, progressive neurological disorders accompany type 2. Type 2 symptoms include absent tendon reflexes, nystagmic dysarthria, cognitive impairment, scoliosis, cerebellar atrophy, and seizure.[2,5]

The clinical features of SNHL in both men and women, as well as ovarian dysfunction in women, along with a karyotype that is typically normal in affected persons, support the diagnosis of Perrault Syndrome 46, XX.[2,6] Additional tests such as a karyotype test and anti-Mullerian hormone (AMH) test can be performed. The eight causative genes (HARS2, HSD17B4, CLLP, C10orf, ERAL1, TWNK, LARS2, and RMND1), all

have biallelic pathogenic mutations that support the diagnosis.[1,7-9] At this time, 18 people with LARS2-Perrault have reported 19 variations.[8] LARS2 mutations usually manifest as Perrault syndrome type 1.[10] There were only 15 cases with mutations in this gene as of 2018, and one of those cases had Perrault syndrome type 2.[10] There is the presence of neuropathic spectrum disorder (ANSD) with bilateral progressive SNHL caused by a CLPP homozygous mutation. On chromosome 19, the mitochondrial protease CLPP is encoded. By decreasing misfolded or damaged proteins, this protease regulates the integrity of mitochondrial proteins, preserving the cell's regular metabolic process. In Perrault Syndrome, CLPP peptidase activity is suppressed, resulting in mitochondrial dysfunction.[4,11,12] It is this dysfunction of mitochondrial protein homeo-stasis that causes Perrault Syndrome.[13] According to another study, people with TWNK mutation-caused Perrault Syndrome exhibit adult neurologic symptoms.[14]

However, about 60% of people with Perrault syndrome identified so far cannot be diagnosed at the molecular level.[3,7,15] Other literature says that the differential diagnosis of Perrault syndrome is Turner syndrome; about half of Turner patients have some degree of hearing disorders. Karyotype analysis can rule out this diagnosis.[2] According to a study of the literature, amenorrhea, elevated gonadotropin levels, and sensorineural hearing loss are prevalent symptoms of Perrault Syndrome despite its clinically significant degree of variability.[16] Uncertainty exists regarding the general pathogenetic link between sensorineural hearing loss and ovarian dysgenesis.[6] A small portion of the broad neurological involvement observed is sensorineural hearing loss in patients with Perrault Syndrome. Magnetic resonance imaging in Perrault Syndrome patients shows cerebral leukodystrophy, cerebellar hypoplasia, etc.[6]

Anti-mullerian hormone (AMH) levels increase between ages 4 and 8 but remain stable through early adulthood. However, throughout childhood, AMH levels are either undetectable or very low. It is unclear whether this indicates early follicular loss or impaired pre- or postnatal folliculogenesis. Despite low AMH levels, all girls go through puberty on their own. This means that although if it only contains a small number of follicles, there are probably enough of them to cause the partial development of secondary sexual characteristics and enable the expansion of the uterus.[7]

People with the 46, XX karyotype for Perrault Syndrome should be diagnosed if they have the following clinical symptoms and family history. There is a spectrum of ovarian dysfunction, from primary ovarian insufficiency (POI) to ovarian dysgenesis. POI is the absence of menstruation before age 40, accompanied by an increase in follicle-stimulating hormone (FSH) levels and a decrease in serum estrogen concentration.[3,17,18]

A developmental disorder known as ovarian dysgenesis is characterized by loss of gonads and supporting cells (granulosa and theca cells, respectively), dysplastic, streaked, or no ovaries. With hypogonadotropic hypogonadism, the serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) increase along with a decrease in the concentration of estrogen in the blood. Upon ultrasound examination, the uterus appears primitive and prepubescent. Autosomal recessive inheritance is supported by family history, including possible parental relatives.[3,17]

From menarche through menopause, when endogenous production starts to diminish, ovarian hormones have a crucial role in regulating bone, cardiovascular, and hormonal health in women.[19] One percent of women have hypogonadotropic hypogonadism, either primary or secondary. In consultation with a pediatric endocrinologist, cyclic estrogen and progesterone may be given to adolescents with amenorrhea to induce withdrawal bleeding and mimic the menstrual cycle after the end of puberty as a treatment for POI.

The age of diagnosis and the level of function loss affect how an ovarian disorder is treated. If the patient has not hit puberty yet, estrogen replacement therapy can be administered to speed up the process. If the patient has entered puberty, oral contraceptive pills should be used to maintain bone health.[2] Estrogen replacement therapy is given until age 50, if there are no contraindications, to reduce the risk of osteoporosis and cardiovascular disease. If the patient intends to become pregnant in the future, she should think about assisted reproduction using donor eggs for in vitro fertilization (IVF) for POI. Before considering conception, women at risk for ovarian failure should investigate donor egg oocyte cryopreservation and measure their uterus.[20] In addition to employing donor eggs, gestational surrogacy can also be used due to premature ovarian failure and frequently underdeveloped uteruses.[2,20]

Treatment for hearing loss can range from more educational materials to cochlear implantation, depending on the severity of the loss and age at the time of loss. This is usually done in close collaboration with otolaryngologists, audiologists, and the child's school system. Regular monitoring for the development of hearing loss is essential. Opioid drugs, such as aminoglycosides and excessive noise, can exacerbate hearing loss. Family education is also needed by informing them that the hearing loss they experience

will be progressive. Perrault syndrome can cause fertility problems. It is essential to screen the proband's siblings so that early identification of the disease might help in timely intervention.[6]

The limitation of this study was that the diagnosis was only made based on the results of anamnesis and laboratory examination. We did not perform karyotype testing, so in this case, the transmissibility of the pathogen was not known to support the diagnosis. This case report provides an overview of the evaluation and how to diagnose patients with Perrault Syndrome. The fact that this case involved a rare hereditary ailment is advantageous. According to the literature, Perrault syndrome is a rare autosomal recessive genetic disorder that affects only about 40 families worldwide, so there is still little existing research related to this syndrome.

CONCLUSION

An uncommon autosomal recessive hereditary condition called Perrault Syndrome is characterized by sensorineural hearing loss (SNHL) and ovarian dysfunction. Ovarian dysfunction includes primary ovarian insufficiency (POI) and gonadal dysgenesis. Perrault Syndrome has a 46, XX karyotype. Additional tests such as karyotyping and anti-mullerian hormone (AMH) tests are not recommended because 60% of people with Perrault Syndrome identified so far cannot be diagnosed at the molecular level. In consultation with a pediatric endocrinologist, cyclic estrogens and progesterone may be given to adolescents with amenorrhea to induce withdrawal bleeding and mimic the menstrual cycle. Before considering pregnancy, women at risk for ovarian failure should consider donor eggs, oocyte cryopreservation, and uterine size. Opioid drugs such as aminoglycosides and excessive noise, which can exacerbate hearing loss, are situations and agents that people with hearing loss should avoid.

DISCLOSURES

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Conflict of interest

There is no conflict of interest.

Patient consent for publication

The patient agreed that her case is published in the report.

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Author contribution

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CASE REPORT

Acquired uterine arteriovenous malformation after cesarean section

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ABSTRACT

Objective: To demonstrate that embolization is a viable and well-established treatment for acquired arteriovenous malformations (AVMs), offering a safe, effective, and less invasive option for patients seeking to preserve fertility.

Case Report: A 20-year-old female presented with recurrent massive vaginal bleeding. Her medical history included a previous cesarean section complicated by a wound infection that necessitated resuturing. Initial diagnostic evaluation with transvaginal color Doppler ultrasound revealed hypervascularity in the uterus surrounding the surgical scar, raising suspicion for a uterine AVM. This diagnosis was subsequently confirmed through angiography. Given the patient's desire to maintain fertility, uterine artery embolization (UAE) was chosen as the treatment modality. The patient underwent multiple embolization sessions, during which embolic agents were administered to occlude the abnormal arteriovenous connections. The procedures were well-tolerated, and post-procedural monitoring indicated a significant reduction in uterine blood flow and resolution of hypervascularity. Follow-up assessments showed complete resolution of symptoms and no further episodes of bleeding. Importantly, the patient's reproductive potential was preserved, and she reported a return to normal menstrual cycles.

Conclusion: Acquired uterine arteriovenous malformation (AVM) is an uncommon but serious complication that can arise following cesarean section and should be considered in cases of persistent postpartum bleeding. This case highlights the efficacy of uterine artery embolization as a treatment for AVMs, offering a minimally invasive alternative to hysterectomy that effectively relieves symptoms while preserving fertility. Early recognition and timely intervention with embolization techniques can significantly improve patient outcomes in similar clinical condition.

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Highlights:

1. Acquired uterine arteriovenous malformation (AVM) is an uncommon sequela of cesarean section, warranting consideration in instances of persistent uterine bleeding in the puerperium.
2. Embolization represents a viable and well-established treatment modality for AVM, providing a safe and efficacious intervention that serves as an alternative, less invasive modality for patients desiring fertility preservation.

INTRODUCTION

Uterine arteriovenous malformation (AVM) is a vascular abnormality characterized by a direct connection between the arterial and venous system within the uterus without any capillary network contribution.[1] Arteriovenous malformation (AVM) is an exceptionally uncommon condition with a reported incidence of approximately 150 cases. Despite its rarity, this disease poses a significant risk of life-threatening complications.[1] This rare condition can be a congenital or acquired lesion.

Congenital uterine AVM is believed to arise from a failure of differentiation during fetal angiogenesis. The embryological arrest or failure in the primitive capillary plexus differentiation results in anomalous capillary speciation and abnormal communication between arteries and veins. Congenital AVM exhibit a propensity for the presence of numerous feeding arteries, which contribute to their extensive vascularization, as well as a considerable number of large draining veins. Consequently, these AVM commonly demonstrate an enlargement beyond the boundaries of the uterus and an invasion into the adjacent pelvic region.[2,3]

The acquired AVM is often associated with previous uterine traumatic procedures such as caesarean section, curettage or pelvic surgery.[4] Acquired AVM can present a wide variety of symptoms. Its incidence and prevalence are difficult to determine because it is often misdiagnosed with retained products of conception and placenta accreta. However, it can cause massive vaginal bleeding, which is potentially life-threatening.

Imaging modalities including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and computerized tomography coronary angiogram (CTA) play a pivotal role in the diagnosis, treatment, and follow-up of uterine arteriovenous malformations (AVMs). Ultrasonography is capable of detecting the presence of anechoic or hypoechoic tubular or sponge-like areas within the normal myometrium and endometrium. However, it is important to note that other conditions may exhibit similar imaging characteristics, such as retained products of conception, gestational trophoblastic disease, or hydrosalpinx. The utilization of color doppler ultrasonography is crucial in obtaining more precise and accurate information in the evaluation of uterine AVMs.

Historically, the management of symptomatic acquired uterine arteriovenous malformations (AVMs) involved the use of hysterectomy. However, advancements in endovascular techniques have offered an alternative and minimally invasive treatment approach for patients who wish to maintain their fertility. In this case report, we present a detailed account of a 20-year-old female patient who experienced recurrent severe bleeding after undergoing a caesarean section. This challenging condition was successfully addressed through a series of uterine artery embolization procedures, leading to favorable outcomes. This report showed that embolization represents a viable and well-established treatment modality for acquired AVM, providing a safe and efficacious intervention, less invasive modality for patients desiring fertility preservation.

CASE REPORT

A 20-year-old Asian woman, multigravida, presented to the emergency room with massive vaginal bleeding. She had a history of caesarean section surgery in the previous four months during her last pregnancy. The patient was also diagnosed with wound infection a month after her surgery and underwent resuturing. No history of hypertension and diabetes. On initial assessment, the patient presented shock symptoms (BP: 91/58 mmHg, HR 118 bpm; RR 26) with moderate pallor. Bleeding was present through the cervix based on speculum examination.

Color doppler ultrasonography showed dominance of pale shades during both systole and diastole represented low-impedance, high-velocity flow within the lesion and a colored mosaic pattern representing turbulent flow was noted. Spectral analysis of the vessels within the lesion confirmed high-velocity flow during both systole and diastole, and a low resistance index. The spectral waveform trace also showed spectral broadening consistent with turbulence and the spectral envelope was irregular. These findings indicated arteriovenous shunts and marked turbulence within the arteriovenous malformation. Spectral analysis of the venous flow revealed high flow velocities and systolic velocity peaks similar to an arterial pattern. The uterine artery velocity waveforms were characterized by high flow velocity and a low resistance index hypervascularity in the uterus around the surgical lesion with RI 0,32 and PSV 138 cm/s suggesting a uterine arterio-venous malformation (Figure 1). The hematological test result was a decline in hemoglobin (8.4 d/dL), and red blood cell (3.04 x 10^6/mm^3) level.

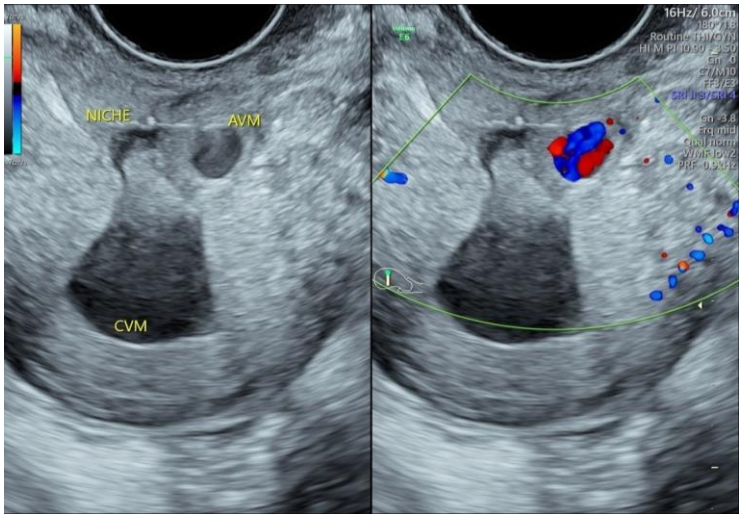

Figure 1. Color Doppler ultrasonography showed a hypervascularity in the uterus around the surgical lesion, suggesting a uterine arterio-venous malformation.

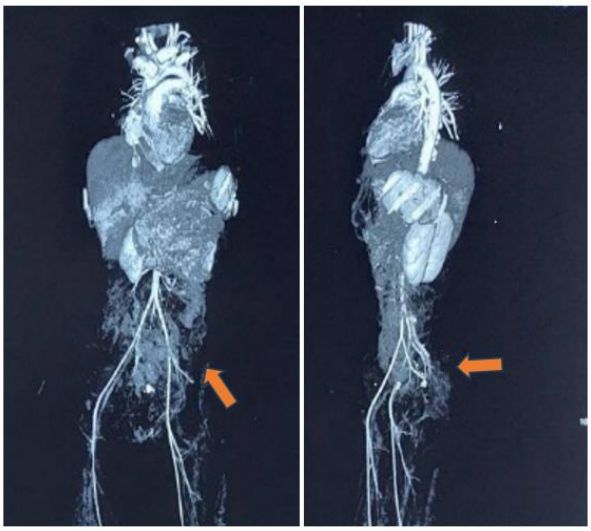

Figure 2. The result of CT angiography confirmed communication with anomalous vessels refer to left uterine arterio-venous malformation (arrow).

The patient's condition was stable after being treated with a blood transfusion. She was moved to the ward for further investigation. The next day, she underwent computed tomography angiography (CTA), which revealed that in the arterial phase, the AVM nidus in the uterus appeared with irregular and inhomogeneous edges. CTA showed hypervascularity of the uterine artery, a branch of the left internal iliac artery, confirming a left uterine arterio-venous malformation (Figure 2).

The patient was scheduled for left uterine artery embolization. Before the embolization, the patient's vital signs deteriorated (BP: 90/60 mmHg, HR 108 bpm; RR 24) with a declining hemoglobin level (4.5 g/dL). The patient was transferred to the ICU for stabilization and subsequently sent to the Cath lab for emergency embolization. The patient's condition improved afterwards. Subsequently, the patient was referred to the interventional radiology department to undergo a computed tomography angiography (CTA) and uterine artery embolization. The procedure involved accessing the femoral artery and performing super-selective microcatheterization of the uterine arteries. During this process, an anomalous vascular pattern was identified in the left uterine artery, characterized by distal angio-dysplasia and arteriovenous fistula.

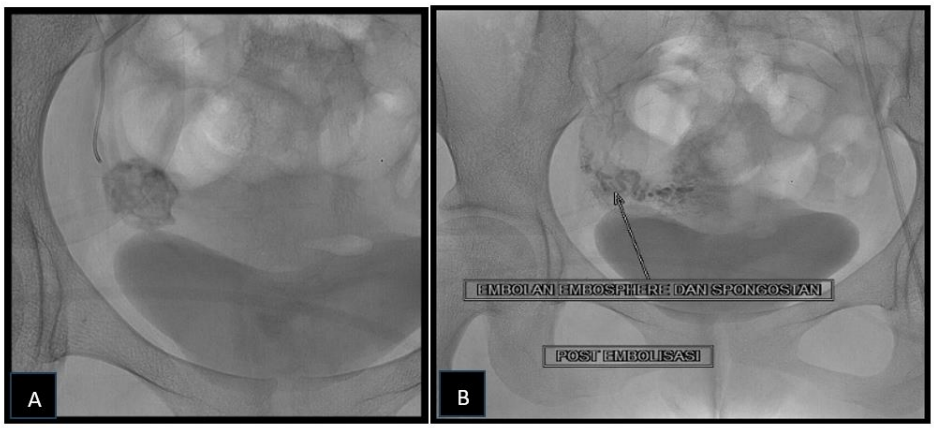

Figure 3. (A) Contrast injection in the left uterine artery showing arteriovenous fistula with ectasic drainage veins; (B) Left uterine artery after embolization.

The uterine artery embolization (UAE) procedure was conducted under moderate sedation, utilizing the left transfemoral approach. Initially, a direct approach was employed to gain access to the left common and internal iliac artery using a 5 French (F) Roberts Uterine Catheter (Cook Medical LLC, 750 Daniels Way, P.O. Box 489, Bloomington, IN 47402-0489 USA). Under the guidance of fluoroscopy, selective embolization was performed into the distal left uterine artery (Figure 3(A)). Non-spherical polyvinyl alcohol 700 microns (PVA) particles were initially chosen, considering the apparently low fistula debit. Subsequent angiographic assessments confirmed satisfactory occlusion of the fistula flow following PVA embolization. Post-embolization angiography demonstrated successful occlusion of the aberrant vessels without any observed vascular complications (Figure 3(B)).

Forty days after the embolization procedure, the patient underwent a follow-up transvaginal ultrasound, which revealed no abnormal findings. Two months later, pelvis magnetic resonance imaging (MRI) was performed, revealing no detectable abnormalities. The patient approved all of the work to be published that includes the personal information and all relevant family members have been informed and have consented to the publication of this information.

DISCUSSION

Around 1 to 2% of cases are attributed to secondary postpartum hemorrhage, which is characterized by causes such as uterine subinvolution, retained products of conception, endometritis, and retained placenta.[6] Less commonly encountered etiologies of secondary postpartum hemorrhage encompass cervical cancer, submucous fibroids, placental adherence, cesarean scar dehiscence, uterine pseudoaneurysm, and uterine rupture.[6,7] Uterine vascular abnormalities, such as arteriovenous malformations (AVMs), and congenital coagulopathies, are implicated in the occurrence of postnatal hemorrhage. Uterine arteriovenous malformation (UAVM), an infrequent and potentially life-threatening condition, serves as a significant cause of excessive bleeding following childbirth. UAVM is characterized by an anomalous connection between the uterine arteries and the venous system. Reported cases of UAVM are limited to fewer than 200 instances. This condition can be classified as either congenital or acquired, with the acquired form often associated with prior cesarean section, curettage, or pelvic surgery.[8,9] In this particular case, the patient's medical history revealed a previous cesarean section performed four months ago, which suggests that the acquired form of uterine arteriovenous malformation (AVM) may be the underlying condition. It is important to note that congenital uterine AVMs and acquired uterine AVMs exhibit distinct pathophysiological processes. Congenital AVMs are believed to arise from the arrest or failure of embryological differentiation of the primitive capillary plexus, resulting in abnormalities in capillary formation and aberrant arteriovenous communication. This leads to the presence of numerous vascularized arteries and enlarged drainage veins in congenital AVMs, often causing them to extend beyond the confines of the uterus and invade the surrounding pelvic structures.[10,11]

Acquired uterine arteriovenous malformations (AVMs) manifest as a result of previous uterine interventions, including pelvic surgery, therapeutic abortion, curettage procedures, or cesarean sections. These interventions contribute to the occurrence of abnormal communi-

cations between arteries and veins, specifically within the venous sinuses of scar tissue where necrotic villi are associated. The healing process following these interventions provides an opportunity for the development of aberrant vascular connections, often characterized by the fusion of arterial and venous vessels. Additionally, acquired AVMs frequently exhibit multiple vascular connections and demonstrate the capacity to invade adjacent anatomical structures.[12,13]

Uterine arteriovenous malformation (AVM) presents with a wide array of clinical manifestations. Vaginal bleeding is the primary and most prevalent symptom, spanning from intermittent spotting to profuse hemorrhage. Other reported presenting symptoms uterine abnormal bleeding and postcoital bleeding. These symptoms can lead to the development of severe anemia. Acquired uterine AVMs commonly exhibit vaginal bleeding in women of childbearing age, especially those who are in the postpartum period or have a history of previous uterine interventions. Accurate diagnosis plays a crucial role in initiating appropriate management strategies. Imaging modalities are indispensable for early detection and effective management, as the diagnosis of uterine AVM cannot be solely established based on clinical evaluation.[14,15]

Ultrasound imaging is a valuable tool for detecting the presence of multiple anechoic or hypoechoic tubular areas, commonly referred to as "sponges," within the myometrium of the normal endometrium. These tubular structures can be visualized and characterized through their distinct ultrasound appearance. However, it is crucial to consider that other pathological conditions may also manifest similar sonographic features. These conditions include retained products of conception, hemangioma, gestational trophoblastic disease, or hydrosalpinx. Therefore, a comprehensive diagnostic approach, including clinical correlation and potentially additional imaging modalities or histopathological evaluation, is necessary to differentiate between these entities and arrive at an accurate diagnosis.[16]

Color Doppler ultrasonography is an essential modality for obtaining more precise and accurate information in medical imaging. In the context of evaluating uterine pathology, such as uterine arteriovenous malformations (AVM), color Doppler ultrasound provides valuable insights. In a normal myometrial signal, color Doppler parameters exhibit specific ranges. These include a peak systolic velocity (PSV) ranging from 9-44 cm/s and a resistive index (RI) ranging from 0.6-0.8. These values serve as reference points for assessing normal vascular flow in the myometrium. However, in the presence of a uterine AVM, color Doppler ultrasound reveals distinct and characteristic features. These include intense vascularization and multidirectional flow pattern. The visualization of juxtaposed red and blue areas indicates the presence of multiple tortuous blood vessels with varying orientations. This phenomenon is a hallmark of uterine AVMs. With color Doppler ultrasound, specific hemodynamic parameters can be assessed to differentiate uterine AVMs from other conditions. Uterine AVMs typically exhibit high velocity flow (mean PSV: 136 cm/s), low resistance flow (mean RI: 0.3), low pulsatility of the arterial waveform, and high velocity and pulsatile venous waveforms. These findings are indicative of abnormal vascular flow pattern associated with uterine AVMs. It is important to note that distinguishing between venous and arterial waveforms can be challenging in the context of uterine AVMs. Additionally, it is not uncommon to observe pulsatile flow in pelvic veins distal to AVMs, deviating from the expected monophasic flow pattern. Initial investigation is often performed by US Color Doppler, which suggests hypervascularity, and this test should include flow velocity measurement.[17,18]

CT angiography (CTA) plays a pivotal role in the comprehensive management of uterine arteriovenous malformations (AVMs), encompassing diagnosis, treatment, and follow-up. It is widely regarded as the "gold standard" for diagnosing AVMs due to its high accuracy and detailed imaging capabilities. CTA allows for the identification and characterization of crucial anatomical and hemodynamic features associated with uterine AVMs. These include bilateral hypertrophy, visualization of feeding uterine arteries, identification of tortuous hypertrophic arterial masses along with large accessory vessels, and early visualization of drainage into hypertrophic veins. These findings provide valuable information for accurate diagnosis and subsequent treatment planning. Beyond its diagnostic capabilities, CTA offers several notable advantages. One such advantage is its rapid acquisition time, allowing for efficient and time-sensitive evaluation of uterine AVMs. Additionally, CTA is widely available, enabling its utilization in various clinical settings, thus facilitating prompt diagnosis and timely intervention.[19,20] The patient underwent a US color Doppler to investigate the bleeding etiology. The evaluation documented a hypervascularity structure above the previous uterus caesarean section scar with an apparent flow reversal suggesting turbulent high-velocity flow, which indicates a suspicion of uterine AVM. Therefore, the patient was scheduled for CT angiography for further investigation. Ultimately, the uterine AVM diagnosis was made by the CTA findings.[21]

A study by Timmerman et al. revealed that ultrasound examination had a low positive predictive value. From 30 cases declared AVM based on color Doppler examination, only three were declared AVM based on

gold standard examination.[22,23] These results were different from El's findings. Gawad et al., where USG and CT-Angiography had a sensitivity of 100%.[24,25] However, this study only used angiography as the gold standard for diagnosing AVM. However, both examinations have their respective roles and functions in diagnosing or determining therapy in AVM case.

The hemodynamic stability of the patients, as well as their desire to preserve fertility, determine therapeutic options for uterine AVM. Resuscitation, emphasizing achieving hemostasis and maintaining tissue perfusion, is performed in post-partum hemorrhage.[26]

Hysterectomy and embolization are the remaining primary treatment options in UAVM. The consideration can be made from the patient's condition and the reproduction expectancy. Hysterectomy represents the definitive therapeutic approach for uterine arteriovenous malformations (AVMs). However, its application is primarily reserved for resource-limited environments or instances where uterine embolization is contraindicated.[27] it remains a viable alternative for individuals who have discontinued their fertility aspirations or in cases where embolization proves ineffective in resolving bleeding. Preservation of reproductive function is typically prioritized, especially in younger patients. Importantly, it should be noted that hemodynamic instability does not represent a contraindication for this procedure.[28] The patient's condition deteriorated, and underwent an emergency embolization. The embolization was performed using N-butyl cyanoacrylate (NBCA) as an embolant agent. Embolization using N-butyl cyanoacrylate (NBCA) material can be considered in patients with active bleeding, unstable hemodynamics, and failed embolization with a gelatin sponge. This material works by polymerizing when in contact with blood and can embolize even in cases of coagulopathy. Trans-arterial embolization is the first-line endovascular therapy used to treat AVMs, especially when multiple arteriovenous shunts exist. If necessary, trans-arterial embolization can also be performed repeatedly. Even though the patient's condition improved after the first embolization, the follow-up US color doppler documented residual UAVM.[29] Hence, the patient required another embolization management. After another embolization series, complete embolization was achieved, and the patient did not experience vaginal bleeding afterwards. Some cases that can be treated with embolization are bleeding due to uterine atony, birth canal lacerations, placental abnormalities, and AVM. This method is fast, can be performed repeatedly and does not require general anesthesia. Apart from that, this method can maintain the function and anatomy of the uterus.

The rebleeding rate in bleeding patients treated with arterial embolization is 5.2-13.5%. The main cause of rebleeding after embolization is recanalization of the embolized artery followed by collateral formation, and it is necessary to look for spontaneous arterial anastomoses such as from the ovarian artery, rotundum artery, middle rectal artery or inferior mesenteric artery. Re-embolization is an effective and safe procedure to do.[30]

In the past, this case could only be managed using arterial ligation or hysterectomy. Since its introduction in 1982, treatment using the arterial embolization method has become more common. This method is less invasive compared to ligation and hysterectomy methods. Apart from that, this method can also have advantages, especially for the patient's fertility function. Several other advantages of this method are shorter hospital stays, CTA-guided examination so that embolization can occur in the right artery, and minimal post-operative injuries.[29,30]

There is limitation to this study. It is a weakness that we only had one case which was fully documented, while other cases of acquired AVM were not fully documented and no surgical intervention had been performed. Our proficiency lies in the thorough documentation and evaluation of the AVM case, encompassing a comprehensive analysis from the pre-embolization phase to the post-embolization phase.

CONCLUSION

Uterine arteriovenous malformation (AVM) is an abnormality of the vasculature characterized by a direct connection between the arterial and venous systems within the uterus, devoid of any capillary network involvement. Uterine AVMs are a rare etiology of profuse and potentially catastrophic vaginal hemorrhage. While hysterectomy represents the definitive therapeutic approach, its implementation is typically avoided in younger patients who still desire fertility. Uterine artery embolization stands as the prevailing treatment modality for symptomatic uterine AVMs. However, obstetricians should be prepared to intervene or repeat the procedure if embolization fails to achieve the desired resolution of bleeding.

DISCLOSURES

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Conflicts of interest

The authors declare no conflicts of interest regarding the publication of this paper.

Patient consent for publication

The patient approved all of the work to be published that includes the personal information and all relevant family members have been informed and have consented to the publication of this information.

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Author contribution

All authors 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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