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Editorial

The Role of Reproduction for the Future of Women's Health

Rajuddin Rajuddin, Nurul Fadliati Maulida

In Indonesia, there were 305 maternal deaths per 100,000 live births in 2015.[1] In 2020, this figure dropped to 189 per 100,000 live births[2]. The World Health Organization (WHO) declared in 2015 that the maternal mortality rate must continue to decrease or be lowered to 105 per 100,000 live births to meet the Sustainable Development Goals (SDGs). This achievement was made possible by upgrades to the reproductive health system, as well as by the efficient allocation of infrastructure, medical personnel, and facilities. In the meantime, inadequate progress has been made in improving community nutrition, providing information and education on family planning and reproductive health, and maintaining clean water and sanitation. Consequently, to accomplish the SDGs and achieve this objective, health professionals and the community must play a positive role in women's reproduction.[3]

Several reproductive illnesses can impact women's future health, including Polycystic Ovary Syndrome (PCOS), the leading cause of infertility in women of reproductive age.[4,5] Due to its global prevalence, affecting between 15 and 20 percent of women, PCOS poses a significant threat to women's future health.[6] Several comorbid risk factors associated with PCOS include infertility, excessive body weight, hypertension, diabetes mellitus, and irregular menstrual periods,[7]. Currently, there is no conclusive explanation for the occurrence of PCOS. The most widely accepted theory attributes PCOS to luteinizing hormone (LH) hypersecretion.[8] The pituitary gland releases more LH due to increased GnRH pulsation in the hypothalamus, leading to ovarian hyperandrogenism and ovulatory failure. Recent research has identified KNDy neurons (Kisspeptin/Neurokinin B/Dynorfin) as the source of GnRH pulsation in PCOS.[9]

Menstrual disorders, such as menorrhagia, metrorrhagia, oligomenorrhea, polymenorrhea, and primary amenorrhea, including Mayer-Kustner-V Rokintanski Syndrome (MRKH) and Testicular Feminization Syndrome (Androgen Insensitivity Syndrome), are commonly observed in women.4,5 Reproductive health is a crucial indicator, given the associations between menstrual cycle disorders (such as PCOS, Diminished Ovarian Reserve (DOR), and Primary Ovarian Insufficiency (POI)), hypothalamic dysfunction, and infertility. It is essential to thoroughly examine data related to menstrual cycle history, secondary sex characteristics, and detailed pregnancy history, as these factors significantly impact women's health in both the short term and long term. This influence extends to aspects such as cancer risk, bone loss, and metabolic disorders.[10]

Reproductive health is influenced by various socio-economic and demographic factors, including poverty, low levels of education, and challenges accessing healthcare in remote areas.[11] A study conducted in Laos revealed that limited reproductive health knowledge, lack of autonomy, and gender inequality were key contributors to elevated rates of child marriage and maternal mortality.[12] A study in Ujjain, Madya Pradesh, India, states that factors that influence maternal and child health are low level of education of children and parents and employment status.[13] Cultural and environmental factors significantly contribute to the elevated maternal death rate, with beliefs such as the idea that having numerous children brings good fortune playing a crucial role. In Nepal, a study revealed that the widespread occurrence of child marriage is driven by societal pressure to start a family at a young age and the limited autonomy granted to children. This implies that even if a child desires to marry early, they may lack the power to decline due to societal expectations and norms.[14]

Verbal abuse from pregnancy care providers and the embarrassment experienced by early-married women act as deterrents, making them unwilling to seek care.[14] Additionally, reproductive health behavior is influenced by parental roles and psychological factors (e.g., the effects of parental divorce).15 Reduced maternal mortality, improved nutrition for children to prevent stunting, enhanced national health system, increased information and education about reproductive health, equitable access to healthcare, family planning, and clean water and sanitation are just a few of the SDGs that Indonesia has been striving to meet. By offering effective prenatal and delivery care, reproductive health education,

and actively supporting family planning, health professionals who specialize in reproductive health play a significant part in lowering the death rate for both mothers and children.3 The community can be better informed and educated to help achieve the Sustainable Development Goals (SDGs), which will lower rates of morbidity and death among mothers and neonates and improve the health of future generations of women.

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Research Article

Knowledge, Attitude, Practice of Pregnant Women and Husband's Support on the Implementation of Pregnancy Exercise

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Abstract

Objectives: To evaluate the knowledge and attitudes of pregnant women and assess the level of support from their partners regarding the adoption of pregnancy exercises in the Tangerang region.

Methods: A quantitative analysis was employed for this study, utilizing a cross-sectional study design.

Results: Data were collected from 49 respondents, revealing a statistically significant relationship ($p=0.031$) between the knowledge of pregnant women and the implementation of pregnancy exercises. Additionally, a highly significant association ($p<0.001$) was observed between the attitudes of pregnant women and their adoption of pregnancy exercises. However, no significant relationship was found between the level of support from husbands and the implementation of pregnancy exercises.

Conclusion: This study concludes that there is a significant correlation between the knowledge and attitudes of pregnant women and the adoption of pregnancy exercises.

Keywords: attitude, husband support, knowledge, pregnancy, pregnancy exercise, prenatal yoga.

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INTRODUCTION

In 2022 The World Health Organization (WHO) updated the recommendation guidelines regarding antenatal care that aims to provide positive pregnancy experience for pregnant mothers.[1] Antenatal care, also known as prenatal care, encompasses a series of activities initiated from conception through delivery. The primary objectives are to prevent, identify, and address conditions that may pose a threat to the health of both the fetus/newborn and the expectant mother. Additionally, it aims to assist women in approaching pregnancy and childbirth as positive experiences, ensuring a healthy pregnancy, a safe delivery, and the birth of healthy babies. One of the key components of antenatal care, as outlined in the Ministry of Health Regulations, is the preparation for a safe delivery. This involves the active participation of pregnant women and their partners in maintaining the health of the mother and making preparations for childbirth.[2]

It is important to understand the normal physiological changes that occur in pregnancy as these will help distinguish them from abnormal adaptations. Despite major advances in health care, to date, the Maternal Mortality Rate (MMR) is still in the range of 189 per 100,000 live births, has almost reached the set target of 183 per 100,000 KH in 2024.3 In the pursuit of expediting the achievement of optimal health status for pregnant women, the community plays a crucial role, both as individuals and organizations. One such role involves conducting classes for expectant mothers. A noteworthy program within the framework of antenatal care is the pregnancy exercise class. These classes, tailored for pregnant women, often take the form of pregnancy exercises. Pregnancy exercises are widely recognized for their benefits in preparing

for childbirth, particularly in terms of muscle relaxation and maintaining proper posture during and after pregnancy.[4]

Numerous studies have explored the various aspects of pregnancy exercise, ranging from its impact on expediting the second stage of labor in vaginal primigravida deliveries, its association with physical and psychological preparedness for childbirth, to its influence on the occurrence of perineal rupture.[5–7] However, there remains a significant gap in the literature concerning the knowledge, attitudes of pregnant women, and the role of husband's support in facilitating pregnancy exercise. This study aims to investigate the relationship between the knowledge and attitudes of pregnant women and the support provided by their husbands in the context of pregnancy exercise implementation.

METHODS

This study utilized a quantitative analysis approach with a cross-sectional study design. Data collection was conducted through online questionnaires distributed via Google Forms after obtaining informed consent from the respondents. The study focused on pregnant women in their second and third trimesters, receiving regular antenatal check-ups at a public healthcare facility (Pusat Kesehatan Masyarakat/ Puskesmas) in the Tangerang region, with a targeted sample size of 50 participants.The questionnaire's validity was assessed through a correlation coefficient test at a significance level of 0.05.

Data collection took place in March 2023, and statistical analysis was carried out using the chi-squared method in SPSS 25.0

RESULTS

Table 1. Sociodemographic Characteristic of Respondents

Variables	Frequency (n)	(%)
Age		
< 35	44	89.8
> 35	5	10.2
Trimester		
II	10	20.4
III	39	79.6
Implementation of pregnancy exercise		
Yes	30	61.2
No	19	38.8

Table 2. The Relationship of Knowledge of Pregnant Women to the Implementation of Pregnancy Exercise

Variable (knowledge)	Implementation of pregnancy exercise				OR (CI 95%)	*P-value*
	yes		no			
	n	%	n	%		
Adequate	17	81.0	4	19.0	4.904	0.031
Lack	13	46.4	15	53.6	(1.312-8.326)	

Table 3. The Relationship between Pregnant Women's Attitudes towards the Implementation of Pregnancy Exercise

Variable (attitude)	Implementation of pregnancy exercise				OR (CI 95%)	*P-value*
	yes		no			
	n	%	n	%		
Positive	20	90.9	2	9.1	17.000 (3.264-88.530)	< 0.001
Negative	10	37.0	17	63.0		

Table 4. The Relationship between Pregnant Women's Husband Support for the Implementation of Pregnancy Exercise

Variables (husband's support)	Implementation of pregnancy exercise				OR (CI 95%)	*P-value*
	yes		no			
	n	%	n	%		
Supported	29	65.9	15	34.1	7.733 (0.792-75.474)	0.130
Unsupported	1	20.0	4	80.0		

DISCUSSION

Based on Table 1, of a total of 49 respondents, 44 (89.2%) of them were women aged under 35 and 5 (10.8%) were aged above 35. The respondents gestational age was divided into two categories, with 39 (79.6%) were on their second trimester and 10 (20.4%) were on third trimester. Thirty of them (61.2%) claimed that they had engaged pregnancy exercise, while another 19 of the respondents (39.8%) had not.

According to the American College of Obstetricians and Gynecologists (ACOG), physical activity, including during pregnancy, offers numerous health benefits. Pregnancy is an opportune time to establish or maintain a healthy lifestyle, with exercise significantly contributing to the well-being of both the mother and fetus. Studies have shown that exercise during pregnancy can reduce the risks of macrosomia, gestational diabetes, cesarean delivery, and lumbar and sciatic pain.[8] This statement is aligned with a study by Putri which states that women who participates in pregnancy exercise classes had significantly lower odds of experiencing prolonged labor, postpartum hemorrhage, and postpartum fever than those in the non-participant group.[9] It is observed in this study that most of the respondents who have adequate knowledge regarding pregnancy exercises are also implementing it in their routines (81.0%). Majority of respondents who lack knowledge regarding pregnancy exercises do not implement it in their routines (53.6%). The calculated p-value of 0.031 confirms a significant relationship between pregnant women's knowledge and the actual implementation of pregnancy exercises.

Bivariate analysis of knowledge and the implementation of pregnancy exercise (Table 3) shows a significant relationship between the two, with a p value of 0,031 (OR 4.904, CI: 1.312-18.326). This is in line with a study in South Sumatera, Indonesia with 76 respondents showing a significant correlation between the two variables with a p value of 0,028.[10] The attitude variable has been shown to be significantly related to pregnant women doing pregnancy exercise (Table 3), with a p-value of 0.001 (OR 17.000, CI: 3.264-88.530). These results are in line with research conducted in South Sulawesi, which stated that there was a significant relationship between attitude and the implementation of pregnancy exercise in pregnant women (p = 0.01).[11]

To increase awareness of the benefits of physical activity during pregnancy, one should understand that social and cultural beliefs can influence health outcomes consequently. Physical activities during pregnancy is influenced by time, lack of child care or feeling unwell during pregnancy, whereas one of the factor that encourages physical activity is family support for refreshment and to prevent health problems in future.[12] Support from family members, friends, and organizations is important for a positive maternal environment. Lack of support are shown to be one of the risks for pregnant woman to develop psychological dysfunction in the offspring. Women with inadequate support were more likely to suffer from multiple psychological distresses. [13]

In addition to that, a study shows a significant positive relationship between family support and antenatal care (ANC). The higher the family support, the higher the scope of a good ANC examination can be accomplished, thus reducing the risk of maternal death.[14] Husband's support is influenced by various factors such as intimacy, self-esteem, and social skills. Husband's support is more influenced by intimacy than other aspects of social interaction. It is shown that the more intimate a person is, the greater the support one gets.[15] However, in the bivariate analysis conducted in this study, the relationship between husband's support and the implementation of pregnancy exercises yielded insignificant results (p=0.130, OR: 7.733, CI: 0.792-75.474). This lack of significance may be explained by findings in Saputra's study, where 53.3% of husbands did not encourage their wives to participate in pregnancy exercises. Various factors might contribute to this, including husbands' lack of awareness about the psychological stress experienced during pregnancy and the influence of cultural and educational backgrounds that assign full responsibility for pregnancy to the wife.[16] Understanding this important role is the first step for a husband to be able to support the mother in having regular antenatal care visits. Mothers who lack support from their husbands tend not to make regular antenatal care visits, this is because the does not have encouragement or motivation from her husband, such as the husband taking the mother to health services, the husband asking about the results of the examination, the husband joining the examination room, the husband giving information about the importance of having an antenatal visit care.[17]

CONCLUSION

There is a significant relationship between knowledge of pregnant women and implementation of pregnancy exercise. In addition to that, a significant relationship exists between the attitude of pregnant women and implementation of pregnancy exercise. However, there is no significant relationship was found between husband's support and the implementation of pregnancy exercises.

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CONFLICT of INTERESTS

The authors declare no conflict of interest in preparing this article.

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Research Article

Impact of COVID-19 Pandemic on Postpartum Contraceptives Method Choice (IUD vs Tubectomy) and Characteristic Aspects: A Retrospective Descriptive Study

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Abstract

Objective: This study aims to assess the impact of the COVID-19 pandemic on postpartum contraceptive methods.

Methods: This retrospective descriptive study was conducted at a single secondary center, utilizing secondary data retrieved from medical records at the Inpatient Installation of Sebelas Maret University Hospital, Surakarta, covering the period from January 2020 to January 2022.

Results: Among users of intra-uterine devices (IUDs), 85% were below 35 years old, 65% were primiparous, 67% had a history of previous injectable contraceptive use, 79% received routine antenatal care, and 51% had education below a college level. These individuals were educated about the importance of contraceptive programs during the COVID-19 pandemic. Sixty-six percent of IUD insertions were conducted via vaginal delivery, and 27% had health facilities within less than 1 km. In contrast, tubectomy contraceptive users comprised 106 patients, with the majority (54%) being aged 35 years or older, all being multiparous, and 25% tested positive for COVID-19. Among tubectomy users, 43% had a history of previous injectable contraceptive use, 85% received routine antenatal care, and 54% had education below a college level. Similar to the IUD group, they were educated about the significance of contraceptive programs during the COVID-19 pandemic. Eighty-four percent of tubectomies were performed via cesarean section, and 27% of patients lived within less than 1 km from health facilities.

Conclusion: The usage rates of intra-uterine devices and tubectomy for contraceptives remained stable during the COVID-19 pandemic. However, there was a decrease in postpartum in-person visits and mobility, coupled with an increase in hospitalizations.Keywords: contraceptive; family planning; intrauterine device; tubectomy.

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INTRODUCTION

An outbreak of pneumonia of unknown origin was detected in China in December 2019, caused by a new coronavirus identified as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2).[1] The World Health Organization (WHO) Emergency Committee declared the corona virus disease (COVID-19) a global health emergency on January 30th, 2020. As per 14th October 2022, the COVID-19 has infected 620,878,405 people, globally.[2] In Indonesia, there were 6,453,864 people infected by COVID-19, with the active cases counted 17,470 (0.3%) daily, the cure rate just reached 6,278,113 people, and death rate for COVID-19 was 158,281 people.[3] The clinical signs and symptoms of COVID-19 in most cases were fever, and some cases have dyspneu.[4]

The COVID-19 pandemic has the potential to significantly disrupt the achievement of family planning programs by 2030. Lockdown measures imposed on communities and the risk of infection among healthcare workers make it imperative to anticipate barriers to reproductive health services during the COVID-19 pandemic.[5] These barriers include a combination of disruptions in the contraceptive supply chain (e.g., barriers to contraceptive production and distribution),

shifts in the focus of the healthcare system (e.g., suspension of certain services and shifting of resources to pandemic response), and reduced demand for sexual and reproductive health services due to reluctance to visit health facilities and mobility restrictions.[6,7]

The rate of unwanted pregnancy in Indonesia reached 40 per 1,000 women of reproductive age with 63% of them terminating the pregnancy by obtaining an abortion. The National Population and Family Planning Agency (BKKBN) reported a 4% reduction in contraceptive use from February 2020 to March 2020 in Indonesia.[8] Increased fertility and sexual activity in the postpartum phase combined with increased difficulty in accessing services in the postpartum period pose certain risks for unwanted pregnancies.[2]

This study purposed to report the impact of the COVID-19 era on postpartum contraceptive method.

METHODS

This study is a retrospective conducted at the inpatient setting of the Sebelas Maret University Hospital from January 2020 to January 2022.

The total sampling technique used for this study contained post partum patients hospitalized in Sebelas Maret University Hospital between January 2020 to January 2022, based on the inclusion and exclusion criteria. This research has gone through a review for the existence of a certificate of ethical feasibility by the ethics committee of the Sebelas Maret University Hospital. Inclusion criteria included all postpartum women at the Inpatient Installation of Sebelas Maret University Hospital who were treated and documented using a postpartum IUDs or tubectomy at the Inpatient Installation of Sebelas Maret University Hospital. The exclusion criteria were patients with incomplete medical record data. Characteristics of the patients included age, parity, education grade, history of antenatal care, history of contraceptive use, mode of delivery, distance accessibility to health facilities, and reasons for contraceptive decisions. Identification of postpartum contraceptives used contraceptive procedures, diagnosis, and dispensing codes.

The independent variables were pregnant women who gave birth and were treated at the Inpatient Installation of Sebelas Maret University Hospital in the period January 2020 to January 2022. The dependent variable was patients with postpartum contraceptive choices, either tubectomy or IUD users. This research only focuses on comparing the IUDs and tubectomy contraceptive methods for several reasons; tubectomy and IUDs are contraceptive methods with high efficacy and low side effects,[9,10] during the COVID-19 pandemic, regulations of social distancing with less outdoor activities have had an impact on reducing the number of patients who come to the hospital compared to the nearest health facility; therefore the COVID-19 condition has a more significant impact on the use of IUDs and tubectomies which require more advanced health facilities, compared to other contraceptive methods, such as birth control pills, implants or injections,[11,12] and the chosen contraceptive methods were adjusted to the research location, as this research was a hospital-based study, the patients who admit specifically for other simple contraceptive method (birth control pills, implants, or injections) were lacking and could not be used as representative data of their population users.

The data regarding the characteristics of tubectomy or IUD users during the COVID-19 Pandemic at Sebelas Maret University Hospital was descriptively presented as a frequency distribution table using Microsoft Excel and then analyzed utilizing Statistical and Product Service Solution (SPSS) 25.0 for Windows. Before carrying out the research, the researcher had obtained ethical clearance from the Health Research Ethics Committee Dr. Moewardi, with number 141 / I / HREC / 2023 as a guarantee that this research has been reviewed for its appropriateness by applicable medical ethics.

RESULTS

This study is based on data from January 2020 – January 2022 with a total of 395 post-partum patients which consist of 106 patients (26%) included as tubectomy contraceptive users, 233 patients (60%) as IUD users, 11 patients (3%) with other contraceptives (interrupted coitus, barrier, hormonal contraceptive), and 45 patients (11%) without any contraceptive at Sebelas Maret University Hospital.

A comparison of demographic data on IUD and tubectomy contraceptive users is presented in Table 1. Based on age, 85% (198 subjects) of IUD users are women with a younger age (< 35 years) compared to tubectomy contraceptive users, where 54% (57 subjects) of the users are

women ≥ 35 years. Regarding parity, both IUD and tubectomy contraceptive users are dominated by multiparous patients, although the percentages are quite far, 65% (152 subjects) and 100% (106 subjects), respectively. This similarity was also found in the history of antenatal care (ANC), where both groups have a population that regularly undergoes ANC and have been given education regarding the urgency of contraceptive usage, especially during COVID-19, with a slightly higher in tubectomy users, 85% (90 subjects) compared to IUD users, 79% (183 subjects). Regarding the mode of delivery, we found that the two groups have very different user characteristics, where 66% (153 subjects) of IUD users are women with a history of spontaneous delivery. In contrast, 84% (89 subjects) of tubectomy contraceptive users are women with history of C-sections.

Other predisposing factors, such as education level, were also analyzed. From the education level, we found that there was no significant difference between users of the two contraceptive methods, where the ratio between patients with high school or below : higher educational level was around 1 : 1 (51%:49% for IUD users and 54 %:46% in tubectomy contraceptive users). Interestingly, based on the history of contraceptive use data, 67% (153 subjects) of IUD users were previously a user of birth control injections. In comparison, only 43% (46 subjects) of tubectomy users previously used birth control injections as their contraceptive method. More importantly, the data shows that 40% (42 subjects) of tubectomy users were previously IUD users, while among IUD users, 20% (49 subjects) chose not to use any contraceptive method before finally deciding to choose an IUD.

In accordance with the focus of this research, which evaluates the effects of COVID-19, we also evaluated the access to primary health facilities. We found that in both groups, 27% of the users could access primary health facilities within a distance of <1 km. The method of tubectomy was also evaluated and revealed that Pomeroy was the most commonly used method, which was performed in 100 subjects (94%) of tubectomy contraceptive users, followed by Kroener, Uchida, and Madlener (2 subjects each).

Table 1. Demographic Data of IUDs and Tubectomy Contraceptive Users

Variables	Frequency n (%)	
	IUDs	**Tubectomy**
Age (y.o.)		
< 35	198 (85)	49 (46)
≥ 35	35 (15)	57 (54)
COVID-19 Infection		
Positive	50 (21)	26 (25)
Negative	183 (79)	80 (75)
Parity		
Primipara	81 (35)	0 (0)
Multipara	152 (65)	106 (100)
Mode of delivery		
Spontaneous	153 (66)	17 (16)
C-Section	80 (34)	89 (84)
History of antenatal care		
Routinely	183 (79)	90 (85)
Not routinely	50 (21)	16 (15)
Educational level		
High school or below	118 (51)	57 (54)
Higher educational level	115 (49)	49 (46)
History of contraceptive		
Pill	29 (12)	10 (9)
Injection	153 (67)	46 (43)
Implant	0 (0)	2 (2)
Intra-uterine devices (IUD)	0 (0)	42 (40)
Others (barrier, coitus interruptus)	2 (1)	2 (2)
None	49 (20)	4 (4)
Access to primary health facilities (km)		
< 1	62 (27)	29 (27)
> 1	171 (73)	77 (73)
Method of tubectomy		
Pomeroy		100 (94)
Kroener		2 (8)
Uchida		2 (8)
Irving		0 (0)
Madlener		2 (8)
Aldridge		0 (0)

DISCUSSION

The COVID-19 widespread postures boundaries to get a postnatal sterilization procedure, counting at the patient and health care provider levels to the policy level. Research by Medicaid reports that at slightest half of the women who desire postnatal sterilization actually undergo the procedure while more than 20% who do not get the desired postpartum sterilization will experience another unwanted pregnancy within that time period in the following year.[2,12] Previous studies reported that healthcare resources are used for personal protective for COVID-19 infections, and the focus on sexual and reproductive health services is hampered which is also affected. Delays in seeking, accessing, and

receiving contraceptives during a pandemic thus increase the risk of maternal death, secondary morbidity due to unwanted pregnancies, and an increased financial burden to deal with these complications by an already strained health care system.[5] The impact of COVID-19 on sexual and reproductive health (SRH) should not be ignored and must be acknowledged as thoroughly as its clinical scope.

Data released by BKKBN in the National Family Planning Program Report regarding the accumulated results of new family planning services for national health insurance participants according to contraceptive methods in 2020 shows that overall, there was a decrease by 4% from February 2020 to March 2020. More detail, the highest decrease occurred in vasectomies (76%), implant removal (16%), IUDs (9%), and condoms (9%). This data also shows that only injectable contraceptives did not experience a decrease. At the same time, other contraceptive methods, such as tubectomy and pills, were also affected, with a decrease of 6% and 4%, respectively.[13] Based on our result, we reported that 60% (233 subjects) of postpartum patients decided to use a IUD contraceptive usage while 26% (106 subjects) decided to chose tubectomy contraceptive usage. As many as 16% of women had given spontaneous delivery chose tubectomy as a postpartum contraceptive whereas 100% of the users were multiparous. In IUD users, 66% of them (153 subjects) had given spontaneous delivery which 35% (81 subjects) of them were a primiparous woman. The average number of patients with postpartum tubectomy contraceptives usage was ≥ 35 years with 57 patients (54%). The present findings contrast with certain prior research outcomes. One study reported a contraceptive usage rate of 83.04% among 3876 women aged 20–24 years, surpassing that of older age groups.[14] In a retrospective cohort study involving 23,965 patients who underwent laparoscopic tubal ligation, the median age for tubectomy was reported as 32.8 years.[15] However, the median age at tubal ligation was 35.5 years.[16] Our study aligns with the result of these studies indicating a prevailing inclination among older women to choose tubal ligation as their preferred contraceptive method. It's noteworthy that the increased availability and growing public acceptance of long-acting reversible contraceptives have led to a reduction in outpatient and interval sterilization procedures.

The World Health Organization (WHO) recommends offering family planning counseling throughout the continuum of maternal health services, including antenatal care (ANC), childbirth, and the postpartum period, which encompasses postnatal care (PNC), child immunization, and well/sick baby clinics. Integrating family planning counseling within these maternal health services enables women to receive comprehensive care without the need for separate visits specifically for family planning services. Moreover, WHO recommends providing family planning education and services to women before their discharge from health facilities following childbirth. This strategy aims to increase women's awareness of the benefits of spacing pregnancies and to improve their knowledge and attitude towards modern contraceptive methods.[17] Many studies have evaluated the effect of family planning counseling during ANC on postpartum modern contraceptive uptake and reported a positive association.[18–20] For example, a study in Northern West Ethiopia indicated that family planning counseling during ANC increased modern contraceptive uptake by six weeks postpartum.[21] Similarly, a study in Nepal indicated that family planning counseling during ANC had improved postpartum contraceptive uptake.[22]

The provision of family planning counseling during ANC services exhibited a notable impact on encouraging the utilization of modern family planning methods in the postpartum period. Consequently, healthcare providers should prioritize the maintenance of seamless care by strengthening the amalgamation of family planning counseling services within ANC and establishing robust referral connections between community resources and healthcare workers.[21] Moreover, during a pandemic scenario, it appears prudent to prioritize the ANC program. Research findings indicate that women with a multiparous status exhibited a higher propensity for contraceptive utilization. Specifically, women identified as multiparous (≥3) showcased a 25.58-fold greater likelihood of utilizing contraceptives.[23] The United States Centers for Disease Control and Prevention conducted a multicenter study known as the Collaborative Review of Sterilization (CREST), which prospectively enrolled over 10,000 women between 1978 and 1986, with a planned five-year follow-up. The study's findings revealed that regret associated with sterilization was lower in nulliparous women compared to women with at least one child. Consequently, a woman without children who wishes to remain child-

free is less likely to experience regret following sterilization compared to a mother who does not desire additional children.[10]

Studies in Mexico reported that 29% postpartum C-section patients used sterilization.[23] This present study showed 89 patients (84%) who underwent tubal ligation through C-sections had a higher risk of regret. There was however no incidence of regret reported during our study period due to the design of the study. This study also highlighted that 90 patients (85%) routinely attended antenatal care activities. This is in accordance which reported the frequency of antenatal care as measured by 75% of prescribed care was altogether related to any postpartum contraceptive.23 In addition, access to contraceptives can also be extended to trained midwives or public health nurses to provide these services to patients. Health facilities can be strengthened by using digital medical devices to reach women's homes and encourage them to use contraceptives without having to visit the crowded health facilities.[24]

This study included 57 patients (54%) who had a history of lower level of education and 115 patients (49%) who had a history of higher levels of education. This result contrasts with a study that describe women who had completed higher education had 2.8 times greater odds of using contraceptives (AOR=2.800; 95% CI=2.181–3.594) than those who had not completed any formal education.[25] Groups of people who have a higher education have better access to family planning services and have a better position in the decision-making process regarding contraceptive use. This is also supported who state that the level of education of women influences the use of modern contraceptives. Groups of people who have a higher education have better access to family planning services and have a better position in the decision-making process regarding contraceptive use.[19] Therefore, it is suggested that health promotion toward contraceptives should be encouraged for those with low education.

Geographical location and the accessibility of health facilities significantly impact contraceptive utilization. In this study, 171 individuals (73%) had to travel more than 1 km to access a health facility. These findings contrast with a cross-sectional study conducted by Roy et al in 2021, which revealed that women residing in rural areas were approximately 65% less likely to use family planning methods compared to their urban counterparts.[5] It is widely accepted that urban regions exhibit higher rates of family planning utilization compared to rural areas. This disparity is attributed to differences in financial circumstances, visits by family planning officers, levels of women's autonomy, and various community characteristics.

Ensuring the availability of effective contraceptives is considered a crucial priority in addressing this issue.[26] Overcoming barriers created by the pandemic to contraceptive services is crucial. Contraception plays a pivotal role in healthcare by empowering reproductive autonomy and reducing unwanted pregnancies.[7] The absence of clear recommendations for postponing pregnancy during the COVID-19 pandemic necessitates individualized decision-making. Hence, it is imperative to provide comprehensive education regarding the importance of contraceptives during both antenatal and postpartum care. [24,26] This study observed the successful performance of postpartum tubectomy procedures at Sebelas Maret University Hospital. The effectiveness of these procedures may be influenced by various factors such as the individual's educational background, utilization of antenatal care, and history of contraceptive use.

In this study, a majority of users of intrauterine device (IUD) contraceptives were below 35 years old, constituting 85% (198 women). This aligns with prior research findings indicating a higher prevalence of contraceptive use among women aged 25-34 years, accounting for 51.2%.[15] Regarding parity, 152 individuals (65%) in this study were classified as multiparous. Studies have shown a higher prevalence of contraceptive utilization among women with multiparous status. Notably, women identified as multiparous (≥ 3 children) exhibited a 25.58-fold higher tendency to use contraceptives. These findings highlight the significant impact of the number of living children and perceptions of an ideal family size on women's attitudes toward contraceptive use. Therefore, a policy perspective is needed to promote better family planning.

The majority of 153 patients (66%) who received IUDs in our study had a history of spontaneous vaginal delivery. This finding was similar to the result of recent retrospective study about prevalence of long-acting reversible contraceptive (LARC) methods utilization and associated factors which revealed that spontaneous vaginal delivery was the most common method of delivery in

IUD users.[27] However, in this study, C-section was only recommended for pregnant women who has obstetric indications and researchers maintain a focus on postpartum contraceptive as an important strategy to promote maternal and newborn health. Service providers need the knowledge and skills to provide reversible long-acting contraceptives (i.e. IUDs and implants) following vaginal and abdominal delivery. In this study, it was reported that 183 people (79%) routinely attended antenatal care activities. This is in accordance with a study conducted by Arero et al in 2022 which reported that receiving counseling during antenatal care were associated with immediate any postpartum reversible long acting contraceptive methods use.[27]

IUD insertion techniques had been standardized using the no-touch and withdrawal technique. The IUD used for postpartum women was so far using a regular IUD, which was inserted in two ways. The first way was by using two fingers (index and middle fingers) where the IUD is clamped between them and inserted into the uterine cavity through the dilated cervix until it was attached to the fundus. The second way was using ring forceps in which the IUD was held at the junction between the two vertical arms and horizontal bar, and it was inserted through the dilated cervical os and pushed deep into the uterine fundus.[28]

The Indonesian Journal of Obstetrics and Gynecology have been studied about the effectivity and safety between R-inserter group and IUD inserted by forceps ring in woman with IUD users. In the R-inserter group, the cumulative rate of expulsion was highest at three months follow up, i.e. 4,3%, and there was no additional expulsion thereafter. Those who suffered from pain and bleeding were treated with mefenamic acid and tranexamic acid, respectively.[28] Three subjects from the R-inserter group had their IUDs removed because of bleeding. Two cases from each group had their IUDs removed because of infection unresponsive to a standard antibiotic treatment. Continuation rates were 93.7%, 93.2% 90.8% and 90.8% each for three, six, nine and 12 months respectively. A multicenter study using CuT 380A IUD inserted by forceps ring during postpartum period reported expulsion rate 13.8%, 16.6% and20.5% each for the first, third and sixth months follow up, respectively. Others showed cumulative expulsion rate 2.67% at three months follow up7% at six months and 12.3% at 12 months there after. The primary and attracting event in the postpartum IUD insertion was high expulsion rate. There was no difference between the R-inserter and ring forceps group, neither in the rate of expulsion nor infection.[28]

Ensuring effective contraceptive services remains an imperative and top priority, necessitating prompt resolution of delays in these services caused by the pandemic. The American College of Obstetricians and Gynecologists (ACOG) emphasizes the critical role of contraceptives in healthcare, aiming to enhance reproductive autonomy and mitigate unwanted pregnancies. The absence of clear guidelines recommending the postponement of pregnancy amid the COVID-19 pandemic underscores the necessity for individualized decision-making. Therefore, comprehensive education spanning from prenatal care to postpartum care regarding the imperative nature of contraceptives becomes essential.[24,26] This study highlights the consistent provision of postpartum Intrauterine Device (IUD) services at Sebelas Maret University Hospital. Factors such as educational level, history of antenatal care, and prior contraceptive usage are influential in determining the adoption of postpartum contraceptive methods.

Numerous studies have outlined the effects of the pandemic on contraceptive services. This particular study delves into the state of contraceptive services and outlines the profile of hospital-based contraceptive users among postpartum women amidst the COVID-19 pandemic. However, it is important to acknowledge certain limitations in this study, notably its retrospective and descriptive design, as well as being conducted in a single-center setting. These limitations might restrict the representation of the findings to the broader population.

This study scrutinized various determinants influencing the choice to use postpartum contraceptives, encompassing educational background, utilization of antenatal care, accessibility, and reasons underlying the refusal of contraceptives.

CONCLUSION

The widespread impact of COVID-19 has affected women's access to contraceptive services, potentially exacerbating existing disparities in the quality of contraceptive care. This, in turn,

poses a threat to women's autonomy. In the short term, understanding how the COVID-19 pandemic affects encounters, utilization, and choices regarding contraceptive care can mitigate adverse effects on sexual and reproductive health. Our results underscore the importance of promoting family planning education among local community workers, particularly concerning pregnancies that are deemed high-risk. It is crucial to give equal attention to healthcare issues during the pandemic, including ensuring affordable family planning services despite social restrictions. This is because a high level of education and the quality of that education significantly influence comprehension and informed decision-making processes.

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CONFLICT of INTEREST

The authors state that the research was conducted without any commercial or financial relationship that could be construed as a potential conflict of interest.

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Research Article

Acceptance and Satisfaction of Indonesian Women Undergoing Visual Inspection with Acetic Acid (VIA) Examination Using Digital Image and the Related Factors

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Abstract

Objective: To determine the acceptance, satisfaction, and willingness to recommend of women undergoing VIA examination with and without digital image and their related factors.

Methods: This was an observational analytic study with cross sectional method. The subjects of this study were adult women undergoing VIA examination with or without digital image in Ulin Regional Hospital, Indonesia. Patients who did not fill the whole questionnaire were excluded from the study. Characteristics analyzed in the study were age, education, occupation, socioeconomic status, source of VIA information, and previous VIA experience. Outcomes analyzed in this study were acceptance, satisfaction, and willingness to recommend.

Results: There were 303 subjects who were included in the study (252 with digital image and 51 without digital image). There were no risk factors of lower acceptance, satisfaction, and willingness to recommend among women undergoing VIA examination. However, the cases of women with low acceptance and satisfaction are associated with lower information of the examination.

Conclusions: Digital IVA examination is a feasible alternative with acceptance, satisfaction, and recommendation rates that are the same as VIA examination without digital imaging.

Keywords: cervical cancer, digital image, Femicam®, visual inspection with acetic acid examination.

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INTRODUCTION

Cervical cancer is the third most prevalent cause of cancer-associated death in women worldwide. Cervical cancer occurs in 1.4 million worldwide, while every year about 231,000 women die from cervical cancer. In addition, the incidence of cervical cancer in Jakarta is known to be 100 per 100,000 adult women.[1]

Cervical cancer is caused by the Human Papilloma Virus (HPV) with the two most common types of HPV, namely 16 and 18. Generally, signs of infection that appear are small pink spots around the genitals that feel itchy or hot like burning. Patients infected with HPV can develop into low-grade lesions, high-grade lesions to cervical cancer if early detection and treatment are not carried out.[2,3] The development required for high-grade lesions to cervical cancer is 10 to 20 years, but in some cases the lesions pre-cancer can develop into cancer within one or two years.[2] Women who experience cervical cancer often occur at the age of 30-40 years and over. The risk factors for a person being infected with HPV in the cervix are: sexual activity aged less than 20 years, frequent change of sexual partners, sexually transmitted infections, family history of cervical cancer, smoking, immunosuppression.[4]

Cervical cancer prevention efforts consist of primary, secondary, and tertiary prevention. Primary prevention is the act of preventing before being exposed to the HPV virus with health

education regarding healthy sexual behavior and HPV vaccination. Secondary prevention is carried out after exposure to the HPV virus by early detection through screening, diagnosis, and immediate therapy of pre-cancerous cervical lesions.[2] Enforcement of the right diagnosis in patients with cervical cancer is needed to determine the appropriate treatment for the tertiary prevention.[5]

Based on the data from the Indonesian Ministry of Health, the coverage of early detection has only reached around 7.6% of the target of 85%.[6] The low coverage of cervical cancer screening is caused by various factors, namely low knowledge due to lack of information regarding the dangers of cervical cancer and how to detect it, concerns about the positive results obtained from the results of screening examinations, as well as the cost of some screening for pre-cancerous cervical lesions which are relatively expensive.[6]

Screening for cervical pre-cancerous lesions can be done using various techniques such as pap smear test, HPV DNA test, and Acetic Acid Visual Inspection (VIA) test. Most hospitals provide facilities for HPV vaccination and Pap test, but only few have VIA facilities and colposcopy.[7] The Pap test is still difficult to attract much interest in developing countries, besides the price is still relatively expensive even though it looks simple in its implementation, it requires complex equipment to detect cervical cancer and patients do not get the results immediately after being examined so that some patients do not return to health facilities and lost the opportunity to get further therapy.[2]

The VIA test is an examination of pre-cancerous lesions using acetic acid, this test uses an easy technique, low cost, and has a high level of sensitivity. Due to the VIA high specificity (92.2%), the use of the VIA test can be an alternative for pre-cancerous lesion screening even in areas that have limited facilities and resources. It is very suitable to be used as cervical cancer screening in developing countries like Indonesia.[8] In carrying out the VIA test procedure, the basic results obtained are in the form of digital images. With currently available technology, the cervical images of women who take VIA tests can be recorded using electronic devices and the results can be explained immediately to women who have IVA tests.[9] The use of digital images of the patient's cervix during counseling after the IVA test examination, it is expected that the patient will have a better understanding of the condition of the cervix so that acceptance and satisfaction will lead to follow-up recommendations and a sense of satisfaction can lead to screening behavior in the surrounding community.

This study aims to compare the acceptance, satisfaction, and willingness to recommend of women undergoing VIA examination with and without digital image and their related factors.

METHODS

This is an observational cross-sectional study performed on women undergoing VIA examination with and without digital images in Ulin Regional Hospital, Indonesia, during the period of June to November 2022. Indonesia. The study population consisted of women who underwent visual inspection with acetic acid (VIA), both with or without the use of digital images, and who met the inclusion criteria while women who did not fill the whole questionnaire were excluded from the study.

The sampling in this study was conducted through simple random sampling, meaning potential subjects were randomized to either the digital image-enhanced VIA examination group or the standard VIA examination group at the time of subject recruitment. Sampling continued until the required sample size was achieved. The sampling will be conducted with a ratio of digital image-enhanced examinations to standard examination at a 3:1 ratio (3 with images: 1 without images).

The examination of VIA was done by a gynecology resident with supervision by an experienced gynecologist with more than 10 years of experience. The examination of VIA was done in accordance to the World Health Organization (WHO) guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.[1] The VIA examination with digital image was done using FEMICAM Medical Camera® (Sarandi Karya Nugraha, Indonesia).[2]

This study used 5% error bound and 95% confidence interval limit, with power of the test considered to be 90%. Variables analyzed in this were age, education, occupation, socioeconomic status, source of VIA information, and previous VIA experience. Outcomes analyzed in this study were acceptance, satisfaction, and willingness to recommend. The acceptance, satisfaction, and willingness to recommend were evaluated using a self-filled questionnaire which had already validated in Indonesia (Appendix 1).

All human studies had been approved by the Research Ethics Committee of Faculty of Medicine, University of Indonesia. All patients who were included in this study had given the informed consent prior to the study. Collected data were then analyzed using SPSS for Macintosh ver. 20. Characteristics of subjects and the symptoms experienced were analyzed descriptively. Bivariate and multivariate analysis was done in order to determine the risk factors of lower acceptance, satisfaction, and willingness to recommend among subjects.

RESULTS

A total of 303 subjects were included in this study, 252 (83.1%) of whom underwent VIA examination with digital image and 51 (16.9%) underwent VIA examination without digital image. Baseline characteristics of subjects can be found in Table 1.

Table 1. Characteristics of Subjects

Characteristics	Frequency (N=30)
Examination Type	
with digital image	252 (83.1)
without digital image	51 (16.9)
Age (median, range)	42 (19-67)
Education	
undergraduate	243 (80.2)
high school	49 (16.2)
elementary	11 (3.6)
Occupation	
employee	154 (50.8)
housewife	149 (49.2)
Income Level (wages)	
> minimum	156 (51.5)
< minimum	147 (49.2))
Information Source	
electronic	85 (28.1)
printed	8 (2.6)
health officer	163 (53.8)
family	47 (15.5)
Previous VIA Experience	
yes	91 (31.4)
no	208 (68.6)
Previous VIA with digital image experience	
yes	236 (77.9)
no	67 (22.1)

Following the analysis of the baseline characteristics of subjects, the distribution of acceptance satisfaction, and willingness to recommend of VIA examination were measured. It is observed that there were only 1 subject with low rate of acceptance and 1 subject with low rate of satisfaction. The results can be found in Table 2.

Table 2. Distribution of Acceptance Satisfaction, and Willingness to Recommend of VIA Examination

Variable	Frequency (%)
Acceptance	
Yes	203 (99.7)
No	1(0.3)
Satisfaction	
Yes	302 (99.7)
No	1(0.3)
Willingness to recommend	
Yes	300 (99.0)
No	3 (1.0)

Following the distribution analysis, the subjects who have undergone VIA examination were analyzed further. The factors affecting acceptance, satisfaction, and willingness to recommend were analyzed and determined. The results can be found in Table 3 for acceptance and Table 4 for satisfaction. However, cross-tabulation table could not be made for willingness to recommend as all of the subjects who had undergone VIA examination had high rate of willingness.

Table 3. Factors Associated with Acceptance of VIA Examination

Characteristics	Acceptance (+)	Acceptance (-)	*P-value*
Examination Type			1.000
with digital image	73 (98.6)	1 (1.4)	
without digital image	21 (100)	0	
Age			0.262
<30	28 (100)	0	
30-40	41 (100)	0	
>40	25 (96.2)	1 (3.)	
Education			0.760
Undergraduate	32 (100)	0	
Senior high school	43 (97.7)	1 (2.3)	
Junior high school	14 (100)	0	
Elementary	5 (100)	0	
Occupation			0.421
Employee	39 (97.)	1(2.5)	
Housewife	55 (10)	0	
Income Level (wages)			0.432
> minimum	54 (100)	0	
< minimum	40 (97.6)	1 (2.4)	
Information source			
Electronic media	23 (95.8)	1 (4.2)	
Printed media	2 (100)	0	
Health officer	53 (100)	0	
Family	16 (100)	0	
Previous VIA with digital image experience			1.000
yes	13 (100)	0	
no	81 (98.8)	1 (1.2)	

Table 4. Factors Associated with Satisfaction of VIA Examination

Characteristics	Satisfaction (+)	Satisfaction (-)	*P-value*
Examination Type			1.000
with digital image	73 (98.6)	1 (1.4)	
without digital image	21 (100)	0	
Age			0.262
< 30	28 (100)	0	
30-40	41 (100)	0	
>40	25 (96.2)	1 (3.8)	
Education			0.119
Undergraduate	32 (100)	0	
Senior high school	44 (100)	0	
Junior high school	13 (92.9)	1 (7.1)	
Elementary	5 (100)	0	
Occupation			0.421
Employee	39 (97.5)	1(2.5)	
Information source			0.849
Electronic media	24 (100)	0	
Printed media	2 (100)	0	
Health officer	52 (98.1)	1(1.9)	
Family	16 (100)	0	
Previous VIA with digital image experience			1.000
Yes	13 (100)	0	
No	81 (98.8)	1(1.2)	
Housewife	55 (100)	0	
Income Level (wage)			1.00
> minimum	53 (98.1)	1(1.9)	
< minimum	41 (100)	0	

DISCUSSION

The VIA examination with digital image has similar acceptance, satisfaction, and willingness to recommend to examination without digital image. Visual inspection examination using acetic acid with digital imagery / digital cervicography (VIA-DC) has begun to be developed around the world with various brands to increase the accuracy of this examination in detecting cervical precancerous lesions.[9–12] One of the tools that has been developed in Indonesia and has been clinically tested is Femicam®.[13] Previous studies have shown that VIA examination with digital images has a higher level of sensitivity and specificity than ordinary VIA examinations.[14]

In this study, it was found that only 1 study subject had poor acceptance or poor satisfaction with the VIA examination, while it was found that all research subjects were willing to recommend the VIA examination. These results indicate that in general the level of acceptance, satisfaction, and willingness to recommend subjects is very high. The results in this study were similar to previous research which showed a high level of satisfaction and acceptance, especially for VIA examination participants who were educated using leaflet media and audiovisual media.[15] In another study conducted in Morocco in 2015, it was also stated that a similar acceptance rate (99%) of VIA examinations without digital images, even in populations with very low awareness of cervical cancer.[16] This is thought to be closely related to the perception of participants that VIA examination can save lives if done properly.[16]

Age is directly related to participation rates and VIA examination expectations.[17,18] Older age is directly related to higher participation rates but concerns about the use of technology are higher than younger test participants.[19] Previous shows that older participants tend to require more intensive communication and a longer time in accepting technology, one of which is VIA examination technology with digital images.[20]

it was found that subjects who had a low level of acceptance, satisfaction level, and desire to recommend tended to have a low-medium level of education. After further investigation, it was discovered that this was related to the subject's ignorance of the benefits of image analysis technology compared to the risks involved in taking pictures during an VIA examination.

The results in this study were similar to research conducted in Bogor, which showed that education level directly influenced perceptions of VIA examinations and other cervical cancer examinations.[21] This was also shown in previous studies which showed that the level of education related to the level of knowledge about cervical cancer, examinations in the framework of early detection of cervical cancer, the dangers posed, and examination methods.[12,21,22]

Based on the analysis conducted, it is known that in general the poor level of acceptance, satisfaction, and desire to recommend is associated with a lack of knowledge and participants' perceptions of the VIA examination conducted, both with digital images and without digital images. Therefore, one of the things that is considered the most important in carrying out VIA examinations is education and counselling.[3] These results are like research which showed that participants underwent VIA examinations with digital images and received counseling and education before and after the action will have a higher level of satisfaction.[12]

CONCLUSION

It is concluded in this study that the VIA examination with digital image has similar acceptance, satisfaction, and willingness to recommend to examination without digital image. Education and informed consent play an essential role to maximize the acceptance and satisfaction of VIA examination. Further research is needed to examine the results by including more data from various different hospitals in order to gain further insight into the acceptance, satisfaction, and willingness to recommend digital VIA examinations.

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CONFLICT of INTERESTS

Authors declared no conflict of interest regarding this article.

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Research Article

The Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, and Length of Cervix as Predictors of Premature Delivery during the Covid-19

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Abstract

Objective: The percentage of neonatal death continues to increase on a yearly basis, in which prematurity is the main cause of mortality. This study determines the descriptive outcomes between neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLT), and cervical length as predictors of preterm birth.

Methods: A retrospective analytical study is conducted using medical records from Dr. Cipto Mangunkusumo National General Hospital. The subjects of this study includes pregnant women diagnosed with preterm delivery in Dr. Cipto Mangunkusumo National General Hospital from April 2020 to June 2021. Data on neutrophil-lymphocyte and platelet-lymphocyte ratios were obtained from a complete blood test during admission. Cervical length is measured using transvaginal ultrasound. The three variables are compared to the control group, which consists of pregnant women with full term delivery.

Results: This study conducted a study with a total of 81 subjects with preterm delivery and 92 subjects with full term delivery. There were no significant difference in neutrophil-lymphocyte and platelet-lymphocyte ratios between preterm and a-term delivery (p=0.795 and p=0.475). Cervical length was significantly longer in preterm compared to full term delivery (24,50 vs 3,15 mm; p = 0,031). The neck cervical length of several participants was not assessed. Cervical length in preterm delivery obtained only 21 patients and data from 10 subjects from the full term group.

Conclusion: The ratio of neutrophil-lymphocyte and platelet-lymphocyte cannot be used as predictors of preterm birth in all pregnant women. To reduce bias in this research, studies with prospective study design with a specified subject criteria are needed.

Keywords: cervical length, neutrophil-lymphocyte ratio, platelet lymphocyte ratio, premature delivery.

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INTRODUCTION

Premature delivery is one of the leading causes of neonatal death in the world. The percentage of neonatal deaths due to prematurity according to WHO was 14% in 2000, which increased to 15% in 2001-2005 and 16% in 2006-2008, and continued to increase to 17% in 2009-2011. In 2010 the number of neonatal deaths due to prematurity was 32,342 out of 73,404 neonatal deaths, which is 44% of all neonatal deaths. Indonesia has a premature incidence rate with perinatal mortality of around 19% and prematurity is the main cause of perinatal mortality.[1]

Until now, clinical findings of early signs of labor are still very difficult to understand and predict, so that overdiagnosis is often found until there is clear evidence of labor.[2] One of the predictors of spontaneous preterm birth is cervical length as measured by transvaginal ultrasonography (USG). It is controversial whether management based on cervical length examination via transvaginal ultrasonography can reduce the incidence of spontaneous preterm birth.[3]

The specific count test is a simple, inexpensive, and available test in most laboratory services. Currently, during the COVID-19 pandemic, the type of count examination is a routine

examination carried out with the aim of knowing the neutrophil-lymphocyte ratio as an indicator for assessing the diagnosis of COVID-19. Several studies have shown an increase in the number of platelets associated with infection, inflammation, and malignancy.[4,5] Recently, the platelet-lymphocyte ratio and the neutrophil-lymphocyte ratio have also been considered as potential markers as markers of inflammation associated with various pathological conditions, one of which is preterm labor.[6]

Based on the reasons mentioned, it is necessary to conduct further research to evaluate the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and cervical length in mothers with spontaneous preterm labor in Indonesia in order to predict early the process of preterm labor that will occur. It is hoped that knowing the relationship between these factors can reduce neonatal morbidity and mortality caused by premature labor in Indonesia in the future.

METHODS

The study is a case-control retrospective analytic study. This study aims to determine the descriptive outcomes between levels of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and cervical length as predictors of preterm labor at Dr. Cipto Mangunkusumo National General Hospital. Secondary data is obtained from medical records in Dr. Cipto Mangunkusumo National General Hospital.

The population in this study consists of pregnant women with premature deliveries at Dr. Cipto Mangunkusumo National General Hospital from April 2020 to June 2021. The inclusion criteria consist of pregnant women with premature deliveries at Dr. Cipto Mangunkusumo National General Hospital in the period from April 2020 to June 2021. Exclusion criteria for the study were patients with incomplete medical record data, i.e. not including identity, diagnosis, neutrophil-lymphocyte ratio, or platelet-lymphocyte ratio. The controls in this study comprised pregnant women who underwent term delivery at Dr. Cipto Mangunkusumo National General Hospital during the same period.

The data taken in this study were patient identity, diagnosis, levels of neutrophil-lymphocyte ratio, platelet-lymphocyte levels, and cervical length. All data were obtained from the patient's medical record. Data on neutrophils, platelets, lymphocytes, neutrophil-lymphocyte levels, and platelet-lymphocyte levels were obtained from a complete blood count and type count when the patient first came to the hospital before delivery took place. Cervical length was obtained from the results of measurements using transvaginal ultrasonography which was performed when the patient first came to the hospital before labor took place.

Categorical data is displayed as amounts and percentages. Numerical data with normal distribution are shown as mean ± standard deviation, while numeric data with abnormal distribution are shown as the mean (minimum – maximum value range). The relationship between neutrophil-lymphocyte levels, platelet-lymphocyte levels, and cervical length with preterm delivery was tested using the T-test if the data were normally distributed or the Mann-Whitney test if the data were not normally distributed. $P < 0.05$ was considered significant.

RESULTS

In this study, a total of 81 subjects with preterm delivery and 92 subjects with full term delivery. The characteristics of the research subjects can be seen in Table 1. Meanwhile, the distribution of diagnoses in pregnant women undergoing preterm labor can be seen in Table 2.

Table 1. Characteristics of Research Subjects

	Premature Delivery (n = 81)	**Term Labor (n = 92)**	***P-Value***
Mother's age (years)	31 (15 – 41)	30 (17 – 43)	0.725M
Gestational age (weeks)	33 (16 – 37)	38 (37 – 41)	<0.001 *M
Leukocyte Level (thousand cells/µl)	13.38 (6.14 – 40.00)	11.70 (4.36 – 29.79)	0.057 M
Platelet Level (thousand cells/µl)	280.95 ± 102.44	279.08 ± 80.87	0.893 T
Neutrophil Level (thousand cells/µl)	10.75 (3.88 – 80.00)	8.90 (3.09 – 26.74)	0.057 M
Lymphocyte Level (thousand cells/µl)	1.71 (0.63 – 16.00)	1.72 (0.29 – 3.52)	0.380 M

Note: M = Mann-Whitney test; T = independent T test

Table 2. Distribution of Diagnosis in Subjects with Premature Delivery

Diagnosis	N (%)
Premature rupture of membranes	18 (22.2)
Antepartum haemorrhage	17 (21.0)
Preeclampsia	11 (13.6)
Oligohydramnios	4 (4.9)
Cervical incompetence	1 (1,2)
Eclampsia	1 (1,2)
Other	29 (35.8)

Patients undergoing preterm labor had a median neutrophil-lymphocyte ratio that was slightly lower than the neutrophil-lymphocyte ratio in patients undergoing term delivery (5.46 vs. 5.50). However, this difference was not statistically significant (Table 3). Patients undergoing preterm labor had a slightly higher mean platelet-lymphocyte ratio than the platelet-lymphocyte ratio in patients undergoing term delivery (146.44 vs. 146.05). However, this difference was not statistically significant (Table 3).

Table 3. Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Premature and Term Labor

	Premature Delivery (n = 81)	Term Labor (n = 92)	*P-Value*
Neutrophil-Lymphocyte Ratio	5.46 (1.03 – 35.17)	5.50 (1.55 – 36.21)	0.795
Platelet-Lymphocyte Ratio	146.44 (17.08 – 481.01)	146.05 (34.47 – 1131.03)	0.475

Note: M = Mann-Whitney test

Not all study subjects underwent cervical length measurements. There were only 21 subjects in the preterm delivery group and 10 subjects in the term delivery group who had cervical length data before delivery. From these subjects, the mean cervical length of the preterm delivery group was 24.50 (0.40 – 37.30) mm. Meanwhile, the mean cervical length in the term labor group was lower at 3.15 (2.50 – 24.00) mm. This difference is considered significant with p-value = 0.031.

DISCUSSION

Preterm labor and delivery are the leading causes of neonatal morbidity and mortality. Although there are various causes of preterm labor, inflammation remains a significant risk factor in preterm labor.[7] Inflammation due to infection is known to be detected in at least 25% of all cases of preterm labor. Some of the most common microorganisms found in the amniotic fluid and the birth canal of mothers with preterm labor are *Ureaplasma urealyticum, Bacteroides ureolyticus, Streptococcus agalactiae, Gardnerella vaginalis,* and *Enterococcus sp.*[8] In addition, chronic inflammation or other immunological abnormalities without foci of infection are also correlated with the incidence of preterm labor. Preterm labor is more common in women with obesity and autoimmune diseases such as SLE, multiple sclerosis, and type I diabetes.[9]

The neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) indicate the proportion of absolute neutrophil and platelet counts to lymphocyte counts, and are obtained from complete blood counts. An increase in the NLR and PLR indicates an increase in the level of inflammation in the body. NLR has been known to have diagnostic value in conditions with local or systemic inflammatory responses such as diabetes mellitus, coronary artery disease, ulcerative colitis, arthritis, and various malignancies. Meanwhile, PLR has a role in atherosclerosis and atherothrombosis in peripheral arterial disease and in monitoring ankylosing spondylitis.[10]

Due to the association between preterm labor and inflammation, NLR and PLR as markers of inflammation are also expected to increase in women with preterm labor. These two markers are also expected to be able to predict preterm labor in pregnant women. The number of vaginal epithelium and neutrophils in preterm labor is higher than in normal pregnancies; 87.5% of subjects obtained a vaginal neutrophil count >5 per field view in the preterm labor compared to the normal labor of 9.4%.[11] A meta-analysis involving 15 articles with 3327 participants found that the NLR was significantly higher in mothers with preterm delivery (p = 0.01). However, there was significant heterogeneity in the studies included in this meta-analysis (p<0.001, I2 = 92.33%).[12]

In a prospective study involving pregnant women aged 34 – 37 weeks with threatened preterm labor, it was found that inflammatory markers such as leukocyte count (p < 0.001), neutrophils (p < 0.001), CRP (p = 0.001) , NLR (p

< 0.001), and PLR (p = 0.003) had higher levels at admission in mothers who later gave birth prematurely. Meanwhile, lymphocyte levels were found to be significantly lower in mothers with preterm delivery (p = 0.012). Of all these markers, on multivariate regression analysis. NLR was found to be the most powerful predictive variable (OR = 1.41; 95% CI 1.32 – 1.51; p = 0.005).[13]

In this study, mothers who underwent preterm labor had higher levels of leukocytes, platelets, neutrophils, and PLR than mothers with term delivery. Mothers who underwent preterm labor also had lower lymphocyte levels than women who delivered at term. However, this difference was not statistically significant. In this study, the NLR was found to be slightly lower in mothers with preterm delivery than in mothers with term delivery, although this difference was also not significant.

Most studies found significantly higher levels of NLR and PLR in mothers with preterm labor.[14] In a prospective study, l found that NLR was significantly higher in women with threatened preterm labor (TPL) than in women without TPL (p<0.001). However, NLR was not significantly different between pregnant women with TPL who eventually gave birth <37 weeks and 37 weeks. This study also found no significant difference in PLR levels between healthy pregnant women and pregnant women with TPL, although the mean PLR was higher in pregnant women with TPL.[15]

Therefore, the difference in the results of this study with other studies may be due to differences in the criteria of the subjects. Because this study is a retrospective study, it also cannot distinguish whether the complete blood count results were taken when the patient was in labor or not. Another study also found that the NLR in mothers with term labor at term was also significantly higher than in women with non-in-partum term labor.[16]

Cervical length is a strong indicator of spontaneous preterm labor. The shorter the length of the cervix, the higher the risk of spontaneous preterm labor in the mother.[17] In women with TPL, the risk of preterm delivery was also higher in women with a shorter, dilated cervix than in a woman with a longer and still closed cervix (p = 0.001).[18]

In this study, there was a significant difference between cervical length in women with preterm labor and term delivery. A previous study found that women experiencing preterm labor had an average age of 29.38 years with shorter cervical length.[19] The cut-off point of cervical length in Ekaputri et al. Study, was 2.65cm with sensitivity of 94.4% and specificity of 65.4%.[20] Nonetheless, the cervical length of mothers with preterm labor in this study was longer than that of mothers with term delivery (24.50 vs 3.15 mm), which was different from the results of previous studies. This is because mothers who underwent caesarean section were not excluded from this study, while cervical length was more involved in spontaneous labor.

The limitation of this study is the retrospective design of the study, as susceptible to bias such as the timing of blood collection or the condition of the mother before delivery. In addition, the inclusion criteria of this study are still quite broad, one of which does not exclude mothers who give birth by caesarean method, so that it can affect the results of the study.

CONCLUSIONS

In this study, it was found that the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) were not significantly different between mothers with preterm delivery and mothers with term delivery. Cervical length was significantly longer in mothers with preterm delivery than in mothers with term delivery. Further research with a prospective design is needed in order to determine more specific subject criteria and reduce bias.

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Research Article

Evaluation of Therapy in Preeclampsia Patients in Several Public and Private Hospitals

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Abstract

Objective: To determine the rationality and effectiveness of therapy in preeclampsia patients at the Inpatient Installation of several public and private hospital in Banyumas area from January-December 2021.

Methods: This study is retrospective, employing purposive sampling for data collection. The data were extracted from the medical records of patients diagnosed with pre-eclampsia at the Inpatient Installation. The sample consisted of 212 patients with a confirmed diagnosis of pre-eclampsia.

Results: From this study, it was found that antihypertensive medications given were methyldopa (52.8%), nifedipine (45.2%), and amlodipine (2%). It was found that the results of the five appropriate analyses were the suitable indication, right patient, proper medication, right dose, and correct route (100%). The antihypertensive medications used were effective in reducing the blood pressure of preeclampsia patients (100%), with an average decrease in systolic pressure by 37 mmHg, an average decrease in diastolic pressure by 22 mmHg, and an average decrease in MAP by 28 mmHg.

Conclusion: Antihypertensives given to preeclampsia patients in several public and private hospitals in Banyumas were rational and effective in reducing the patient's blood pressure.

Keywords: antihypertensives, effectiveness, preeclampsia, rationality.

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INTRODUCTION

Pregnant women with preeclampsia have a very high risk of developing eclampsia, HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets), and an increased risk of death for pregnant women. Moreover, preeclampsia had long-term effects post-delivery, such as increase in blood pressure, BMI, and CRP level [1].In Indonesia, maternal deaths in 2020 were caused by three leading causes, including bleeding as many as 1,330 cases, hypertension/ high blood pressure in pregnancy as many as 1,110 cases, and circulatory system disorders as many as 230 cases[2]. Meanwhile, in 2018, the most common causes of maternal deaths in Central Java included pre-eclampsia/eclampsia (36.80%), hemorrhage (22.60%), infection (5.20%), and other causes (35.40%)[3]. In Banyumas Regency, the prevalence of maternal mortality rate (MMR) is relatively high at 67.84 per 100,000 live births[4].

One of the factors influencing the occurrence of maternal mortality due to pre-eclampsia is the presence of irrational therapy because irrational antihypertensive therapy can cause the risk of hypotension and potential side effects on the fetus, so when choosing medications during pregnancy, the level of maternal and fetal benefits must outweigh the risks to allow safe and rational treatment[5]. According to research, 77 cases

of medication-related problems were found, including wrong indication medications in 8 cases (10.4%), underdose in 53 cases (68.8%), and overdose in 16 cases (20.8%). Medication-related problems can lead to the non-achievement of therapeutic targets in treating pre-eclampsia patients. They can increase the risk that is higher than the benefits obtained[6].

One of the therapies given to pre-eclampsia patients is methyldopa. Methyldopa is an alpha-2 adrenergic receptor agonist antihypertensive medication. It is the first line of hypertension treatment for pregnant women with chronic hypertension because it is the safest and has a large margin of safety. However, methyldopa has minor peripheral effects that can reduce sympathetic tone and arterial blood pressure but do not affect pulse frequency and renal blood flow[7]. Using methyldopa in patients with severe pre-eclampsia can reduce VEGF (Vascular Endothelial Growth Factor) levels by 10% at 250 mg and reduce levels by 57% at 500 mg. Methyldopa can also reduce Mean Arterial Pressure (MAP) to normal limits. The standard value of MAP ranges from 70 to 100 mmHg[8]. This study aimed to determine the pattern of medication use, rationality, and effectiveness of therapy in pre-eclampsia patients at Wijayakusuma Purwokerto Hospital, Banyumas Regional General Hospital, Prof. Dr. Margono Soekarjo Purwokerto Regional General Hospital and Budhi Asih Purwokerto Mother and Child Hospital for January-December 2021.

METHODS

The Muhammadiyah University of Purwokerto Health Research Ethics Commission has ethically approved this research with the numbers KEKP/ UMP/24/1/2022 and KEKP/UMP/19/1/2022. This research is a type of non-experimental research. The research method us in this study is a retrospective method with data collection using purposive sampling. The retrospective method was used because this study requires existing data that occurred in 2021, namely in the form of medical records of pre-eclampsia patients at the Inpatient Installation of Purwokerto Hospital, Banyumas Regional General Hospital, Prof. Dr. Margono Soekarjo Purwokerto Regional General Hospital and Budhi Asih Purwokerto Mother and Child Hospital from January to December 2021.

The research instruments used in this study include data collection sheets, 2016 Indonesia Society of Obstetricians and Gynecologist guidelines, and patient medical records (medical reports). The collected data included patient names, medical record numbers, ages, medication history, disease history, pregnancy history, allergy history, diagnosis, complaints, gestational age, laboratory data, and clinical information (respiration rate, blood pressure, pulse, body temperature). Additionally, the medication list comprised details such as dose, duration, and frequency.

The obtained data were classified based on patient characteristics, including age, disease diagnosis (classified according to pre-eclampsia), gestational age, and medical history. This classification was presented in tabular form. Additionally, the pattern of antihypertensive medication use is depicted as a percentage (%).

The rationality of treatment was assessed by comparing the collected data with the treatment criteria outlined in the official literature, specifically the 2016 Indonesia Society of Obstetricians and Gynecologists guidelines. The results were processed in percentage form and presented in tables. Effectiveness was evaluated through bivariate analysis using the Wilcoxon method, which assesses the relationship or influence between two or more variables.

RESULTS

This study evaluates the rationality and effectiveness of therapy in pre-eclampsia patients at the inpatient installation of Wijayakusuma Purwokerto Hospital, Banyumas Regional General Hospital, Prof. Dr. Margono Soekarjo Purwokerto Regional General Hospital and Budhi Asih Purwokerto Mother and Child Hospital from the period January-December 2021 based on a decrease in blood pressure of pregnant women diagnosed with pre-eclampsia to determine the effectiveness of therapy and five right, namely the right patient, the suitable indication, the right medication, the correct dose and the proper administration to determine the rationality of therapy. Based on the data obtained, there were 928 medical records of pregnant women with mild and severe pre-eclampsia. The number of medical records that met the study's inclusion criteria was 212, and 716 data met the exclusion criteria due to incomplete medical record data, not getting antihypertensive therapy, having no proteinuria lab data, and having a history of hypertension.

Patient Characteristics

The results of the analysis of the characteristics of preeclampsia patients in the inpatient installation of public and private hospitals in Banyumas can be seen in Table 1.

Table 1. Characteristics of Patients Diagnosed with Preeclampsia inpatients Installations of Public and Private Hospitals in Banyumas from January-December 2021

Characteristics	Number of Patients (n = 212)	(%)
Age (Years)		
17-25	49	23.13
26-35	88	41.50
36-45	75	35.37
Gestational Age (weeks)		
0-14	0	0
14-28	6	2.84
28-42	206	97.16
Proteinuria (Dipstick examination)		
+1	76	35.84
+2	52	24.52
+3	75	35.37
+4	9	4.27
Comorbidities		
None	203	95.77
Asthma	5	2.35
Hemorrhoids	1	0.47
Anemia	2	0.94
Scoliosis	1	
Gestational Status		
G1	61	28.77
G2	61	28.77
G3	45	21.22
G4	33	15.59
G5	10	4.71
G6	2	0.94

Pattern of Antihypertensive Medication Use

The analysis of antihypertensive medication use patterns in pre-eclampsia patients in inpatient installations of public and private hospitals in Banyumas can be seen in Table 2.

Table 2. Data on the Use of Antihypertensives in Pre-Eclampsia Patients at Public and Private Hospitals in Banyumas

Medication	Dosage (mg)	Number of Patients	Average Duration of Therapy (Days)
Methyldopa	250	43	2
	500	145	3
Nifedipine	10	165	3
Amlodipine	5	2	1
	10	10	2

Rationality Evaluation of Antihypertensive Treatment

The analysis of the rationality of antihypertensive treatment in pre-eclampsia patients in inpatient installations of public and private hospitals in Banyumas can be seen in Table 3.

Table 3. Rationality of Antihypertensive use in Pre-Eclampsia Patients in Public and Private Hospitals in Banyumas

Rationality Criteria	Amount of Use		(%)	
	Appropriate	Inappropriate	Appropriate	Inappropriate
Right patient	212	0	100	0
Right indication	212	0	100	0
Right medicine	212	0	100	0
Correct dose	212	0	100	0
Correct method of administration	212	0	100	0

Evaluation of the Effectiveness of Antihypertensive Treatment

The results of the analysis of the effectiveness of antihypertensive treatment in pre-eclampsia patients in inpatient installations of public and private hospitals in Banyumas can be seen in Table 4.

Table 4. Effectiveness of Antihypertensive use in Preeclampsia Patients in Public and Private Hospitals in Banyumas

Blood Pressure Value	Before (mmHg)	After (mmHg)
Systolic	160	123
Diastolic	101	79
Mean Arterial Pressure (MAP)	121	93

DISCUSSION

Based on Table 1, the highest age group is the early adult age category (26-35), with as many as 88 patients (41.50%), and late adulthood (36-45), with as many as 75 patients (35.37%). This result parallels previous research on the proportion of pregnant women who experience preeclampsia, with the highest percentage occurring in the age group 20-35 years by 70.59%[9]. Furthermore, another study states that patients diagnosed with preeclampsia with the highest percentage are in the age category 26-35 years and 36-45 years by 43% and 34%[10]. At the age of >30/35 years, it is prone to hypertension and eclampsia, which is caused by changes in tissues and there are also changes in the birth canal that are not as flexible as pregnant women under 30/35 years of age[11,12].

Characteristics of patients based on gestational age, the highest percentage was obtained in the third trimester of pregnancy, namely 206 patients (97.16%). This result parallels previous studies, which found that 100% of the incidence of preeclampsia occurred in third-trimester pregnancy[9,10]. Another study showed that term pregnancy had a higher risk of severe preeclampsia-eclampsia compared with preterm pregnancy. However, the severity of complications in preeclampsia had an association with preterm delivery [13,14]. This result is reciprocal with the theory of placental implant ischemia, which states that preeclampsia increases with increasing gestational age. As fibrinogen levels increase, risk for early-onset preeclampsia are higher in pregnant women. Increased fibrinogen levels are part of an exaggerated inflammatory response and subsequent endothelial activation, which is currently believed to be the primary pathophysiological mechanism in preeclampsia[15].

Preeclampsia patients who have proteinuria levels with the highest percentage are +1, which is 76 patients (35.84%), and +3, as many as 75 patients (35.37%). In preeclampsia, one of the manifestations is proteinuria; usually, much protein passes through the glomerular capillaries but does not enter the urine. Compensation and selectivity of the glomerular all inhibit the transport of albumin, globulin, and other high molecular weight proteins across the glomerular wall. Proteinuria that occurs in preeclampsia results from hypertension in pregnancy that causes blood perfusion in the kidneys and a decrease in glomerular filtration rate so that high molecular weight proteins leave the glomerulus and cause protein in the urine or proteinuria[16].

The most preeclampsia patients were in the G1 / first pregnancy and G2 / second pregnancy categories, namely 61 patients (28.77%). The results of this study are in accordance with the statement that patients who are first pregnant as primigravida are 6-8 times more likely to experience preeclampsia than patients who have been pregnant or multigravida[17]. Furthermore, preeclampsia is more common in patients who first conceive or primigravida compared to patients who have had previous pregnancies or multigravida; this is due to the formation of blocking antibodies caused by stress factors experienced by patients who first conceive or primigravida in the face of childbirth. Gravida status is one of the factors that can influence the incidence of preeclampsia in pregnant women[18].

The use of methyldopa is more often used as therapy if the patient's clinical condition has blood pressure between 140-160/90-110 mmHg; the results of this study are in step with the 2016 Indonesia Society of Obstetricians and Gynecologist reference standard, which states that methyldopa is indicated to lower blood pressure in preeclampsia patients with blood pressure more than 140/90 mmHg. Methyldopa treatment has been reported to prevent the subsequent development of severe hypertension during pregnancy. It has not been shown to affect uteroplacental or fetal hemodynamics or well-being, and associated with fewer adverse infant outcomes, including respiratory distress, seizure and sepsis[19]. While the administration of nifedipine is more often used as therapy if the patient's clinical condition has a blood pressure of more than 160/110 mmHg, the results of this study are consistent with the 2016 Indonesia Society of Obstetricians and Gynecologist reference standard, which states that nifedipine is used if the patient's blood pressure is more than 160/110 mmHg. However, the concomitant use of calcium channel blockers with magnesium sulfate to prevent seizures requires special attention, as the concomitant administration of these medications has been reported to cause circulatory collapse and neuromuscular blockade[19].

Appropriate Patient

Assessment of appropriate patients in this study is based on contraindications to antihypertensives used and compared with the patient's medical

history and whether antihypertensives used in pregnant women are safe or not based on the Pregnancy Risk Category of the medication. Based on research conducted on 212 medical record data for preeclampsia patients at the Inpatient Installation of Public and Private Hospitals in Banyumas for the period January-December 2021. It was found that the value of the accuracy of selecting antihypertensive medications based on the right patient was 100% appropriate for the patient; the assessment of the right patient was based on the patient's pathology and physiological conditions and did not cause contraindications in the patient. Methyldopa is under Pregnancy Risk Category B, acts in the central nervous system, and is the most commonly used antihypertensive medication for pregnant women with chronic hypertension. Methyldopa has a wide safety margin (safest). Contraindications to using methyldopa are for patients with active liver disease (acute hepatitis, cirrhosis hepatitis)[7]. Nifedipine and amlodipine are popular and widely used Pregnancy Risk Category C medications in pregnant women diagnosed with preeclampsia that act as selective, natriuretic renal arteriolar vasodilators and increase urine production. Amlodipine has been used in pregnancy, but safety data are lacking[19]. Excessive use of CCBs has been reported to cause fetal hypoxia and acidosis. This circumstance is due to relative hypotension following CCB administration[7].

Appropriate Indication

Assessment of appropriate indication in this study is based on whether or not antihypertensive treatment is suitable for the diagnosis and blood pressure of the patient. Based on 2016 Indonesia Society of Obstetricians and Gynecologist, antihypertensives are given if the systolic blood pressure is more than 140 mmHg or the diastolic level is more than 90 mmHg. Based on research conducted on 212 medical record data for preeclampsia patients at the Inpatient Installation of Public and Private Hospitals in Banyumas for the period January-December 2021. It was found that the value of the accuracy of selecting antihypertensive medications based on appropriate indications was 100% correct indications; the assessment of appropriate indications was based on the selection of medications for patients, whether according to the doctor's indications and diagnoses. Antihypertensive therapy has not been shown to reduce fetal growth restriction, placental abruption, or superimposed preeclampsia or to improve perinatal outcomes. The most important indication for antihypertensive administration in pregnancy is maternal safety in preventing cerebrovascular disease. However, the decrease in blood pressure should be gradual, not exceeding 25% in 1 hour, to prevent a decrease in uteroplacental blood flow[7]. The goal of treating hypertension in pregnancy is also to protect pregnant women from high blood pressure, which is dangerous and impacts the continuation of pregnancy, growth, and maturation of the fetus[20].

Appropriate Medication

Assessment of appropriate medications in this study is based on the accuracy of the selection of antihypertensive medications that are safe for pregnant women and compared with the 2016 Indonesia Society of Obstetricians and Gynecologist reference standards. Based on research conducted on 212 medical record data for preeclampsia patients at the Inpatient Installation of Public and Private Hospitals in Banyumas for the period January-December 2021. The value of the accuracy of selecting antihypertensive medications based on appropriate medications is 100% appropriate medications according to the reference standards used. Based on 2016 Indonesia Society of Obstetricians and Gynecologist, the antihypertensive medications given are the Calcium Channel Blocker (CCB) group in the form of nifedipine and the α2-adrenergic agonist group in the form of methyldopa and if the patient's blood pressure is 140-160/90-110 mmHg, the patient is given methyldopa. If the patient's blood pressure exceeds 160/110 mmHg, the patient is given nifedipine[7].

Correct Dose

This study's assessment of the correct dose is based on administering antihypertensive medications to patients within the recommended minimum dose and daily dose range based on the 2016 Indonesia Society of Obstetricians and Gynecologist reference standard. Based on research conducted on 212 medical record data for preeclampsia patients at the Inpatient Installation of Public and Private Hospitals in Banyumas for the period January-December 2021. The value

of the accuracy of selecting antihypertensive medications based on the correct dosage was 100% correct dosage according to the reference standards used. According to the 2016 Indonesia Society of Obstetricians and Gynecologist reference standard, nifedipine's recommended peroral dose range is 10-30 mg, amlodipine is 5-10 mg, and methyldopa is 250 mg-500 mg. If the dose is too low, it causes the medication in the blood to have levels below the therapeutic range, which causes the medication to be unable to provide the desired effect. At the same time, if the dose is too high, it causes the medication in the blood to have levels exceeding the therapeutic range, which causes the medication to have a toxic effect[21]. Therefore, administering antihypertensive medications must pay attention to the accuracy of the dose given to patients to obtain therapeutic success and achieve normal blood pressure[22]. Providing medication doses that are not following standards can significantly impact patients. If the dose of medications listed on the prescription is inappropriate, then the patient fails to get the correct treatment related to the disease[23].

The Correct Method of Administration

Assessment of the correct dose in this study is based on when the medication is used as it should be; if the medication has been given according to the instructed method, it can be said to be the right way of administration[24]. Based on research conducted on 212 medical record data for preeclampsia patients at the Inpatient Installation of Public and Private Hospitals in Banyumas for the period January-December 2021. It was found that the value of the accuracy of selecting antihypertensive medications based on the correct method of administration was 100% correct method of administration. Administration of nifedipine is better given orally because using sublingual nifedipine can increase the risk of sudden maternal hypotension and fetal problems due to placental hypoperfusion. Sudden hypotension may be exacerbated by concomitant magnesium sulfate (used as a treatment or prophylactic agent for eclampsia attacks with severe preeclampsia)[20].

Based on Table 4, 212 data showed a decrease in blood pressure after administration of antihypertensive medications. Data from patients with an average initial systolic blood pressure of 160 mmHg and after antihypertensive administration showed a decrease in systolic blood pressure to an average of 123 mmHg, besides that diastolic pressure also decreased from an average initial diastolic blood pressure of 101 mmHg decreased diastolic blood pressure to an average of 79 mmHg and MAP blood pressure also decreased from an average initial MAP blood pressure of 121 decreased MAP blood pressure to an average of 93 (Table 4). This result shows that taking antihypertensive medications reduces blood pressure and is safe for pregnant women without causing side effects for both mother and fetus. These results are parallel with research, which states that in the use of hypertension medications in pre-eclampsia patients, 197 respondents (100%) experienced a decrease in blood pressure after being given antihypertensive medications[25].

Treatment using methyldopa is more often used when the patient's blood pressure is between 140-160/90-110 mmHg; the data is also compatible with the 2016 Indonesia Society of Obstetricians and Gynecologist reference standard, which states that methyldopa is indicated for lowering blood pressure in pre-eclampsia patients, with blood pressure greater than 140/90 mmHg and methyldopa is proven to prevent an increase in the severity of pre-eclampsia disease to severe pre-eclampsia and has no adverse effect on uteroplacental or fetal hemodynamics or fetal well-being[26]. Methyldopa is usually started at 250-500 mg orally 2-3 times daily, with a maximum dose of 3 g daily. The maximal effect of the medication is achieved 4-6 hours after taking it, and it takes 10-12 hours before the kidneys excrete it7. A long-term follow-up study of infants born to women treated with methyldopa during pregnancy found no increased incidence of general health or mental health problems. In addition, methyldopa can be combined with other antihypertensives to achieve the desired blood pressure target[27].

Both nifedipine and amlodipine are more often used as therapy if the patient's clinical condition has a blood pressure of more than 160/110 mmHg; the results of this study are consistent with the 2016 Indonesia Society of Obstetricians and Gynecologist reference standard, which states that the CCB group is used if the patient's blood pressure is more than 160/110 mmHg. Peroral administration of nifedipine for pre-eclampsia patients is usually given at a dose of 20-30 mg/ day 2-3 times per day; nifedipine at this dose can reduce blood pressure in pre-eclampsia patients.

Giving nifedipine for 2-5 days can reduce blood pressure. Nifedipine has a short mechanism of action that increases the frequency, intensity, and duration of angina pectoris associated with acute hypotension[7]. Nifedipine is fast-acting within 10-20 minutes after oral administration with fewer side effects, so it is often used prenatally. Very little calcium channel blocker is excreted in an intact form via the kidneys, so there is no need for dose adjustment in patients with impaired renal function. The main side effect of nifedipine is due to excessive vasodilation. Symptoms observed include dizziness or headache due to meningeal artery dilatation, hypotension, reflex tachycardia, facial flushing, nausea, vomiting, peripheral edema, cough, and pulmonary edema[28]. Amlodipine, with a dose between 2.5 to 10 mg, can be given once a day because it has a long half-life. A once-daily dose can reduce blood pressure that lasts for 24 hours. Administration of amlodipine does not cause acute hypotension because the onset of action of amlodipine is slow[29].

CONCLUSION

The antihypertensive medications used in preeclampsia patients in several public and private hospitals in Banyumas were α2-adrenergic agonist group, namely methyldopa by 52.8% and Calcium Channel Blocker (CCB) group, namely nifedipine by 45.2 % and amlodipine by 2 %. The rationality of medication used in preeclampsia patients in public and private hospitals in Banyumas obtained from indicators such as right patient, suitable indication, proper medication, right dose, and right route of administering the medication were 100%. The effectiveness of therapy in preeclampsia patients can reduce patient blood pressure, with an average decrease in systolic pressure by 37 mmHg, an average decrease in diastolic pressure by 22 mmHg and an average decrease in MAP by 28 mmHg.

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Research Article

Body Composition Parameters, Adiponectin, Leptin and Adiponectin/ Leptin Ratio are Correlated with LH/FSH Ratio in Women with PCOS but not in Women without PCOS

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Abstract

Objective: To investigate the correlation between body composition parameters, adiponectin, leptin and the adiponectin/ leptin ratio and the LH/FSH ratio in women with polycystic ovary syndrome (PCOS).

Methods: A cross-sectional study was conducted at Reproductive Cluster Yasmin, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, with sixty women with PCOS and sixty healthy women as controls (matched for age and BMI). Body composition parameters, including body weight, body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), percent body fat (PBF), visceral fat area (VFA), percent subcutaneous fat (PSF) and skeletal muscle mass (SMM), were measured; levels of fasting glucose, fasting insulin, testosterone, and sex hormone binding globulin (SHBG) were measured; and homeostatic model assessment for insulin resistance (HOMA-IR) values, anti-Mullerian hormone (AMH), free androgen index (FAI), Ferriman-Gallwey (FG) score, adiponectin levels, leptin levels, adiponectin/leptin ratio, LH, FSH and LH/FSH ratio were measured.

Results: Body composition parameters (body weight, BMI, WC, WHR, PBF, VFA, PSF, SMM) were not significantly different between women with PCOS and controls. Fasting insulin ($P<0.05$), HOMA-IR ($P<0.05$), AMH ($P<0.01$), FAI ($P<0.01$), FG score ($P<0.01$) and LH/FSH ratio ($P<0.05$) were higher in PCOS women. Adiponectin ($P<0.01$) was lower in PCOS women, while leptin and the adiponectin/leptin ratio were not significantly different between groups. Most of body composition parameters, adiponectin, leptin and adiponectin/leptin ratio were correlated with HOMA-IR in both groups. SMM was positively correlated with the LH/FSH ratio, while body weight, BMI, WC, PBF, VFA, and PSF were inversely correlated with the LH/FSH ratio in PCOS patients but not in controls. WHR was not correlated in either group. Leptin ($r=-0.278$; $P<0.05$) was negatively correlated with the LH/FSH ratio only in the PCOS group. Adiponectin ($r=0.394$; $P<0.01$) and the adiponectin/leptin ratio ($r=0.413$; $P<0.01$) were also positively correlated with the LH/FSH ratio only in the PCOS group. AMH was correlated with the LH/FSH ratio, whereas testosterone level, FAI, FG score, fasting insulin level and HOMA-IR value were not correlated with the LH/FSH ratio in PCOS women.

Conclusion: Most of the body composition parameters, leptin, adiponectin and the adiponectin/leptin ratio were significantly correlated with HOMA-IR in both groups. However, correlations of those parameters with LH/FSH ratio were found only in PCOS but not in women without PCOS. Adiponectin and leptin may play a significant role in the mechanism of neuroendocrine disorders in PCOS, which is characterized by an increased LH/FSH ratio.

Keywords: adiponectin, adiponectin/leptin ratio, body composition, HOMA-IR, leptin, LH/FSH ratio, PCOS.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is known to be the most common endocrine disorder in women of reproductive age, with a prevalence of approximately 5 to 20%.[1] The clinical features of PCOS include menstrual irregularity, hirsutism and infertility.[2] Obesity and insulin resistance are metabolic disorders that are often found in women with PCOS.[3] In addition, the presence of neuroendocrinological disorders in the form of increased LH levels and the LH/FSH ratio is commonly encountered in women with PCOS.[4] Both insulin resistance and an increased LH/FSH ratio are associated with chronic anovulation, hyperandrogenemia, polycystic morphology of the ovary, increased levels of AMH and disruption of the sex hormone feedback mechanism to the pituitary and hypothalamus.[5,6] Therefore, insulin resistance and an increased LH/FSH ratio, among other factors such as genetic, epigenetic and environmental factors, are thought to be important parts of the complex pathogenesis of PCOS.

Previous studies have shown a strong relationship between dysregulated adipokine expression and the onset of glucose intolerance and insulin resistance in PCOS women.[7,8] Adipose tissue secretes adipokines, most notably leptin and adiponectin.[9,10] Leptin is thought to be importantly involved in regulating food intake, metabolism, and reproduction. Some studies found significantly higher leptin levels in PCOS women than in those who have regular menstruation, and leptin levels were positively correlated with insulin resistance.[9-11] A study shows that giving insulin sensitizer can reduce leptin and insulin levels and improve reproductive function in PCOS patients.[12] In contrast, adiponectin improves insulin sensitivity and has an anti-inflammatory effect. Previous studies have shown a reduction in adiponectin levels in PCOS women with insulin resistance and obesity.[10,13-15] Furthermore, the adiponectin/leptin ratio is considered a potent indicator of insulin resistance and has the potential to be used as a marker of PCOS.[10] The association between adipokines and neuroendocrine disorders in PCOS has also been studied previously.[11,16,17]

Studies have demonstrated that visceral obesity is associated with an elevated risk of metabolic syndrome.[18-20] Measurement of body weight or BMI alone cannot describe the distribution of fat mass from different body parts and cannot predict the occurrence of insulin resistance. Therefore, body composition measurements are considered a better method to differentiate peripheral and visceral body fat, as well as fat-free mass, and to predict the risk of metabolic disorders in PCOS women.[21] Body composition can be easily measured using bioelectrical impedance analysis, which is noninvasive, inexpensive and reliable.[22] Studies have demonstrated that body composition parameters are different between women with PCOS and controls. Moreover, body composition parameters were correlated with increased leptin levels and lower adiponectin levels in PCOS women.[23-25]

Obesity and metabolic syndrome, particularly insulin resistance, have become epidemic diseases and are closely linked to the prevalence of PCOS. Given the ongoing development of the theory on PCOS pathogenesis, it is crucial to conduct further research exploring the relationship between anthropometric profiles and adipokines in connection with insulin resistance and the LH/FSH ratio. Therefore, this current study aimed to investigate the correlation between body mass composition parameters, levels of leptin and adiponectin, the adiponectin/leptin ratio, and HOMA-IR values, as well as the LH/FSH ratio in women with PCOS.

METHODS

Sample Collection

PCOS was diagnosed according to the Revised 2003 consensus on diagnostic criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004)[2], identified as any two of the following three criteria: clinical and/or biochemical signs of hyperandrogenism, oligo- or anovulation, and polycystic ovarian morphology determined by ultrasonography. This is a cross-sectional study with a total of 120 women of reproductive age divided into two groups of sixty, one with PCOS and the other as controls. Based on the sample size formula for this study, the minimum sample needed reached 56 samples with SD from previous research of 14.96 and the proportion difference from this study of 10.01; hence, the study settled with sixty samples. The samples were recruited from the Yasmin Clinic, Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, from September

2021 until August 2022. Patients with any other cause of hyperandrogenism or oligomenorrhea, such as Cushing's syndrome, congenital adrenal hyperplasia, hypothyroidism, or significant increases in serum prolactin levels, were excluded. In addition to the exclusion criteria, no subjects had taken medications known to disrupt the function of the HPG axis, such as corticosteroid, hormonal therapy, antiepileptic, or antipsychotic drugs in the last 6 months.

The subjects were taken using consecutive sampling technique until the minimum number of samples have been reached. The enrolled patients underwent comprehensive physical examination, USG, and laboratory examination. Another sixty healthy women without both menstrual disturbance and hyperandrogenism were recruited as controls. Both groups of PCOS and controls were then divided equally into two groups based on their body mass index (BMI) according to the Asia Pacific criteria, which states that normal weight is classified as 18.5-22.9 kg/ m^2 and obese is classified as more than 25 kg/ m^2. From all subjects, 5 ml whole-blood samples were obtained in the follicular phase (until Day 5 of the menstrual cycle) after overnight fasting (10 to 12 h). Fasting was done to have accurate results for fasting glucose and fasting insulin levels to evaluate HOMA-IR. The Ferriman-Gallwey (FG) score and free androgen index (FAI) were calculated to investigate hyperandrogenism. The FG score was evaluated by measuring terminal hair growth on eleven different body areas with a scale from 0 to 4 each based on the FG scoring system and the cut off found for PCOS in Asia.[26] FAI is a measurement of the biologically active testosterone levels in the blood, evaluated by multiplying 100 with the total testosterone level divided with the SHBG level. Homeostatic model assessment for insulin resistance (HOMA-IR) was measured to investigate insulin resistance. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo Hospital (KET-/197/ UN2.F1/ETIK/PPM.00.02/2021). Written informed consent was obtained from each subject.

Hormone, Glucose, and SHBG Measurements

The levels of total testosterone (T), luteinizing hormone (LH), follicle-stimulating hormone (FSH), fasting insulin, anti-Müllerian hormone (AMH), and sex-hormone binding globulin (SHBG) were measured using TOSOH (Tosoh India Pvt. Ltd., Mumbai, India) following the manufacturer's protocols. All samples intended for examination were previously thawed, diluted, and then placed into a 500 µl sample cap. Subsequently, the sample cap and reagent were inserted into the instrument. The diluent was filled, the buffer tank was washed, and the waste tank was emptied. The sample identity was entered into the software, followed by pressing the start button on the instrument, leading to the appearance of the hormone level results. Additionally, the levels of adiponectin, leptin, and fasting glucose were measured using ELISA kits based on each component utilizing the sandwich ELISA principle.

Assessment of Body Composition

Body composition parameters were measured using the bioimpedance method with an Omron HBF 375 (Omron Body Fat Analyzer HBF-375; Omron, Bannockburn, Illinois) according to the instructions provided by the manufacturer. The selected body composition parameters measured in this study were weight (kg), BMI (kg/m^2), percent body fat (PBF) (%), visceral fat area (VFA) (cm^2), percent subcutaneous fat (PSF) (%), and skeletal muscle mass (SMM) (kg). Waist circumference (WC) was measured between the iliac crest's superior border and the ribs' inferior border using a tape measure with subjects standing, whereas hip circumference (HC) was measured over the buttocks at the maximum circumference. The waist-to-hip ratio (WHR) is defined as WC/HC.

Statistical Analysis

The data are presented as the mean ± SE (standard error) for demographic and endocrine characteristics. The collected data were normalized using the Kolmogorov–Smirnov test to determine the data distribution. Correlation tests between the dependent and independent variables were performed using the Pearson test if both numeric variables tested had a normal distribution or using the Spearman test if they did not have a normal distribution. A value of $p < 0.05$ was considered to indicate significance. The statistical analysis was performed using SPSS version 26.0.

RESULTS

The demographic and endocrine characteristics of women with PCOS and the control women are presented in Table 1. Compared to controls, body composition parameters (weight, BMI, WC, WHR, PBF, VFA, PSF, SMM) did not significantly differ between women with PCOS and controls (Table 1). Fasting glucose was not significantly different, but fasting insulin levels (P<0.05) and HOMA-IR value (P<0.05) were elevated in PCOS women; therefore, insulin resistance was significantly increased in PCOS women compared to controls. AMH was significantly elevated in PCOS women compared with controls (P<0.01). Testosterone and SHBG did not significantly differ between the two groups; however, the FAI (P<0.01) and FG score (P<0.01) were significantly higher in women with PCOS. Adiponectin (P<0.01) levels were significantly decreased in PCOS women, while leptin levels and the adiponectin/leptin ratio were not significantly different between groups. LH and FSH were not significantly different between groups, while the LH/FSH ratio was significantly higher in the PCOS group.

Table 1. Characteristics of Women with and without PCOS

Characteristics	PCOS (Mean ± SE)	Non PCOS (Mean ± SE)	*P-value*
Age (years)	26.02 ± 0.45	25.47 ± 0.57	0.452
Weight (kg)	64.47 ± 1.83	74.48 ± 12.30	0.422
BMI (kg/m^2)	26.19 ± 0.75	24.42 ± 0.80	0.109
WC (cm)	81.70 ± 1.65	79.07 ± 1.50	0.242
WHR	0.81 ± 0.08	0.81 ± 0.08	0.611
PBF (%)	32.69 ± 0.76	32.58 ± 0.73	0.916
VFA (cm^2)	7.37 ± 0.76	6.14 ± 0.62	0.212
PSF (%)	29.82 ± 0.85	28.97 ± 0.80	0.465
SMM (kg)	24.37 ± 0.31	25.15 ± 0.41	0.128
Fasting glucose (mg/dL)	95.61 ± 1.29	93.08 ± 1.11	0.140
Fasting insulin (uIU/mL)	15.11 ± 2.41	9.32 ± 0.88	0.026*
HOMA-IR (%)	3.49 ± 0.58	2.19 ± 1.62	0.036*
AMH (ng/mL)	12.66 ± 0.92	4.99 ± 0.38	0.000**
Testosterone (ng/dL)	76.68 ± 5.44	57.09 ± 9.32	0.072
SHBG (nmol/L)	51.92 ± 8.42	71.32 ± 5.10	0.051
FAI	7.92 ± 0.82	4.03 ± 0.66	0.000**
FG score	6.47 ± 0.37	3.19 ± 0.31	0.000**
Adiponectin (ng/mL)	4.88 ± 0.33	6.95 ± 0.49	0.001**
Leptin (ng/mL)	6.99 ± 0.60	5.65 ± 0.54	0.101
Adiponectin/Leptin ratio	1.51 ± 0.31	5.63 ± 2.98	0.172
LH (mIU/mL)	10.56 ± 0.65	9.94 ± 3.17	0.850
FSH (mIU/mL)	7.09 ± 0.26	6.69 ± 0.54	0.514
LH/FSH ratio	1.49 ± 0.07	1.11 ± 0.16	0.033**

Note: BMI=body mass index; WC=waist circumference; WHR=waist:hip ratio; PBF=percent body fat; VFA=visceral fat area; PSF=percent subcutaneous fat; SMM=skeletal muscle mass; HOMA-IR= homeostatic model assessment for insulin resistance; LH=luteinizing hormone; FSH=follicle stimulating hormone; SHBG=sex hormone binding globulin; FAI=free androgen index; FG score=Ferriman Gallwey score.*P<0.05 = significant difference. **P<0.01 = significant difference.

A subgroup analysis was performed based on BMI (lean and obese PCOS), as shown in Table 2. WC (P<0.01), PBF (P<0.01), VFA (P<0.01) and PSF (P<0.01) were higher in the obese group, while SMM (P<0.01) was higher in the lean PCOS group. Interestingly, the WHR was similar between the 2 groups. Fasting insulin levels (P<0.01) and HOMA-IR value (P<0.01) were elevated in obese PCOS patients, while fasting glucose levels were not different between the groups. FAI (P<0.01) was elevated in obese women, SHBG (P<0.01) was higher in lean PCOS women, and AMH and testosterone levels were not significantly different between groups. Significant differences in adiponectin, leptin, and the adiponectin/leptin ratio (P<0.01) between the two groups were also observed. Adiponectin levels (P<0.01) and the adiponectin/leptin ratio (P<0.01) were lower in obese subjects, whereas leptin levels (P<0.01) were higher. Interestingly, the LH/FSH ratio (P<0.05) was elevated in lean compared to obese PCOS patients.

Table 2. Characteristics of Obese and Lean PCOS Women

Characteristics	PCOS group (Mean ± SE)		*P-value*
	Obese (n = 30)	Lean (n = 30)	
Age (years)	26.23 ± 0.65	26.03 ± 0.52	0.638
Weight (kg)	76.07 ± 1.87	52.86 ± 0.94	0.000**
BMI (kg/m2)	30.94 ± 0.79	20.53 ± 0.28	0.000**
WC (cm)	91.67 ± 1.78	71.73 ± 1.02	0.000**
WHR	0.83 ± 0.01	0.81 ± 0.10	0.083
PBF (%)	37.3 ± 0.71	28.10 ± 0.60	0.000**
VFA (cm2)	11.77 ± 0.99	2.99 ± 0.21	0.000**
PSF (%)	35.03 ± 0.86	24.61 ± 2.95	0.000**
SMM (kg)	22.85 ± 0.38	25.89 ± 1.57	0.000**
Fasting glucose (mg/dL)	94.10 ± 1.29	91.03 ± 1.41	0.223
Fasting insulin (uIU/mL)	22.60 ± 4.36	6.80 ± 0.67	0.001**
HOMA-IR (%)	5.16 ± 1.05	1.81 ± 0.21	0.003**
AMH (ng/mL)	12.00 ± 1.28	13.31 ± 1.33	0.479
Testosterone (ng/dL)	73.52 ± 7.45	62.75 ± 5.34	0.566
SHBG (nmol/L)	27.99 ± 1.83	78.60 ± 7.85	0.004**
FAI	10.30 ± 1.30	5.75 ± 1.18	0.003**
FG score	6.6 ± 0.56	6.33 ± 0.48	0.721
Adiponectin (µg/mL)	3.85 ± 0.35	5.90 ± 0.49	0.001**
Leptin (ng/mL)	9.78 ± 0.86	4.21 ± 0.45	0.000**
Adiponectin/Leptin ratio	0.51 ± 0.08	2.51 ± 0.56	0.001**
LH (mIU/mL)	9.58 ± 0.87	11.54 ± 0.94	0.129
FSH (mIU/mL)	7.16 ± 0.32	6.45 ± 0.51	0.788
LH/FSH ratio	1.32 ± 0.08	1.90 ± 0.12	0.017*

Note: BMI=body mass index; WC=waist circumference; WHR=waist:hip ratio; PBF=percent body fat; VFA=visceral fat area; PSF=percent subcutaneous fat; SMM=skeletal muscle mass; HOMA-IR= homeostatic model assessment for insulin resistance; LH=luteinizing hormone; FSH=follicle stimulating hormone; SHBG=sex hormone binding globulin; FAI=free androgen index; FG score=Ferriman Gallwey score. *P<0.05 = significant difference. **P<0.01 = significant difference.

Body weight, BMI, WC, PBF, VFA and PSF had a significant positive correlation, while SMM had a negative correlation with HOMA-IR value in both PCOS women and controls, as shown in Table 3. However, WHR only had a significant positive correlation with HOMA-IR value in PCOS women. Testosterone had a negative correlation with HOMA-IR value only in the PCOS group, while FAI was positively correlated with HOMA-IR value only in the control group. SHBG had a negative correlation with HOMA-IR value in both groups, while AMH and FG scores did not correlate with HOMA-IR value in either group. Fasting insulin had a positive correlation with HOMA-IR value in both groups, whereas fasting glucose was not correlated with HOMA-IR value in either group. Leptin levels in women with PCOS and controls had a positive correlation with HOMA-IR, while adiponectin levels were negatively correlated with HOMA-IR value in both groups.

Body weight, BMI, WC, PBF, VFA, and PSF were negatively correlated with the LH/FSH ratio, while SMM was positively correlated with the LH/FSH ratio only in PCOS patients, while WHR was not correlated with the LH/FSH ratio in either group. FG score, testosterone, SHBG and FAI scores did not correlate with the LH/FSH ratio in PCOS patients and controls. Fasting glucose was positively correlated with the LH/FSH ratio only in PCOS patients; in contrast, fasting insulin was correlated with the LH/FSH ratio only in the control group. HOMA-IR value did not correlate with the LH/FSH ratio in either group. AMH also had a positive correlation with the LH/FSH ratio in PCOS women but not in controls. This study also found that leptin levels had a negative correlation with the LH/FSH ratio only in the PCOS group. Interestingly, adiponectin levels and the adiponectin/leptin ratio were also found to only positively correlate with the LH/FSH ratio in the PCOS group, not in the control group.

Table 3. Correlation between Metabolic Characteristics and LH/FSH Ratio and HOMA-IR Value in Women with and without PCOS

Characteristics	HOMA-IR				LH/FSH Ratio			
	PCOS (n = 60)		Control(n = 60)		PCOS (n = 60)		Control(n = 60)	
	r	p-value	r	p-value	r	p-value	r	p-value
Age (years)	0.020	0.878	-0.127	0.334	0.151	0.251	-0.025	0.847
Weight (kg)	0.618	0.000**	0.478	0.000**	-0.365	0.004**	-0.028	0.831
BMI (kg/m^2)	0.626	0.000**	0.361	0.005**	-0.373	0.003**	-0.044	0.739
WC (cm)	0.637	0.000**	0.441	0.000**	-0.324	0.011*	-0.111	0.399
WHR	0.268	0.038*	0.120	0.359	-0.017	0.895	-0.071	0.591
PBF (%)	0.604	0.000**	0.347	0.007**	-0.333	0.009**	-0.001	0.997
VFA (cm2)	0.561	0.000**	0.449	0.000**	-0.349	0.006**	-0.055	0.674
PSF (%)	0.668	0.000**	0.491	0.000**	-0.335	0.009**	-0.046	0.725
SMM (%)	-0.572	0.000**	-0.324	0.012*	0.294	0.023*	-0.036	0.786
FG score	-0.110	0.402	0.294	0.056	0.071	0.591	-0.046	0.769
Testosterone (ng/dL)	-0.419	0.001**	0.121	0.359	0.242	0.062	0.234	0.071
SHBG (nmol/L)	-0.594	0.000**	-0.576	0.000**	0.098	0.458	-0.034	0.796
FAI	0.125	0.342	0.475	0.000**	0.111	0.400	0.224	0.086
Fasting blood glucose (mg/dL)	-0.083	0.532	0.225	0.084	0.306	0.019*	-0.178	0.175
Fasting blood insulin (uIU/mL)	0.969	0.000**	0.855	0.000**	-0.226	0.083	0.314	0.015*
HOMA-IR (%)					-0.202	0.122	0.635	0.063
AMH (ng/mL)	-0.230	0.077	-0.156	0.233	0.317	0.014*	0.194	0.138
Leptin (ng/mL)	0.707	0.000**	0.499	0.000**	-0.278	0.031*	0.123	0.347
Adiponectin (µg/mL)	-0.285	0.028*	-0.365	0.004**	0.349	0.006**	0.010	0.937
Adiponectin/Leptin ratio	-0.642	0.000**	-0.523	0.000**	0.413	0.001**	-0.081	0.541

Note: r=correlation coefficient; BMI=body mass index; WC=waist circumference; WHR=waist to hip ratio; PBF=percent body fat; VFA=visceral fat area; PSF=percent subcutaneous fat; SMM=skeletal muscle mass; HOMA-IR= homeostatic model assessment for insulin resistance; LH=luteinizing hormone; FSH=follicle stimulating hormone; SHBG=sex hormone binding globulin; FAI=free androgen index; FG score=Ferriman Gallwey score. *P<0.05 = significant correlation (2-tailed). **P<0.01 = significant correlation (2-tailed).

DISCUSSION

Studies have revealed that in PCOS patients, metabolic disorders characterized by insulin resistance or hyperinsulinemia and the presence of neuroendocrine disturbances in the form of increased LH levels or LH/FSH ratio are characteristics that are often found along with ovulation disorders, hyperandrogenism, and infertility.[18] An elevated LH/FSH ratio is specifically identified in cases of polycystic ovarian syndrome (PCOS).[19] Furthermore, an association was assumed between adipose tissue and metabolic and neuroendocrine disorders. Depres suggested that visceral obesity might activate the hypothalamus-pituitary-adrenal axis.[18] Adipose tissue, as an endocrine organ, produces adipokines such as leptin and adiponectin, which have been shown to be associated with the occurrence of insulin resistance and metabolic syndrome. Measuring body composition parameters can differentiate fat tissue in the visceral area from other areas, which is more useful in predicting the risk of insulin resistance rather than just measuring BMI.[27] In this study, the focus was on the relationship between parameters of body composition, insulin resistance, levels of leptin and adiponectin, adiponectin/leptin ratio, and LH/FSH ratio in women with PCOS. To our knowledge, this study is the first to investigate the relationship between body composition parameters and the LH/FSH ratio in women with PCOS.

The characteristics of PCOS patients and controls were initially compared. No differences were found in body composition parameters between PCOS patients and controls, contrary to reports from previous studies.[23-25] However, our result was similar to the findings.[28] Furthermore, body composition parameters between obese patients with PCOS and controls, as well as lean PCOS patients and lean controls was not significantly difference. These conflicting results might be due to the different methods of measuring body composition parameters between those studies. The present study used the bioimpedance method, which was indicated to be reliable in measuring body composition parameters.[22] Moreover, the heterogeneity of PCOS pathophysiology and influences of race and environment might contribute to this dissimilarity.

Although body composition did not significantly differ between the two groups, fasting insulin level and HOMA-IR value were higher in women with PCOS, showing enhanced risk of glucose intolerance and insulin resistance in PCOS women. These results were in accordance with other studies.[22,23,29] Based on our study, it is assumed that factors other than biometrics of body composition, such as adipokines, may contribute to insulin resistance in women with PCOS.

Studies have shown a clear association between insulin resistance, glucose intolerance, and disrupted adipokine secretion, particularly adiponectin and leptin, in PCOS-afflicted women.[15,30-32] The current study also uncovered significant differences in adiponectin levels between PCOS and control groups, supporting the notion of insulin resistance due to reduced adiponectin or increased leptin activity. Interestingly, our findings revealed comparable leptin levels across both groups, consistent with earlier studies.[32,33] Adiponectin's role as a potent insulin sensitizer underscores its significance in PCOS-associated insulin resistance. Conversely, leptin, a crucial regulator of energy balance and adiposity, exhibited elevated levels in PCOS women, aligning with prior studies.[7,10,29] Furthermore, the adiponectin/leptin ratio, a key metric, was consistently lower in PCOS cases than controls.[9-11] A parallel study echoed our observations, showing reduced adiponectin levels and no substantial difference in leptin levels in PCOS individuals.[34] This collective evidence underscores the disrupted state of adipokine equilibrium in PCOS, accentuating its association with insulin resistance.

When the coefficient correlation between body composition and HOMA-IR value was investigated, the results found that VFA, which describes visceral fat and PSF as subcutaneous fat markers, positively correlated with HOMA-IR value in both women with PCOS and controls. Similar results also applied to body weight, BMI, and WC. In contrast, SMM, which describes skeletal muscle mass, was negatively correlated with HOMA-IR value in both groups. The results are in accordance with a study that expressed that increasing muscle mass will improve insulin sensitivity and reduce the risk of developing type 2 diabetes.[35]

Moreover, the outcomes revealed intriguing associations: body composition parameters (body weight, BMI, WC, PBF, VFA, and PSF) positively correlated with the LH/FSH ratio, whereas SMM exhibited a negative correlation. Notably, women without PCOS exhibited no such correlations between body composition and the LH/FSH ratio. Supporting our findings, reported a weak negative correlation between body fat percentage and LH in PCOS women but not controls.[23] This implies that although body composition does not substantially differ between PCOS patients and controls, additional variables foster these correlations in PCOS patients. This study pioneers the exploration of body composition's association to the LH/FSH ratio in PCOS women. Furthermore, AMH levels exhibited a positive correlation with the LH/FSH ratio in only PCOS women, aligning with the findings of other studies.[36,37] This could be attributed to the presence of AMH type 2 receptor (AMHR2) in both hypothalamus and pituitary organs.[38]

Moreover, our results showed that leptin levels were negatively correlated with the LH/FSH ratio in women with PCOS but not in controls. These results were in line with a study[16], whereas other studies showed the opposite results.[11,17] The relationship between leptin and LH secretion has been investigated with the conclusion that leptin could affect the hypothalamus and pituitary in the regulation of GnRH pulsatility and LH secretion.[39,40] In addition, the present study found a significant positive correlation between adiponectin levels and the adiponectin/leptin ratio with the LH/FSH ratio in women with PCOS but not in controls. Similar observations were also demonstrated.[14,15] Previous studies demonstrated that adiponectin receptors, Adipor1 and Adipor2, were found on pro-opiomelanocortin (POMC) and neuropeptide Y (NPY) neurons in the arcuate nucleus[41] in addition to being discovered in the anterior pituitary.[42] These outcomes suggest a role for adiponectin in energy homeostasis.

One of the hypotheses of the occurrence of neuroendocrinological disorders in PCOS is the disruption of the sex steroid hormone feedback mechanism in the hypothalamus and pituitary due to exposure to increased androgen levels.[43] However, our study did not show a significant correlation between testosterone levels, FAI, FG scores and LH/FSH ratio in PCOS women or in controls. Other studies have also demonstrated the association of insulin resistance with increased LH and LH/FSH ratio[44,45]; however, this study did not find any significant correlation between both fasting insulin and HOMA-IR.

Interestingly, our study revealed that the LH/

FSH ratio was significantly higher in lean women with PCOS. Conversely, the HOMA-IR value was lower in lean women with PCOS compared to obese women with PCOS. This finding provides further confirmation for the proposed hypothesis, which suggests the existence of two phenotypes of PCOS based on genetic and hormonal analysis. These phenotypes are the 'Reproductive' type, characterized by elevated levels of LH, SHBG, and BMI with relatively low insulin levels, and the 'Metabolic' type, characterized by high BMI, insulin, and glucose levels accompanied by low LH and SHBG.[46] Further investigation is needed to explore this issue. Additionally, the diagnosis and therapeutic approach for these two types of PCOS may vary according to their respective pathophysiology.

Limitations of the present study were the small sample size of both PCOS women and controls recruited from a single center in Indonesia. Therefore, larger studies in populations of diverse backgrounds are required to confirm the results.

CONCLUSION

In conclusion, our study sheds light on the intricate web of metabolic and hormonal interplay in women with PCOS. Through a comprehensive analysis of various factors, this study unraveled a few significant insights. Firstly, there was a nuanced relationship between insulin resistance, adiponectin, and leptin levels in PCOS women. The elevation of HOMA-IR was found to be associated with a decrease in adiponectin, and conversely, an increase in leptin levels. This finding underscores the importance of addressing insulin resistance as a key factor in PCOS-related metabolic alterations. Furthermore, the intricate relationship between AMH and the LH/FSH ratio became evident. Our results indicated that an increase in AMH levels was associated with a higher LH/FSH ratio in PCOS women. This emphasizes the complex influence of hyperandrogenism on the reproductive hormonal balance in PCOS. Notably, we uncovered compelling links between body composition parameters, leptin and adiponectin levels, the adiponectin to leptin ratio, and the LH/FSH ratio in PCOS women. The present study showed that the dysfunction of adipose tissues associated with the dysregulation of adipokines may play a significant role in the mechanism of neuroendocrine disorders in PCOS, which is characterized by an increased LH/FSH ratio and therefore requires further investigation. These associations were not observed in the control group, highlighting the specificity of these interactions to the PCOS population. In summation, our study not only enriches our understanding of the intricate mechanisms underpinning PCOS but also underscores the need for a multifaceted approach when considering therapeutic interventions. As we continue to decipher the pathophysiology of PCOS, our findings offer a steppingstone towards more targeted and effective management strategies for this complex syndrome.

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CONFLICT OF INTEREST

There is no conflict of interests in this paper.

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Research Article

Serum Vitamin D Levels, Visual Analog Scale Dysmenorrhea Score, and Endometriosis ASRM Classification: a Relationship Study

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Abstract

Objective: To assess the correlation between vitamin D levels, dysmenorrhea intensity measured by the visual analogue scale (VAS), and the stage of endometriosis determined by the American Society of Reproductive Medicine (ASRM) grading score.

Methods: A cross-sectional study was conducted involving 37 women diagnosed with suspected endometriosis who met the inclusion and exclusion criteria. The aim was to determine the correlation between vitamin D levels, dysmenorrhea VAS scores, and the ASRM endometriosis stage at RSUP Dr. Mohammad Hoesin Palembang from November 2021 to April 2022. Bivariate analysis was employed to assess correlation, utilizing Pearson's correlation test and the Spearman Rank correlation test as an alternative method.

Results: There was a significant positive correlation between vitamin D levels and the VAS score for dysmenorrhea (r = 0.678; p = 0.000) and a very strong positive correlation between vitamin D levels and the degree of endometriosis (r = 0.774; p = 0.000) based on Spearman Rho's correlation test.

Conclusion: There is a significant relationship between vitamin D levels with the VAS score of dysmenorrhea and the degree of endometriosis ASRM.

Keywords: american society of reproductive medicine, endometriosis, visual analogue scale, vitamin D.

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INTRODUCTION

Endometriosis, an estrogen-dependent gynecologic disease, is characterized by the presence of endometrial functional tissue (endometrial glands and stroma) implanted ectopically outside the uterine cavity. It affects thirty-five to fifty percent of reproductive-age women, although many cases are suspected to be underdiagnosed. Commonly reported symptoms include dysmenorrhea, infertility, or both.[1] Some women experience severe pain, with prevalence varying from 3% to 33%, which can be incapacitating for 1-3 days, significantly impacting their ability to move. Consequently, these complaints often greatly affect the patient's quality of life.[2,3]

Increased concentrations of PGE2 and PGF2α which are higher in the menstrual fluid of patients with dysmenorrhea are thought to be the most

potent cause of pain, especially PGF2α. Until now, the etiology of endometriosis itself is still unclear, but several studies have suggested the possibility of an influence on vitamin D levels. Previous studies have also suggested that there is a strong association between vitamin D deficiency and other factors, which determines a wide range of polymorphic clinical manifestations where menstrual disorders are important in pubertal women. Vitamin D receptors and 1α-hydroxylase enzymes, responsible for catalyzing the formation of D3 from its precursor, 25(OH)D, are expressed in the uterus and immune system cells. This presence leads to the belief that vitamin D may offer benefits in preventing uterine abnormalities.[4]

Vitamin D is a group of fat-soluble steroids derived from cholesterol. Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) are the two main forms of vitamin D. Vitamin D can work after binding to its receptors (vitamin D receptors or VDR) which are located throughout the body, including blood vessels and reproductive tissues, such as the uterus, ovaries, and placenta. The existence of VDR in reproductive tissue makes many hypotheses that vitamin D has a relationship with endometriosis.[5,6] In further research, it is known that vitamin D has a role in reducing the severity of endometriosis, thereby reducing the degree of the pain by lowering pro-inflammatory cytokine levels and prostaglandin biological activity.[6]

Another factor, activity, and body mass index (BMI) was known to be associated with dysmenorrhea and the degree of endometriosis. The level of activity also had a strong and significant positive correlation with the VAS dysmenorrhea score and the degree of endometriosis. Physical activity increases systemic levels of various cytokines with anti-inflammatory properties. Striated muscle is identified as an endocrine organ, which through contraction, stimulates the production and release of myocytokines, which can influence and alter metabolism and cytokine production in tissues and organs. Evidence suggests that symptoms associated with endometriosis result from localized peritoneal inflammatory reactions caused by ectopic endometrial implants. Regular physical exercise appears to have a protective effect against diseases involving inflammatory processes as it induces an increase in systemic cytokine levels with anti-inflammatory and antioxidant properties and acts by reducing estrogen levels.[7]

While with BMI, although previous studies have shown that there no association between BMI and the degree of dysmenorrhea[8] and the incidence of endometriosis[9], higher BMI is often associated with chronic inflammation, which could be a contributing factor in both pain and discomfort associated with dysmenorrhea and endometriosis potentially worsen the. Obesity is also often associated with lower levels of physical activity.[10] Reduced physical activity can lead to decreased endorphin release, which might affect pain perception during dysmenorrhea. Also higher BMI associated with increased prostaglandin production which plays a role in uterine contractions and menstrual pain.[11]

Therefore, this study aimed to analyze the correlation between serum vitamin D levels and the intensity of dysmenorrhea, measured using the *visual analogue scale* (VAS), as well as the stage of endometriosis, determined by the American Society of Reproductive Medicine (ASRM) grading score. In addition, this study also assessed the relationship between body mass index (BMI) and activity on the VAS score of dysmenorrhea and the degree of endometriosis.

This comprehensive investigation into the relationship between endometriosis, dysmenorrhea, vitamin D, and additional factors such as activity and BMI aims to explore the potential impact of vitamin D on the severity of endometriosis and its symptoms. By delving into these interactions, this study endeavors to offer valuable insights into an area that remains incompletely understood, thereby contributing to a deeper comprehension of the involved mechanisms.

METHODS

A cross-sectional study was carried out to examine the correlation between serum vitamin D levels with dysmenorrhea VAS scores and endometriosis ASRM in RSUP Dr. Mohammad Hoesin Palembang in the period November 2021 to April 2022. The sample consisted of 37 women who were diagnosed with suspected endometriosis and planned for a laparotomy or laparoscopic procedure. The sample size was determined using the correlation coefficient from a study conducted (0.783),[12] and the formula for correlation calculation was used to establish the sample size. The formula included a 99% level of significance and 99% statistical power. Samples were selected using total sampling

according to the day the patient was diagnosed with endometriosis. The inclusion criteria for this study encompassed women between the ages of 18 and 50 years, diagnosed with endometriosis based on intraoperative findings corroborated by anatomical pathology examinations, who had not undergone hormonal therapy, and expressed willingness to participate in the study. Conversely, individuals with a recent history of vitamin D intake within the last 2 weeks, a medical history of malignancy, kidney disease, or those currently pregnant were excluded from participation.

The concentration of Vitamin D was measured by RSMH laboratory using the ELISA method using a blood sample of up to 5 mL drawn from the cubital fossa vein. The results were categorized into normal (> 30 ng/mL), insufficiency (21 – 29 ng/mL) and deficiency (< 20 ng/mL).[13] While the degree of dysmenorrhea was measured with VAS score by using visual pain assessment tools, in the form of a 10 cm line equipped with an illustration of facial expressions when experiencing pain. The scores were categorized into no pain (0), mild (1-3), moderate (4-6), severe (7-9) and very severe (10).[14] On the other hand, the American Society for Reproductive Medicine (ASRM) classification was used to determine the staging of endometriosis and were classified into grade I (score 1-5), II (score 6-15), III (score 16-40) and IV (score > 40).[15]

The statistical analysis was conducted using SPSS version 20. Bivariate analysis was done to evaluate the correlation between vitamin D levels and dysmenorrhea VAS scores. Regarding the correlation between vitamin D levels and the endometriosis ASRM grading score, the analysis involved the Pearson correlation test, complemented by the Spearman Rank correlation test as an alternative. All analyses were conducted using a 95% confidence interval.

RESULTS

Thirty-seven women participated in the study, ranging in age from 22 to 48 years, with an average of 34.41 ± 6.86 years, and an average BMI of 24.12 ± 3.34 kg/m2 (range 18.2 – 31.2 kg/m2). In addition, as many as 67.6% of patients experienced infertility and 32.4% of them were not infertile (Table 1).

Table 1. Demographics, Clinical and Laboratory Characteristics

Characteristic	Total (n)	(%)
Age		
Mean ± SD	34.41 ± 6.86	
Median	33	
Min-Max	22 – 48	
Body Mass Index (kg/m²)		
Mean ± SD	24.12 ± 3.34	
Median	23.5	
Min-Max	18.2 – 31.2	
Body Mass Index		
Underweight	1	2.7
Normoweight	22	59.5
Overweight	12	32.4
Obese class I	2	5.4
Surgery		
Laparoscopy	31	83.8
Laparotomy	6	16,2
Parity		
Infertile	25	67.6
Non-infertile	12	32.4
Vitamin D (ng/ml)		
Mean ± SD	19.08 ± 7.05	
Median	17.6	
Min-Max	7.4 – 33.1	
Deficiency	25	67.6
Insufficiency	8	21.6
Normal	4	10.8
VAS		
Mean ± SD	4.43 ± 1.66	
Median	5	
Min-Max	2 – 8	
VAS Score		
Mild	13	35.1
Medium	19	51.4
Severe	5	23.5
Endometriosis Degrees		
Grade I	2	5.4
Grade II	2	5.4
Grade III	3	8.1
Grade IV	30	81.0
Activity		
Low	19	51.4
Medium	13	35.1
High	5	13.5

The study revealed a significant prevalence of vitamin D deficiency among endometriosis patients, affecting 67.6% of the sample, with an average vitamin D level of 19.08 ± 7.05 ng/ml (range 7.4 – 33.10 ng/ml). The majority of participants reported moderate VAS scores for dysmenorrhea (51.4%), with an average VAS score of 4.43 ± 1.66 (score range 2 – 8). Furthermore, the study indicated a high prevalence of grade IV endometriosis cases (81.1%) within the sample, and most participants engaged in light physical activity on a daily basis (51.4%) (Table 1).

The results of the Spearman Rho's correlation test revealed a significant positive correlation between vitamin D levels and the VAS score for dysmenorrhea (r = 0.678; p = 0.000, Table 2) and a very strong positive correlation between vitamin D levels and the degree of endometriosis (r = 0.774; p = 0.000, Table 3). This implies that patients with vitamin D deficiency tended to experience more severe dysmenorrhea symptoms and a higher degree of endometriosis, while those with normal vitamin D levels had milder dysmenorrhea and less advanced endometriosis

Table 2. Correlation of vitamin D Levels with VAS Dysmenorrhea Scores

Characteristic	VAS score			*P-value*	r
	Mild	Medium	Severe		
Vitamin D, n (%)				0.001*	0.678
Deficiency	4 (100)	0 (0)	0 (0)		
Insufficiency	6 (75.0)	2 (25.0)	0 (0)		
Normal	3 (23.1)	17 (68.0)	5 (20.0)		

Spearman Rho's test, *p < 0.05

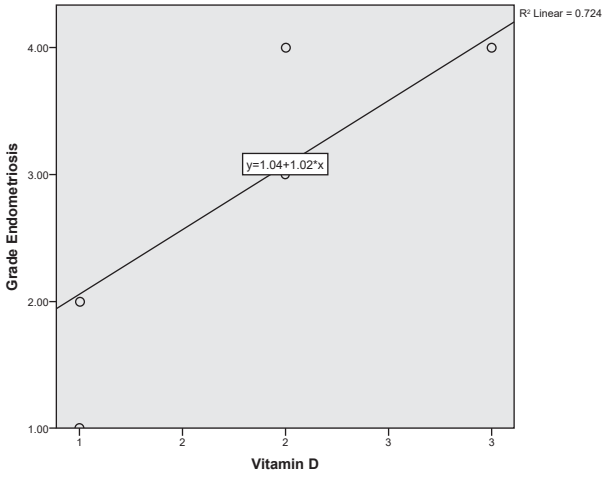

Figure 1. Graph of the correlation of vitamin D with the VAS score

Table 3. Correlation of vitamin D Levels with Degree of Endometriosis

Characteristic	Degree of endometriosis				*P-value*	r
	Grade I	Grade II	Grade III	Grade IV		
Vitamin D, n (%)					0.000*	0.774
Deficiency	2 (50.0)	2 (50.0)	0 (0)	0 (0)		
Insufficiency	0 (0)	0 (0)	3 (37.5)	5 (62.5)		
Normal	0 (0)	0 (0)	0 (0)	25 (100)		

Spearman Rho's test, *p < 0.05

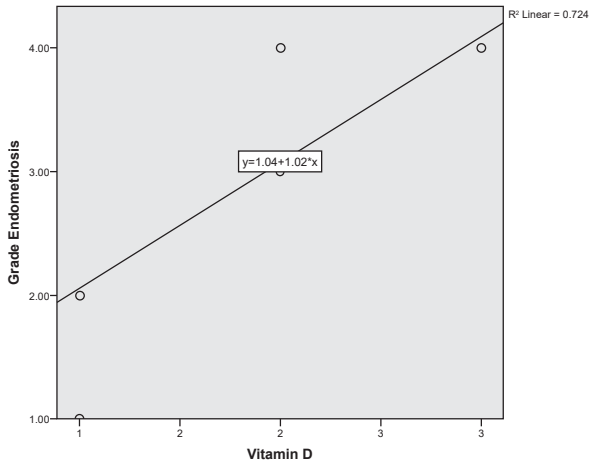

Figure 2. Graph of the correlation of vitamin D with degree of endometriosis

The results of the study, as shown by the Spearman Rho's test (Table 4), shed light on the relationship between body mass index (BMI), physical activity, and the degree of endometriosis and the severity of dysmenorrhea. Notably, the correlations between BMI and these parameters were found to be weak and insignificant, with a positive correlation coefficient of 0.259 for dysmenorrhea VAS score and 0.176 for the degree of endometriosis. In contrast, the relationship between physical activity and these variables was more pronounced and significant. The study demonstrated a strong and significant positive correlation between activity and dysmenorrhea VAS scores (r = 0.638; p = 0.000) and a moderate and significant positive correlation between activity and the degree of endometriosis (r = 0.536; p = 0.001). These findings suggest that higher levels of physical activity are associated with milder dysmenorrhea symptoms and a lower degree of endometriosis and vice versa, while BMI has a limited impact on these parameters in this study group.

Table 4. Correlation between Body Mass Index with VAS Score and Degree of Endometriosis

Variabel	Variabel	N	r	*P-value*
Body Mass Index Activity	VAS score	37	0.259	0.176
	Degree of endometriosis	37	0.176	0.299
	VAS score	37	0.638	0.000*
	Degree of endometriosis	37	0.536	0.001*

Spearman Rho's test, *p < 0.05

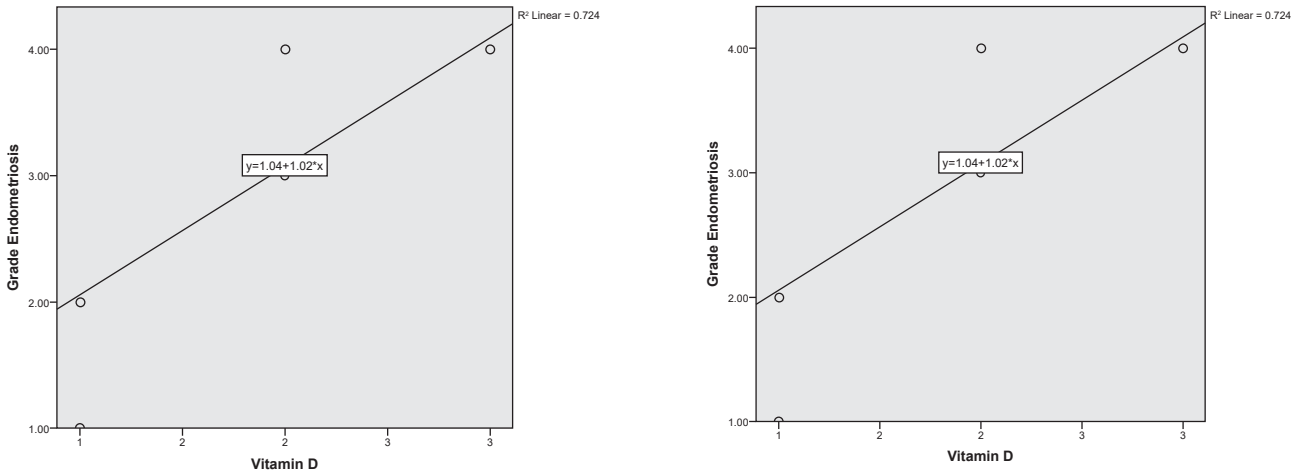

Figure 3. Correlation between Body Mass Index with VAS Score and Degree of Endometriosis

DISCUSSION

In this study, 37 women were involved, and the mean age of endometriosis patients was 34.41 ± 6.86 years (range 22 – 48 years). This is in line with the study which found that the average age of endometriosis patients was 34.22 ± 6.54 years (range 18 – 45 years).[16] These results were not much different from where the average age of the patients was obtained. endometriosis in the two treatment groups in their study amounted to 33.4 ± 0.892 years and 34.7 ± 0.925 years.[17] Similarly, a study reported an average age of endometriosis patients of 33.3 ± 6.23 years.[18]

In this study, most endometriosis patients had a normoweight body mass index (59.5%) with an average BMI of endometriosis patients in this study of 24.12 ± 3.34 kg/m^2 (range 18.2 – 31.2 kg/m^2). Another study found similar results which reported endometriosis patients BMI was reported to be 23.48 ± 1.90481.[19] The average BMI of endometriosis patients ranged from 22.46 to 23 kg/m^2.[20] A greater average BMI of 27.1 ± 0.752 kg/m^2 and 27.8 ± 0.710 kg/m^2.[11] Research found a lower mean BMI of 21.1 (15.2–33.5 kg/m^2) and reported no difference in mean BMI between endometriosis patients and healthy controls ($p > 0.05$).[9]

In this study, 67.6% of endometriosis patients had vitamin D deficiency, with an average vitamin D level of 19.08 ± 7.05 ng/ml (range 7.4 – 33.10 ng/ml). Vitamin D receptor expression was found to be significantly lower in samples from endometriosis patients than in samples from normal endometrium in both the proliferative phase (12.88% vs 20.12%) and the secretory phase (10.32%; 21.51%), according to research ($p < 0.05$). Vitamin D could be used as a targeted therapy for endometriosis seeing as vitamin D deficiency plays a significant role in its pathogenesis. Research has suggested several possible reasons for lower vitamin D levels in endometriosis patients, one of them is dietary habits. Previous studies have shown that a higher intake of dairy products and 1,25-dihydroxy vitamin D3 is associated with a decreased risk of endometriosis.[21]

One of the most prevalent complaints in women with gynecologic problems is dysmenorrhea, including endometriosis. The visual analogue scale (VAS) was used in this study to quantify the pain associated with endometriosis. The results showed that most endometriosis patients complained of moderate pain (51.4%). According to the VAS score, it was also observed that patients with vitamin D deficiency tend to experience moderate to severe pain. Vitamin D has a very strong correlation with dysmenorrhea pain in endometriosis patients, where the more deficient levels of vitamin D, the more severe the pain is felt. The association between vitamin D levels and dysmenorrhea lies in the pathogenesis of dysmenorrhea, where prostaglandins are released from endometrial cells. Vitamin D and vitamin D receptors work on many organs, one of which is the endometrial cells, and play an important role in reducing the production of prostaglandins.[22]

In this study, there were differences in vitamin D levels based on dysmenorrhea pain scores. This may be due to vitamin D regulating the immune system in chronic inflammatory responses. Inflammatory processes can influence the metabolism of vitamin D and may lead to lower vitamin D levels in individuals with more severe menstrual pain. With Vitamin D supplementation, the production of anti-inflammatory cytokines is increased and that of pro-inflammatory cytokines is decreased.[20] The active form of vitamin D, calciferol, also known to control prostaglandin production.[23]These results are in line with research which involved 372 women reporting a negative correlation between serum 25(OH)D levels and pain index ($r = -0.612$; $p = 0.044$). Most of women with mild dysmenorrhea (VAS score 1 -3) have vitamin D insufficiency, meanwhile those with moderate dysmenorrhea (VAS score 4-7) have vitamin D deficiency.[6] Furthermore, several studies compared vitamin D levels and VAS score in groups which given vitamin D supplementation and groups given a placebo or no intervention. The results in the group given vitamin D supplementation had a significantly lower VAS score.[1,14,24] Vitamin D supplementation reduced pain intensity with a reduction of 1.0 score at week 4 and 1.5 scores at week 8 ($p< 0.001$).[25] A clinical trial comparing the effects of vitamin D administration with a placebo on the VAS score of patients with endometriosis who had undergone laparoscopy. The findings reported that giving vitamin D to patients who had undergone ablative surgery had no discernible effect.[20]

Vitamin D exhibits a notable correlation with the degree of endometriosis. This study revealed discernible differences in vitamin D levels corresponding to the severity of endometriosis, indicating a robust and significant negative

correlation between vitamin D levels and the degree of endometriosis. Lower vitamin D levels were consistently associated with more severe degrees of endometriosis, aligning with findings from a meta-analysis demonstrating a negative correlation between vitamin D status and disease severity (stage III–IV vs stage I–II: SMD − 1.33 ng/mL, 95% CI − 2.54 to − 0.12; p=0.03). Numerous additional studies have also indicated a similar relationship between vitamin D levels and the severity of endometriosis in affected women.[12,26,27] In vitro and animal studies have suggested that vitamin D supplementation leads to regression of endometriotic implants, decreased invasion, and reduced proliferation.[28] The role of vitamin D in inhibiting cell proliferation can be explained by understanding the role of vitamin D in the cell cycle. The vitamin D 1,25(OH)2D3-VDR system stops the cell cycle at the G0-G1 transition through several mechanisms. 1,25(OH)2D3 activates VDR directly by binding to the p21 promoter and inducing its expression. 1,25(OH)2D3 also increased the expression of p15, p16, p18, and p27 which had an impact on cell inhibition, especially the transition phase from G1 to S. Therapy with 1,25(OH)2D3 could inhibit cell proliferation. Microarray analysis demonstrated the upregulation of several genes that regulate the cell cycle, including the kinase 1-activated p21 and p53. Therefore, vitamin D is considered to play a strong role in cell differentiation and proliferation through direct regulation of the cell protein cycle.[29]

Most endometriosis patients in this study did light physical activity (51.4%). Based on the correlation test, activity and VAS scores showed a strong and significant positive correlation. This result is in line with the study that reported a strong correlation between physical activity and dysmenorrhea (p = 0.000; r = -0.650). In addition, physical activity also correlates with the degree of endometriosis, patients with mild physical activity tend to have a severe degree of endometriosis and vice versa. Exercise was known as a non-specific pain relief method by enhancing blood flow in the pelvic region and triggering the release of beta-endorphins. It contributes to the prevention and alleviation of dysmenorrhea by reducing stress levels and improving mood. Exercise also lowers body fat, which is linked to a higher prevalence of dysmenorrhea.[30]

A cross-sectional study involving 1009 participants with endometriosis indicated that pain symptoms could potentially be alleviated by exercise performed the day before. Those who engaged in physical activity at least three times a week tended to report reduced pain symptoms. Conversely, a systematic review, encompassing 3 clinical trials and involving 109 participants, aimed to explore the association between exercise and endometriosis symptoms. The physical activities provided encompassed flexibility and strength training, cardiovascular fitness, and yoga, conducted independently one to four times a week for durations of 8-24 weeks without supervision. However, due to heterogeneity and various confounding factors, a meta-analysis could not be conducted in this study. Consequently, further investigation is required to comprehensively understand the relationship between exercise and its impact on endometriosis symptoms.[31]

CONCLUSION

In this study, serum vitamin D levels exhibited a significant positive strong correlation with the VAS dysmenorrhea score (r = 0.678; p = 0.000), along with a very strong positive correlation with the degree of ASRM endometriosis (r = 0.774; p = 0.000). To enhance our comprehension of the complex interplay among serum vitamin D levels, dysmenorrhea, and endometriosis, future research should prioritize several key areas. Primarily, addressing the limitation of the current study's relatively small sample size is crucial. Conducting research with a larger and more diverse participant pool would enhance the generalizability and robustness of the findings. Longitudinal studies tracking changes in these variables over time would elucidate causality and the dynamic nature of these relationships. Furthermore, investigating additional potential confounding variables, such as dietary practices, lifestyle factors, and other health-related aspects, could offer nuanced insights into these associations. Moreover, employing random sampling strategies instead of patient selection based on the day of diagnosis would mitigate bias in participant selection, resulting in a more representative cohort of women affected by endometriosis. This adjustment would ultimately yield more precise and valuable outcomes for future research endeavors.

LIMITATION of STUDY

The limitation of this study is based on a relatively

small sample size of 37 women, which may limit the generalizability of the findings. A larger and more diverse sample would provide a more comprehensive understanding of the correlation between serum vitamin D levels, dysmenorrhea, and endometriosis. Also, because the sample was selected using total sampling on the day of endometriosis diagnosis. This could introduce selection bias, as patients diagnosed on specific days may not represent the broader population of endometriosis patients. The study design is also cross-sectional, which only allows for the observation of correlations at a single point in time. Longitudinal or prospective studies could provide insights into how these variables change over time and potentially establish causality.

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Case Report

Mosaic Form of Turner Syndrome

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Abstract

Objective: To report a case of breast growth disorder in a mosaic form of Turner Syndrome. Turner syndrome is a chromosomal condition characterized by small height and primary ovarian insufficiency that affects one in every 2500 female births. Mosaicism is likely to occur when monosomy X develops in only a few cells during development. The clinical presentation of Turner syndrome mosaicism is atypical, with symptom severity varying based on the number of affected cells. This case discusses issues with secondary sex development, including mild hyperandrogenism, and explores how combination hormonal treatment can aid in enhancing secondary sex development.

Method: Case Report.

Case: A 21-year-old woman presented with chief complaint of the lack of breast enlargement. She exhibited normal genitalia internally and externally and had a regular menstrual cycle. Karyotyping revealed a mosaic pattern of 45, X/46, XX (1 percent/99%) with normal estradiol levels and elevated testosterone levels (indicating mild hyperandrogenism). The patient underwent two cycles of hormone therapy using Ethinyl Estradiol and Drospirenone, resulting in breast growth progression from Tanner stage 1 to Tanner stage 2.

Conclusion: Mosaicism in Turner syndrome is plausible, and the severity of clinical symptoms correlates with the number of defective chromosomes. The presentation of Turner syndrome mosaicism varies, and therapy should be tailored to address specific symptoms. While breast development is observed in some girls with Turner Syndrome, instances of breast growth disorder may occur, involving estrogen activity and estrogen receptor sensitivity. Although the exact cause of impaired breast growth remains unknown, administering estrogen in such cases can improve secondary sexual characteristics.

Keywords: mild hyperandrogenism, mosaicism, turner syndrome.

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INTRODUCTION

Turner syndrome (TS), also known as congenital ovarian hypoplastic syndrome, is characterized by a woman's X chromosome being partially or fully absent, resulting in small stature, primary ovarian insufficiency, gonadal dysgenesis, and infertility. This disease affects one out of every 2500 female newborns.[1,2] Some cases of Turner syndrome are monosomy X (45,X), 5-10% are long arm X duplications (46,X,i(Xq)), and the rest are 45,X mosaicism with one or more extra cells.[3]

"Classic" Turner syndrome refers to cases in which the X chromosome is fully absent, whereas "Mosaic" Turner syndrome refers to cases in which the defect only affects the X chromosome of a few cells of the body, with few or no symptoms. The mosaic pattern 45,X/46,XX has the highest frequency of all the mosaic patterns (36%). Turner syndrome mosaicism results in an unusual clinical presentation.[1,3]

CASE

A 21-year-old woman presented with chief complaint of the lack of breast enlargement, and

her height and weight were 150 cm and 43 kg, respectively. The internal and external genitalia have typical appearances, and menstruation occurs on a regular basis. Without clinical hyperandrogenism, karyotyping revealed 45, X/46, XX (1 percent /99 percent) (Figure 1) with normal estradiol levels and increased testosterone levels (mild hyperandrogenism) without virilization (Table 1).

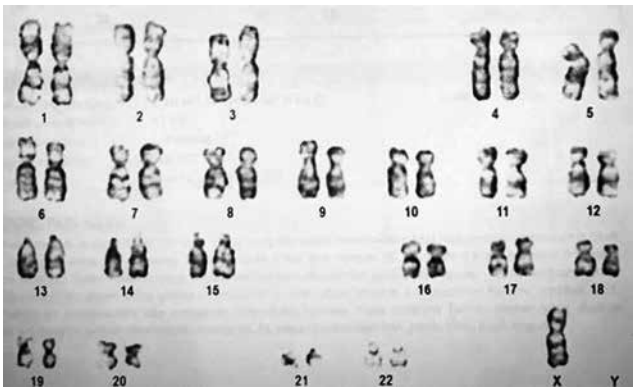

Figure 1. Karyotyping Report

Table 1. Hormone Levels Measured before and after Treatment

Laboratory Test	before Treatment	after Treatment
Prolactin	10.48 ng/ml	
Estradiol	153 pg/ml	62 pg/ml
Testosteron	34.38 ng/dl	39.29 ng/dl

At Tanner stage 1, the examination of secondary sex development revealed small, undeveloped breasts and no hair in the armpits. Over the course of two cycles, the patient received hormone therapy comprising a combination of Ethinyl Estradiol and Drospirenone, resulting in breast growth progression from Tanner stage 1 to Tanner stage 2 (Figure 2).

Figure 2. Tanner 2 Secondary Sexual Development Disorder (after therapy)

DISCUSSION

Turner syndrome (TS) is a condition wherein a woman's X chromosome is entirely or partially lost. The incidence of TS occurs in 1 in 2000 to 2500 live-born girls, and it is the only monosomic syndrome in which individuals can survive.[4]

45,X is the traditional karyotype for TS. In a recent research, only 45 percent of individuals had the traditional karyotype; the rest had a mosaic karyotype (45,X/46,XX or 45,X/47,XXX), a karyotype with structural abnormalities on the X chromosome (eg i(Xq) or i(Xp)), or a karyotype with a Y chromosome or chromosomal fragment.[2]

Short stature, infertility, estrogen deficiency, hypertension, elevated liver enzymes, middle ear infection, micrognathia, bone age retardation, decreased bone mineral content, cubitus valgus, and underdevelopment during the first postnatal year are the most common physical abnormalities affecting women with TS.[2,5] Hypothyroidism, diabetes, heart disease, osteoporosis, congenital abnormalities (heart, urinary system, face, neck, ears), neurovascular disease, and liver cirrhosis, as well as colon and rectal cancer, are all considerably more common in women with TS.[6]

The occurrence of two or more lineages of cells with distinct genotypes emerging from a single zygote in a single human is known as genetic mosaicism. Postzygotic mutations cause genetic mosaicism. The zygote is generated when a sperm (23 chromosomes) and an ovum (23 chromosomes) fuse together. The zygote then divides through mitosis to form the full human body. Ideally, all zygotic offspring would possess identical genomes, but this is not always the

case. Mosaicism occurs during one of the phases following the formation of the zygote.[7]

Mosaicism stems from genetic abnormalities occurring in either the germline or somatic cells of the body, such as single nucleotide variations, chromosomal aberrations, copy number variants, among others. It can occur randomly or originate from stem cells. The extent and proportion of cells affected by mosaicism dictate the specific tissue impacted, which may range from non-gonadal tissue only, solely gonadal tissue, to affecting all bodily tissues. The quantity of cells involved dictates the phenotypic expression. Depending on triggering factors, this expression might manifest during pregnancy, after delivery, or even later in life.[7]

The X chromosome may be lost during early embryonic cell division in people with Turner syndrome with mosaicism. As a result, some cells have just one copy of the X chromosome (45, 21+X0), whereas others have two copies (46, 21+XX). Mosaic people experience less severe symptoms.[8]

In this case, the karyotype revealed a mosaic pattern of 45, X/46, XX (1 percent/99 percent) with normal estradiol levels, a mild increase in testosterone, and regular menstruation. Despite these findings, we remain concerned about the presence of a breast disorder evident at Tanner stage 1. Breast development occurs in early embryonic life and progresses to form lactiferous ducts and the mammary gland by the 8th month of fetal development. Thelarche, marking the onset of puberty, typically begins between ages 8 and 13. During childhood and puberty, the breast bud and mammary gland enlarge under the influence of steroid hormones-estrogen and progesterone. Estrogen stimulates the development of adipose tissue and lactiferous ducts, while progesterone induces alveolar budding and lobular growth.[9]

The regular menstruation shows the estrogen activity in this patient, however the breast development may indicate unsatisfactory estrogen activity. It may be caused by estrogen-receptor resistance. The action of estradiol affects breast development and involves estrogen receptor α. Both estrogen receptors α and β are encoded by Esr1 and Esr2, respectively. Studies on Esr1 knockout mice demonstrate hypoplastic uteri and multicystic ovaries without corpus luteum, while the ablation of ESR2 leads to reproductive abnormalities.[10]

Several case reports have described the occurrence of Turner syndrome mosaicism, which is characterized by a low percentage of chromosomal deletions and is an unusual characteristic of TS. A 40-year-old lady presented with an inguinal lump and was subsequently diagnosed with mosaic-shaped TS (45X/46XX). After 26 years of marriage, the lady has never had a period and has never been pregnant. Physical examination revealed a 5'1" (155 cm) height, acceptable breast development but tiny nipples, and no pubic or axillary hair. The inguinal mass has ovotestis sonomorphology and an atrophic uterus, as shown on ultrasound. Turner Mosaic Syndrome was verified by the karyotype, which showed 46XX (96%)/45X (4%).[3]

A case of Turner syndrome mosaicism was also described in a 58-month-old lady with small height. Except for his low height and cubitus valgus, he exhibits no TS dysmorphology. Turner syndrome mosaicism karyotype 45,X (18 cells)/47,XXX (7 cells) was discovered by cytogenetic analysis of 25 blood lymphocytes.[11]

The most consistent phenotypic finding is short stature. However, current research suggests that individuals with mosaic TS have an increased likelihood of experiencing menstruation and achieving pregnancy. Gonadal dysgenesis stands as a defining characteristic of TS, with approximately 90% of patients requiring hormone replacement therapy (HRT) to initiate puberty. Nonetheless, a subset of children with TS does undergo spontaneous pubertal maturation and menarche, occurring in about 10% of cases in monosomy 45,X. Patients with TS mosaicism such as 45X/47XXX exhibit a higher propensity for spontaneous menstruation. Fertility is generally diminished in TS, albeit the degree varies based on the specific chromosomal mutation. Women with mosaicism for a normal cell lineage of 46, XX, a cell lineage of 47,XXX, or an extremely distal Xp deletion are more likely to experience spontaneous fertility.[11,12]

The clinical presentation in this case is notably unique, particularly with the presence of mild hyperandrogenism. However, the authors have not conclusively determined the cause of hyperandrogenism. In Turner syndrome, manifestations of hyperandrogenism can occur in cases of mosaicism or upon detecting a Y chromosome through PCR and FISH array examinations. Notably, in this case, neither the presence of a Y chromosome nor virilization was identified. The primary concern regarding the presence of a Y chromosome lies in the elevated risk of developing gonadoblastoma or other

tumors. However, the role of the Y chromosome in oncogenesis remains controversial. In instances where there is suspicion, laparoscopy may be necessary to ascertain the presence of gonads. Nevertheless, in this particular case, there appears to be a tendency toward non-identification of gonads.[13,14]

Therapy in this case

The treatment administered is mostly determined by the clinical presentation. In this case, hormonal tablets (drospirenone and ethynyl estradiol) were used to treat secondary sex development problem, and after two cycles of treatment, secondary sex development progressed from tanner 1 to tanner 2. The improvement after hormonal therapy was seen in parameter of breast development and axillary hair, growing from tanner 1 to tanner 2.

Hormonal treatment is required to induce and maintain secondary sex development in this scenario. The 2016 International Turner Syndrome Meeting in Cincinnati suggested that estrogen replacement medication be begun between the ages of 11 and 12, and gradually escalated to adult doses over the course of 2-3 years.[15]

Due to the lack of X chromosome, one with TS may be involved in the risk of developing skin neoplasms, colorectal cancer and CNS tumor.[16] The risk of cancer are given with the administration of ethynyl estradiol. In the oral contraceptive therapy, ethynyl estradiol level range from 20 mcg to 50 mcg, which may increase the activity of Human Temolerase Reverse Transcriptase (hTERT). Inhibition of hTERT in immortal cells will lead to telomere shortening and apoptotic cells death, therefore hTERT activity indicate immortal and proliferation of cancer cells. Estrogen Receptor and Estrogen Response Element will cause the hTERT gene expression.[17]

To lower the risk of cancer, including endometrial cancer and/or breast cancer linked with extended estrogen exposure, progestins should be introduced when bleeding has occurred or after 2 years of estrogen therapy. To reduce bleeding, progesterone may be administered for 10 days each month, and adult women with TS should continue to take combination estrogen and progesterone.

The choice of progesterone type is according to the patient's clinical condition. Hyperandrogenism in this case is a consideration for the clinician to administer drospirenone. The use of fourth-generation combined oral contraceptive with novel progestine drospirenone have natural progesterone effect, including anti-mineralocorticoid and anti-androgen activities.[18] The other progesterone type that can be administered is nomegestrol acetate, which has a good tolerability profile and neutral metabolic characteristic. It is selective for receptor binding progesterone and have smaller activity against many steroid receptor, which gives no androgenic, estrogenic, glucocorticoid and mineralocorticoid effect.[19]

Fertility in this case

Fertility in TS individuals is normally poor, however it varies depending on the genetic abnormalities detected. Women with mosaicism for the 46,XX normal cell lineage, the 47,XXX cell lineage, or the most distal Xp deletion are more likely to have spontaneous fertility.[10] Even if a woman with TS experiences spontaneous menarche and normal menstrual cycles, ovarian failure will ultimately develop, and the odds of miscarriage and life-threatening cardiovascular problems (aortic dissection and severe hypertension) remain substantial, even during pregnancy.[9] Pregnancy in a woman with Turner syndrome, whether with an autologous oocyte or from a donor, is considered high risk since it might induce maternal and fetal difficulties. Any woman with TS who intends to become pregnant should be informed about the following informations;[20] Increased risk of miscarriage, Increased risk of fetal chromosomal abnormalities in pregnancies fertilized with autologous oocytes, High risk of maternal morbidity and mortality due to cardiovascular and metabolic complications, Obligation to transfer only one embryo in case of IVF-DO, to minimize the risk of multiple pregnancy, Increased risk of CS due to medical complications and narrow pelvic outlet in patients with Turner syndrome, The need for close follow-up by a multidisciplinary team, preferably in a tertiary care center, Risk of obstetric and neonatal complications (IUGR, prematurity, preeclampsia).

While research data is limited, it appears that women with Mosaic Turner Syndrome have a lower risk of cardiovascular and obstetric complications. Therefore, it is advisable for these women to undergo a comprehensive preconception checkup to assess their risks and for subsequent follow-up.[20]

CONCLUSION

Mosaicism in Turner syndrome remains a possibility, and the severity of clinical symptoms corresponds to the extent of defective chromosomes. The variability of mosaicism in Turner syndrome necessitates therapy tailored to the presenting symptoms. This case highlights secondary sex development issues accompanied by mild hyperandrogenism. Despite the patient's regular menstruation indicating estrogen activity, the breast development remains at Tanner stage 1. Breast growth disorder may involve estrogen activity and sensitivity of estrogen receptors, and the administration of combination hormonal treatment can aid in enhancing secondary sex development.

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CONFLICT of INTEREST

The authors have no conflicts of interest to disclose.

AVAILABILITY of DATA and MATERIALS

The data that support the findings of the present study are available in Medical Record Department of Dr. Moewardi Hospital, Surakarta.

Patient Consent for Publication

Patient provided consent for publication.

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Case Report

Unusual Location: Omental Ectopic Pregnancy Interesting Case Report

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Abstract

Objective: Omentum pregnancy is an ectopic pregnancy in the abdominal cavity. The event has high morbidity and mortality. The purpose of this case is to present a rare case of abdominal ectopic pregnancy that occurred in a young woman.

Methods: Case report.

Results: A 22-year-old woman at 16 weeks gestation presented with abdominal pain and clinical shock. Examination results revealed pregnancy outside the womb, with an estimated fetal weight of 193 grams and positive heart activity. The patient underwent laparotomy surgery, revealing that the pregnancy had occurred in the omentum organ with placental attachment.

Conclusion: In this case, emergency management began with the patient's reception in the emergency department, followed by laparotomy exploration. After a meticulous surgery, the pregnancy's location was identified in the omentum, and the evacuation of pregnancy products was performed. The patient received treatment for several days until being discharged home. Early diagnosis and interprofessional management are crucial if similar conditions are suspected in the future to prevent morbidity.

Keywords: abdominal cavity, ectopic pregnancy, omental pregnancy.

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INTRODUCTION

Ectopic pregnancy refers to fertilization and implantation outside the uterine cavity, including the fallopian tubes, cervix, ovaries, uterine horn region, and abdominal cavity.[1] Approximately 0.34% to 1.3% of all ectopic pregnancies are abdominal pregnancy, with only 9% found in omentum.[2] Abdominal pregnancy is a rare form of ectopic pregnancy within the peritoneal cavity, exclusive of the fallopian tubes, ovaries, broad ligament, and cervix. It is associated with high maternal and fetal morbidity and mortality.[3,4] Some of the risk factors identified include a history of pelvic inflammatory disease (PID), a history of previous ectopic pregnancies, previous spontaneous abortion, and uterine deformities.[5] A literature review on Medline for the period 1958-2012 reported only 16 cases of omental pregnancy.[6] Considering the very few case reports of omental pregnancy and the absence of clinical symptoms that appear in early pregnancy, the diagnosis is delayed and requires immediate identification before rupture occurs. Sign and symptoms in patients vary depending on the site of implantation, and only 20-40% of cases are diagnosed before surgery.[7] In this case report, we will report the multiparous pregnant woman with hemoperitoneum due to ruptured omental ectopic.

CASE

A 22-year-old woman, 16 weeks gestational age gravida 2 presented to the emergency department (ED) of Gadjah Mada Academic Hospital, Yogyakarta, and was referred from another hospital with complaints of abdominal pain felt since 2 weeks ago. She was a healthy woman without known illnesses. Since her menarche was 14 years old, previous menses were regular every month, and there was no delay in her menses. Sudden complaints became more aggravating and felt throughout the abdomen from the day before the patient entered the hospital until the patient had difficulty standing

up and defecating. The patient does not know that she is pregnant. When the first complaint appears, it does not interfere with the activity, so the patient does not check her condition. When complaints incriminate the patient to check her condition and an ultrasound examination is carried out, it is said that the patient has a pregnancy outside the uterus.

The patient was then given temporary treatment with anti-pain, but complaints did not decrease, and the patient was referred to our hospital. Clinically, the vital signs examination found that the patient's tension was already very low, 89/60mmHg and a pulse rate of 105 beats per minute. For physical examination of the abdomen, pressure pain was found in the entire abdomen. The vaginal examination was essentially normal, without bleeding seen. Furthermore, an ultrasound examination was carried out and revealed an empty uterus with pregnancy products with a biparietal diameter (BPD) 38.2 mm, femur length (FL) 20.9 mm, estimated fetal weight 193 grams, with cardiac activity positive and intra-abdominal free fluid positive. (Figure1)

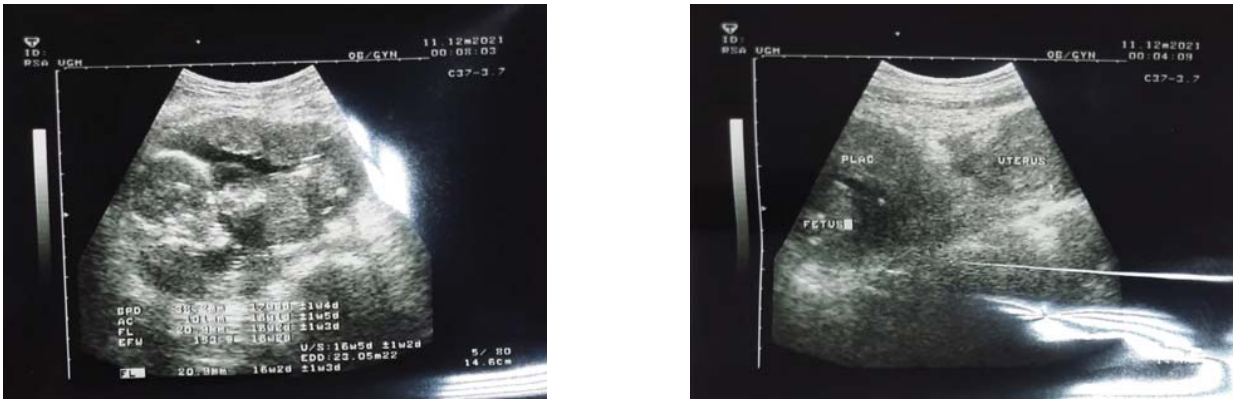

Figure.1 Sonography: Appearance of pregnancy products in the abdominal cavity.

The day after the patient's treatment, a laparotomy exploration of collaboration between the obstetrician and gynecologists and general surgeon is carried out. (Figure 2) In the surgery report, evacuation of abdominal pregnancy products has been carried out, and there is also internal bleeding due to placental separation and omental adhesions. (Figure 3) After surgery the patient is placed in an intensive room for one day following the development of the condition and is then transferred to general ward. Patient receive postoperative packet red cell treatment along with other therapies such as anti-pain, and antibiotics. Patients are also given education to mobilization gradually with a programmed diet as needed. The treatment of complaints gradually improved, the patient recovered and was discharged home five days later. The patient was discharged several days with a case of omental pregnancy.

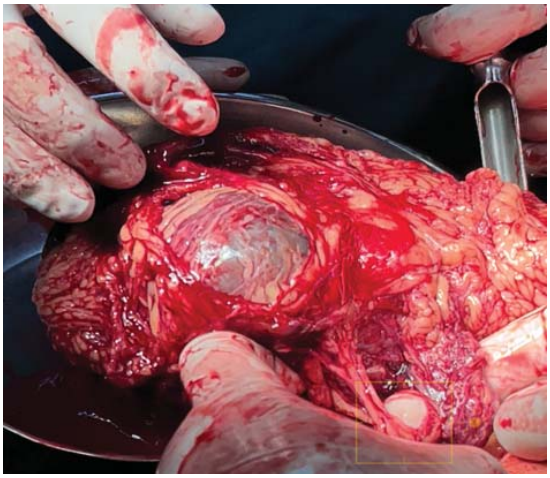

Figure.2 Pregnancy products on omentum tissue

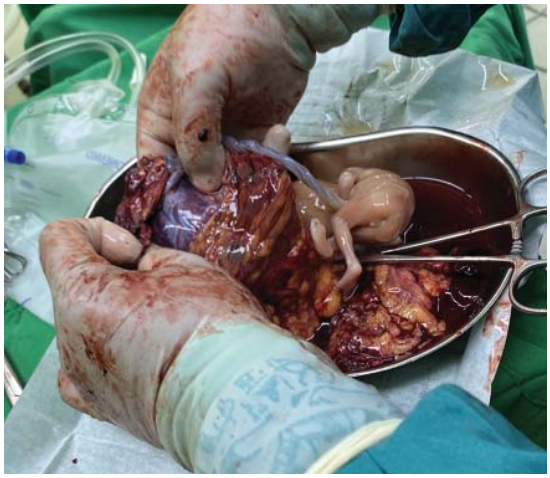

Figure.3 The fetus along with the placenta to the abdominal omentum tissue.

DISCUSSION

Ectopic pregnancy (the term ectopic comes from the Greek word ectopic) means to be outside, and abnormal implantation as gestational growth creates the potential for organ rupture because only the uterine cavity can accommodate the growing fetus.[1] Early diagnosis is important so that treatment and results obtained are optimal.[8] An optimal fallopian tube environment is required to facilitate oocyte transport, fertilization, and migration of the early embryo to the uterus for implantation. Transport of oocytes and embryos through the tubes, with the help of smooth muscle contractions and ciliary lining, is influenced by several local factors, including immunological, hormonal, toxin, and infection.[9] There is an increase in pro-inflammatory cytokine activity, which causes tubal damage, so cell transport does not go well. Chlamydia trachomatis infection causes the production of interleukin-1 by tubal epithelial cells, which later recruits neutrophils and damages the fallopian tubes.[9–11]

Half women with an ectopic pregnancy were found to have no risk factors.[12] Several of the identified risk factors for ectopic pregnancy include a history of ectopic pregnancy and previous fallopian tube surgery, using an intrauterine device, suffering from pelvic inflammatory disease, congenital uterine anomalies, infertility, history of smoking, endometriosis, use of assisted reproductive technology and history of pelvic of abdominal surgery.[13] Among the risk factors described above, women with a history of previous ectopic pregnancy have a greater chance of recurrence, and this will increase to 25% if the is a history of ectopic pregnancy in two or three previous pregnancies.[12]

What is interesting about this case is that in this patient there were no risk factors that support the occurence of ectopic pregnancy. In this woman, the previous pregnancy history was done normally and did not have a history of any surgery. Previous labor history is also by vaginally. Then the complaints he got also appeared after a few weeks until the second trimester. In abdominal ectopic pregnancy, this condition makes it difficult for practitioners to diagnose early until advanced management.

The incidence of ectopic pregnancy is estimated in the general population to be 1 to 5% in patient using assisted reproductive technology. Ectopic pregnancies occurring outside the fallopian tubes account for less than 10% of all ectopic pregnancies. Pregnancies implanted in the abdominal cavity are approximately 1,3%. In one of the studies conducted in Indonesia regarding the incidence profile of ectopic pregnancy. Of the 98 samples, 30,6% of the patients had a range of 26-30 years, the use of hormonal contraception was found more often than an intrauterine device, 7% of patients were repeat cases, 12,1% of patient had a history of surgery in the abdominal or pelvic area, and most ectopic pregnancies were found in the first pregnancy and as many as 26,4% of patient accompained by aggravating infection.[14]

Women with an ectopic pregnancy will complain of pelvic pain, but not all ectopic pregnancies will have this feature. Women of reproductive age who complain of pelvic pain, abdominal pain, nausea/vomiting, dizziness, and vaginal bleeding should be determined whether the patient is pregnant.[12,15] The examiner needs to identify various risk factors for ectopic pregnancy in the patient's history, such as history of previous ectopic pregnancy and history of fallopian tube damage (history of pelvic inflammatory disease, tubal surgery) of pregnancy with assisted reproductive technology.[16–18]

Signs and symptoms of ruptured ectopic pregnancy, such as hemodynamic instability or acute abdomen need to be evaluated and treated promptly. In addition to the physical and obstetric examination, it is necessary to carry out other supporting examinations to confirm an ectopic pregnancy. Diagnostic minimal evaluation of suspected ectopic pregnancy by transvaginal ultrasound examination. Then to confirm pregnancy, serial examination with transvaginal ultrasonography and serum hCG level was carried out.[12]

Interventions for treating ectopic pregnancies include the administration of systemic methotrexate, surgery, and expectancy. Candidates of expectant treatment must be asymptomatic and have no evidence of rupture or hemodynamic instability.[19] Patients with low hCG levels can be treated with a single and double-dose methotrexate (MTX) protocol if hCG levels are high. Surgical treatment, including salpingostomy or salpingectomy, is required when the patient has features of intraperitoneal bleeding, and symptoms of ectopic rupture of hemodynamic instability.[12] Patients with relatively low beta hCG levels have a better prognosis following treatment with a single dose of MTX. On the other hand, if the patient's hemodynamic

are unstable, they tend to be more at risk of worsening due to haemorrhagic shock or other complications.[19,20]

Abdominal pregnancy, especially in omentum, is an interesting case where it is rare. Many cases of ectopic pregnancy occur in the fallopian tube and found a history that supports the occurrence of cases such as a history of previous ectopic pregnancies, smoking, damage to tubal tissue due to infections like PID, and use of assisted reproductive organs. However, in this case none of these risk factors were found and this condition is supported by literature that states there are some cases of ectopic pregnancy that do not have risk factors.

CONCLUSION

Omentum ectopic pregnancy is a rare occurrence where treatment in the form of diagnosis and therapy must be carried out immediately. Suspicion of omentum pregnancy should be considered if you find complaints of abdominal pain in pregnant women. In this case, the clinical symptoms of omentum pregnancy are uncertain. Most patients have sudden abdominal pain even though this condition is only discovered after a few weeks of pregnancy. The point that needs to be considered is that an in-depth history and examination are needed to confirm this incident. Because this condition is rare clinicians are expected to be vigilant about the condition to avoid possible morbidity and mortality that can occur.

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Systematic Review

Carbetosine, a Long-acting Oxytocin Agonist, as a Uterotonic in the Prevention of the Occurrence of Postpartum Bleeding

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Abstract

Objective: To evaluate the comparative effect of carbetocin versus other uterotonic agents (misoprostol and oxytocin) in preventing postpartum bleeding.

Methods: Medical search engines such as Pubmed, Google Scholar, and Cochrane were used for literature searches. The literature covered the period from 2013 to 2023. Keywords used were "Carbetocin" or "long-acting oxytocin" and "uterotonic", "post-partum hemorrhage" or "post-partum bleeding." Data analysis was conducted using the RevMan 5.4 application.

Results: This study involved 12 clinical trials involving a total sample of 32,312 people. Based on forest plot analysis, it was found that patients receiving carbetocin therapy had a 0.42 times lower risk of developing postpartum compared to those receiving other uterotonic agents (misoprostol and oxytocin) (OR: 0.42; 95% CI: 0.26-0.68; p<0.0004; with heterogeneity p<0.00001, I2 85%)

Conclusion: Carbetocin, with its effectiveness and efficacy, can be considered as one modality for preventing postpartum hemorrhage in comparison to other uterotonic agents, such as misoprostol and oxytocin. In addition to that, it can benefit women at risk of having a major obstetric hemorrhage.

Keywords: carbetosin, clinical trial, meta-analysis, uterotonic.

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INTRODUCTION

Maternal deaths are estimated to occur at a rate of 140,000 annually, or 1 woman every 4 minutes, according to World Health Organization (WHO) data. Additionally, postpartum bleeding may cause up to 25% of maternal deaths. Estimated that 100,000 maternal deaths occur annually.[1] Nearly a quarter of all maternal deaths worldwide occur after childbirth, with postpartum hemorrhage being the leading cause in low-income nations like Indonesia.[2-4]

Postpartum hemorrhages are defined as blood losses of at least 500 mL and more than 1000 mL after vaginal and cesarean deliveries respectively.[5] The WHO's current recommendation for preventing postpartum hemorrhage involves aggressively managing the third stage of labor. The most important element of actively treating the third stage of labor is using uterotonic medicines beforehand, which has been found to prevent postpartum hemorrhage by up to 50%. Currently, oxytocin serves as the primary treatment for preventing postpartum hemorrhage. Nonetheless, challenges arise due to its short half-life and activity.[6] However, in many low- and middle-income nations, exposure to heat in areas without access to cold-chain transit and storage cannot ensure its efficacy. Quality issues like impurities and insufficient active ingredients are also mentioned as issues with using such oxytocin.[5]

Studies have investigated the efficacy of oxytocin and carbetocin in reducing postpartum hemorrhage. Since 1997, the long-acting oxytocin analog carbetocin has successfully stopped postpartum bleeding.[7,8] In previous research, the effects of carbetocin 100 mg intramuscularly (IM) and oxytocin 5 IU intramuscularly (IM) were compared. The carbetocin group required less uterotonics and had much less bleeding. After extensive research, it was shown that IM carbetocin reduced postpartum hemorrhage more effectively than oxytocin. Previous studies

have shown that uterine contractions can commence in less than two minutes after the initial carbetocin dose and persist for up to two hours.[2,7,8]

To date, only a limited number of meta-analyses and systematic reviews have addressed the role of carbetocin, a long-acting oxytocin agonist, in preventing postpartum hemorrhage. Therefore, further investigation is necessary to elucidate the role of carbetocin in reducing postpartum bleeding. This gap in research prompted the authors of this meta-analysis to examine the use of carbetocin, a long-acting oxytocin agonist, as a uterotonic agent in preventing postpartum hemorrhage.

METHODS

Search engines such as PubMed, Google Scholar, and Cochrane were utilized for literature searches spanning the years 2013 through 2023. Keywords included "Carbetocin" or "long-acting oxytocin" and "uterotonic," along with "postpartum hemorrhage" or "postpartum bleeding." Data analysis was performed using the RevMan 5.4 program. Inclusion criteria were as follows pregnant women with a higher risk of preterm labor who used carbetocin as a uterotonic to prevent postpartum hemorrhage; evaluation of the efficacy of carbetocin, a long-acting oxytocin agonist, as a uterotonic; and the availability of adequate odds ratio (OR) data accompanied by 95% confidence intervals. Reviews, case reports, correspondence, conference abstracts, and duplicated data were excluded from consideration.

RESULTS

Based on the quality assessment of the study using the New Ottawa Scale for the analysis of Randomized Control Trials, the fundamental research has good quality (Table 1.)

Table 1. Quality of the Study

Author, year	1	2	3	4	5	6	7	8	Criteria
Amornpetchakul, 2017	√	-	√	√	√	√	√	√	Good
Elbohoty, 2016	√	√	√	-	√	√	√	√	Good
Elgaforelsharkwy, 2013	√	√	√	√	√	√	-	√	Good
Hsu, 2021	√	√	-	√	√	√	√	√	Good
Ibrahim, 2020	√	√	√	√	-	√	√	√	Good
Maged, 2015a	√	-	√	√	√	√	√	√	Good
Maged, 2015b	√	√	√	√	√	-	√	√	Good
Razali, 2016	√	√	√	-	√	√	√	√	Good
Salem, 2019	√	-	√	√	√	√	√	√	Good
Taheripanah, 2017	√	√	√	√	√	-	√	√	Good
Whigham, 2018	√	-	√	√	√	√	√	√	Good
Widmer, 2018	√	√	√	-	√	√	√	√	Good

All included studies in this meta-analysis had a low risk of bias, according to Cochrane's review of the risk of bias using a risk of bias checklist (Table 2).

Table 2. Risk of Bias Analysis

Author, year	Signaling question			Default risk of bias
	1.1	1.2	1.3	
Amornpetchakul, 2017	Y	PY	N	Low
Elbohoty, 2016	Y	Y	N	Low
Elgaforelsharkwy, 2013	Y	PY	NI	Low
Hsu, 2021	PY	Y	N	Low
Ibrahim, 2020	Y	PY	N	Low
Maged, 2015a	Y	PY	PN	Low
Maged, 2015b	PY	PY	N	Low
Razali, 2016	Y	PY	N	Low
Salem, 2019	Y	Y	N	Low
Taheripanah, 2017	PY	PY	PN	Low
Whigham, 2018	Y	PY	N	Low
Widmer, 2018	PY	PY	N	Low

*Y/PY = "Yes" or "Probably yes"; N/PN = "No" or "Probably no"; NI = "No information"

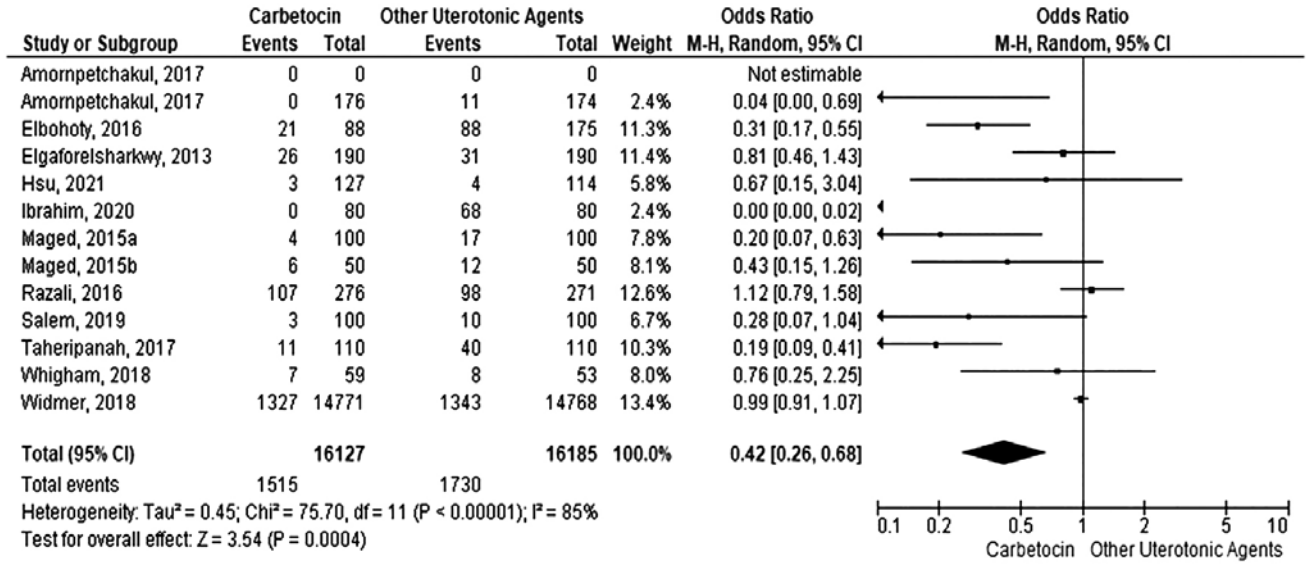

Figure 1. Forest plot for carbetocin vs. other uterotonic agents

This study involved 12 clinical trials involving a total sample of 32,312 people. Based on forest plot analysis, it was found that patients receiving carbetocin therapy had a 0.42 times lower risk of developing postpartum compared to those receiving other uterotonic agents (misoprostol and oxytocin) (OR: 0.42; 95% CI: 0.26-0.68; p<0.0004; with heterogeneity p<0.00001, I2 85%) (Figure 1).

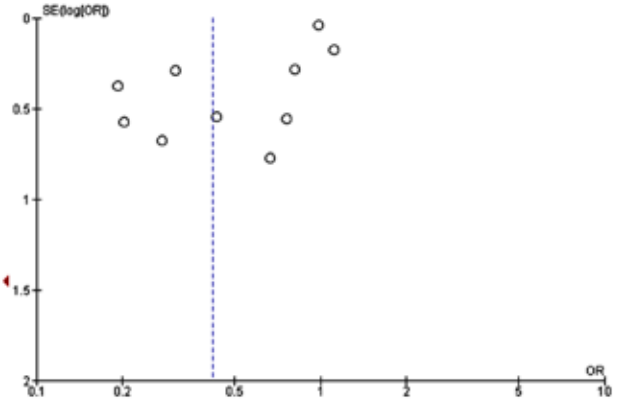

Figure 2. Tunnel plot for carbetocin vs. other uterotonic agents in preventing post-partum hemorrhage.

DISCUSSION

Our current meta-analysis compared the effectiveness of carbetocin as a uterotonic drug in reducing the risk of postpartum hemorrhage. Patients administered carbetocin exhibit a significantly lower risk of bleeding compared to those receiving other uterotonic treatments.

Previous research involved a comparison between carbetocin and oxytocin to prevent postpartum hemorrhages. This study revealed that carbetocin reduced the necessity for uterotonics particularly those who underwent cesarean deliveries. However, vaginal delivery did not yield the same outcomes. The study found no significant difference between using carbetocin, oxytocin, or another control in terms of reducing the risk of postpartum hemorrhage, which is defined as any blood loss greater than 500 ml, or the threat of severe PPH, which is defined as a condition of blood loss greater than 1000 ml.[9]

The uterine tone can be improved with carbetocin, a synthetic long-analog of oxytocin. According to a prior study, intravenous carbetocin administration to postpartum individuals can induce tetanic uterine contractions that start after two minutes and persist for six. The rhythmic contraction was then generated for 60 minutes following the carbetocin injection.[10] Carbetocin has a half-life of 40 minutes, approximately four to ten minutes longer than oxytocin, with an optimal dosage of 100 µg intravenously.[11] The oxytocin receptor (OXTR) in the uterine smooth muscle can specifically bind carbetocin. The rhythmic contractions of the uterus can be induced by this method. Additionally, it might intensify prior contractions and raise the uterine muscular tone. Following intramuscular injection of carbetocin, the intravenous administration of the drug can trigger contractions for 60 and 120 minutes.[12]

Carbetocin is equally effective as syntometrine but has fewer adverse effects in preventing primary PPH after vaginal birth. A different study showed that a single injectable carbetocin dosage of 100 g decreased postpartum blood loss more efficiently and with fewer side effects. There was no difference between intramuscular carbetocin

and intravenous oxytocin in a randomized study between the frequency and severity of PPH in high-risk women. The prevention of PPH in high-risk women after vaginal birth was demonstrated in a more recent trial to be more successful with injectable carbetocin than oxytocin. Carbetocin outperforms syntometrine in avoiding PPH after vaginal delivery, according to a thorough review of 11 research.[12]

A prior study comparing intravenous administration of carbetocin and oxytocin in a hypertensive pregnant woman who underwent elective cesarean section demonstrated that carbetocin was more effective in reducing both intraoperative and postoperative blood loss compared to oxytocin. Additionally, the postoperative hemoglobin levels in the carbetocin group did not significantly differ from the preoperative levels, while the oxytocin group showed a decrease in hemoglobin levels.[13] However, recent research has shown minimal disparity in the efficacy of carbetocin and oxytocin solutions for manual placental removal. Similarly, there were no significant differences in the need for blood transfusions between the two groups.[14]

Carbetocin was compared with other control agents, including misoprostol. According to the previous study, carbetocin exhibited a more beneficial effect than misoprostol in reducing the risk of postpartum hemorrhage. Various factors were analyzed in the study, including decreased hemoglobin levels, the requirement for additional oxytocic substances, uterine massages, blood pressure monitoring, and adverse drug effects for each intervention. The study findings revealed that, compared to carbetocin, misoprostol significantly lowered hemoglobin levels after delivery ($p=0.025$). Additionally, the third stage of labor was shorter ($p=0.001$), and there was less blood loss ($p<0.001$) in the misoprostol group. Moreover, individuals in the carbetocin group required fewer additional oxytocic medications and uterine massages. Furthermore, the study indicated that misoprostol led to more adverse medication responses than carbetocin ($p<0.001$). Notably, the misoprostol group experienced significantly higher incidences of fever, shivering, and diarrhea with p-values of 0.006, 0.050, and 0.028, respectively. Additionally, blood pressure levels among individuals administered misoprostol were notably higher at 30 and 60 minutes post-delivery compared to those receiving carbetocin, extending up to 60 minutes after delivery.[15]

Despite its effectiveness, the cost of using carbetocin warrants consideration. In comparison to alternative treatments like oxytocin, carbetocin incurs higher costs. An earlier study demonstrated that oxytocin exhibited a higher mean cost-effectiveness than carbetocin. Specifically, the mean cost-effectiveness ratio for oxytocin was 4944 USD, whereas for carbetocin, it was 3874 USD.[13]

The limitation in this study is that we did not perform a sub-group analysis on the factors that are likely to influence the occurrence of postpartum bleeding, as in patients with differences in bleeding risk.

CONCLUSION

Due to its effectiveness and efficiency, carbetocin stands as a viable method in preventing postpartum hemorrhage. Moreover, it holds promise in benefiting women at high risk of experiencing significant obstetric bleeding.

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