Editorial

The Role of Social Obstetrics and Gynecology in the Coverage of Cervical Cancer Screening in the Era of Health Transformation in Indonesia

Junita Indarti

Cervical cancer remains a major concern in Indonesia, with statistics from the 2021 Indonesian Health Profile showing that it ranks second only to breast cancer in terms of incidence, with 36.633 cases (17.2% of all cancers in women). Furthermore, it has a significant mortality rate, with 21.003 deaths (19.1% of all cancer-related deaths). When compared to the incidence of cervical cancer in 2008, there is a twofold increase.

According to GLOBOCAN 2020 data, Indonesia continues to have a substantially higher incidence of cervical cancer (24.4 per 100.000 population) than other emerging nations such as Malaysia and India. The incidence of cervical cancer in Indonesia is still very high, even when compared to wealthy nations like Singapore, which is Indonesia's neighbour.

The contributing factor to this high incidence rate is the low screening coverage. Until 2021, only about 6.83% of women aged 30-50 years underwent cervical cancer screening with the VIA method. In 2023, the screening coverage in Indonesia is 7.02%, with the target for cervical cancer screening coverage in 2023 being 70%.

Without fast and effective action, these cervical cancer rates will continue to rise, causing a significant socio-economic burden and a decrease in the quality of individual life. Social Security Agency of Health (*BPJS Kesehatan*) notes that cervical cancer is ranked second in catastrophic illness, with costs amounting to around Rp 3.5 trillion for 2.5 million cases in 2020. Approximately 70% of cancer patients arrive at an advanced stage, incurring high treatment costs, and this situation certainly burdens the Social Security Fund of Indonesia.

In the midst of these challenges, Indonesia's efforts to accelerate the improvement of cervical cancer prevention are related to the transformation of the healthcare system, which includes five pillars of healthcare transformation: primary care transformation, referral service, healthcare financing system, healthcare workforce, and healthcare technology. These five pillars can support two strategies for cervical cancer prevention, namely primary prevention through HPV vaccination and secondary prevention through early detection of cervical cancer.

The development of innovative screening methods and prevention approaches has become essential in addressing the challenge of screening coverage to make it more effective, affordable, and easily accessible. The cervical cancer screening methods used in Indonesia include VIA, Pap smear, and HPV DNA testing, as well as HPV DNA testing and VIA (co-testing).

VIA remains the preferred screening method due to its affordability compared to HPV DNA testing and Pap smear. However, the challenge is that, in addition to training healthcare personnel, a comprehensive referral process needs to be established for positive results if they cannot be managed at the primary healthcare facilities.

Another screening method is HPV DNA testing, which has a very high sensitivity, ranging from 80-95%. It is more effective in detecting precancerous lesions and can be performed by untrained healthcare personnel, self-sampling, or collected from urine samples. Some studies suggest that the concordance between samples taken by healthcare professionals and those taken by patients themselves is not significantly different, ranging from 80-95%. Currently, research has been conducted in various countries, including Indonesia, to develop HPV DNA testing using urine samples to make the screening process more accessible. Some of these studies reported that the sensitivity of HPV DNA testing from urine samples ranges from 63.9% to 87.5%. In addition to its high sensitivity, both self-administered HPV DNA testing and urine-based testing can accommodate unscreened patients due to factors like embarrassment, lack of time, and transportation obstacles that hinder screening.

Despite having many advantages, the implementation of HPV DNA testing in Indonesia still faces the challenge of high costs. However, there are now locally produced HPV DNA tests available at a lower and more affordable price, which was originally priced at Rp 600.000-800.000 but has now been reduced to Rp 148.850. Therefore, the estimated costs incurred when using the screening method multiplied by the number of women of reproductive age who are required to be screened with HPV DNA testing amounts to Rp. 4.422.641.281.650.

Considering that cervical cancer has wide-ranging health and socio-economic impacts on women in Indonesia, it is necessary to have more stringent regulations requiring women to undergo routine screenings. The Role of Social Obstetrics and Gynecology has the potential to support cervical cancer screening coverage and help reduce the extensive impact of this disease by developing evidence-based strategies. Efforts to improve cervical cancer prevention should be continuously promoted by various stakeholders. Likewise, the subsequent management of all these screening methods requires referral services with fast and integrated access and coordination between screening centres and healthcare facilities. Collaboration between the Central and Regional Governments, Hospitals, Community Health Centres, Professional Organizations, and the community is essential for the realization of better health and quality of life for Indonesian Women.

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Research Article

Hospital Cost vs INA-CBGs Claim for Obstetrics Procedure In Soe Rural General Hospital, East Nusa Tenggara

Tarif Rumah Sakit vs Klaim INA-CBGs untuk Prosedur Obstetrik di Rumah Sakit Umum Daerah SoE, Nusa Tenggara Timur

Raymond Surya[1,2], Ascobat Gani[1], Yudianto B. Saroyo[3]

[1] Faculty of Public Health Universitas Indonesia, Depok
[2] Specialist of Obstetrician-Gynecologist, RSUD SoE,
Timor Tengah Selatan District Nusa Tenggara Timur
[3] Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Indonesia
Dr. Cipto Mangunkusumo Hospital, Jakarta

Abstract

Objective: To depict the discrepancy and analyze the difference between hospital cost and INA-CBGs claim in obstetrics' cases in SoE Rural General Hospital, Timor Tengah Selatan regent, East Nusa Tenggara.

Methods: This is an observational descriptive study using medical record documents of spontaneous vaginal, assisted vaginal, and cesarean delivery cases from the period of October to December 2022. We included all completed billing documents on that period. Cases paid by fee-for-service and local government were excluded. Data analysis was conducted using IBM SPSS Statistic 23.0

Results: From the total of 323 delivery cases recorded in SoE Rural General Hospital, only 245 cases were included. Most subjects were patients aged around 30 years old, referred from primary healthcare facility in the district, were in term pregnancy, and in 3rd class inpatient rooms. The median of length of stay (LOS) in vaginal delivery (spontaneous and assisted) and cesarean delivery were 2 days and 3 days, respectively. Mean difference between hospital cost to INA-CBGs claim was 67% to 158% for either vaginal or cesarean delivery based on class inpatient room. We found that hospital cost was always higher than claim cost based on INA-CBGs claim.

Conclusion: There is a significant discrepancy between hospital cost and INA-CBGs claim (from 67% to 158%) for obstetric services in SoE Rural General Hospital.

Keywords: hospital cost, INA-CBGs claim, obstetric.

Abstrak

Tujuan: *Untuk memberikan gambaran perbedaan dan menganalisis perbedaan antara tarif RS dengan klaim INA-CBGs pada kasus obstetrik di RSUD SoE, Timor Tengah Selatan, Nusa Tenggara Timur.*

Metode: *Studi deskriptif observasional menggunakan dokumen rekam medis dari kasus persalinan pervaginam spontan, persalinan pervaginam dengan alat, dan seksio sesarea dari Oktober hingga Desember 2022. Kami memasukkan seluruh dokumen billing yang lengkap. Dokumen biling yang dibayarkan mandiri dan oleh pemerintah lokal dieksklusi. Analisis data dengan menggunakan IBM SPSS Statistik 23.0.*

Hasil: *Dari 323 persalinan yang terekam di RSUD SoE, hanya 245 kasus diinklusikan. Kebanyakan subjek berusia 30 tahun, dirujuk dari puskesmas, kehamilan cukup bulan, dan ruang perawatan kelas 3. Angka median dari lama rawat pervaginam (baik spontan maupun dengan alat) adalah 2 hari dan seksio sesarea 3 hari. Rerata perbedaan tarif RS dengan klaim INA-CBGs ialah 67% hingga 158% baik persalinan pervaginam maupun seksio sesarea berdasarkan ruang kelas perawatan. Kami menemukan angka tarif RS selalu lebih tinggi cukup jauh dari klaim INA-CBGs.*

Kesimpulan: *Terdapat perbedaan antara tarif RS dan klaim INA-CBGs (antara 67 hingga 158%) untuk prosedur obstetrik di RSUD SoE.*

Kata kunci: *tarif RS, klaim INA-CBGs, obstetrik.*

INTRODUCTION

The World Health Organization (WHO) defines health as a state of complete physical, mental, and social well-being, not merely the absence of disease or infirmity [1]. According to the Law of the Republic of Indonesia Number 36 of 2009, health is essential for everyone to live productively in society and the economy. Health services are established either individually or collectively in organizations to promote health, prevent and treat diseases, and enhance the well-being of individuals, families, groups, and society[2]. Indonesian Minister of Health Regulation Number 3 of 2020 about hospital's classification stated that hospital is a health service institution which carries out individual health service comprehensively through outpatient, inpatient, and emergency unit [3]. To enhance patient's satisfaction, hospital should maintain health service quality as customer expectation in order to meet patient's satisfaction. One of them is through appropriate cost in accordance with treatment offered by the hospital.

In the era of Universal Health Coverage (UHC), payments at health facilities aim to improve quality, provide patient-oriented services, and increase efficiency without rewarding providers for over- or under-treatment or adverse events. In Indonesia, *Badan Penyelenggara Jaminan Sosial Kesehatan* (BPJS) manages the national health insurance system (JKN) as part of UHC. One of the fundamental payment system in JKN to hospitals is a prospective payment or bundling system known as Indonesia Case Based Groups (INA-CBGs) [4]. Indonesian Minister of Health Regulation Number 76 of 2016 authorizes INA-CBGs to be implemented in Indonesia [5].

Based on data from the Badan Pusat Statistik (BPS) in 2020, Indonesia's maternal mortality rate (MMR) remains high, at approximately 189 per 100,000 live births[6]. Meanwhile, the World Health Organization (WHO) has set a global target of reducing maternal mortality to less than 70 per 100,000 live births by 2030[7]. JKN aims to support this vision by addressing the three delays that contribute to maternal deaths, ensuring easy access to health services for all women [8].

The disparity in INA-CBGs claims for deliveries can pose obstacles to reducing MMR directly and indirectly. The Indonesian national report for 2018 indicated that cesarean sections accounted for over 17.6% of delivery modes in Indonesia9. Previous studies have revealed differences between actual hospital costs and INA-CBGs claim rates, with negative differences observed for both vaginal and cesarean delivery procedures [9,10]This disparity between costs and claims prompts hospitals to manage their expenses through cost containment measures, including enhancing efficiency, payment systems, and service standardization[10]. Therefore, this study aims to determine and analyze the difference between hospital cost and INA-CBG claim for delivery cases either spontaneous vaginal delivery or cesarean section in RSUD SoE, Timor Tengah Selatan district, East Nusa Tenggara. RSUD SoE is the only one referral hospital for regent of Timor Tengah Selatan, East Nusa Tenggara; thus, complicated delivery cases in primary health care will be referred to this hospital.

METHODS

This observational descriptive study was conducted in RSUD SoE, Timor Tengah Selatan district, East Nusa Tenggara using patients' billing documents for cases of spontaneous vaginal delivery and cesarean section cases from October to December 2022. These billing documents consisted of total patients' billing during hospitalized/treatment and successful INA-CBG claim. We included all completed billing documents on that period. Cases paid by fee-for-service and local government were excluded. Total sampling was employed to collect cases, and the flowchart illustrating our case recruitment process is presented in Figure 1.

Demographic characteristics consisted of age, referral status, gestation, parity, gestational age, complication, length of stay (LOS), and inpatient hospital class. Gravidity defines as the number of pregnancies both current and past regardless of pregnancy outcome. Parity is the number of pregnancies after 20 weeks and 0 days of gestation regardless of the number of fetuses or outcomes. Gestational age is calculated by (280-estimated due date-reference date)/7 and it is written in both weeks and days. Pregnancy complications include hypertension, pre-labor rupture of membranes (PROM), preterm labor, post-term, twin pregnancy, intrauterine fetal demise (IUFD), failed of induction, previous cesarean section (CS), fetal distress, abnormal placentation, malpresentation, dystocia 1st or 2nd stage of labor, cephalopelvic disproportion (CPD), primary infertility, condyloma, and HIV. Pre-labor rupture of membranes (PROM) is spontaneous

rupture of membranes occurring before onset of labor11. Preterm happens less than 37 weeks and 0 days [11]. Intrauterine fetal demise (IUFD) defines as the delivery of fetus without showing sign of life, indicated by absent breathing, heartbeats, pulsation of umbilical cord, or definite movements of voluntary muscles, regarding to greater than 20 weeks of gestation or birth weight greater than or equal to 500 grams [12]. Malpresentation is any presentation other than a vertex presentation [11]. Dystocia is characterized by the slow or abnormal progression of labor. Meanwhile, cephalopelvic disproportion is a discrepancy between the size of maternal pelvis and fetal head precluding vaginal delivery [13]. Length of stay (LOS) is a measure the length of time elapsed between hospital discharge and admission [14]. Inpatient classroom is divided into one, two, and three based on Regulation of Government of the Republic of Indonesia Number 47 of 2021 [15].

Hospital cost includes summary of the surgery procedures, medication, nursing, laboratory, room charges, disposable medical supplies, consultations, supportive items, and blood transfusions. This hospital cost refers to the Regulation of Timor Tengah Selatan Regent Number 24 of 2021 about hospital cost in Timor Tengah Selatan district [16]. INA-CBGs claims follows the guidelines of the Regulation of Indonesian Minister of Health Number 69 of 2013 in which the claims are different based on 5 regions. RSUD SoE falls under regional 5 for class C hospitals [17]. Cost difference signify the disparity between hospital costs and INA CBG claim. Proportion in percentage is calculated as the mean variable cost divided by the average hospital cost. This study did not require ethical clearance due to the use of secondary data using medical records. However, it has been approved by the head of RSUD SoE under number RSUD.35.01.02/244/2023.

The data were described descriptively. To assess the normality data, we used Kolgomorov-Smirnov test and univariate test to describe each variable also frequency distribution. IBM SPSS Statistic 23.0 was also used for the data analysis.
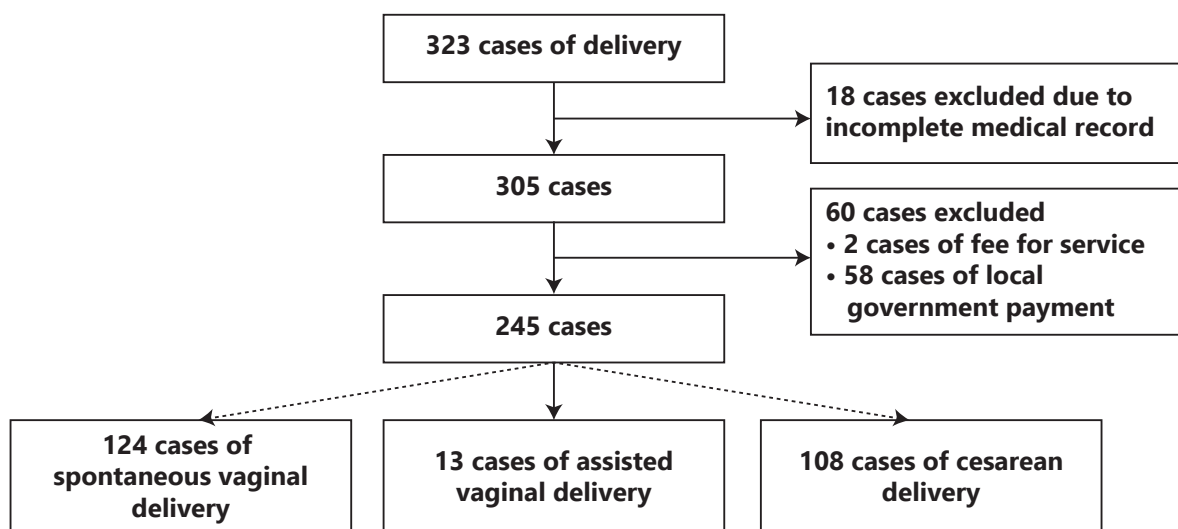

Figure 1. Flow chart of recruiting cases in this study

RESULTS

Out of 323 cases of delivery either vaginal or cesarean section in RSUD SoE during this study, only 305 were well-recorded cases due to the absence of electronic medical records (EMR) usage. Approximately 60 cases were excluded because they were paid for using the fee-for-service method or local government payment, which did not align with the case mix system according to JKN. Table 1 depicted the demographic characteristics of patients included in this study. Most of them aged around 30 years old, referred from primary health care in the district, term pregnancy, and 3rd class of inpatient hospital room. For LOS, the median both in spontaneous vaginal delivery and assisted vaginal delivery was 2 days; meanwhile, for cesarean delivery, it was 3 days. Statistically, there was significant differences in age and LOS among the groups ($p < 0.05$).

Table 1. Demographic Characteristics in this Study

	Spontaneous Vaginal Delivery (N=124)	Assisted Vaginal Delivery (N=13)	Cesarean Delivery (N=108)	P-value
Age (years old) (median (min-max))	29 (14-46)	30 (17-36)	32 (19-49)	0.047[a]
Referral (N, %)				
Polyclinic	12 (9.7)	1 (7.7)	15 (13.9)	
Primary health care	57 (46.0)	9 (69.2)	43 (39.8)	
Clinic	12 (9.7)	0	31 (28.7)	
Other hospital	2 (1.6)	0	1 (0.9)	
No referral	41 (33.1)	3 (23.1)	18 (16.7)	
Gravidity (median (min-max))	2 (1-8)	2 (1-5)	2 (1-9)	0.632[a]
Parity (median (min-max))	1 (0-7)	1 (0-4)	1 (0-6)	0.917[a]
Gestational age (weeks) (median (min-max))	39 (26-44)	39 (33-43)	40 (36-42)	0.125[a]
Complication (N, %)				
Hypertension	9 (7.3)	0	15 (13.9)	
PROM	12 (9.7)	0	2 (1.9)	
Preterm labor	6 (4.8)	0	0	
Post-term	4 (3.2)	0	1 (0.9)	
Twin pregnancy	3 (2.4)	0	0	
IUFD	7 (5.6)	0	0	
Failed of induction	0	0	8 (7.4)	
Previous CS	1 (0.8)	0	20 (18.5)	
Fetal distress	0	2 (15.4)	12 (11.1)	
Abnormal placentation	0	0	6 (5.6)	
Malpresentation	2 (1.6)	0	19 (17.6)	
Dystocia 1st or 2nd stage	12 (9.7)	11 (84.6)	16 (14.8)	
CPD	0	0	6 (5.6)	
Primary infertility (patient's value)	0	0	1 (0.9)	
Condyloma	0	0	1 (0.9)	
HIV	0	0	1 (0.9)	
None	68 (54.8)	0	0	
Length of stay (LOS) (days) (median (min-max))	2 (1-5)	2 (1-3)	3 (2-10)	<0.001[a]
Inpatient Hospital Class (N (%))				
I	4 (3.2)	0	9 (8.3)	
II	14 (11.3)	1 (7.7)	13 (12.0)	
III	106 (85.5)	12 (92.3)	86 (79.6)	

a. Kruskal Wallis non-parametric test. PROM: Prelabor rupture of membrane. IUFD: Intrauterine fetal demise
CS: Cesarean section. CPD: Cephalopelvic disproportion. HIV: Human Immunodeficiency Virus
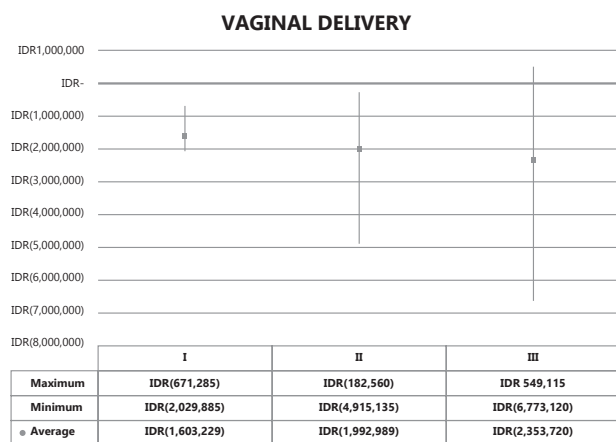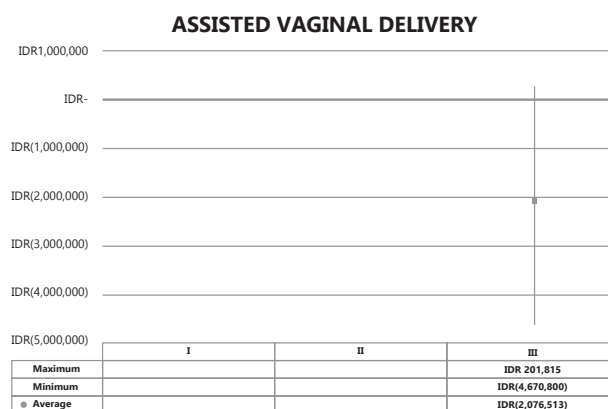
Table 2 showed the summary, mean, percentage, and different component of hospital cost in RSUD SoE to INA-CBGS claim based on methods of delivery. For spontaneous vaginal delivery, the mean difference in hospital costs compared to INA-CBGS claims ranged from 67% to 129%. Meanwhile, the mean difference between 92% and 109% was described for assisted vaginal delivery based on inpatient hospital class. Also, the mean difference from 87% to 158% was shown in cesarean delivery appropriate to inpatient hospital class. Figure 1 to 3 depicted the average, minimum, and maximum value of difference between hospital costs and INA-CBGS claims according to vaginal delivery, assisted vaginal delivery, and cesarean delivery; respectively. All analyzed data showed that hospital cost was always higher than INA-CBGS claim. In spontaneous vaginal delivery and assisted vaginal delivery, the highest mean cost was contributed by non-surgery procedure around 26-34%. Meanwhile, in cesarean delivery, the highest proportion of hospital cost was coming from surgery procedure (55-59%).

Table 2. Summary, Mean, Percentage, and Different Component of Hospital Cost in RSUD SoE to INA-CBGS Claim for Obstetrics Cases (spontaneous, assisted vaginal, and cesarean delivery) According to the Inpatient Hospital Class.

| Obstetric Cases | Inpatient Hospital Class | | | | | | | | | | | | | | |
| | Spontaneous Vaginal Delivery | | | | | | Assisted Vaginal Delivery | | | | Cesarean Delivery | | | | | |
	I (IDR)	p-value (%)	II (IDR)	p value (%)	III (IDR)	p-value (%)	II (IDR)	p-value (%)	III (IDR)	p-value (%)	I (IDR)	p-value (%)	II (IDR)	p-value (%)	III (IDR)	p-value (%)
Number of cases (N)	4		14		106		1		12		9		13		86	
LOS (average) (days)	2		2		2		2		2		4		3		3	
Hospital cost (average)	3,993		4,087		4,183		4,604		3,989		13,574		15,006		12,847	
Lowest hospital cost	2,963		2,508		1,257				2,502		11,308		11,206		1,782	
Highest hospital cost	4,414		7,241		10,461				6,308		17,284		31,463		26,681	
Non-surgery procedure (mean)	1,100	28	1,273	31	1,410	34	1,200	26	1,200	30	7,935	58	8,320	55	7,527	59
Lowest	1,000		1,000		1,000				1,200		6,935		6,935		369	
Highest	1,200		2,400		5,700				1,200		11,435		11,437		11,435	
Medicine (mean)	407	10	427	10	578	14	390	8	476	12	2,180	16	3,717	25	2,133	17
Lowest	316		315		104				210		1,735		1,857		250	
Highest	462		742		7,048				1841		2,403		20,784		8,520	
Nursing (mean)	880	22	1,174	29	991	24	1346	29	943	24	1,008	7	742	5	856	7
Lowest	445		401		65				155		446		577		161	
Highest	1,068		2,395		2,506				1,964		2,728		1.077		7.621	
Laboratory (mean)	332	8	359	9	369	9	343	7	392	10	508	4	511	3	600	5
Lowest	243		243		75				210		46		221		66	
Highest	391		636		832				771		882		1,044		6,619	
Room charge (mean)	750	19	846	21	710	17	900	20	728	18	1,121	8	1,055	7	1,163	9
Lowest	600		360		50				540		730		630		25	
Highest	900		1,980		1,800				1,260		1,500		1,230		2,790	
Disposable medical supplies (mean)	100	3	88	2	95	2	100	2	77	2	119	1	107	1	121	1
Lowest	100		50		25				25		100		100		25	
Highest	100		150		500				200		150		125		1,500	
Consultation (mean)	350	9	182	4	154	4	175	4	177	4	261	2	250	2	255 5	2
Lowest	200		100		25				75		225		150		23	
Highest	750		375		400				275		300		375		900	
Supporting item (mean)	100	3	123	3	138	3	150	3	114	3	211	2	184	1	201	2
Lowest	100		100		50				50		150		150		100	
Highest	100		200		532				246		299		300		600	
Blood transfusion (mean)	N/A		N/A		1,033	25	N/A		N/A		1,860	14	1,240	8	930	7
Lowest					620						1,860		1,240		620	
Highest					1,240						1,860		1,240		1,860	
INA-CBGS claim (average)	2,390		2,094		1,829		2,394		1,912		7,258		6,224		4,983	
Difference (average)	-1,603	-67	-1,993	-95	-2,354	-129	-2,210	-92	-2,077	-109	-6,316	-87	-8,782	-141	-7,864	-158

IDR: Indonesian Rupiah. P: Proportion* All values in thousand rupiah

VAGINAL DELIVERY

	I	II	III
Maximum	IDR(671,285)	IDR(182,560)	IDR 549,115
Minimum	IDR(2,029,885)	IDR(4,915,135)	IDR(6,773,120)
● Average	IDR(1,603,229)	IDR(1,992,989)	IDR(2,353,720)

Figure 1. Average, minimum, and maximum value of difference between hospital cost and INA-CBGs claim for vaginal delivery

ASSISTED VAGINAL DELIVERY

	I	II	III
Maximum			IDR 201,815
Minimum			IDR(4,670,800)
● Average			IDR(2,076,513)

Figure 2. Average, minimum, and maximum value of difference between hospital cost and INA-CBGs claim for assisted vaginal delivery

CESAREAN DELIVERY

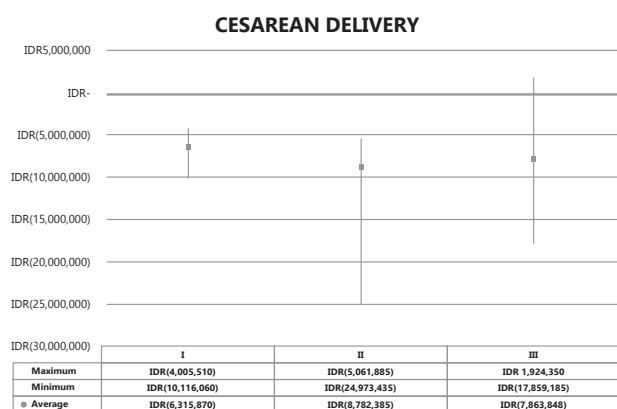|	I	II	III
Maximum	IDR(4,005,510)	IDR(5,061,885)	IDR 1,924,350
Minimum	IDR(10,116,060)	IDR(24,973,435)	IDR(17,859,185)
Average	IDR(6,315,870)	IDR(8,782,385)	IDR(7,863,848)

Figure 3. Average, minimum, and maximum value of difference between hospital cost and INA-CBGs claim for caesarean delivery

DISCUSSION

There was a significant difference between hospital cost in RSUD SoE and INA-CBGs claim. The hospital costs are determined per service details according to the standard costs outlined by Regulation of Timor Tengah Selatan Regent Number 1 of 2021 concerning the redistribution of public services, and Number 24 of 2021 concerning hospital costs in the Timor Tengah Selatan district [16,18]. On the other hand, INA-CBGs claims are calculated based on diagnosis code grouping (ICD-X) with prospective payment method. Prospective payment method means that the payment is carried out by health service known before providing treatment to the patients. The cost divided into regional area and hospital type has been set by Regulation of Indonesian Minister of Health in 2016 [5].

The determination of hospital cost considers several aspects such as society's ability to pay, hospital services based on sophisticated degree of treatment and inpatient classroom, providing cost relief for poor people as appropriate to General Directorate of Medical Services corporation with BPJS.[19] The summary of the actual hospital cost, it showed that non-surgery or surgery procedure contributed to the highest hospital actual cost (26-59%). Meanwhile, disposable medical supplies and supporting item became the two lowest of hospital actual cost around 1-3%.

Several factors contribute to the significant cost difference between the hospital and INA-CBGs claims, including coding accuracy, efficiency, remuneration, hospital management, and clinical pathways. In the implementation of INA-CBGs claims, accurate coding is crucial, as it

impacts the grouper results within the INA-CBGs application, and is inherently linked to the claimed costs. Observation indicated that certain claimed diagnoses and procedures were inconsistent with reality. Most reports contained codes for mild levels of claim severity, although, as the sole referral hospital in the Timor Tengah Selatan district, more moderate to severe claim codes would be expected. For instance, the omission of blood transfusions from the procedure list for INA-CBGs claims could affect the severity of the diagnosis. The improper completion of claim records by non-health providers led to the under-recording of disease severity and performed procedures in the actual INA-CBGs claim. A previous study concluded that internal accuracy in recording diagnoses and procedures significantly impacts INA-CBGs claims[20].

In the case of cesarean delivery, surgery procedures exceeded the INA-CBGs claims. Efficiency should be instituted in all aspects of actual hospital costs. Surgery procedures encompass the costs of operating theater usage, anesthesia and obstetric medications, and surgical tools. Hospital managers should assess the high cost associated with this procedure's contribution to the overall cost. Efficiency initiatives can begin with the planning of generic medications used in the hospital, purchasing medications through e-catalogs, promoting standard drug formularies, arranging medications and surgical tools within operating theaters, conducting laboratory examinations in line with medical indications, and holding evaluation meetings to discuss monthly claim differences within the management[21].

Through efficiency, cost control is necessary to maintain economic stability in a hospital without regarding the health quality of services. Efficiency has the role to balance between cost and good quality of health services[22]. Several determinants of hospital efficiency consist of competition, LOS, bed occupancy rate (BOR), ratio of doctors and nurses to patients, use of technology, family structure, and health policy [23].

Given that RSUD SoE functions as a local public service agency (BLUD), the hospital manager must consider the financial aspect. Currently, the hospital's income is allocated as 60% for operational expenditures and 40% for remuneration. This allocation should be inverted, resembling the structure of RSUD Budhi Asih in Jakarta, where 60% is dedicated to remuneration. The remuneration system, known as the medical services fee, is built upon three

fundamental principles: pay for position, pay for performance, and pay for people[21,24]. Therefore, to apply those basic principles, there was a need of indexing to produce the scores including basic index, positioning index, competency index, emergency index, risk index, performance index, and employees' attendances. By revising the remuneration system, it can be a motivation for hospital health workers to perform efficiency to minimalize the difference of costs.

To control hospital expenses is through standardization of service such as reducing the variation in services and increasing the procedure of cost-quality control in high-cost and also high-volume cases. A case manager should run these tasks to manage the hospital [10]. Unfortunately, there was no case manager in RSUD SoE, yet. Thus, the expenses of hospital actual cost in both vaginal and cesarean delivery can exceed 67-158% higher than INA-CBGs claim. Apart from that, the LOS of vaginal delivery and cesarean delivery was around 2 and 3-4 days, consecutively. LOS longer than expected will increase the hospital expenses which contribute to higher cost than INA-CBGs claim. Therefore, the implementation of clinical pathways is paramount for enhancing efficiency. Despite the substantial monthly delivery rates at the hospital, clinical pathways have not been introduced for either vaginal or cesarean deliveries. As a matter of fact, numerous deliveries take place at the hospital each month. Clinical pathways involve the integration of diagnosis and treatment, incorporating evidence-based medical service standards and measurable nursing care objectives during hospitalization. This implementation aligns with clinical governance principles aimed at maintaining and enhancing health service quality within affordable cost boundaries. It's crucial for a case manager to oversee this implementation[22].

CONCLUSION

There was a significant difference of hospital cost and INA-CBGs claim for obstetric services in RSUD SoE. To minimalize the disparity cost between hospital and INA-CBGs claim, several strategics include filling the accurate diagnosis and surgery procedure supervised by health providers, performing efficiency, stating good remuneration to hospital health workers, and controlling hospital through clinical pathway.

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Partum Mothers' Experience Regarding Support during the COVID-19 Pandemic

Pengalaman Ibu Bersalin Mengenai Dukungan selama Pandemi Covid-19

Ria H. Sari, Farida Kartini, Menik S. Daryanti

Universitas Aisyiyah Yogyakarta

Abstract

Objective: To investigate the experiences of mothers giving birth with regard to family support and the assistance of health workers during the COVID-19 pandemic.

Methods: A descriptive phenomenological approach was employed for this research, following the framework standards for reporting qualitative research (SRQR). Thirteen individuals participated in the study, comprising seven mothers giving birth, three husbands, two midwives, and one parent. The research was conducted at the Mlati II Health Center in Sleman Regency, specifically in Cabakan Hamlet, Sumberadi, Kec. Mlati, Kab. Sleman, Special Region of Yogyakarta, during January-February 2022. The choice of location was based on specific criteria set by the researchers. Data collection took place online due to practical reasons, with informants being contacted to choose between online or offline interviews. Purposive sampling was used for informant selection, and in-depth interviews lasting approximately one hour each were conducted via WhatsApp, Zoom, or phone calls, with prior agreement from the informants. The interviews followed a semi-structured format.

Results: Two main themes emerged from the data analysis: the emotional experiences of mothers during labor and their various needs. The COVID-19 pandemic had a significant impact, leading to feelings of anxiety, fear, tension, and the need for comfort and confidence. These psychological needs were categorized into verbal support, including encouragement, communication, and reassurance, as well as tactile support, involving gestures such as stroking, holding, and back rubs. Mothers also expressed spiritual needs, such as prayer and maintaining positive thoughts for a smooth delivery and the health of the baby. Nutritional needs, encompassing healthy and balanced eating, were identified as essential during childbirth. Support from husbands, family members, and health workers played a crucial role in reassuring mothers and educating them about COVID-19 prevention, contributing to a positive birthing experience.

Conclusion: The provision of positive support during childbirth can facilitate a normal delivery and instill confidence in mothers.

Keywords: childbirth, covid-19 pandemic, experience, maternity, support.

Abstrak

Tujuan: *Untuk mengetahui pengalaman ibu bersalin mengenai dukungan keluarga dan tenaga kesehatan selama pandemi covid-19.*

Metode: *Desain penelitian ini menggunakan pendekatan fenomenologi deskriptif sehingga untuk melengkapi pelaporan menggunakan framework standards for reporting qualitative research a synthesis of recommendations (SRQR). Jumlah informan yang digunakan dalam penelitian ini yaitu 13 orang, yang terdiri atas 7 ibu bersalin, 3 suami, 2 bidan dan 1 orang tua. Penelitian ini dilakukan di Puskesmas Mlati II di Kabupaten Sleman, di Dusun Cabakan, Sumberadi, Kec. Mlati, Kab. Sleman Daerah Istimewa Yogyakarta. Penelitian ini dilakukan pada bulan Januari-Februari 2022, alasan pemilihan tempat ini adalah berdasarkan kriteria peneliti. Metode dalam penelitian dilakukan secara online. Peneliti memiliki beberapa alasan praktis untuk mengumpulkan data secara online. Peneliti menghubungi informan untuk menanyakan apakah bersedia di wawanacara secara online atau offline. Rekruitmen informan pada penelitian ini menggunakan purposive sampling. Peneliti melakukan indepth interview dengan informan secara online melalui media whatsapp, zoom dan telepon seluler kurang lebih satu jam tiap individu dengan perjanjian terlebih dahulu dengan informan. Wawancara yang digunakan dalam penelitian ini semi structure.*

Hasil: *Didapatkan 2 tema yaitu tanda-tanda persalinan dan kebutuhan ibu bersalin. Dampak pandemi covid-19 membuat ibu merasa was-was atau kekhawatiran, takut dan cemas, tegang, berusaha nyaman, berusaha tenang dan rasa percaya diri. Kebutuhan psikologis ini terbagi menjadi dua bagian yaitu dukungan secara verbal dan dukungan secara sentuhan. Dukungan secara verbal seperti menyemangati, di ajak ngobrol, memberikan dukungan, mendampingi, ramah, komunasi, percaya diri, siaga, pelayanan bagus, harus kuat, menyayangi dan perhatian. Dukungan secara sentuhan seperti di elus-elus, mengusap keringat, pegang kepala, menggosok-gosok punggung dan menggosok perut. Kebutuhan spiritual yang didapatkan ibu selama proses persalinan yaitu zikir, berdoa, dan selali berpikir positif agar persalinan lancar dan bayi sehat. Kebutuhan nutrisi ibu bersalin seperti makan-makanan yang sehat, makanan bergizi seimbang, minum air putih untuk tenaga mengejan. Dukungan yang diberikan oleh suami, keluarga dan tenaga kesehatan membuat ibu merasa tenang dan mendapatkan edukasi terhadap penyebaran covid-19 agar mendapatkan persalinan yang positif.*

Kesimpulan: *Dukungan yang positif akan memberikan persalinan normal dan ibu percaya diri.*

Kata kunci: *dukungan, ibu bersalin, pandemi covid-19, pengalaman, persalinan.*

INTRODUCTION

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as COVID-19, caused a global public health emergency. The COVID-19 pandemic was initially reported in Wuhan, China, in December 2019. Globally, over 2 million people have tested positive for the virus, and nearly 140 thousand individuals have tragically lost their lives[1].

The COVID-19 pandemic has had a profound impact on hospital organizations, healthcare workers, and societies in affected countries. Visits to hospitalized patients have been significantly restricted and, in some cases, entirely prohibited as a preventive measure to curb the spread of COVID-19. These measures have been implemented by governments to mitigate the risk of transmission. Specifically, during childbirth, only one person has been permitted to accompany the birthing process, and visits from other individuals have been prohibited while patients are in the hospital.[2].

Globally, maternal mortality is still very high, around 295,000 women. In developing countries, maternal mortality is still high, around 415 per 100,000 live births, more than 40 times higher than European countries and almost 60 times higher than Australia and New Zealand[3]. Maternal and perinatal deaths are often the result of complications that do not manifest suddenly but rather develop over time. These complications may include miscarriage, uterine rupture, sepsis during the postpartum period, postpartum hemorrhage, preeclampsia, and eclampsia.[4].

Pregnancy and childbirth are normal physiological events that occur in a woman's life[5]. Positive birth experiences will increase the bond between mother and baby[6]. Negative birth experiences can have profound effects on mothers, potentially leading to feelings of despair despair, being traumatized to give birth, and postpartum depression[7].

The current condition is with the outbreak of Covid-19 during hospitalization so that restrictions on visitors during childbirth and referrals are limited by health facilities, causing isolation and helplessness for pregnant women. Counseling regarding birth plans must consider the new stress on the mother, so that the mother can choose the right health facility for delivery[8].

Changes in service to maternal service practices have an impact on delivery. During the Covid-19 pandemic there was a change in the rules that women in labor could not be accompanied by their families, causing women to feel anxious and afraid. Health service policies and delivery practices must support safe and comfortable services. Women who get safe and comfortable services during the Covid-19 pandemic can make mothers get positive experiences [9].

Based on the above discussion, it is deemed necessary to conduct research on how mothers experience childbirth regarding family support and health workers during the pandemic Covid-19. This is important considering that support is one of the most important things for the smooth delivery process, the support given from husbands, family and health workers is needed by mothers.

Mothers during the perinatal period need support from family and health workers to provide positive information that aims to prevent anxiety and fear during the delivery process. The collaborative approach provided by health workers must be fulfilled both physically, psychologically, emotional and socially. Mother-centred education and information is very important for psychological safety against uncertainty and unexpected experiences during labor during the pandemic covid-19 [10].

Based on data obtained from the Health Department (Dinkes) of Sleman, the number of mothers giving birth was 13,470. The number of deliveries at the public health center (puskesmas) Mlati II in 2019 was around 536 births [11]. Preliminary studies conducted by researchers had an impact on the number of deliveries during the Covid-19 pandemic. During the pandemic the average delivery was 10-15 per month. The Community Health Center continues to carry out delivery assistance during the Covid-19 pandemic. If there is a room disinfection schedule, the patient will be transferred to another facility.

The COVID-19 pandemic has led to significant changes in the services provided at healthcare facilities, including the restriction of family accompaniment during childbirth. However, at Puskesmas Mlati II in Sleman, mothers giving birth still receive assistance from their families. Despite this, the atmosphere, which can be described as less conducive due to COVID-19, intensifies maternal anxiety and worry. Elevated levels of anxiety and worry can have detrimental effects on the childbirth process and a mother's psychological well-being.

This study aims to explore the experiences of mothers giving birth concerning family support

and interactions with healthcare workers during the COVID-19 pandemic at Puskesmas Mlati II in Sleman. The research seeks to provide valuable information, knowledge, education, and insights to mothers giving birth regarding the significance of family support and healthcare worker involvement during the COVID-19 pandemic.

Social support offered to mothers during childbirth plays a vital role in boosting their self-confidence and enthusiasm for the birthing process. Such support can take various forms, including instrumental, emotional, informational, and appraisal support[12]. Spiritual is a person's relationship with an entity outside himself. Fear and anxiety about pain during childbirth cannot be separated from one another. There is a relationship between religion and anxiety[13].

METHODS

This research design uses qualitative research[14]. The approach used in this study uses descriptive phenomenology[15]. The approach using qualitative research is more appropriate to use to gain an in-depth understanding of research on the experiences of birth mothers regarding support during the pandemic covid-19[16]. Qualitative research is usually difficult to evaluate because the reporting is incomplete, so the Standard Reporting Synthesis of Recommendations (SRQR).

Retrieval of informants in this study was carried out online. This study used a purposive sampling technique[17]. The informants used in this study were 7 mothers giving birth, 3 informants from husbands, 1 informant from parents and 2 informants from registered health center midwives who were willing to sign informed consent. Ethical Clearance with number 1437/KEP-UNISA/I/2022.

This research was conducted at the Mlati II Health Center in Sleman Regency in Cabakan Hamlet, Sumberadi, Kec. Mlati, Kab. Sleman, Special Region of Yogyakarta 55286. This research was conducted in January-February 2022, the reason for choosing this place was based on the researchers' criteria.

The criteria for the researchers were mothers who gave birth at the Mlati II Health Center in Sleman, mothers who gave birth at the age of 20-35 years, were at full term of gestation and mothers who gave birth used cell phones to communicate on both Android and iOS.

Researchers conducting In-depth individual interviews (IDI) are used as the most powerful tool to gain an understanding of humans and dig deep information[18]. The application of the in-depth interview method conducted in this study was the fastest and most appropriate method used by researchers during the pandemic Covid-19.

In this study, researchers were not directly present at the research location. Researchers conducted in-depth interviews with informants online via whatsapp, zoom and cell phones for approximately one hour per individual with prior agreement with the informant.

The source triangulation used was the husband of the mother who gave birth, the family, namely parents and health workers, namely the midwife who worked at the Mlati II Health Center in Sleman.

The triangulation technique in this study uses documentation that aims as evidence that researchers are conducting research on informants and interview guides to ask for data needs by researchers.

Time triangulation in this study was carried out in the morning until noon which was directed to meet the person in charge of MCH. Researchers coordinated with midwives to request data on mothers who gave birth at the Mlati II Health Center. After obtaining the birth mother's data, the researcher contacted the informant via chat on WhatsApp with the aim of obtaining valid data information.

The interview schedule in this study was in accordance with the wishes of the informant and when the informant's baby was sleeping the aim was to obtain clearer, valid and proven data in obtaining data sources.

RESULTS

Table 1. Characteristics of Informants

Code	Age	number of children	Profession
P1	23	1	Housewife
P2	25	1	Housewife
P3	26	1	Private Sector Employee
P4	24	1	Housewife
P5	25		Housewife
P6	25	2	Housewife
P7	23	1	Housewife
B1	28	1	Entrepreneur
B2	30	1	Entrepreneur
B3	29	1	Private Sector Employee
Bd 1	52		Senior Midwife/ DIV Midwifery
Bd 2	35		Midwife / DIII Midwifery
IK 1	60		Housewife

The main informants of this study were mothers who gave birth at the Mlati II Health Center.

The results of interviews with mothers who give birth show the needs that are needed by the mother during the delivery process, namely psychological needs. This psychological need is divided into two parts, namely support and emotional. Informants revealed that during the delivery process they received support from their husbands, family, health workers both verbally and by touch.

Verbal Support

The interviews on support for informants verbally indicated that support was provided such as encouraging, being invited to chat, providing support, accompanying, friendly, communicating, confident, alert, good service, having to be strong, loving and caring. The following are the informants' expressions regarding the support given during labor verbally to informants P1, P2, P4, P5, P6, Bd 1, Bd 2, C1, B1, B2, B3.

"Always say come on sis, miss you can come on, great miss, you can do it. Give support to me, tell me you have to stay asleep even for one minute, you shouldn't be afraid" (P1)

"Yes, my husband accompanies me, supports, encourages, gives drinks, feeds, fans. Yes like. Come on, my dear, our child will be born. Soon we will be father and mother (more or less like that sis)" (P2)

"The midwives were also good, all friendly too, from my prenatal check up to the birth the midwives were always good and patiently the midwife directed me to be rapid after rapid directed to the observation room but apparently there was no opening yet directed to go home" (P4)

"This is my first experience giving birth, Miss. Alhamdulillah, I was born normally and the midwife who helped me provided good service" (P5)

"The service there is good, sis. Every time I get sick and have cramps like that, the midwife says it's opening and the midwife is on standby to come, check and check my baby's heart" (P6)

"Support given by my husband is good. Even though the mother feels scared, her husband can still accompany her, but it is recommended that the husband use an N-95 mask like that" (BD 1)

"Jenengan is struggling, this is the soul of the women here. Jenengan has to fight, his son also struggles to get out, so Jenengan has to be enthusiastic like that. I hope the birth goes smoothly, sis" (BD 2)

"You have to be enthusiastic, you have to be strong, you have to do that. You have to be calm, you have to be patient and your husband provides food and drink" (C1)

"I'm giving support, come on, keep spirit, you can do it soon, our child will be born, you have to be strong to face it for the sake of our child" (B1)

"I'm giving support, come on, keep spirit, you can do it soon, our child will be born, you have to be strong to face it for the sake of our child" (B2)

"Yesterday my mother-in-law offered a prayer that the delivery would go smoothly, the mother and baby would be healthy. Always think positively that women's nature is like that. And reminding you that you have to eat and drink too so you have energy" (B3)

Touch Support

The interviews obtained this sub-theme, informants revealed that they received touch support such as being stroked, wiping sweat, holding their heads, holding hands, rubbing their backs and rubbing their stomachs. The following are expressions of support in touch with informants P1, P2, P5, P7, Bd 1, Bd 2, B1, B2.

"Don't get massages, sis, because you can't just be stroked. I was carried to the bathroom for fear of getting tired" (P1)

"I stroked my wife's stomach, because she felt pain" (P1)

"Even wiping sweat too sis" (P2)

"He stroked my head and held my hand so that my heart would be calm and my mind sis" (P5)

"Hold hands and fan sis" (P5)

"My husband always kisses my forehead, rubs my back, strokes my stomach" (P7)

"Like that, when there is his, he also rubs his back, strokes and so on" (Bd 1)

"Support provided by the husband is in the form of a support system such as attention and feeding" (BD 2)

"I stroked his stomach and gave massages, fed him food and drink" (B1)

"I stroked his stomach and massaged his back, fed him food and drink and asked him to tell stories to reduce his anxiety" (B2)

"I stroked his stomach inviting his sister to tell stories and massaged his back" (B3)

DISCUSSION

Data collected from informants who gave

birth during the COVID-19 pandemic revealed that, fundamentally, their childbirth experiences were not significantly different from those before the pandemic. However, it was noted that the predominant difference during the pandemic was the heightened level of fear experienced by mothers. Throughout the COVID-19 pandemic, the analysis of the data identified two main themes: "Signs of Labor" and "Maternal Needs During Labor."

Regular uterine contractions or cervical dilatation are basic indicators of labor regardless of the phase or stage. Physiological processes that increase uterine muscle changes from contractions will continue to get stronger as the time of delivery approaches [19]. The urge to push on the mother is to hold her breath while pushing which lasts for 10 seconds or more when the opening of the cervix is complete [20].

Mothers who are struggling to give birth to children really need support from the people they care about, especially from their husbands. The support provided by the husband can add strength and make the mother feel valued and loved. The support system provided by the family and health workers is also important for mothers to increase their enthusiasm to meet their baby, who has been waiting for nine months with great hope.

Verbal Support

The establishment of trust and good communication between health workers and mothers will fulfill spontaneous and smooth deliveries. Examination procedures during labor can be determined by the conditions that occur. The friendship and closeness of health workers is very important to mothers in providing quality services throughout the life cycle [21].

Health workers must provide the best service to the mother during the delivery process in accordance with the current SOP and notify what handling is done during the delivery process[22]. The support provided by the husband during the birth process can provide a sense of care and establish a harmonious relationship between mother and husband. The presence of a husband during the birth delivery process can provide a feeling of calm, comfort, feeling appreciated so as to reduce anxiety [23].

Mothers who get high self-efficacy from husbands, families, and health workers will have a lower incidence of postpartum depression.

Families that provide support to mothers during childbirth will make mothers feel loved, cared for, valued so as to reduce fear, stress and depression after childbirth [24].

Touch Support

Family support is needed by the mother during the birth process. Especially the presence of childbirth assistance, namely the husband. A husband who gives a touch, such as touching his wife's hand with feeling, will give a more calm and comfortable feeling in facing labor [25]. The husband plays a vital role in accompanying the mother during the childbirth process. His support goes beyond just financial assistance; it encompasses emotional and psychological support as well. This support is characterized by love and care, boosting the mother's self-confidence, and showing her respect. The husband also maintains open and honest communication, gives undivided attention, and is genuinely caring and responsive. Furthermore, he stands prepared to embrace the responsibilities of parenthood, demonstrating readiness to become a loving and supportive parent.

CONCLUSIONS

The support given by husbands to mothers can add strength, feel calm, comfortable so that mothers feel valued and feel confident and empowered. husband's high self-efficacy during the delivery process during the covid-19 period will make the mother feel calm and relaxed in facing childbirth so that excessive fear and anxiety is reduced.

The support provided by parents and husband is an inseparable unit during the birth process. The support provided by the family is no less important during the pandemic covid-19. Families can also provide online support such as video calls and telephone calls to mothers because of the policy regarding childbirth assistance, only one person is allowed.

Families can also provide online support such as video calls and telephones to mothers because of the policy regarding birth assistance that only allows one person. Before the mother gives birth, the family encourages the mother to be able to give birth normally, must not give up, must be enthusiastic, the women are here and pray.

Support provided by health workers during the delivery process is in the form of emotional

support can make mothers feel valued, more confident and feel what they feel about pain and fear during labor. Good social relationships between mothers and health workers can create a positive birth experience and reduce pain during labour. Despite the Covid-19 pandemic, health workers, particularly midwives, consistently followed the Standard Operating Procedures (SOP) while providing services. In addition to their regular duties, they implemented measures to prevent the transmission of Covid-19.

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| Research Article |

The Use of Maternal Early Obstetric Warning Score (MEOWS) as a Tool to Predict Treatment Needs in the Intensive Care Unit in Severe Preeclampsia Patients

Penggunaan Maternal Early Obstetric Warning Score (MEOWS) sebagai Parameter Prediksi Kebutuhan Perawatan Intensive Care Unit (ICU) Pasien Preeklamsia Berat

Ratu A.D. Putri, Imelda E.B Hutagaol

Department of Obstetrics and Gynecology
Arifin Achmad Hospital Universitas Riau
Pekanbaru

Abstract

Objective: To determine the cut-off point of the Modified Early Obstetric Warning System (MEOWS) scores for severe preeclampsia patients to enhance clinical surveillance and responsiveness for determining the appropriate level of care.

Methods: A retrospective cross-sectional study design was employed, involving 282 samples selected from medical record data of research subjects at Arifin Achmad Hospital in Pekanbaru. The research variables included preeclampsia (PEB), MEOWS score, and the place of care. The research sample was categorized into two groups: those with high MEOWS scores (MEOWS $\geq$ 8) and those with low MEOWS scores (MEOWS < 8). Data were processed and statistically analyzed using SPSS, with sensitivity and specificity measurements conducted using the Receiver Operating Characteristic (ROC) curve.

Results: Statistically significant differences were found in the MEOWS score thresholds between the two groups. The calculated cut-off point for the MEOWS score was determined to be 7.57 (rounded to 8). There was a significant association between MEOWS scores $\geq$ 8 and the need for Intensive Care Unit (ICU) care (Relative Risk [RR] 0.35; 95% Confidence Interval [CI]: 0.157–0.788; p = 0.009) as well as the risk of Intrauterine Fetal Demise (IUFD) (RR 1.04; 95% CI 1.02–1.06).

Conclusion: The MEOWS score can serve as a valuable parameter for early detection of ICU care requirements in severe preeclampsia patients, thereby enhancing clinical surveillance and responsiveness.

Keywords: ICU, MEOWS, severe preeclampsia.

Abstrak

Tujuan: Mencari batasan nilai (cut off point) skor MEOWS pasien PEB dalam menentukan tempat perawatan untuk peningkatan survelens klinis serta daya tanggap.

Metode: *Penelitian dilakukan dengan desain studi potong lintang retrospektif pada 282 sampel dari data rekam medis subjek penelitian di RSUD Arifin Achmad Pekanbaru. Variable penelitian berupa PEB, Skor MEOWS dan tempat perawatan Sampel penelitian dibagi menjadi dua kelompok, yaitu skor tinggi (MEOWS ≥8) dan rendah (MEOWS <8). Data Kemudian diolah dan dianalisa secara statistic menggunakan SPSS Pengukuran sensitifitas dan spesifitas menggunakan kurva Receiver Operating Characteristic (ROC).*

Hasil: *Perbedaan batasan nilai skor MEOWS antar kelompok memiliki perbedaan yang bermakna secara statistic. Hasil perhitungan mendapatkan cut off point skor MEOWS adalah 7.57 (dibulatkan menjadi 8). Terdapat hubungan bermakna antara skor MEOWS ≥8 dengan kebutuhan perawatan di ICU (RR 0,35; CI 95%: 0,157–0,788; p=0,009) dan risiko terjadinya IUFD (RR1,04; 95% CI1,02 – 1,06).*

Kesimpulan: *Skor MEOWS dapat digunakan sebagai parameter untuk deteksi dini kebutuhan perawatan ICU pada pasien preeklamsia berat, untuk peningkatan survelens klinis serta daya tanggap.*

Kata kunci: *MEOWS, ICU, PEB.*

INTRODUCTION

Severe preeclampsia is one of the leading causes of maternal death.[1-6] Preeclampsia is a pregnancy-related condition characterized by new-onset hypertension that occurs after 20 weeks of gestation, often in the later months, with or without proteinuria.[7,9] The course of severe preeclampsia is complex, and it can deteriorate at any point during pregnancy. Therefore, there is a need for a user-friendly method to detect it.[7-11] Modified Early Obstetrics Warning Score (MEOWS) is one of the parameters that can be used for early detection of high-risk obstetric patients, to prevent or reduce the risk of aggravation that occurs, by placing patients according to the level of care and needs of the patient.[12-15] MEOWS was introduced in obstetric units in the United Kingdom to reduce maternal mortality by enhancing the early detection of clinical signs of deterioration in women at risk of critical illnesses.[16-18]

Score	3	2	1	0	1	2	3
Temperature		≤35 °C	35-35.9 °C	36-37.4 °C	37.5-37.9 °C	38.0-38.9 °C	≥39 °C
Systolic BP	≤69	70-79	80-89	90-139	140-149	150-159	≥160
Diastolic BP			≤49	50-89	90-99	100-109	≥110
Pulse		<40	40-49	50-99	100-109	110-129	≥130
Respiratory Rate	≤10			11-19	20-24	25-29	≥30
AVPU				Alert	Responds to Voice	Responds to Pain	Unconscious
Urine output mLs/hr	<10	<30		Not Measured			

Figure 1. Modified Early Obstetrics Warning Score (MEOWS)[14]

In 2017, female deaths due to pregnancy or childbirth occurred daily, with an estimated 810 women losing their lives. Data from the Ministry of Health reveals that Indonesia ranks second among ASEAN countries with the highest Maternal Mortality Rate (MMR).2 The alarming MMR figures have prompted the government to implement structural interventions, one of which is the inclusion of MMR reduction targets in the National Medium-Term Development Plan (RPJMN) for 2020-2024, emphasizing the importance of providing appropriate levels of care.[6] The objective of this study is to determine the cut-off point for MEOWS scores in severe preeclampsia patients, aiming to enhance clinical surveillance and responsiveness in determining the appropriate level of care.

METHODS

This research was conducted at RSUD Arifin Achmad in Pekanbaru, Riau Province, using a retrospective cross-sectional study design. The study sample consisted of 282 participants who met the inclusion and exclusion criteria. Inclusion criteria included pregnant patients diagnosed with severe preeclampsia and superimposed preeclampsia, who were receiving treatment at Arifin Achmad Hospital. Exclusion criteria encompassed patients with a history of heart disease, lung disease, liver, and/or kidney disease. The measurement instrument employed was the MEOWS score. Subsequently, the samples were categorized into two groups: those with high MEOWS scores (MEOWS ≥ 8) and those with low MEOWS scores (MEOWS < 8).

The research data comprised secondary data extracted from patients' medical records. Subsequently, this data was collected, processed, and statistically analyzed using the Statistical Package for Social Sciences (SPSS) software, version 25, from Chicago, IL, USA. The analysis aimed to determine relationships between variables using the Pearson test. Sensitivity and specificity measurements were conducted utilizing the Receiver Operating Characteristic (ROC) curve to assess the relationship between the MEOWS score and ICU care. The analysis yielded a cut-off point for the MEOWS score, along with an associated Area Under the Curve (AUC) value.

RESULTS

The primary objective of this study is to determine the cut-off point for MEOWS scores in patients with Preeclampsia (PEB). This cut-off point will serve as a predictive tool used to determine the appropriate level of care for PEB patients, thereby enhancing clinical surveillance and responsiveness. Table 1 presents the characteristics of the study subjects, including an average age of 33.26±5.42 years, an average parity of 1.97±0.95, a Body Mass Index (BMI) of 26.77±3.25 (kg/m2), 100% utilization of care guarantee insurance, 77.0% receiving treatment in the ICU room, and an incidence of Intrauterine Fetal Demise (IUFD) in 96.1% of cases. The research data underwent normality and homogeneity tests, followed by the Pearson test to determine whether there was a significant difference in the means of the two sample groups. The data was statistically processed parametrically and is presented in the form of detailed tables and curves.

Table 1. Characteristics Participants

Variable	Value (n=282)	RR (CI 95%)
Age (years old)	33.26±5.42	2.40 (2.34 – 2.46)
Parity	1.97±0.95	1.19 (1.14 -1.23)
Body Mass Index (Kg/m²)	26.77±3.25	1.60 (1.52 – 1.69)
Guarantee	100	1.01 (1.002 – 1.03)
Place of Care		
ICU	23.0	1.77 (1.72 – 1.82)
Non-ICU	77.0	
IUFD	3.9	1.04 (1.02 -1.06)

The data is then analyzed to assess diagnostic tests. The analysis used to evaluate the diagnostic test's ability employs the Receiver Operating Characteristic (ROC) curve to determine accuracy, sensitivity, and specificity levels through the Area Under the Curve (AUC). Test performance is considered good if AUC ≥ 0.7. The results of the ROC curve analysis in this study (Figure 2) yielded an AUC value of 0.826 for the MEOW score (95% CI, 0.699 – 0.953) (Table 2). This indicates that the MEOW score has a high diagnostic value in predicting the need for ICU care in patients with severe preeclampsia
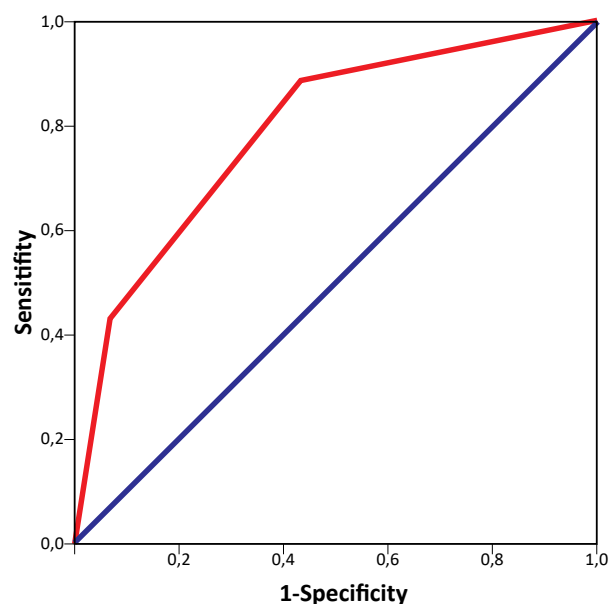

Figure 2. ROC curve

Table 2. Area Under the Curve

Area	Std. Error	Asymptotic Sig	Asymptotic CI 95%
0.826	0.065	0.000	0.699 – 0.953

The number of samples in this study amounted to 282. The characteristics of the IGD ≥8 MEOWS score were 28 subjects and the IGD <8 MEOWS score was 254 subjects. Patients treated in the ICU amounted to 65 subjects and those treated other than in the ICU amounted to 217 subjects. Figure 2 shows the optimal cut-off sensitivity and specificity image between MEOW scores with ICU care is 7.57 (rounded to 8). This study can be one of the screenings in determining the level of care of severe preeclampsia patients.
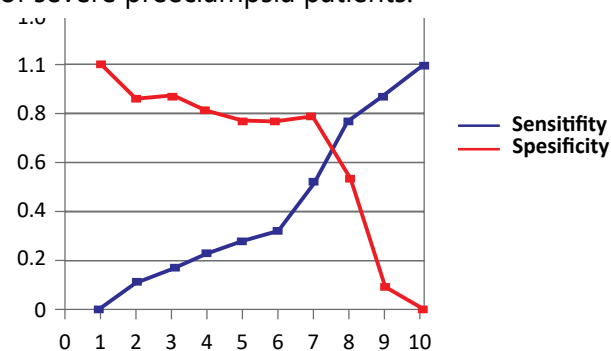

Figure 3. cut off point value MEOWS

Table 3. Relationship between the MEOWS and the Need for Treatment in the ICU

MEOW score	ICU treatment		%	RR (95% CI)	*P-value*
	Yes	No			
> 8 (high)	16	12	4.3	0.35 (0.157 – 0.788)	0.009
< 8 (low)	53	201	18.8	1 (referent)	

Table 4. Relationship between the MEOWS the risk of occurrence of IUFD

MEOW score	IUFD		%	RR (95% CI)	P-value
	Yes	No			
> 8 (high)	5	23	8.2	8.98 (2.545 – 31.721)	0.000
< 8 (low)	6	248	2.1	1 (referent)	

Table 3 data shows that the p-value of 0.009 (p< 0.05), means that there is a relationship between MEOW scores and ICU care in this study. with an RR value of 0.35 indicates that patients with high MEOWS scores are 0.35 times more likely to be admitted to the ICU than those with low MEOWS scores. Secondary outcomes of this study were illustrated through Table 4 which showed patients with high MEOWS scores had a 0.35 times higher likelihood of ICU care infants than those with low MEOWS scores.

DISCUSSION

The characteristics of the study subjects revealed an average age of 33.26±5.42 years, an average parity of 1.97±0.95, a Body Mass Index (BMI) of 26.77±3.25 (kg/m2), with 100% utilizing care guarantee insurance, 77.0% receiving treatment in the ICU room, and an incidence of Intrauterine Fetal Demise (IUFD) at 96.1%. According to studies by the World Health Organization (WHO), there is a global infant mortality rate of 10,000,000 individuals annually. Indonesia has the highest perinatal death rate, underscoring the need for extensive and high-quality improvements in healthcare services. Multiple factors, including maternal, fetal, and placental factors, contribute to infant mortality[19-21]. Maternal factors encompass the mother's age, gestational age, and illnesses such as preeclampsia, eclampsia, diabetes mellitus, and premature rupture of membranes (PROM). Hypertensive disorders during pregnancy are responsible for approximately 5% of intrauterine deaths. It has been demonstrated that the risk of fetal mortality is higher in mothers diagnosed with preeclampsia during the preterm period.[21]

The results of the ROC curve analysis in Figure 2 of this study yielded an AUC (Area Under the Curve) value for the MEOW score of 0.826 (95% CI, 0.699 – 0.953) (Table 2). Figure 2 illustrates the optimal cut-off point, balancing sensitivity, and specificity, for MEOW scores in relation to ICU care, which was found to be 7.57 (rounded to 8). The analysis employed the Receiver Operating Characteristic (ROC) curve to assess the diagnostic test's accuracy, sensitivity, and specificity by measuring the AUC. A diagnostic test is considered to have good diagnostic value when AUC ≥ 0.7 [15-17]. These findings indicate that MEOW scores exhibit a high diagnostic value for predicting the need for ICU care in severe preeclampsia patients.

The proportion of MEOWS scores associated with ICU care showed a p-value of <0.05 and an RR of 8.98 (95% CI; 2.545 – 31.721), indicating that patients with high MEOWS scores were 0.35 times more likely to be admitted to the ICU than those with low MEOWS scores. Similarly, the proportion of MEOWS scores in relation to the incidence of IUFD had a p-value of <0.05 with an RR of 8.98 (95% CI; 2.545 – 31.721). Methods such as the Early Warning Score, early warning system, and rapid response system have been known since 1999. However, the Early Warning System used at that time was considered challenging to apply to obstetric patients due to the physiological changes they undergo during pregnancy and the postpartum period. In 2013, the Intensive Care National Audit and Research Centre Case Mix Programme Database developed the Modified Early Obstetrics Warning Score (MEOWS) to facilitate the early detection of high-risk obstetric patients. This is achieved through a combination of statistical scoring and clinical decisions. This study serves as a valuable screening tool for determining the level of care required for severe preeclampsia patients. It is consistent with research conducted at Norfolk and Norwich University Hospital and Sardjito Hospital, which suggests that MEOWS can effectively predict the need for ICU.[14,18]

CONCLUSION

The MEOW score can serve as a parameter for the early detection of ICU treatment needs in severe preeclampsia patients, enhancing clinical surveillance and responsiveness.

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Research Article

Expansion Grade and Morphokinetic Parameters Associated with Aneuploidy Status of Embryo Fifth Day

Tingkat Ekspansi dan Parameter Morfokinetik yang Diasosiasikan dengan Status Aneuploid pada Hari ke lima Sebuah Embrio

Achmad K. Harzif[1,2], Muharam Natadisastra[1], Dwi A. Suryandari[3], Retno A. Werdhani[4], Wisnu Jatmiko[5], Arief Boediono[6,7], Hartanto Bayuaji[8], Budi Wiweko[1,2]

[1]Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Indonesia
Dr. Cipto Mangunkusumo General Hospital, Jakarta
[2]Human Reproductive, Infertility, and Family Planning Cluster
Indonesian Medical Education and Research Institute, Jakarta
[3]Departement of Biology
[4]Departement of Community Medicine
Faculty of Medicine, Universitas Indonesia, Jakarta
[5]Faculty of Computer Science Universitas Indonesia, Jakarta
[6]Faculty of Veterinary Medicine Bogor Agricultural University, Bogor
[7]Indonesian Reproductive Science Institute (IRSI)
Research and Training Centre, Jakarta
[8]Departement of Obstetrics and Gynecology
Faculty of Medicine Universitas Padjajaran, Bandung

Abstract

Objective: To determine the potential of examining embryo morphology, and morphokinetic parameters in predicting the chromosomal status of embryos.

Methods: This study is a cross-sectional that requires patients undergoing IVF followed by chromosome examination with NGS that was conducted at the IVF Center at Pondok Indah Hospital and Morula IVF Center at Bunda Hospital from December 2021 to December 2022. Each embryo that reaches the blastocyst stage on day 5 or 6 will be washed and put into a PCR tube for a week; then, embryologists annotate them to determine morphological assessment and morphokinetic parameters using Time-Lapse Microscopy. The chi-square test was used to analyse bivariate variables.

Results: One hundred twenty-four samples were collected on day 5 of patients undergoing the IVF procedure. 50.8% of the samples were aneuploid chromosomes, and 49.2% were euploid. The morphokinetic characteristics median was 3.86 fold. It was found that expansion grade, time to pro-nuclear fading, and time to the synchrony of the third cell cycle were significantly associated with euploid status (p = 0.000; 0.041 and 0.036).

Conclusion: The expansion grade has been proven as the most influential component for accurately predicting the ploidy status of embryos.

Keyword: blastocyst, embryo, euploid status, expansion grade, morphokinetics.

Abstrak

Tujuan: Untuk mengetahui potensi pemeriksaan morfologi embrio, dan parameter morfokinetik dalam memprediksi status kromosom embrio.

Metode: Penelitian ini merupakan penelitian potong lintang yang memerlukan pasien yang sedang menjalani program bayi tabung yang dilanjutkan dengan pemeriksaan kromosom dengan NGS yang dilakukan di Pusat IVF RS Pondok Indah dan Pusat IVF Morula RS Bunda pada bulan Desember 2021 hingga Desember 2022. Setiap embrio yang mencapai tahap blastokista pada hari ke 5 atau 6 akan dicuci dan dimasukkan ke dalam tabung PCR selama seminggu; kemudian, ahli embriologi membuat anotasi untuk menentukan penilaian morfologi dan parameter morfokinetik menggunakan Mikroskop Time-Lapse. Uji chi-square digunakan untuk menganalisis variabel bivariat.

Hasil: Seratus dua puluh empat sampel dikumpulkan pada hari ke 5 dari pasien yang menjalani prosedur IVF. 50,8% sampel adalah kromosom aneuploid, dan 49,2% adalah euploid. Median karakteristik morfokinetik sebesar 3,86 kali lipat. Ditemukan bahwa tingkat ekspansi, waktu menuju pemudaran pro-nuklir, dan waktu hingga sinkronisasi siklus sel ketiga berhubungan secara signifikan dengan status euploid (p = 0,000; 0,041 dan 0,036).

Kesimpulan: Tingkat ekspansi telah terbukti sebagai komponen yang paling berpengaruh dalam memprediksi status ploidi embrio secara akurat.

Kata kunci: blastosist, embrio, status euploid, tingkat ekspansi, morfokinetik.

INTRODUCTION

In vitro fertilization (IVF) is an assisted reproductive technology used to achieve pregnancy on infertile couples. The pregnancy rate of IVF is between 30-40%, with endometrial recetivity and embryo being the most influential factors for successful implantation.[1, 2] Therefore, additional methods needs to be performed on embryos to increase implantation success and result in pregnancy and birth.[3] Study compared the pregnancy rate between day-2 and day-3 embryos found no significant difference. However, embryo quality was identified as a potential factor affecting pregnancy rates.[4] One way to ensure that the embryo quality is through the use of Preimplantation Genetic Testing for Aneuploidy (PGT-A) or Preimplantation Genetic Screening (PGS). These procedures are carried out to ensure the embryo does not have any aneuploid chromosomes. This procedure requires a biopsy of the blastomeres in the 8-cell phase or the trophectoderm in the blastocyst phase. It also requires high expertise as well as expensive equipment and reagents. In addition, there is no clear evidence yet that this invasive procedure does not cause injury to the embryo, and there is the possibility of undetected mosaic or segmental aneuploidy.[3] This has led IVF practitioners to consider non-invasive embryo selection methods.

Embryo visual assessment is a well-established and commonly used method for selecting embryos by examining their morphology under a microscope at specific time points. Various parameters are evaluated at different stages of development to gather information about the embryo's quality. Although the scoring criteria may vary among fertility clinics, most assess cleavage-stage embryos based on: fragmentation, presence, number, and nuclei size. Similarly, blastocyst-stage embryos are assessed based on the number and symmetry of blastomeres. It is crucial to standardize the timing of these assessments. Embryonic development is highly dynamic; even assessments conducted on the same day can yield different results between day and night. The highlights are the importance of conducting frequent embryo examinations to gather more comprehensive information about their developmental progress and viability over time.[5-7] Nevertheless, it is important to acknowledge that this assessment necessitates the removal of embryos from the culture medium within the incubator and relies on the expertise of an embryologist. Therefore, the involvement of human factors such as embryologist's expertise cannot be eliminated.[8, 9]

Considering the natural variations in embryo development speed, the time element becomes crucial when assessing embryo morphology; consequently, evaluations at specific time points need to be performed daily. Time-lapse microscopy techniques have been devised to continuously analyses embryo morphology at regular intervals, spanning just a few minutes. Time-lapse microscopy holds significance as it allows for the observation of embryos without necessitating their removal from the incubator, there by maintaining the optimal conditions for embryo development.[10] The study demonstrated that using time-lapse technology resulted in a significantly higher pregnancy rate than conventional methods (67.32% vs. 57.22%; p = 0.0410) and live birth rate (65.37% vs. 55%; p = 0.0380).[11]

The time-lapse imaging displays the changes occurring in the nuclear and cytoplasmic components within the culture medium. The recorded videos are annotated at specific time points and developmental stages. The morphokinetic assessment of the embryo begins during the early stages, starting from the moment of syngamy and progressing through the stages of 2-cell, 3-cell, 4-cell, 5-cell, 6-cell, and 9-cell embryos (t1 – t9), and later at the time of partial compaction. In the final stages, the morphokinetic assessment encompasses genomic activation, the morula stage, blastulation, blastocyst formation, and blastocyst expansion. An embryo is referred to as a morula when over 90% of it has undergone compaction; while a blastocyst is characterized by a crescent-shaped embryo with fluid filling the central cavity.[12]

Many studies have been conducted to build non-invasive models by associating embryo morphology, morphokinetics, and euploidy status. Some studies have reported that euploid status is significantly related to the morphological or morphokinetic characteristics of the embryo. The euploid rate was significantly higher for embryos with good morphology (73.2%) than for those with average (50%) or poor morphology (40%; p=0.001). It was also found that the inner cell mass (ICM) and trophectoderm (TE) are strongly associated with the euploidy rate.[13] Moreover, study reported that blastocyst expansion was the most significant factor associated with euploid

status (p = 0.045).[14]

The study showed that the mean of time to pro nuclear fading (tPNf), Time to 2 cells (t2), Time to 5 cells (t5), Duration of second cells cycle (cc2), Duration of second cells cycle (cc3), Difference between t5 and t2 (t5-t2) were significantly delayed in aneuploidy embryos.[15] Additionally, it was observed that the early breakdown of pronuclei is a potential marker of euploid embryos. A study conducted suggests that t3 and t5-t2 associate significantly with chromosome abnormality. Aneuploid embryos appeared to have delayed tSC, tSB, and tB compared to euploid embryos.[10]

The invasiveness of the procedure, cost, and fear of embryo damage caused by PGT-A examination to determine the ploidy status of an embryo's chromosomes have created a need for another method that is simpler, cheaper, and non-invasive, and that has at least the same ability to predict aneuploidy in embryos. Morphological assessment alone is ineffective since embryos that have good morphology do not necessarily have normal chromosomes. Therefore, this study aims to determine the potential of examining embryo morphology, and morphokinetic parameters in predicting the chromosomal status of embryos.

METHODS

This research is a cross-sectional study to determine the relationship between embryo morphology and chromosomal status, and blastocyst morphology. Research has been done on embryo culture from patients undergoing in vitro fertilization (IVF). Samples were taken at the IVF Centre at Pondok Indah Hospital and Morula IVF Centre at Bunda Hospital from December 2021 – December 2022. Examinations were conducted at the PGS/PGD Cluster Human Reproduction, Infertility and Family Planning (HRIFP) IMERI FMUI laboratory and the Diagnostic and Research Centre biomolecular laboratory FMUI to analyse the Next Generation Sequencing (NGS). Non-probability consecutive sampling was used, in total 124 samples were analyzed. Samples included in this study are the embryo on day 5 of patients undergoing IVF, followed by chromosome examination with NGS. Samples were excluded if the embryo did not turn into a blastocyst on day 5 of culture, failed to take part in the chromosome examination due to the absence of embryos that could be biopsied, biopsy showed a mosaic embryo, and if the

embryo were not cultured.

Oocyte in metaphase II stage, which have been taken by a specialist in obstetrics and gynecology, were then carried out to do intracytoplasmic sperm injection (ICSI) procedure. The oocytes that have been injected with sperm cells will have the pronucleus examined 18-20 hours post-ICSI to determine whether the oocytes are fertilized or not. Fertilized oocytes will form 2 pronuclei (2pn) and then be cultured until the third day. On the fifth day, the oocytes will be cultured separately in blast assist without phenol red media. Embryo developments will then be recorded and photographed every day to assess its morphological quality using the morphokinetic time-lapse. Embryos that reach the blastocyst stage will undergo a trophectoderm biopsy.

The morphology of the inner cell mass was categorized into three groups: A, B, and C. Group A represented a good morphology, characterized by a high number of compacted cells. Group B indicated a moderate morphology with fewer cells and less compaction. Group C represented a poor morphology with very few cells and an absence of compaction. Similarly, the trophectoderm morphology was categorized into groups A, B, and C. Group A denoted a good morphology with a cohesive layer formed by numerous cells. Group B indicated a moderate morphology with fewer cells and loosely arranged structure. Group C represented a poor morphology with a small number of larger cells. The expansion grade was classified on a scale from 1 to 6. Grade 1 indicated the initial stages of blastocyst development. Grade 2 represented a blastocoel occupying more than 50% of the embryo. Grade 3 denoted a blastocoel occupying the entire embryo, indicating a complete blastocyst. Grades 4, 5, and 6 indicated the expanding blastocyst with thinning trophectoderm, the embryo starting to hatch, and the embryo fully hatched, respectively.

We conclude the morphokinetic characteristic. To enhance the accuracy of a morphokinetic evaluation, it is essential to have a device capable of documenting the evolving embryo with precision. Time-lapse microscopy (TLM), which involves the utilization of a specialized microscope capable of capturing microscopic changes, allows for closer observation of embryos, enabling the tracking of their development and changes over time. TLM comprises various key components, including a microscope equipped with phase contrast or fluorescent capabilities, a real-time imaging digital camera, computer software controlling the

camera, and an incubator providing an optimal environment for the embryo.[16] In this study TLM assessed for the embryo begin from the early stages (pro-nuclear fading) to the final stages (blastocyst). The duration of cycle and time of synchrony were also evaluated.

Each embryo that reaches the blastocyst stage on day 5 or 6 will be informed to the patient. A biopsy will be performed if the patient wishes to undergo a chromosomal examination. Each embryo will be placed in a separate medium. Then, 4 to 10 cells from the trophectoderm will be taken from each embryo by perforating the pellucida zone with a laser under microscope, creating a hole that is by 6-9 μm in size. The collected trophectoderm cells will then be washed in a drop containing PBS and 10% PVP solution. The washed cells will be placed into a PCR tube containing 2.5 μl of the same medium. The cells will then be stored with the temperature of -20oC for a week, before the chromosomes were examined using the NGS method. The morphology of day five embryos obtained by time-lapse microscopy were annotated by embryologists to carry out morphological assessments. All variables that have been assessed to predict the chromosomal status of the embryo will then be included in creating a prediction model to determine which model has the best diagnostic ability. Finally, all data were analyzed using percentages, means, and medians for abnormal distributions. Bivariate analysis employed the chi-square test for categorical variables, unpaired t-tests and the Mann-Whitney test for numerical variables.

ETHICAL CONSIDERATION

This study has been approved by the ethics committee of the Faculty of Medicine Universitas Indonesia.

RESULTS

One hundred forty-eight samples were collected from embryo culture and embryo biopsies on day 5 of patients undergoing the IVF procedure. Samples were screened based on exclusion and inclusion criteria resulting in 24 samples being excluded from the study because the PGT-A results showed mosaic chromosomes. Final data processing and analysis were carried out on 124 samples. Morphological characteristics and PGT-A results were described in Table 1. Out of the total samples, 50.8% exhibited aneuploid chromosomes, while 49.2% exhibited euploid chromosomes. The morphology of the inner cell mass is predominantly Category A (54%); morphology of the trophectoderm showed that Categories A and B are slightly different (37.9% and 40.3%, respectively), and 36.5% of embryos reach expansion grade 3.

Table 1. Morphological Embryo Characteristics

Characteristic		Description (n= 124)
Inner cell mass morphology	Category A	67 (54)
	Category B	42 (33.9)
	Category C	15 (12.1)
Trophectoderm morphology	Category A	47 (37.9)
	Category B	50 (40.3)
	Category C	27 (21.8)
Expansion grade	Grade 1	26 (21)
	Grade 2	41 (33.1)
	Grade 3	45 (36.3)
	Grade 4	9 (7.3)
	Grade 5	3 (2.4)
	Grade 6	0 (0)
PGT-A chromosomes status	Euploid	61 (49.2)
	Aneuploid	63 (50.8)

*Categorical variables are presented by percentage n (%)

Morphokinetics data were extracted from time lapse-monitoring to determine the length of time it takes for the embryo to divide and reach the blastocyst stage (tB). The morphokinetics characteristics were described in table 2. It can be seen that the embryos need about 100.49 ± 10.19 (107.94 – 111.57) hours to reach the blastocyst stage and becomes a complete blastocyst after 107.19 hours (91.2 – 140.20).

Table 2. Morphokinetics Characteristics

Characteristic	Description (n= 124)
Time to pro nuclear fading (hour); tNPf	20.91 (5.23 – 53.02)
Time to 2 cells (hour); t2	25.64 (6.56 – 64.02)
Time to 3 cells (hour); t3	36.00 (8.15 – 67.93)
Time to 4 cells (hour); t4	38.10 (10.73 – 68.43)
Time to 5 cells (hour); t5	48.52 ± 9.26 (46.88 – 50.17)
Time to 6 cells (hour); t6	52.22 (23.48 – 86.27)
Time to 7 cells (hour); t7	53.77 (28.15 – 88.02)
Time to 8 cells (hour); t8	60.91 (30.90 – 100.81)
Time to compact (hour); tSC	80.44 ± 11.77 (78.35 – 82.55)
Time to morula (hour); tM	88.10 ± 10.86 (86.10 – 90.03)
Time to start blastocyst (hour); tSB	100.49 ± 10.19 (107.94 – 111.57)
Time to blastocyst (hour); tB	107.19 (91.2 – 140.20)
Duration of second cells cycle (hour), cc2 (t3 – t2)	10.65 (1.34 – 17.67)
Time of the synchrony of the second cell cycle (hour); s2 (t4 – t3)	1.35 (0.00 – 16.5)
Duration of third cells cycle (hour); cc3 (t5 – t3)	12.69 (1.36 – 33.57)
Time of the synchrony of the third cell cycle (hour); s3 (t8 – t5)	15.34 (0.83 – 102.25)

*Numerical variables with normal distribution are presented in mean ± standard deviation and variables with a non-normal distribution are presented as the median.

Bivariate analysis was performed to assess variables related to euploid and aneuploid chromosomal status and were described in Table 3. It was found that expansion grade has significant value on predicting PGT-A chromosome status (p=0.000). The expansion grade was categorized in ordinal (Grade 1-2; Grade 3-6) and nominal (Grade 1 – 5); both categorizations showed that the expansion grade has significant value, consequently (p=0.000; p=0.001). However, several other variables, such as the morphology of the inner cell mass and the trophectoderm, did not show any significant differences in chromosome status.

Table 3. Results of Morphological Bivariate Analysis with PGT-A Chromosome Status

Variable	Euploidy PGT – A (n=61)	Aneuploidy PGT – A (n=63)	P-value	OR	(95%CI)
Inner cell mass morphology					
Category A	36 (53.7)	31 (46.3)	0.531[a]		
Category B	18 (42.9)	24 (57.1)			
Category C	7 (46.7)	8 (53.3)			
Inner cell mass morphology					
Category A	36 (53.7)	31 (46.3)	0.18[a]	1.48	0.73 – 3.02
Category B dan C	25 (43.9)	32 (56.1)		Comparison	
Trophectoderm morphology					
Category A	24 (51.1)	23 (48.9)	0.948[a]		
Category B	24 (48)	26 (52)			
Category C	13 (48.1)	14 (51.9)			
Trophectoderm morphology					
Category A	24 (51.1)	23 (48.9)	0.444[a]	1.12	0.54 – 2.33
Category B dan C	37 (48.1)	40 (51.9)		Comparison	
Expansion Grade					
Grade 1 – 2	23 (34.3)	44 (65.7)	0.000[a]	3.82	1.81 – 8.07
Grade 3 – 6	38 (66.7)	19 (33.3)		Comparison	
Expansion Grade					
Grade 1	10 (38.5)	16 (61.5)	0.001[a]		
Grade 2	13 (31.7)	28 (68.3)			
Grade 3	26 (57.8)	19 (42.2)			
Grade 4	9 (100)	0 (0)			
Grade 5	3 (100)	0 (0)			

[a]Categorical variables were analyzed using the chi square test with continuity correction, presented in the form of n (%), p value, OR and 95%CI

The results of morphokinetic bivariate analysis with PGT-A chromosome status are described in Table 4. Only tNPf and ss3 showed significant results, with p-value of 0.041 and 0.036, respectively.

Table 4. Results of Morphokinetic Bivariate Analysis with PGT-A Chromosome Status

Variable	Euploidy PGT – A (n=61)	Aneuploidy PGT – A (n=63)	*P-value*	Average Ranking	(95%CI)
Time to pro nuclear fading (hours); tNPf	19.88 (11.05 – 53.02)	21.91 (5.23 – 30.65)	0.041[a]		
Time to 2 cells (hours); t2	25.01 (19.67 – 64.02)	25.96 (6.56 – 33.43)	0.301[a]		
Time to 3 cells (hours); t3	35.13 (23.44 – 67.93)	36.36 (8.15 – 47.62)	0.397[a]		
Time to 4 cells (hours); t4	37.76 (26.13 – 68.43)	38.43 (10.73– 53.79)	0.430[a]		
Time to 5 cells (hours); t5	48.23 ± 10.54	48.81 ± 7.97	0.727[b]	-0.58	-3.88 – 2.72
Time to 6 cells (hours); t6	50.52 (32.99 – 86.27)	52.51 (23.48 – 79.85)	0.342[a]		
Time to 7 cells (hours); t7	54.28 (41.22 – 88.02)	53.67 (28.15 – 83.25)	0.986[a]		
Time to 8 cells (hours); t8	60.92 (44.34 – 100.81)	60.09 (30.9 – 100.35)	0.479[a]		
Time to compact (hours); tSC	81.17 ± 11.80	79.73 ± 11.79	0.498[b]	1.43	-2.75 – 5.63
Time to morula (hours); tM	88.17 ± 11.84	88.02 ± 9.91	0.938[b]	0.15	-3.72 – 4.03
Time to start blastocyst (hours); tSB	100.10 ± 10.04	100.88 ± 10.63	0.676[b]	-0.77	-4.45 – 2.90
Time to blastocyst (hours); tB	105.22 (91.2 – 138.25)	108.85 (96.36 – 140.20)	0.227[a]		
Duration of second cells cycle (hours); cc2 (t3 – t2)	10.63 (1.56 – 15.50)	10.67 (1.34 – 17.67)	0.446[a]		
Time of the synchrony of the second cell cycle (hours); s2 (t4 – t3)	1.42 (0.00 – 16.30)	1.33 (0.00 – 16.75)	0.492[a]		
Duration of third cells cycle (hours); cc3 (t5 – t3)	12.58 (1.36 – 33.57)	13.58 (3.73 – 27.21)	0.073[a]		
Time of the synchrony of the third cell cycle (hours); s3 (t8 – t5)	17.46 (1.42 – 47.67)	13.43 (0.83 – 102.25)	0.036[a]		

[a]Numerical variables with abnormal data distribution were analyzed using the Mann Whitney test, presented in the form of median (minimum – maximum), p-value and average ranking

[b]Numerical variables with normal data distribution were analyzed using unpaired t-test, presented in the form of mean ± standard deviation, p-value, mean difference and 95%CI

DISCUSSION

Morphological characteristics have been studies for determine embryo selection. A study conducted examined the relationship between morphology and the euploid status of the cleavage and embryo blastocyst. It was found that 40.6% of good embryo morphology are euploid, 29.3% were in moderate and 25.8% were in poor; no significant difference was found between the morphology of the cleavage phase and the euploid number (p=0.254). Assessment of embryos in the blastocyst phase found a significant difference in the euploid rate which were 73.2% with good morphology, 50% were moderate and 40.5% were poor (p=0.001). It was also found that the grade of inner cell mass and trophectoderm were related to the euploid number of embryos in blastocyst phase.[13] Carried out a research study that employed multiple logistic regression analysis to determine the most influential morphological grading factor affecting the euploidy status of embryos. Among the three grading factors evaluated (TE, ICM, expansion), the blastocoel expansion grade emerged as the most influential factor (odds ratio: 1.261; P = 0.045).[14] However, this study found that inner cell mass and trophectoderm morphology did not significantly correlate with euploid status (p = 0.531; 0.948). Interestingly, only the expansion grade showed a significant value with a p-value of 0.000 (OR 3.82; 95% CI 1.81 – 8.07).

A study conducted by Desai et al. reported that expansion grade had a stronger correlation with clinical pregnancy (OR 7.10; 95% CI, 2.73 – 19.5 ; p<0.001) and live birth rate (OR 7.19; 95% CI,

2.68 – 20.27 ; p<0.001) than other morphologic characteristics in frozen embryo transfer. A different significant implanted rate was reported within the same expansion grade on day 6 and 5 (36% vs 58%; p<0.001). In bivariate analysis, TE and ICM were also significant in affecting clinical pregnancy and live-birth rate. But both ICM and TE score were influenced by blastocyst expansion. Furthermore, the expansion grade was categorized as either an expanded blastocyst (grade 3 to 4) and a non-expanded blastocyst (grade 1 to 2). The result showed that the likelihood of clinical pregnancy and live birth were four times higher in expanded blastocyst. In conclusion, their study provides evidence that the expansion grade is the most crucial factor influencing blastocyst implantation in FET cycles.[12]

Another study showed that expansion score strongly predicted successful clinical pregnancy and live birth independently. Study demonstrated that expanded blastocyst with normal ICM and suboptimal TE had high implantation rate. Assume that TE did not independently impact implantation rate.[17]

Instead of predicting pregnancy and implantation rate, we correlated the expansion grade with euploidy status. In this context, aneuploid embryo has a lower chance of establishing a pregnancy and live birth compare with euploid embryo (5.8% vs 59.6%; 5.0% vs 46.7%).[18] A study reported that the kinetics of blastocyst expansion are associated with euploid status. The expansion of embryo affected by aquaporin water channels which allow extracellular liquid to flow into trophectoderm. The inflow results from the increase of ion concentration regulated by the sodium/potassium pump. Aneuploidy is a genomic condition characterized by an imbalance in chromosome number, resulting in both generalized and chromosome-specific cellular deficits. Moreover, imbalance chromosome causes slower cell division, which reduces cellularity and leads to less robust expansion of the blastocoel.[19-21]

Our study revealed only time to pro-nuclear fading (tPNf) and time of the synchrony of the third cell cycle (s3; t8 – t5) showed significant results (p = 0.041 and 0.036) operating Time-lapse Miscroscopy. In a retrospective study carried out embryos that underwent biopsy on the third day were subjected to morphokinetic assessment using time-lapse technology. The study observed that the most significant variables for predicting

chromosomal abnormalities were the duration of division from 3 blastomeres to 5 blastomeres (cc3, OR=2.095; 95% CI=1.356 – 3.238) and the time interval between 2-cell and 5-cell stages (t5–t2, OR=2.095; 95% CI=1.763–4.616). A meta-analysis that incorporated various morphokinetic parameters to assess embryo development. According to their findings, embryos that exhibited rapid division and shorter durations of 2-cell and 3-cell stages had a higher rate of successful implantation. In a separate study it was demonstrated that time-lapse microscopy (TLM) combined with a specific algorithm that could identify the risk of aneuploidy without the need for Preimplantation Genetic Screening (PGS). TLM serves as a valuable selection tool in cases where PGS is recommended but not feasible due to factors such as economic, legal, social constraints, or even when PGS is not indicated for certain patients.[15, 22]

One of the studies assessing morphokinetic parameters associated with euploid or aneuploid status in embryos was conducted on 1730 blastocysts that were biopsied. There was a significant difference in the average time required to reach blastocyst (tB) between the euploid embryo group of 110.2 hours compared to the aneuploid group of 112.8 hours (p<0.001). Also obtained the difference between the time needed to reach expanded blastocyst (tEB) and the time to reach blastocyst hatching (tHB).[23]

Study reported that tPNa, tPNf, t2, t5, tSB, s3, s3 are significant associate with ploidy status of embryo (p = 0.010; 0.001; 0.010; 0.010; 0.040;0.006;0.040). The mechanism of aneuploidy embryo impact on morphokinetic remains elusive. Between the appearance of pronuclei and their fading, chromosome arrangement, histone modifications, and transcriptional activity occur. The variety length of the S and G2 phases reflects the extent of DNA synthesis. As a result, the synthesis of a different amount of genetic material can alter the standard timeline of pronuclear appearance. In conclusion, euploid status might play a role in determining the morphokinetic patterns of embryos.[24]

CONCLUSION

This study concludes that expansion grade could be a potential factor for accurately predicting the ploidy status of embryos. Moreover, only the time to pronuclear fading and the synchrony of the third cell cycle in morphokinetic parameters

are significantly associated with ploidy status.

STRENGHT AND LIMITATION

This study evaluates, envies, and strengthens the previous studies that morphology embryo and morphokinetic parameters impact embryo euploid status. However, only 124 embryos were analysed; further studies should be performed using bigger samples to establish an accurate non-invasive methods predictive model for embryo selection.

CONFLICT of INTEREST

The author declare that they have no conflict of interest.

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Research Article

The Low Level of Serum 1,25-Dihydroxyvitamin D3 and Calcium in Preeclampsia Women and Its Impact on Maternal Outcomes

Kadar Serum 1,25-Dihidroksivitamin D3 dan Kalsium yang Rendah pada Perempuan Preeklamsia dan Dampaknya terhadap Luaran Maternal

Hudila R. Karmia[1], Yusrawati[1], Tara Fadhillah[2]

[1]Division of Fetomaternal Obstetrics and Gynecology
[2]Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Andalas
Dr. M. Djamil General Hospital
Padang

Abstract

Objective: To investigate the association of serum 1,25-dihydroxyvitamin D3 (1,25[OH]2D3) and calcium levels in pregnancy with the risk of preeclampsia and its impact on maternal outcomes.

Methods: This cross-sectional observational study was conducted in the Obstetrics and Gynecology Department at Dr. M. Djamil Padang General Hospital from May 2021 to April 2022. Patients with normal pregnancy, diagnosed with preeclampsia, and willing to sign the informed consent were included in this study. Blood serum samples from patients were collected and examined with an ELISA kit. The collected data were then statistically analyzed with univariate and bivariate analysis.

Results: The serum 1.25(OH)2D3 levels strongly correlate with maternal outcomes (systolic and diastolic blood pressure) among preeclampsia patients, with p-value = <0.0001. The serum 1.25(OH)2D3 levels in preeclampsia were significantly lower than in normal pregnancy (88.73 ± 42.22 vs. 111.11 ± 52.49 pg/ml), with p-value = 0.033. The serum calcium levels in preeclampsia patients were significantly lower compared to normal pregnant women's (8.67 ± 0.49 vs. 9.55 ± 0.93 mg/dL), with p-value = <0.0001. However, there was no association between serum $1.25(OH)_2D_3$ and serum calcium levels in pregnancy.

Conclusion: Serum levels of 1,25-dihydroxyvitamin D3 and calcium in preeclampsia were significantly lower than in normal pregnancy. Serum 1,25-dihydroxyvitamin D3 levels were also found to have a significant correlation with systolic and diastolic blood pressure in preeclamptic patients. These findings reinforce the suggestion of the importance of vitamin D and calcium supplementation during pregnancy to reduce the risk of preeclampsia and to achieve better maternal outcomes.

Keywords: 1.25-Dihydroxyvitamin D3, calcium, hypertension, pregnancy, preeclampsia.

Abstrak

Tujuan: Mengetahui hubungan antara kadar serum 1,25-dihidroksivitamin D3 (1,25[OH]2D3) dan kalsium pada kehamilan dengan risiko preeklamsia dan pengaruhnya terhadap luaran maternal

Metode: Studi observasional potong lintang ini dilakukan di Departemen Obstetri dan Ginekologi RSUP Dr. M. Djamil Padang dari Mei 2021 hingga April 2022. Pasien dengan kehamilan normal, terdiagnosis preeklampsia, dan bersedia menandatangani informed consent diinklusi dalam penelitian ini. Sampel serum darah dari pasien dikumpulkan dan diperiksa dengan ELISA-kit. Data yang terkumpul kemudian dianalisis secara statistik dengan analisis univariat dan bivariat.

Hasil: Kadar serum 1,25(OH)2D3 memiliki hubungan yang kuat dengan luaran maternal (tekanan darah sistolik dan diastolik) pada pasien preeklamsia, dengan nilai p = <0,0001. Kadar serum 1,25(OH)2D3 pada preeklampsia lebih rendah secara signifikan dibandingkan kehamilan normal (88,73 ± 42,22 vs 111,11 ± 52,49 pg/ml), dengan p-value = 0,033. Kadar kalsium serum pada pasien preeklampsia juga secara signifikan lebih rendah dibandingkan ibu hamil normal (8,67 ± 0,49 vs 9,55 ± 0,93 mg/dL), dengan p-value = <0,0001. Namun, tidak ada hubungan antara kadar serum 1,25(OH)2D3 serum dengan kadar serum kalsium pada kehamilan.

Kesimpulan: Kadar serum 1,25-dihidroksivitamin D3 dan kalsium pada preeklamsia lebih rendah secara signifikan dibandingkan kehamilan normal. Kadar serum 1,25-dihidroksivitamin D3 juga ditemukan memiliki korelasi yang signifikan dengan tekanan darah sistolik dan diastolik pada pasien preeklamsia. Temuan ini memperkuat saran akan pentingnya suplementasi vitamin D dan kalsium selama kehamilan untuk menurunkan risiko preeklamsia dan untuk mendapatkan luaran maternal yang lebih baik.

Kata kunci: 1,25-Dihydroxyvitamin D3, kalsium, hipertensi, kehamilan, preeklamsia.

INTRODUCTION

The maternal mortality rate (MMR) is an important indicator of a nation's health status. However, the MMR in Indonesia is still remarkably high, which is 305 per 100,000 live births, the second rank after Laos among ASEAN countries.[1] The majority of maternal mortality cases are preventable, which are mostly caused by post-partum hemorrhage, infection, preeclampsia or eclampsia, prolonged or delayed parturition, and unsafe abortion.[2]

Preeclampsia (PE) is one of the direct causes of maternal death with prevalence around 5-8% globally. Pregnant women with PE are characterized by elevated blood pressure (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) and proteinuria (>300 mg/24 hours) after 20 weeks gestation, with maternal organ dysfunctions. If untreated, this condition can cause further complications including eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), liver abnormality, retinal detachment, and diffuse intravascular coagulopathy.[3] PE will not only negatively affect maternal health but also impact fetal growth and development, which correlates with higher fetal morbidity and mortality.[4]

PE is a multifactorial pathological condition that occurs as an accumulation of maternal, placental, and fetal factors.[5] Many studies have shown that low levels of vitamin D links to the development of PE. This is related to the function of vitamin D in providing an immunomodulatory effects and regulating blood pressure through the renin-angiotensin system (RAS).[6] Sunlight is the main source of vitamin D. UVB rays from the sun are absorbed by the skin and convert 7-Dehydrocholesterol into Previtamin D3, which is then spontaneously converted into vitamin D3 (Cholecalciferol). This vitamin D enters the blood circulation and is hydrolyzed in the liver into 25-Hydroxyvitamin D (25[OH]D). This inactive metabolite is then activated in the kidneys to 1.25-Dihydroxyvitamin D (1.25[OH]$_2$D).[7] Vitamin D is brought from mother to fetus through an active form of 1.25(OH)$_2$D. Damage to the blood vessel cells in the placenta and kidney causes failure of 1.25(OH)$_2$D synthesis and impact on blood pressure regulations, causing an increase in blood pressure. This stage is the clinical stage of the etiopathogenesis of PE.[8]

1.25(OH)$_2$D inhibits the production of pro-inflammatory cytokines in the human placenta. As seen in the placenta of preeclamptic women, 1.25(OH)$_2$D reduced the secretion of pro-inflammatory cytokines, tumor necrosis factor-α, and interleukin-6. 1.25(OH)$_2$D can also interfere placental Th1 cytokine production, which is increased in PE.[9] In addition, plasma 1.25(OH)$_2$D and plasma renin activity were found to be inversely correlated. The RAS is essential in controlling blood pressure and is involved in the hemodynamic dysregulation of PE. In PE, plasma levels of active renin which stimulate signaling to increase systemic blood pressure, are higher than in normotensive women. 1.25(OH)$_2$D can decrease renin gene transcription through a vitamin D receptor-dependent process (VDR).[6,10]

Hypertension during pregnancy is not only influenced by a deficiency of vitamin D but can also be affected by low calcium levels, which can trigger the release of renin or parathyroid hormone (PTH). This release, in turn, leads to an increase in intracellular calcium levels in vascular smooth muscle.[11] Previous studies have shown that serum concentration of 1.25(OH)$_2$D in pregnancy was positively correlated with calcium uptake.[8] Sixty percent of patients with preeclampsia have hypocalcemia.[12] In addition, a meta-analysis of 10 studies also found that calcium supplementation was associated with a significant reduction in the incidence of preeclampsia.[13] In contrast, a study found no significant difference in serum calcium levels between the preeclampsia and normal pregnancy groups.[14]

To evaluate the risk of PE based on vitamin D status, most studies examined 25(OH)D as a biomarker of vitamin D. Whereas 1,25(OH)$_2$D levels also have significant contributions to the pathophysiology of PE, and only limited studies focus on this active metabolite. There are also different results of the relationship of calcium levels to the occurrence of preeclampsia, while it is also essential to the development of PE. Therefore, we are interested in investigating the association of 1.25(OH)$_2$D$_3$ and calcium levels in pregnancy with the risk of preeclampsia and its impact on maternal outcomes.

METHODS

This cross-sectional observational study examined the association between vitamin D and calcium levels in pregnant women with preeclampsia and normal pregnancy. This study was carried out in the Obstetrics and Gynecology Department at Dr. M. Djamil Padang General

Hospital from May 2021 to April 2022. The inclusion criteria were pregnant women with normal pregnancy and diagnosed with PE, willing to follow the study, and signing an informed consent sheet. Malabsorption, concurrent PE, thyroid, renal, and hepatic abnormalities; ineligible serum owing to damage; and dropped individuals were the exclusion criteria. Samples were collected by consecutive sampling. Blood serum samples (5mL) from patients were collected and examined with an ELISA kit (R&D system).

The data were initially processed with univariate analysis to evaluate the subjects' characteristics, including age, parity, BMI, gestational age, and maternal outcomes (systolic and diastolic blood pressure, mean arterial pressure, serum levels of 1.25-Dihydroxyvitamin D3 and calcium). Then, the subsequent bivariate analysis was performed to analyze the significance of 1.25-Dihydroxyvitamin D3 and calcium levels between normal pregnancy and PE. Data normality was assessed based on the Shapiro-Wilk test. All p values < 0.05 was considered statistically significant. This study has been approved by the Health Research Ethics Committee of Andalas University (approval number: 339/KEPK/2021).

RESULTS

A total of 80 pregnant women were observed in this study, 40 women with normal pregnancy and 40 women with preeclampsia.

Table 1 shows the characteristics of patients in this study. The mean age of patients with normal pregnancy was older than the PE. Patients with PE had a higher BMI than normal pregnant. In both groups, the number of patients with multiparity was higher than those who with the first pregnancy. The gestational age in patients with normal pregnancy was higher than in PE patients. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were found higher in the patients with PE compared to normal pregnant women. The levels of 1.25-Dihydroxyvitamin D3 and calcium in normal pregnancy were higher than in PE patients, which were 111.11 ± 52.49 vs. 88.73 ± 42.22 pg/ml and 9.55 ± 0.93 vs. 8.67 ± 0/49 mg/dL, respectively.

Table 1. Subject Characteristics

Characteristics	Normal Pregnancy (n = 40)	Preeclampsia (n = 40)
Age (years), mean±SD	33.13 ± 4.99	30.48± 6.82
Parity, n (%)		
Primipara	6 (15.0)	16 (40.0)
Multipara	34 (85.0)	24 (60.0)
BMI (kg/m^2), mean±SD	22.75 ± 3.24	26.73 ± 5.30
GA (weeks), mean±SD	37.50 ± 1.22	32.58± 5.10
SBP (mmHg), mean±SD	117.40 ± 7.21	164,63 ± 18,93
DBP (mmHg), mean±SD	76.00 ± 5.06	101.30 ± 7.67
MAP (mmHg), mean±SD	89.60 ± 4.54	122.03 ± 10.15
1,25(OH)$_2$D (pg/ml), mean±SD	111.11 ± 52.49	88.73 ± 42.22
Calcium (mg/dL), mean±SD	9.55 ± 0.93	8.67 ± 0.49

BMI=Body Mass Index; GA=Gestational Age; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; MAP=Mean Arterial Pressure

Our study showed a significant difference of 1.25-Dihydroxyvitamin D3 serum value in PE and normal pregnancy (72.53 vs. 99.18 pg/ml; p = 0.33). Similarly, the serum calcium level of pregnant women with PE is significantly lower than normal pregnant women (8.67 vs. 9.55 mg/dL; p = <0.0001), as seen in Table 2. The result of linear regression statistical test showed that there was no correlation between serum 1,25(OH)$_2$D$_3$ and serum calcium level (r=0.167; p=0.302).

Table 2. The Differences of Serum 1,25-Dihydroxyvitamin D3 and Calcium Levels between Normal Pregnancy and Preeclampsia

Variables	Normal Pregnancy (n = 40)	Preeclampsia (n = 40)	*P-value*
1.25-dihydroxyvitamin D3 (pg/ml)	99.18 (34.38-263.62)	72.53 (25.86-215.23)	0.033*
Calcium (mg/dL)	9.55 (7.70-11.80)	8.67 (7.60-10.30)	<0.0001*

*Values are presented in median (min-max)

The current study also evaluated the difference of 1.25-dihydroxyvitamin D3 regarding maternal outcomes in pregnant women with PE. We found that there was a significant difference in the levels of 1.25-dihydroxyvitamin D3 based on systolic blood pressure, diastolic blood pressure, and gestational age, but not in term of body mass index. The details are provided in Table 3.

Table 3. The Differences of Serum 1.25-Dihydroxyvitamin D3 Levels based on Maternal Outcomes among Patients with Preeclampsia

Maternal Outcomes	1,25-Dihydroxyvitamin D3 (pg/ml) median (min – max)	P-value
Systolic Blood Pressure		<0.0001*
Hypertension (n = 15)	127.40 (59.19-215.23)	
Severe hypertension (n = 25)	66.62 (25.86-168.80)	
Diastolic Blood Pressure		<0.0001*
Hypertension (n = 30)	86.28 (57.05-215.23)	
Severe hypertension (n = 10)	52.80 (25.86-76.12)	
Gestational Age		0.026*
Early onset (n = 19)	67.43 (25.86-168.80))	
Late onset (n = 21)	86.38 (52.40-215.23)	
Body Mass Index		0.586
Normal weight (n = 16)	67.97 (41.73-168.80)	
Overweight (n = 16)	87.56 (25.86-215.23)	
Obesity (n = 8)	71.37 (52.40-133.92)	

DISCUSSIONS

Age, parity, and body mass index (BMI) are the risk factors for the occurrence of preeclampsia. Our study showed that PE patients were younger than the normal pregnancy. A previous study also found a relationship between maternal age and preeclampsia, in which mothers under 20 were at higher risk for preeclampsia. The reason was linked to normal trophoblast cell invasion failure, which might result in spiral arterioles not adapting correctly.[15]

This study also showed that 60% of pregnant women with PE are multiparous. However, this finding is different with the study result that reported there was an association of parity and the occurrence of severe preeclampsia, which primigravida mothers have 1.6 times higher risk than mothers with multigravida.[16]

The BMI indicates the individual's nutritional status to determine normal, underweight, overweight, or obese. In Asia-Pacific, a BMI ≥ 25 kg/m^2 is categorized as obese. Obesity is one of the risk factors for PE. Our study reported that the BMI of normal pregnant was lower than that of PE patients, but there was no significant association (p>0.05). This finding is different to the study result that BMI has a strong correlation to vitamin D levels in PE patients.[17]

A study reported that PE commonly occurs in the late-onset (GA $\geq$34 weeks) than in the early onset (GA <34 weeks).[18] However, our study different results, indicating that PE was more frequently present in early onset cases (32 weeks) compared to late onset cases (38 weeks). Furthermore, we identified a significant association between gestational age and serum 1.25(OH)$_2$D levels in PE patients. PE can occur both in early and late-onset pregnancy. Mothers with a history of chronic hypertension were at higher risk for early-onset PE. Additionally, maternal with a family history of chronic hypertension were higher for late-onset PE.[19]

The current study found that in normal pregnancy had lower blood pressure (SBP, DBP, and MAP) compared to PE patients. The SBP difference between in normal pregnant women and PE patients was also shown in the previous study, with the recurrence of PE being higher 1.94 times than the normal pregnancy.[20] In normal pregnancy, the RAS activation is upregulated to increase the secretion of renin, angiotensin I, and II into circulation. In PE, the levels of renin, angiotensin I, and II circulations were lower than the normal pregnancy. However, the plasma receptor for renin and the autoantibody towards angiotensin II were activated to stimuli signaling.[21]

This study also reported that 1.25(OH)$_2$D serum level was associated with systolic and diastolic blood pressure (p<0.0001) in PE patients. Vitamin D, including its active form 1,25(OH)2D, is known to have various effects on blood pressure regulation. It can affect the renin-angiotensin-aldosterone system (RAAS), which

plays a central role in blood pressure regulation. Vitamin D may also have anti-inflammatory and vasodilatory effects that could influence blood pressure. Some studies have investigated the relationship between vitamin D levels, including 1,25(OH)2D, and blood pressure in women with preeclampsia. Sasan et al. stated that sufficient vitamin D levels can lower arterial blood pressure.[20] A supplementation of >100 nmol/L 25(OH)D can lower SBP and DBP as much as -7.5 mmHg and -4,4 mmHg, respectively.[22]

In this study, we reported that the serum levels of 1.25 dihydroxy vitamin D in PE patients were lower than in normal pregnancy. Meanwhile, the need for vitamin D during pregnancy is higher as it is necessary for the mother's health and the fetus's development. In PE, poor control of effector T cells by regulatory T-sets can lead to altered placental invasion, resulting in the release of vasoconstrictive factors by the placenta and consequently causing maternal hypertension and proteinuria. $1.25(OH)_2D$, through its immunomodulatory role, helps maintain immune homeostasis and prevents placental vasoconstriction, so the risk of preeclampsia can be reduced.[23]

A relationship between vitamin D and PE and the association with maternal blood pressure. An increase of vitamin D 30 nmol/L will reduce the risk for PE during pregnancy.[24] This is because sufficient vitamin D will maintain gene transcription of renin and lower the plasma receptor activation towards angiotensin II, lowering blood pressure.[21] Furthermore, a study also showed that the lower serum vitamin D would increase the risk for high blood pressure. The study also reported that 1,25-dihydroxyvitamin D could suppress the increase of blood pressure by modulating blood vessel protection and function.[25] A meta-analysis of 27 randomized clinical trials concluded that Vitamin D administration in pregnancy was significantly associated with a reduced risk of preeclampsia. The higher dose of vitamin D supplementation, the less risk of PE. This result suggests that vitamin D supplementation can be a practical preventive strategy for the incidence of PE in pregnancy.[26]

Not only it affects the RAS, but vitamin D also causes hypertension by taking a role in calcium homeostasis. It stimulates the generation of calcium transporters, increases calcium reabsorption in the kidney, and induces osteoclastic calcium release in bones. To compensate for this lower Ca2+ concentration

in the plasma caused by a vitamin D deficit, the main cells in the parathyroid gland secrete more parathyroid hormone (PTH) that can further cause elevated blood pressure.[27]

This study shows a higher calcium level in normal pregnancy than in PE patients. A study by Dhungana et al. also reported a similar finding, which serum calcium level was lower in preeclampsia (8.10 ±0.56mg/dl) than control (9.59 ±0.62 mg/dl) with p<0.001.[28] A strong association between calcium levels in both normal pregnancy and PE, in which the calcium levels in pregnant women with PE were significantly lower.[29] Calcium is one of the most abundant substances in human body to support various physiologic functions, such as growth and development, neuronal excitability process, neurotransmitter releasing, muscle contraction, membrane integrity, and blood clotting.[30] During pregnancy, several physiological changes occur to maintain maternal homeostasis, while also maintain and support the growth and development for the fetus.[31]

Low calcium levels contribute to the progression of preeclampsia (PE) or hypertension during pregnancy. Decreased calcium levels lead to elevated parathyroid and renin hormone release, ultimately increasing intracellular calcium in the blood. High intracellular calcium in vascular smooth muscle results in increased vascular resistance and vasoconstriction, leading to high blood pressure. During pregnancy, factors such as hemodilution, increased urinary excretion, and calcium mineral transfer from the maternal to fetal circulation progressively reduce calcium concentration[30] However, in the second and third trimesters, calcium metabolism and absorption are heightened. Sufficient calcium levels during this period reduce uterine smooth muscle contractions and help prevent delivery complications and premature birth[30,31] A meta-analysis conducted by the Cochrane Pregnancy and Childbirth Group reported that pregnant women with poor calcium intake can reduce their risk of preeclampsia and premature delivery by receiving high-dose calcium supplementation (1 g/day).[32]

CONCLUSIONS

This study found that pregnant women with preeclampsia were typically younger, multiparous, had higher BMI, and experienced early-onset preeclampsia. Additionally, the

study revealed a strong correlation between serum 1,25-dihydroxyvitamin D3 levels and maternal outcomes, including systolic and diastolic blood pressure, among preeclampsia patients. Moreover, the serum levels of both 1,25-dihydroxyvitamin D3 and calcium were significantly lower in preeclampsia compared to normal pregnancies. However, no association was observed between serum 1.25(OH)2D3 and serum calcium levels during pregnancy. We suggest that Vitamin D supplementation need to be prioritized by the public health system as an affordable and safe method to lower the risk of PE among pregnant women, as it also have a positive impact on maternal outcomes.

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Research Article

COVID-19 Infection and the Preeclampsia in Pregnant Women

Infeksi COVID-19 dengan Preeklamsia pada Ibu Hamil

Cindy M. Pradana[1], Dita D. Parti[2], Elly N. Sakinah[3]

[1]Undergraduate Student Program
[2]Department of Obstetrics and Gynecology
[3]Department of Pharmacology
Faculty of Medicine, Universitas Jember

Abstract

Objective: To determine the relationship between COVID-19 infection and preeclampsia in pregnant women at RSD dr. Soebandi Jember.

Methods: This study used cross-sctional study with simple random sampling. The data is secondary data from medical records of 118 pregnant women who checked their pregnancies from March 2020 to December 2021 at RSD dr. Soebandi Jember and analyzed with chi-square test and logistic regression test.

Results: Multivariate analysis showed that there were a relationship between COVID-19 infection with preeclampsia. COVID-19 is the most risky variable with an OR of 4.045 (95% CI 1.595 – 10.259). This condition happens because COVID-19 infection triggers down-regulation of RAS which make the failure of spiral artery remodelling and preeclampsia.

Conclusion: There is a relationship between COVID-19 infection and the incidence of preeclampsia in RSD dr. Soebandi Jember.

Keywords: COVID-19, preeclampsia, renin-angiotensin system (RAS), SARS-CoV-2.

Abstrak

Tujuan: Untuk mengetahui hubungan antara infeksi COVID-19 dengan kejadian preeklamsia pada ibu hamil di RSD dr. Soebandi Jember.

Metode: Penelitian ini merupakan studi potong lintang dengan pengambilan sampel menggunakan simple random sampling. Penelitian ini menggunakan data sekunder rekam medis 118 ibu hamil yang memeriksakan kehamilannya mulai Maret 2020 hingga Desember 2021 di RSD dr. Soebandi Jember dan dianalisis dengan uji statistik Chi-square dan uji regresi logistik.

Hasil: Analisis statistik menunjukkan terdapat hubungan antara infeksi COVID-19, usia, dan obesitas dengan kejadian preeklamsia di RSD dr. Soebandi Jember. Variabel COVID-19 merupakan variabel yang paling berisiko terhadap terjadinya preeklampsia dengan OR 4,045 (95% CI 1,595 – 10,259). Hal ini terjadi karena infeksi COVID-19 memicu down-regulasi pada RAS yang mengakibatkan kegagalan remodelling arteri spiralis dan preeklamsia

Kesimpulan: Terdapat hubungan antara infeksi COVID-19 dengan kejadian preeklamsia di RSD dr. Soebandi Jember.

Kata kunci: COVID-19, preeklamsia, renin-angiotensin system (RAS), SARS-CoV-2.

INTRODUCTION

Coronavirus Disease 2019 or COVID-19 is caused by SARS-CoV-2 virus. WHO designated COVID-19 as a world pandemic on March 11, 2020. SARS-CoV-2 spread to almost all countries, including Indonesia.[1] Based on data from the Indonesian Ministry of Health, as of January 3, 2022 there were 4,263,433 confirmed cases of COVID-19 in Indonesia. Pregnant women are a group who vulnerable being infected by COVID-19 due to physiological changes during pregnancy.[2] Pregnant women with COVID-19 infection also have worse clinical outcomes than non-pregnant women with COVID-19 infection.3 Based on data from the Indonesian Ministry of Health on July 30, 2021, there were 2,179 pregnant women died and 18% of them died because of COVID-19.

Pregnant women with COVID-19 are at risk of developing preeclampsia, fetal death, and premature birth.[3] and preeclampsia being a significant contributor to perinatal and maternal mortality.[4] Although the exact cause of preeclampsia remains uncertain, the theory of endothelial dysfunction plays a crucial role in its development. Endothelial dysfunction has also been observed in COVID-19 patients.[5] Both endothelial dysfunction occured in COVID-19 and preeclampsia. Previous research indicates that pregnant women with severe COVID-19 face a fivefold higher risk of developing preeclampsia compared to those with asymptomatic COVID-19. However, the existing academic literature on the connection between COVID-19 infection and preeclampsia in pregnant women is limited, and the World Health Organization (WHO) has not provided specific guidance on managing pregnant women with COVID-19.[6] Identifying the relationship between COVID-19 infection and preeclampsia in pregnant women is of paramount importance for determining appropriate treatment and reducing the mortality rate. There have been 29 reported cases of pregnant women with both COVID-19 and preeclampsia at RSD dr. Soebandi Jember from March 2020 to December 2021. Considering of these conditions, we are interested in researching this study.

METHODS

This study is a cross-sectional design and involves pregnant women who underwent pregnancy check-ups at RSD dr. Soebandi Jember between March 2020 and December 2021. The samples were selected using a simple random sampling method, resulting in the inclusion of 118 medical records of pregnant women who met the specified exclusion and inclusion criteria.

The inclusion criteria encompassed pregnant women with both COVID-19 infection and preeclampsia in pregnancies beyond 20 weeks of gestation, provided that complete medical records were available. Pregnant women with COVID-19 infection who had a prior history of hypertension, kidney failure, nephrotic syndrome, anasarca edema, eclampsia, or stroke were excluded from the study. Data analysis was conducted using SPSS version 24.

After 118 samples were collected, bivariate analysis is performed by chi-square test. There are nine variables to be analyzed, namely COVID-19, age, education, work, delivery method, gravida, history of diabetes mellitus, obesity, and baby birth weight. The COVID-19 variable is divided into two criteria, yes and no. The age variable is divided into two criteria, high risk (>35 years) and low risk (≤35 years). Education variable is divided into two criteria, incomplete (junior high school, elementary, no school) and complete (college, senior high school). Work variable is divided into two criteria, yes and no. The gravida variable is divided into two criteria, primigravida and multigravida. The variable history of diabetes mellitus is divided into two criteria, yes and no. Obesity variable is divided into two criteria, yes and no. Variable baby birth weight is divided into two criteria, low (<2500 grams) and normal (≥2500 grams). After the bivariate analysis, the variables with p value < 0.25 would be re-analyzed in multivariate analysis to find the most risky factor for preeclampsia. Multivariate analysis was performed using backward LR method of logistic regression test. This study has passed the ethical coincidence test by the Ethics Commission of Medical Faculty, Jember University, as certified under the ethic No: 1575/H25.1.11/KE/2022.

RESULTS

Table 1. Characteristics of Samples

Variable	Preeclampsia				Normal				Total	
	COVID-19		Normal		COVID-19		Normal			
	N	%	N	%	N	%	N	%	N	%
Age (y o)										
<20	0	0	0	0	0	0	1	0.85	1	0.85
20-35	19	16.1	8	6.78	30	25.42	24	20.34	81	68.64
>35	10	8.47	10	8.47	0	0	16	13.57	36	30.51
Education										
College	0	0	2	1.69	0	0	4	3.39	6	5.08
Senior High School	19	16.1	4	3.39	8	6.78	20	16.95	51	43.22
Junior High School	5	4.24	7	5.92	15	12.71	11	9.32	38	32.20
Elementary School	4	3.39	5	4.24	7	5.93	6	5.09	22	18.65
No Education	1	0.85	0	0	0	0	0	0	1	0.85
Work										
Yes	2	1.69	2	1.69	6	5.08	2	1.69	12	10.17
No	27	22.88	16	13.57	24	20.34	39	33.05	106	89.83
Delivery method										
Vaginal	14	11.86	10	8.47	5	4.24	25	21.19	54	45.76
Abdominal	15	12.71	8	6.78	25	21.19	16	13.56	64	54.24
Gravida										
Multigravida	8	6.78	8	6.78	25	21.19	23	19.5	64	54.24
Primigravida	21	17.8	10	8.47	5	4.24	18	15.25	54	45.76
History of Diabetes Mellitus										
No	13	11.02	8	6.78	25	21.19	30	25.42	76	64.4
Yes	16	13.56	10	8.47	5	4.24	11	9.32	42	35.6
Obesity										
No	7	5.93	8	6.78	25	21.19	18	15.25	58	49.15
Yes	22	18.64	10	8.47	5	4.24	23	19.5	60	50.85
Baby birth weight (gram)										
>3500	1	0.85	0	0	4	3.39	3	2.54	8	6.78
2500-3500	12	10.17	8	6.78	21	17.8	29	24.58	70	59.32
<2500	16	13.56	10	8.47	5	4.24	9	7.62	40	33.9

Table 2. The Relationship between COVID-19 and Preeclampsia

Variable	Preeclampsia		Normal		Total		*P-value*	OR	CI 95%	
	N	%	N	%	N	%			Lower	Upper
COVID-19										
Normal	18	15.25	41	34.75	59	50		1.000	Reference	
COVID-19	29	24.58	30	25.42	59	50	0.039	2.202	1.037	4.677

Table 3. Relationship between Risk Factors and Preeclampsia

Variable	Preeclampsia		Normal		Total		*P-value*	OR	CI 95%	
	N	%	N	%	N	%			Lower	Upper
Age (y o)										
≤35	27	22.88	55	46.61	82	69.49		1.000	Reference	
>35	20	16.95	16	13.56	36	30.51	0.021	2.546	1.141	5.682
Education										
Complete	25	21.19	32	27.12	57	48.31		1.000	Reference	
Incomplete	22	18.64	39	33.05	61	51.69	0.387	0.722	0.345	1.513
Work										
Yes	4	3.39	8	6.78	12	10.17		1.000	Reference	
No	43	36.44	63	53.39	106	89.83	0.628	1.365	0.387	4.819
Delivery Method										
Vaginal	24	20.43	30	25.42	54	45.76		1.000	Reference	
Abdominal	23	19.49	41	34.75	64	54.24	0.347	0.701	0.334	1.471
Gravida										
Multigravida	16	13.56	48	40.68	64	54.24		1.000	Reference	
Primigravida	31	26.27	23	19.49	54	45.76	0.000	4.043	1.850	8.836
History of Diabetes Mellitus										
No	21	17.8	55	46.61	76	64.4		1.000	Reference	
Yes	26	22.03	16	13.56	42	35.6	0.000	4.256	1.912	9.475
Obesity										
No	15	12.71	43	36.44	58	49.15		1.000	Reference	
Yes	32	27.12	28	23.73	60	50.85	0.002	3.276	1.507	7.121
Baby Birth Weight (gram)										
≥2500	21	17.8	57	48.31	78	66.1		1.000	Reference	
<2500	26	22.03	14	11.86	40	33.9	0.000	5.041	2.220	11.446

Table 4. Multivariate Analysis of Factors Influencing Preeclampsia

	Variable	*P-value*	OR	CI 95%	
				Lower	Upper
Step 1	COVID-19	0.027	3.110	1.140	8.483
	Age	0.346	2.057	0.459	9.208
	Gravida	0.621	1.490	0.307	7.235
	DM	0.999	0.000	0.000	
	Obesity	0.362	1.788	0.513	6.230
	BBW	0.999	0.001	0.000	
Step 2	COVID-19	0.017	3.302	1.235	8.827
	Age	0.163	2.508	0.690	9.125
	DM	0.999	0.000	0.000	
	Obesity	0248	1.990	0.619	6.394
	BBW	0.999	0.001	0.000	
Step 3	COVID-19	0.016	3.343	1.250	8.941
	Age	0.221	2.207	0.621	7.845
	Obesity	0.230	2.047	0.636	6.593
	BBW	0.311	2.091	0.501	8.719
Step 4	COVID-19	0.003	4.045	1.595	10.259
	Age	0.019	3.306	1.215	8.991
	Obesity	0.009	3.110	1.332	7.261

These result support previous research that any relationship between COVID-19 infection and the incidence of preeclampsia.[7]

DISCUSSION

The results of bivariate analysis showed that COVID-19, age, gravida, history of diabetes mellitus, obesity, and baby birth weight had significant relationship with preeclampsia. Meanwhile, education (p = 0.387), occupation (p = 0.628), and delivery method (p = 0.347) did not have a relationship with preeclampsia. The results of the multivariate analysis indicate that the COVID-19 variable (p = 0.003) has the most significant influence on the occurrence of preeclampsia at RSD dr. Soebandi Jember, with an odds ratio (OR) of 4.045. In conclusion, pregnant women who contract COVID-19 have a 4.045 times higher risk of developing preeclampsia compared to pregnant women without a COVID-19 infection.

These results support previous research that any relationship between COVID-19 infection and the incidence of preeclampsia. COVID-19 infection can trigger down-regulation of the Renin-Angiotensin System (RAS) due to binding of SARS-CoV-2 to the ACE2 receptor.[7] ACE2 or Angiotensin Converting Enzyme-2 is an enzyme which converts angiotensin II to angiotensin 1-7.[8] Down-regulation of the Renin-Angiotensin System (RAS) is characterized by decreased levels of angiotensin 1-7, angiotensin which acts as a vasodilator. This decrease of angiotensin 1-7 levels triggers an increase in the systemic arterial vasoconstrictive effect of angiotensin II, including spiral artery vasoconstriction.[9] This condition can lead to failure of spiral artery remodelling. The failed spiral artery remodelling leads to placental ischemia and increased oxidative stress. Oxidative stress can cause angiogenic imbalance by increasing the expression of sFlt-1 as an antiangiogenic protein. The angiogenic imbalance triggers endothelial dysfunction which later causes preeclampsia.[10]

The results also support previous research which stated that COVID-19 infection can trigger preeclampsia through increased coagulation cascade activity. Increased activity of coagulation cascade is characterized by changes in PT (prothrombin time), BT (bleeding time), a PTT (activated Partial Thromboplastin Time), CT (clotting time).[11] The other research also stated that COVID-19 infection is known to increase the inflammatory response which is characterized by an increase in the value of CRP (C-reactive protein), D-dimer, and NLR (neutrophil lymphocyte ratio) which in turn triggers occurrence of preeclampsia.[12]

Multivariate analysis in Table 4 shows that age is associated with preeclampsia. Pregnant women >35 years have a 3,306 times risk of developing preeclampsia compared to pregnant women ≤35 years. The results support previous research which states that ages > 35 years are more at risk of developing preeclampsia because of vascular degeneration. This degeneration of blood vessels occurs due to decrease in nitric oxide and increase in oxidative stress with age.[13] Vascular degeneration can cause endothelial dysfunction through platelet aggregation and impaired prostaglandin metabolism.[14] This condition triggers vasoconstriction and can potentially lead to cardiovascular and nephrological disorders.[15]

Multivariate analysis in Table 4 also shows that obesity is associated with preeclampsia. Obese pregnant women have a risk of 3,110 times of developing preeclampsia compared to normal or non-obese pregnant women. The results supports previous research which states that obese pregnant women are more at risk of developing preeclampsia because lipids can be found in the placenta and can interfere placental invasion.[16] In addition, the complement system also has an important role in increasing the risk of preeclampsia in obese pregnant women. Complement system can be activated locally, by adipose tissue, and systemically, by the liver or other organs. The complement system functions to protect the body from pathogens and plays a role in physiological processes, such as regulating the humoral immune response. The complement system must be lowered to allow adequate placentation because the embryo has paternal and maternal antigens, but is simultaneously activated to protect fetus and mother from pathogens. In obesity, there is an increase of the complement system activation due to the high amount of adipose tissue. The increase of complement system can trigger placentation disorders which lead to preeclampsia.[17]

CONCLUSION

The COVID-19 variable shows a significant relationship with preeclampsia. Pregnant women with COVID-19 have a 4.045 times higher risk of developing preeclampsia compared to pregnant women without a COVID-19 infection at RSD dr. Soebandi Jember.

LIMITATION OF STUDY

This study did not examine the relationship between the severity of COVID-19 and the degree of preeclampsia in pregnant women.

FUTHER RESEARCH RECOMMENDATION

Future researchers can use a larger number of samples and use different research methods, such as cohorts, to minimize research bias. Future researchers are also expected to be able to deepen this research topic by analyzing the relationship between the severity of COVID-19 and the degree of preeclampsia in pregnant women.

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Research Article

Infertile Couple and Pregnancy Outcomes for Patients Undergoing a Pregnancy Program in the Rural Area of Nagekeo District, Flores, East Nusa Tenggara

Pasangan Infertil dan Luaran Kehamilan pada Pasien yang Menjalani Program Kehamilan di Kabupaten Nagekeo, Flores, Nusa Tenggara Timur

Chatarina L. S. D. Dando[1], Angga Dominius[1], Jacob T. Salean[2]

[1]General Practitioners
[2]Department of Obstetrics and Gynecology
Aeramo Hospital Flores Nagekeo Regency

Abstract

Objective: To elucidate the characteristics of infertile couples residing in the rural area of Nagekeo Regency and assess the outcomes of their participation in the local pregnancy program.

Methods: We conducted a descriptive study at Aeramo Regional General Hospital (RGH) in Nagekeo Regency, Flores, East Nusa Tenggara (ENT), utilizing a total sampling technique from January 2020 to April 2022. A total of 56 couples participated in this study.

Results: The analysis revealed that infertile couples at Aeramo RGH were typically aged between 23 and 35 years, with an average infertility duration exceeding 4 years. Primary infertility was the predominant condition (89.3%), with 55.4% of male partners exhibiting obesity. A significant number of male participants reported alcohol and cigarette consumption. Data were insufficient to determine the prevalence of infertility in men versus women. Notably, the outcomes of the pregnancy program in this region did not demonstrate significant improvements.

Conclusions: This study identified potential risk factors such as smoking, alcohol consumption, and obesity that may contribute to infertility; however, it did not establish a strong correlation between these factors and infertility. Moreover, the pregnancy program's outcomes were inconclusive, likely due to limited diagnostic and treatment resources in the area.

Keyword: infertility characteristics, pregancy program, pregnancy outcomes.

Abstrak

Tujuan: Mendeskripsikan karakteristik pasangan infertil di Kabupaten Nagekeo serta mengetahui hasil luaran kehamilan bagi pasangan yang mengikuti program kehamilan di daerah tersebut.

Metode: Penelitian ini merupakan penelitian deskriptif yang dilakukan di Rumah Sakit Umum Daerah (RSUD) Aeramo, Kabupaten Nagekeo, Flores, Nusa Tenggara Timur. Dengan menggunakan teknik total sampling pada periode Januari 2020 - April 2022, terdapat 56 pasangan yang bergabung dalam penelitian ini.

Hasil: Hasil penelitian kemudian dianalisis secara univariat dan didapatkan usia pasangan infertil di Aeramo RGH adalah antara 23 - 35 tahun dengan durasi infertilitas lebih dari 4 tahun. Infertilitas primer dan obesitas pada pria mendominasi masing-masing kelompok yaitu 89,3% dan 55,4%. Mayoritas laki-laki mengonsumsi alkohol dan rokok. Tidak ditemukan data yang cukup untuk menentukan apakah infertilitas terjadi pada laki-laki atau perempuan. Hasil dari program kehamilan yang dilakukan di daerah ini belum menunjukkan hasil yang signifikan.

Kesimpulan: Karakteristik yang memicu faktor risiko seperti merokok, mengonsumsi alkohol dan obesitas. Meskipun pada penelitian ini belum didapatkan korelasi yang kuat dari faktor risiko tersebut pada infertilitas. Hasil dari program kehamilan belum menunjukkan hasil yang signifikan karena modalitas diagnostik dan pengobatan yang sangat terbatas.

Kata kunci: karakteristik infertilitas, luaran kehamilan, program hamil.

Correspondence author. Chatarina L.S.D. Dando. General Practitioner. Aeramo Hospital. Flores Nagekeo Regency. Email; atindando@gmail.com

INTRODUCTION

Infertility is defined as the inability to conceive after unprotected sexual intercourse for 12 months or more. It is categorized as either primary or secondary infertility. Approximately 48 million couples worldwide experience infertility.[1]

Data from the Indonesian In Vitro Fertilization Association (PERFITRI) in 2017 found that infertility occurred in 1,712 men and 2,055 women. Currently, over 20% of couples grapple with infertility issues.[2]

For many couples, the period of infertility treatment is the most stressful of their lives. In developing countries, the desire to reproduce can be met with societal stigmatization, leading to diminished self-esteem and depression. Furthermore, the pursuit of parenthood often results in a decreased desire for sexual activity when conception remains elusive.[3]

A higher infertility rate in a country can contribute to a reduced birth rate, potentially resulting in a less productive workforce, increased dependency on labor, and a growing elderly population.[4]

Risk factors for infertility are often linked to an individual's lifestyle. In men, infertility can stem from issues related to sperm quality, while in women, structural or hormonal abnormalities may be the cause.[1]

Hence, it is crucial to assess and research infertility. This study aims to present data regarding the characteristics of infertile couples and the outcomes of pregnancy programs in Nagekeo Regency, Flores, East Nusa Tenggara (NTT). The objective is to provide a reference for the local Health Office and the Ministry of Health of the Republic of Indonesia, facilitating the development of appropriate infertility management strategies in rural areas.

METHODS

This research comprises a descriptive study conducted at the Regional General Hospital (RSUD) Aeramo in Nagekeo Regency. The data were collected from both primary and secondary sources. Primary data were gathered through direct interviews, employing questionnaires administered to respondents, while secondary data were extracted from medical records at Aeramo Hospital.

The study population consisted of infertile couples who had participated in a pregnancy program at the Gynecology Clinic of Aeramo Hospital. Utilizing a total sampling technique from January 2020 to April 2022, a total of 56 couples were included in the study.

The collected data were subsequently subjected to univariate analysis using SPSS Version 25. This analysis aimed to provide a descriptive overview of the characteristics and pregnancy outcomes associated with the conducted pregnancy program. The results of this study have been presented in tabulated form, aligning with relevant theories.

RESULTS

The results of the analysis of respondent characteristics are presented below.

Table 1. Respondent Characteristics

Variables	n = 56
Age of Female	
25 – 30	23 (41.1)
31 – 35	17 (30.4)
36 – 40	15 (26.8)
41 – 45	1 (1.8)
46 – 50	0
Age of Male	
25 – 30	9 (16.1)
31 – 35	23 (41.1)
36 – 40	16 (28.6)
41 – 45	7 (12.5)
46 – 50	1 (1.8)
Types of Infertility	
Primary	50 (89.3)
Secondary	6 (107)
Duration of Infertility (year)	
1	9 (16.1)
2	10 (17.9)
3	9 (16.1)
4	5 (8.9)
>4	23 (41)
Female Body Mass Index (BMI)	
Obesity	26 (46.4)
Non Obese	30 (53.6)
Male	
Obesity	31 (55.4)
Non Obese	25 (44.6)
Smoking History	
Female	
Yes	0 (0)
No	56 (100)
Male	
Yes	33 (58.9)
No	23 (41.1)
Alcohol History	
Female	
Yes	0 (0)

No	56 (100)
Male	
Yes	35 (62.5)
No	21 (37.5)
Sperm Analysis	
Normospermia	12 (21.4)
Asthenozoospermia	9 (16)
Oligoasthenozoospermia	3 (5.4)
Leucospermia	
Normospermia	3 (5.4)
Oligozoopermia	3 (5.4)
Teratozoospermia	2 (3.6)
Asthenoteratozoospermia	1 (1.8)
No Laboratory Result	23 (41)
Female's Comorbidities	
PCOS	6 (10.71)
Ovarian Cyst	3 (5.4)
Uterine Myoma	3 (5.4)
not specific etiology	3 (5.4)
Endometriosis	2 (3.6)
Unknown	39 (69.6)

Table 2. Pregnancy Outcomes

Result	n = 56
Pregnant	12 (21.4)
Not Pregnant	44 (78.5)

DISCUSSIONS

The highest prevalence of infertility was observed in women aged 25-30 years (41.1%) and in men aged 31-35 years (41.1%). Previous studies have consistently demonstrated that the risk of infertility tends to rise with age.[5]

Based on Borumandnia's research, the prevalence of primary infertility in men and women in the Southeast Asian region is lower when compared to secondary infertility.[6] These results are not in accordance with this study, because the primary infertility rate is higher than secondary infertility.

The duration of infertility in married couples is predominantly greater than 4 years (41%). This finding aligns with prior research, which has shown that as the duration of infertility increases, the degree of infertility also tends to rise, often resulting in a smaller number of oocytes obtained.[5]

Obesity is one of the characteristics of infertile couples. In this study, obesity in men (55,4%) was higher than in women (46.4%). Obesity can trigger infertility in men through changes in semen parameters such as sperm concentration, motility, viability, morphology, DNA integrity and mitochondrial function.[7] Obesity and overweight

in women can trigger menstrual dysfunction and anovulatory conditions.[8]

In this study, 58.9% of male respondents were active smokers, while none of the women smoked. Active smoking has been associated with an increased incidence of infertility. Moreover, the delay in conception appears to be directly correlated with the number of cigarettes smoked daily, with active smokers experiencing a 54% higher delay in achieving conception. Among women, smoking can accelerate ovarian follicular depletion and the loss of reproductive function. In men, smoking often leads to reduced sperm concentration, motility, and/or morphology when compared to non-smokers.[9]

Alcohol consumption is associated with sperm apoptosis and spermatogenesis defects that cause low total sperm count and concentration. More than a third of men who consume >5 units of alcohol per week experience partial or total spermatogenic arrest.[10] The results of this study showed that 62.5% of men (35 people) actively consumed alcohol, while no women consumed alcohol.

The causes of infertility in women include ovulation disorders, reduced ovarian reserves, abnormalities in the reproductive system or chronic diseases.[11] In this study, 69.6% of women who experienced infertility had unknown causes, PCOS (Polycistic ovary syndrome) as much as 10.71%, ovarian cysts (5.4%), uterine myoma (5.4%), secondary amenorrhea (5.4%), and endometriosis (3.6%). PCOS puts women 10 times at risk of infertility.[12] Among the male respondents, a total of 21 individuals (37.5%) exhibited sperm abnormalities. The most prevalent sperm abnormality observed was asthenozoospermia (16%). Notably, 90% of male infertility cases are attributed to abnormalities in sperm count parameters [Reference 5]. However, it's important to acknowledge the limitations of this research, as 41% of male respondents did not undergo sperm analysis.

In this study, the outcome of the pregnancy program indicated a success rate of 21.4%, with 12 women successfully conceiving within one cycle of the three-month pregnancy program. The program utilized conventional methods, consisting of a natural pregnancy program involving the analysis of infertility causes using available diagnostic modalities, namely Ultrasonography (USG) and sperm analysis examinations. When suspicions of reproductive diseases were identified in women and men,

management was provided, including education to modify risk factors and medication tailored to the underlying causes. However, it's important to note that this study did not assess the significance of the pregnancy program at Aeramo Hospital in relation to pregnancy success. The relationship between the management provided and pregnancy outcomes was not analyzed.

CONCLUSION

The majority of infertility cases were observed in women aged 25-30 years (41.1%) and in men aged 31-35 years (41.1%). Primary infertility was the most prevalent type (89.3%). The duration of infertility exceeded 4 years in 41% of cases. A significant proportion of men were obese, with a prevalence of 55.4%, while 46.4% of women were obese. Additionally, the majority of men in the study were smokers (58.9%) and consumed alcohol (62.5%). It is essential to acknowledge data limitations, particularly regarding the results of male sperm analysis and female comorbidities. In terms of pregnancy outcomes, only 21.43% of participants achieved pregnancy, while 78.57% did not. This study did not identify a strong correlation between these risk factors and infertility. Furthermore, the pregnancy outcomes of couples undergoing the pregnancy program at Aeramo Hospital did not yield significant results, primarily due to the limited availability of diagnostic and management modalities.

SUGGESTION

It is necessary to conduct bivariate to multivariate analytical research on each of these infertility risk factors for the incidence of infertility in rural areas of Nagekeo Regency,to provide valuable data on causal relationships, which, in turn, can inform future infertility prevention measures.

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| Research Article |

Optimal Omega-3 Intake: A Natural Way to Ease Primary Dysmenorrhea Severity

Asupan Omega-3 yang Optimal: Cara Alami untuk Mengurangi Derajat Dismenore Primer

Benedicta A. Widyatmoko, Edihan Mardjuki

School of Medicines and Health Sciences
Universitas Katolik Atma Jaya Indonesia
Jakarta

Abstract

Objective: To examine the link between adequate omega-3 intake and degree of primary dysmenorrhea in Atma Jaya preclinical medical students

Methods: This cross-sectional study of 126 female students who experienced primary dysmenorrhea started from August to October 2022. Data was collected through the distribution of google forms containing the Working ability, Location, Intensity, Days of pain, Dysmenorrhea (WaLLID) score and Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ). According to Recommended Dietary Allowance (RDA), daily intake of omega-3 fatty acids is sufficient if it is ≥ 1.1 g/day. Data were processed using Microsoft Excel and SPSS and analyzed by a 2x3 Chi-square test.

Results: The findings showed that the majority of the respondents who consumed optimal omega-3 fatty acids, 17.5% (22 people), had primary dysmenorrhea with mild pain and also had a low percentage of severe primary dysmenorrhea, 3.2% (4 people). The link between adequate intake of omega-3 fatty acids with the degree of primary dysmenorrhea in female medical students showed significant test results (p=0.046).

Conclusion: There is a significant link between optimal intake of omega-3 and degree of primary dysmenorrhea in Atma Jaya preclinical medical students (p<0.005).

Keywords: intake, medical student, menstruation, primary dysmenorrhea, omega-3 fatty acids.

Abstrak

Tujuan: *Mengetahui hubungan asupan omega-3 yang optimal dengan derajat dismenore primer pada mahasiswi prelinik kedokteran Atma Jaya.*

Metode: *Penelitian potong lintang terhadap 126 mahasiswi yang mengalami dismenore primer ini di mulai sejak Agustus hingga Oktober 2022. Pengumpulan data dilakukan melalui penyebaran google form secara daring berisi kuesioner Working ability, Location, Intensity, Days of pain, Dysmenorrhea (WaLLID) score dan Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ). Asupan asam lemak omega-3 dikategorikan menjadi cukup apabila asupan harian ≥ 1.1 g/hari sesuai dengan Angka Kecukupan Gizi (AKG). Program yang digunakan untuk pengolahan data adalah Ms. excel dan SPSS, sedangkan untuk uji analisis data menggunakan Chi-square 2 x 3.*

Hasil: *Penelitian menunjukkan bahwa mayoritas responden dengan asupan asam lemak omega-3 yang optimal yaitu 17.5% (22 orang) merupakan penderita dismenore primer dengan derajat nyeri ringan serta memiliki persentase dismenore primer berat yang sangat kecil yaitu 3.2% (4 orang). Hubungan antara kecukupan asupan asam lemak omega-3 dengan derajat dismenore primer pada mahasiswi kedokteran menunjukkan hasil uji yang signifikan (p=0.046).*

Kesimpulan: *Adanya hubungan yang signifikan antara asupan omega-3 yang optimal dengan derajat dismenore primer pada mahasiswi preklinik Kedokteran Atma Jaya (p<0.005).*

Kata kunci: *asupan, asam lemak omega-3, dismenore primer, mahasiswi kedokteran, menstruasi.*

INTRODUCTION

Dysmenorrhea, commonly referred to as lower abdominal pain, is a common occurrence in the majority of women during menstruation.[1] Primary dysmenorrhea is caused by changes in prostaglandin levels and uterine contraction activity, which affect the narrowing of uterine blood vessel and active contractions.[2] Within the Indonesian population, approximately 64.25% of women experience dysmenorrhea, with primary dysmenorrhea resulting in 54.89%.[3] Primary dysmenorrhea affects 87.5% of young women in Central Jakarta.[4] The presence of primary dysmenorrhea can significantly affect an individual's quality of life. Some women complained on impaired mobility, as well as a feeling of discomfort in carrying out their daily activities.[5]

Primary dysmenorrhea is the most frequent problem that occurs during menstruation due to prostaglandin hypersecretion and uterine myometrial contractions.[6] Age at menarche, duration of menstruation, body mass index (BMI), food intake, and physical activity are all risk factors for primary dysmenorrhea. Consuming foods rich in omega-3 decreases the likelihood of experiencing pain associated with dysmenorrhea and based on a systematic review, omega-3 contribute in inhibiting the production of arachidonic acid, thereby inhibiting the production of prostaglandins and reducing myometrial and vessel contraction.[7] There are three primary forms of omega-3 fatty acids: Alpha Linolenic Acid (ALA), Eicosapentaenoic Acid (EPA), and Docosahexaenoic Acid (DHA). Plant oils contain a rich amount of ALA including flaxseed, soybean, and canola oil. Meanwhile, DHA and EPA can be found in a variety of seafoods, including salmon, tuna, and others.[8] Based on PERMENKES no. 28 of 2019 regarding the Recommended Dietary Allowance (RDA) for Indonesian Society, adequate intake of omega-3 fatty acids for women over 13 years is 1.1 g/day.[9]

A previous study found that giving omega-3 rich fish oil supplements for two months resulted in a significant reduction in the intensity of menstrual pain. This is linked to the formation of EPA omega-3 fatty acids from series 3 prostaglandins and thromboxanes (PGE3 and TXA3) and series 5 leukotrienes (LT5), both of which are anti-inflammatory mediators.[10] Aside of being anti-inflammatory, omega-3 fatty acids are also analgesic, inhibiting pain transmission by blocking the activity of mitogen-activated protein kinase, which is involved in modulating central sensitization caused by inflammation and neuropathic pain.[11] However, there are only few studies that show that consuming omega 3 through daily food intake can reduce the severity of primary dysmenorrhea, so based on this and existing theory, the primary objective of this study is to examine the potential association between sufficient intake of omega-3 and the degree of primary dysmenorrhea.

METHODS

This study employs an analytical observational design, specifically a cross-sectional approach. The target of this study was preclinical students at the Atma Jaya School of Medicine and Health Sciences with a sample selection system, such as purposive sampling technique which is a technique for matching samples according to the respondent's criteria. The inclusion criteria for this study were students from School of Medicine and Health Sciences Atma Jaya Class of 2019-2021 who have primary dysmenorrhea during menstruation. The exclusion criteria for this study were female students who are unwilling to be respondents, fill inaccurate information, or have gynecological diseases. This filtration from the respondent's criteria resulted 126 respondents in total.

The research procedure begins with the distribution of dysmenorrhea history and working ability, location, intensity, days of pain, and dysmenorrhea (WaLLID) questionnaires to select respondents who meet the criteria. The severity of dysmenorrhea pain is categorized using the WaLIDD score. A score of 0 signifies an absence of dysmenorrhea, while scores ranging from 1 to 4 represent mild dysmenorrhea, scores from 5 to 7 indicate moderate dysmenorrhea, and scores from 8 to 12 indicate severe dysmenorrhea. The validity and reliability of this WaLIDD questionnaire have been tested (Cronbach's alpha = 0.723). [12]

Furthermore, a Semi-Quantitative Food Frequency Questionnaire (SQ-FFQ) was distributed to determine the adequacy of omega-3 fatty acid intake.[13] This questionnaire includes a list of foods high in omega-3 fatty acids culled from the USDA's Nutrisurvey and Food Central databases (USDA). Respondents will be asked to fill out a questionnaire based on the frequency of consumption of each food.

The data collected will represent daily intake of omega-3 that will be categorized as sufficient if it is greater than 1.1 grams/day according to the Recommended Dietary Allowance (RDA).[9] The data analysis will involve Microsoft Excel and the Statistical Package for Social Science (SPSS) with a 2 x 3 Chi-square test.

RESULTS

Table 1. Subject Characteristics

Characteristics	N	%
Age (years old)		
17-18	39	30.9
19-20	74	58.7
21-23	13	10.3
Age at Menarche		
10-11	35	27.7
12-13	67	53.1
14-15	24	19.0
Menstrual cycle		
Regular	91	72.2
Irregular	35	27.8
Period length (days)		
3-4	4	3.2
4-5	36	28.6
5-6	61	48.4
>6	25	19.8
Analgesic use		
Yes	20	15.9
No	106	84.1
Total	126	100

There were 126 respondents who satisfied the specified inclusion and exclusion criteria. The subjects' characteristics in this study included their age, menarche, regularity of the menstrual cycle, period length, and use of analgesics during menstruation (Table 1). The respondents' ages ranged from 17 to 23, with the majority (58.7%) between the ages of 19 and 20. Most of the respondents had menarche at age 12-13 years (53.1%), experienced menstruation with regular cycles (72.2%), had a menstrual duration of 5-6 days (48.4%), and did not require analgesics (84.1%).

Table 2. Degree of Primary Dysmenorrhea and Omega-3 Intake

	N	%
Degree of Primary Dysmenorrhea		
Mild pain	53	42.1
Moderate pain	46	36.5
Severe pain	27	21.4
Omega-3 Intake		
Adequate	37	29.4
Inadequate	89	70.6

Table 2 shows the distribution of primary dysmenorrhea degrees among respondents, with mild pain (N=53;42.1%), moderate pain (N=46;36.5%), and severe pain (N=27;21.4%). The distribution of omega-3 fatty acid intake in Table 2 shows that a large percentage of respondents, 89 people (70.6%), had inadequate omega-3 intake. The average intake per day of omega-3 fatty acids was 0.89 grams/day among 126 respondents. The average intake is classified into the low intake category (<1.1 grams/day).

Tabel 3. Average Intake of Omega-3 Food Sources in Respondents

Omega-3 Food Sources	Average Daily Intake (mg)	Omega-3 Food Sources	Average Daily Intake (mg)
Fried rice	27.31	Goat meat	0.09
White bread	5.65	Cow meat	15.25
Biscuit	36.24	Meatball	8.52
Biscuit with cream	62.41	Meat sausage	6.56
Instant noodles	15.75	Chicken sausage	5.92
Tofu	194.08	Catfish	4.55
Fried tofu	135.53	Gurame (fish)	22.65
Tempeh	10.45	Mujaer (fish)	0.50
Mungbean milk	0.18	Tongkol (fish)	5.79
Mungbean porridge	0.02	Salmon (fish)	11.19
Soybeans	1.45	Tuna (fish)	18.34
Deep-fried peanuts wrapped with flour	1.00	Mackarel (fish)	24.53
Peanut wrapped with flour	0.25	Sarden (fish)	11.32
Greenpeas	0.08	Chicken egg	76.24
Chicken liver	0.24	Chicken egg (raw)	0.88
Cooked chicken	29.77	Instant cereal	19.24
Fried chicken	27.99	Avocado	0.83
Fried chicken breast (fast-food)	23.74	Ambon banana	3.51
Fried chicken thigh (fast-food)	14.92	Kepok banana	0.15
Chicken intestine satay	0.49	Ice cream	12.14
Chicken feet	0.23	Fish oil	45.67

According to the SQ-FFQ analysis, there are 43 omega-3 fatty acid food sources in total, which are classified as carbohydrates, plant protein sources, animal protein, cereals, fruit, snacks, and supplements. Based on Table 3, the food source of omega-3 fatty acids with the highest average daily intake of omega-3 is tofu (194 mg/day), which is classified as a plant protein source.

Following tofu, the highest average daily intake of omega-3s is found in chicken eggs (76.2 mg/day), biscuits (62.4 mg/day), cereals (19.2 mg/day), fish oil (45.6 mg/day), and chicken meat (29.7 mg/day). Other than that, high omega-3 intake was found in mackerel (24.53 mg/day), tuna (18.34 mg/day), and gurame (22.65 mg/day) in the fish group.

Tabel 4. Crosstabulation of Omega-3 Fatty Acids Intake and Primary Dysmenorrhea Degree

Variable		Primary Dysmenorrhea Degree			Total (%)	*P-value*
		Mild **N (%)**	**Moderate** **N (%)**	**Severe** **N (%)**		
Omega-3 Fatty Acids Intake	Adequate	22 (17.5)	11 (8.7)	4 (3.2)	37 (29.4)	0.046
	Inadequate	31 (24.6)	35 (27.8)	23 (18.3)	89 (70.6)	
	Total	53 (42.1)	46 (36.5)	27 (21.4)	126 (100)	

According to Table 4, there were 37 respondents (29.4%) who had an adequate intake of omega-3 fatty acids. The majority of those who had an adequate intake had mild primary dysmenorrhea, which was 21 respondents (17.5%). Meanwhile, 11 respondents (8.7%) went through moderate primary dysmenorrhea, and 4 respondents (3.2%) experienced severe primary dysmenorrhea. There were 89 people (70.6%) among those who had inadequate omega-3 fatty acids, with 31 respondents (24.6%) experiencing mild primary dysmenorrhea, 35 respondents (27.8%) experiencing moderate primary dysmenorrhea, and 23 respondents (18.3%) experiencing severe primary dysmenorrhea. The results from Chi-square test table 2 x 3 shows a significance value (p) of 0.046 (p<0.05), indicating a statistically significant link between omega-3 fatty acid intake and the degree of primary dysmenorrhea.

DISCUSSION

The respondents in this study varied in age from 17 to 23, with the majority of respondents aged 19-20 years (58.7%). Discovered the highest prevalence of primary Dysmenorrhea occurred within the age range of 19 to 20 (42.6%).[14] 53.1% of respondents had menarche at age 12-13 years. This findings aligns with RISKESDAS analysis regarding the mean age of menarche in women in DKI Jakarta Province, which is 12.44 years, and in North Jakarta districts/cities, which is 12.58 years.[15]

In terms of menstrual cycle regularity, the majority of respondents reported having regular menstrual cycles (72.2%). Similar findings were reported in a study on female students at

Faculty of Medicine Universitas Andalas, where most respondents (86%) had regular menstrual cycles.[16] The distribution of period length showed the highest number at 5-6 days (34.9%). Women experience menstrual bleeding for an average of 5 days, with heavier bleeding occurring during the initial 3 days of menstrual cycle.[17] Analgesics are used to relieve pain in some people who have primary dysmenorrhea or pain. According to statistical information, 15.9% of all respondents required analgesics during menstruation.

Degree of Primary Dysmenorrhea

Based on the results, 53 respondents (42.1%) had primary dysmenorrhea with a mild degree of pain, followed by 46 respondents (36.5%) had moderate pain, and 27 respondents (21.4%) had severe pain. This is consistent with the findings of a study, which showed that the majority of respondents, 29 respondents (40.3%), experienced mild primary dysmenorrhea pain.[18] Research conducted on medical students at the University of HKBP Nommensen Medan using the WaLLID scoring system, the average primary dysmenorrhea wwas 4.48. This score of 4.48 indicates mild primary dysmenorrhea.[19]

Primary dysmenorrhea is related to various factors, such as biological, psychological, and lifestyle factor. Biological factors vary in menarche age, menstrual duration, and dysmenorrhea in the family. Psychological factors are generally related to stress, depression, and anxiety. Social factors can be affected by a lack of social support. Daily dietary intake is an example of a lifestyle factor. According to a study conducted on female students at a Chinese University woman

with early menarche and irregular menstrual cycles have more intense menstrual pain.[20] The majority of respondents in this study had primary dysmenorrhea with mild pain, which can be attributed to the previously mentioned factors. As shown by Table 1, most of the respondents in this study had normal menarche age and period length, as well as a regular menstrual cycle, which can contribute to a mild degree of dysmenorrhea. In the end, the variation in the degree of primary dysmenorrhea in women is due to the production of different prostaglandin hormones.

Omega-3 Fatty Acids Intake

According to the result of a univariate test for omega-3 fatty acid intake, 89 respondents (70.6%) had inadequate intake (1.1 gram/day) and 37 respondents (29.4%) had adequate intake (>1.1 gram/day). Similar findings were found in R. Suzan's (2018) study of students at the Faculty of Medicine, University of Jambi, who discovered that 70% of the respondents, or 42 respondents, did not get enough omega-3 fatty acids.[21] However, discovered that the results are opposite where the respondents have an average intake of omega-3 in the adequate category, 1.18 grams/day (> 1.1 grams/day).[22] This could be due to differences in the SQ-FFQ used to assess omega-3 fatty acids intake.

A lack of omega-3 fatty acid intake in college students can be affected by various factors, including a lack of nutrition knowledge and a high fast-food diet. research conducted through interviews with samples, most people had insufficient knowledge about good eating habits, such as eating a lot of fast food. [23]

Relationship between Omega-3 Fatty Acids Intake and Degree of Primary Dysmenorrhea

According to the result of a univariate test for omega-3 fatty acid intake, 89 respondents (70.6%) had inadequate intake (1.1 grams/day) and 37 respondents (29.4%) had adequate intake (>1.1 grams/day). Based on Table 4 showed that the majority of those who consumed adequate omega-3 fatty acids, 21 respondents (17.5%), had primary dysmenorrhea with mild pain. Respondents who consumed adequate omega-3 fatty acids had a very low percentage of severe primary dysmenorrhea, 3.2% (4 respondents). Meanwhile, respondents with an inadequate intake of omega-3 fatty acids in the severe primary

dysmenorrhea group were 23 respondents (18.3%) out of a total of 27 respondents (21.4%). The 2 x 3 Chi-square test results indicated a significant (p=0.046) correlation between adequate omega-3 fatty acid intake and the degree of primary dysmenorrhea in medical students.

A systematic review and meta-analysis study found that omega-3 fatty acids could reduce the severity of primary dysmenorrhea (p<0.001).[24] This is coherent with the research results which show that the more omega-3 fatty acids a person consumes, the less pain they experience from primary dysmenorrhea. Regarding the effect of consuming omega-3 and vitamin E supplements on reducing the degree of primary dysmenorrhea pain on women aged 18-25 years stated that there were significant results from consuming these supplements on reducing primary dysmenorrhea. [25] Giving fish oil supplements rich in omega-3 for two months reduced the intensity of menstrual pain significantly.[10] Primary dysmenorrhea is caused by the synthesis of prostaglandins, which can cause strong contractions in the uterus, resulting in cramps, abdominal discomfort, lower back pain, nausea, vomiting, headaches, and other symptoms. Omega-3 fatty acids inhibits the production of arachidonic acid, which then inhibits the production of series 2 prostaglandins and reduces myometrial contraction.[7]

During menstruation, progesterone levels fall, followed by the production of arachidonic acid. Arachidonic acid with cyclooxygenase enzymes produces series 2 prostaglandins, which are proinflammatory to the uterus. Consumption of omega-3 fatty acids increases prostaglandin series 3 by acting as a substrate for the cyclooxygenase enzyme. This results in a decrease in prostaglandin series 2 and an increase in prostaglandin series 3. Prostaglandin series 3 is an anti-inflammatory that also reduces myometrial contractions, reducing ischemia and pain during menstruation.[26]

CONCLUSIONS

Omega-3 fatty acids intake in respondents seemed to be inadequate or less than the Recommended Dietary Allowance (RDA) (<1.1 grams/day), in as many as 89 people (70.6%). Meanwhile, 37 people (29.4%) reported an adequate intake of omega-3 fatty acids. The majority of respondents had mild primary dysmenorrhea, with the distribution being mild

(42.1%), moderate (36.5%), and severe (21.4%). The majority of respondents with adequate omega-3 intake (17.5%) had mild primary dysmenorrhea, while the percentage of severe primary dysmenorrhea was very low, at 3.2%. The findings of this study provide evidence supporting a link between the consumption of omega-3 fatty acids and primary dysmenorrhea severity. ($p < 0.05$)

Further research can be conducted using more specific and less biased methods, such as the intervention of omega-3 fatty acid intake to see its effect on the degree of primary dysmenorrhea in women. Future research can also measure omega-3 serum levels to compare omega-3 fatty acid intake and the degree of primary dysmenorrhea for each individual.

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Research Article

The prevalence of lower urinary tract symptoms in Caesarean section patients' first and seventh day of postpartum

Perbandingan Prevalensi Gejala Saluran Kemih Bawah pada Ibu Postpartum Hari pertama dan Hari Ketujuh secara Sectio Caesarea

Austin Julian¹, Johannes C. Prihadi², Yuma S. S. Indrajaya³

¹ Study Program of Medicine
² Department of Surgery
³ Department of Obstetrics and Gynecology
School of Medicine and Health Science
Universitas Katolik Indonesia Atma Jaya
Jakarta

Abstract

Objective: To compare the prevalence of Lower Urinary Tract Symptoms (LUTS) on the first day and the seventh day postpartum in Caesarian section patient

Method: This cross-sectional study utilized the ICIQ-FLUTS LF (ICIQ-Female Lower Urinary Tract Symptoms-Long Form) and a questionnaire to screen for risk factors among postpartum patients who underwent C-section delivery at Santo Antonius Hospital, Pontianak, West Kalimantan. Data were collected twice, 12 hours after urinary catheter removal and on the seventh day of the postpartum period. The study sample consisted of 95 respondents.

Results: Among the 111 total respondents, the majority were under 35 years old, multiparous, classified as obese, had no family history of Lower Urinary Tract Symptoms (LUTS), and had not used diuretics or traditional medicine. Significant differences were observed in the prevalence of LUTS between the first and seventh days of the postpartum period. Most symptoms showed a decrease on the seventh day, except for six symptoms: insensible urinary incontinence, hesitancy, urinary retention, feeling of incomplete emptying, bladder pain, and dysuria, which increased.

Conclusion: In conclusion, our study suggests that the duration of the postpartum period affects the prevalence of LUTS following C-section delivery. However, it's important to acknowledge the limitations of this study, which may impact the understanding of LUTS progression during the postpartum period.

Conclusion: In conclusion, we concluded that the duration of the postpartum period affects the LUTS after delivery with the method of C-section, but this study has many limitations which may affect the progressivity of LUTS in the Postpartum period.

Keywords: Caesarean Section, ICIQ FLUTS Long From, Lower Urinary Tract Symptoms, Postpartum period.

Abstrak

Tujuan: Untuk membandingkan prevalensi Gejala Saluran Kemih Bawah di hari pertama dan hari ketujuh postpartum pada pasien Sectio Caesarea.

Metode: Desain penelitian berupa studi potong li.ntang dengan pengumpulan data menggunakan kuesioner terstruktur ICIQ FLUTS-LF dan kuesioner skrining dasar penelitian yang dilakukan 2 kali yaitu 12 jam setelah pelepasan kateter dan postpartum hari ke 7. Subjek penelitian ini adalah semua ibu postpartum dengan metode SC yang memenuhi kriteria inklusi dan eksklusi penelitian di RS Santo Antonius Pontianak, Kalimantan Barat. Jumlah sampel pada penelitian ini adalah 95 responden

Hasil: Pada penelitian ini didapatkan subjek sebesar 111 responden yang mayoritasnya berusia kurang dari sama dengan 35 tahun, multipara, status gizinya obesitas, tidak memiliki riwayat keluarga yang mengalami LUTS, tidak mengkonsumsi obat-obatan tradisional dan obat-obatan diuretik. Terdapat perbedaan signifikan di prevalensi LUTS hari 1 dan 7 postpartum SC dengan mayoritas dari 16 gejala LUTS yang didata mengalami penurunan di hari ketujuh dibanding hari pertama, terkecuali 6 gejala LUTS yang mengalami peningkatan di hari ketujuh yaitu Insensible Urinary Incontinence, Hesitansi, retensio urin, perasaan tidak lampias setelah berkemih, nyeri kandung kemih, serta disuria.

Kesimpulan: Dalam penelitian ini, peneliti menyimpulkan bahwa durasi masa postpartum berpengaruh pada keluhan LUTS yang dialami pasca persalinan secara Sectio Caesarea, akan tetapi, penelitian ini memiliki keterbatasan yang dimana terdapat banyak oleh faktor-faktor risiko tertentu yang dapat berpengaruh terhadap progresivitas LUTS

Kata kunci: Sectio Caesarea, ICIQ FLUTS Long Form, Gejala Saluran Kemih Bawah, Masa Pasca Persalinan, Masa nifas, Postpartum.

INTRODUCTION

The postpartum period represents the body's functional recovery to its pre-pregnancy state and typically extends for 6-8 weeks following delivery. During pregnancy, various changes occur in the mother's body, encompassing alterations in anatomy, physiology, and hormonal levels, including changes in the urinary tract[1,2]. Lower Urinary Tract Symptoms (LUTS) do not constitute a diagnosis but rather reflect a subjective sensation that may indicate alterations or disorders in lower urinary tract function. LUTS can be categorized based on urinary phases, including storage symptoms, voiding symptoms, and post-micturition symptoms[3].

Previous studies have examined the relationship between the prevalence of Lower Urinary Tract Symptoms (LUTS) during pregnancy and the six weeks following childbirth, revealing a decrease in LUTS prevalence during the six-week postpartum period compared to the prevalence during pregnancy [4].

A study was conducted with primipara subjects to investigate the relationship between labor methods and the incidence of Lower Urinary Tract Symptoms (LUTS). This investigation involved the observation of participants for 45 days during the final trimester of pregnancy and continued for ten days postpartum. The study revealed a decrease in symptoms such as frequency, urgency, nocturia, and urge urinary incontinence during the postpartum period. However, it also noted an increase in cases of LUTS attributed to urinary loss among subjects who underwent vaginal delivery, which may be associated with persistent stress [5].

Research on the impact of the C-section delivery method on the function of the lower urinary tract in the postpartum period is still rare in Indonesia. In C-section deliveries, various factors, including the anesthesia method employed and the use of catheters during surgery, can contribute to the development of Lower Urinary Tract Symptoms (LUTS). This research aims to provide an overview of LUTS and assess the impact of the C-section delivery method on LUTS during the postpartum period. It does so by comparing the prevalence of LUTS on the first and seventh days postpartum.

METHODS

This research is an analytical descriptive study with a cross-sectional study approach. Research data collection was conducted from January - March 2022. The target population of this study is all postpartum patients with the C-Section delivery method at the Saint Antonius Hospital in Pontianak. The sample size in this study was 111 respondents, whereas sampling was carried out with the simple random sampling method.

This study aims to compare Lower Urinary Tract Symptoms (LUTS) on the first and seventh days postpartum in cases involving the Caesarean Section delivery method. The variables under investigation in this study are independent variables, specifically the prevalence of LUTS on the first day and LUTS on the seventh day postpartum. Data collection commenced with an explanation of the research to the subjects, followed by the completion of informed consent forms. Additionally, sociodemographic data about the subjects and LUTS were collected 12 hours after the removal of the catheter. The data was obtained through the administration of the ICIQ-Female Lower Urinary Tract Symptoms Long Form (ICIQ-Fluts LF) questionnaire, either via Google Forms or through interviews for those unable to complete the Google Form. Subsequently, a similar data collection process was repeated on the seventh day postpartum during the follow-up visit. The collected data was then subjected to descriptive analysis, and the prevalence of LUTS on the first and seventh day postpartum was compared using the Wilcoxon non-parametric test.

RESULTS

Table 1 shows the sociodemographic description of the research subject. Patients included in the aging ≤ 35 years were 93 people (83.8%), and as many as 18 were in the age category of > 35 years. Forty-eight people (43.2%) were included in the primipara category and 63 people (56.8%) were categorized as multipara. Subjects with normal BMI (Body Mass Index) were 53 people (47.7%), while people with BMI that were categorized as overweight were 58 people (52.3%). One hundred eight subjects (97,3%) do not have a family history of previous LUTS, and a small portion of subjects (2,7%) had a family history of LUTS. One hundred six respondents (95.5%) did not consume herbal or traditional medicines and 5 respondents (4.5%) had consumed herbal or traditional medicines. The subjects who did not consume diuretic drugs were 110 respondents (99.1%), while the subjects

who took diuretic drugs were 1 person (0.9%).

Table 1. Sociodemographic Characteristic of Subject

Sociodemographic characteristic of subject	n	%
Age (y o)		
≤ 35	93	83.8
> 35	18	16.2
Parity		
Primipara	48	43.2
Multipara	63	56.8
Body Mass Index		
Normal	53	47.7
Overweight	58	52.3
Family History of LUTS		
Yes	3	2.7
No	108	9.73
History of consuming traditional or herbal medicine		
Yes	5	4.5
No	106	95.5
History of consuming diuretic medicine		
Yes	1	0.9
No	110	99.1

LUTS observed in this study amounted to 16 symptoms grouped based on the phases of urination, including the storage symptoms, voiding symptoms, post-micturition symptoms, and other symptoms. LUTS assessment of the respondents used the ICIQ-Fluts LF questionnaire. The respondents who answered 0 on the questionnaire question were categorized as non-LUTS patients and respondents who answered on a scale of 1 or higher were considered positive LUTS patients. Table 2 compares the prevalence of LUTS on the first and seventh day of the postpartum in the C-section delivery method. Ten symptoms of LUTS decreased on the seventh day of postpartum. However, six symptoms, including Insensible Urinary Incontinence, Hesitancy, Urinary Retention, Feeling of incomplete emptying, bladder pain, and dysuria increased on the seventh day of postpartum.

Table 2. LUTS Prevalence on the First and Seventh Day of Postpartum

LUTS	First day	%	Seventh day	%
Storage symptoms				
Frequency	55	49.1	43	38.4
Nocturia	77	68.8	57	50.9
Urgency	30	26.8	21	18.8
Urge UI	9	8.0	4	3.6
Stress UI	9	8.0	6	5.4
Insesible UI	3	2.7	4	3.6
Voiding symptoms				
Hesitancy	13	11.6	36	32.1
Straining	14	12.5	6	5.4
Intermitten stream	9	8.0	4	3.6
Noctural enuresis	11	9.8	1	0.9
Slow stream	8	7.1	2	1.8
Urinary retention	2	1.8	14	12.5
Ability to stop urine flow	33	29.5	12	10.7
Post-micturition sympstoms				
Feeling of incomplete emptying	22	19.6	56	50.0
Other symptoms				
Bladder pain	31	27.7	73	65.2
Dysuria	11	9.8	44	39.3

Table 3 shows the significance of the difference in the prevalence of LUTS in the postpartum period. Based on the Wilcoxon test analysis, all symptoms have a p-value value lower than 0.05, which indicates the significant difference in the prevalence of LUTS on the first and seventh day of the postpartum period in C-section delivery method patients.

Table 3. Comparison of LUTS on the First and the Seventh Day of Postpartum

LUTS	First day	%	Seventh day	%	P-value*
Storage symptoms					
Frequency	55	49.1	43	38.4	0.024
Nocturia	77	68.8	57	50.9	0.044
Urgency	30	26.8	21	18.8	0.000
Urge UI	9	8.0	4	3.6	0.000
Stress UI	9	8.0	6	5.4	0.000
Insesible UI	3	2.7	4	3.6	0.000
Voiding symptoms					
Hesitancy	13	11.6	36	32.1	0.000
Straining	14	12.5	6	5.4	0.000
Intermitten stream	9	8.0	4	3.6	0.000
Noctural enuresis	11	9.8	1	0.9	0.000
Slow stream	8	7.1	2	1.8	0.000
Urinary retention	2	1.8	14	12.5	0.000
Ability to stop urine flow	33	29.5	12	10.7	0.000
Post-micturition sympstoms					
Feeling of incomplete emptying	22	19.6	56	50.0	0.000
Other symptoms					
Bladder pain	31	27.7	73	65.2	0.040
Dysuria	11	9.8	44	39.3	0.000

* Wilcoxon test

DISCUSSION

This study records the demographic characteristics of subjects considered to be at risk for Lower Urinary Tract Symptoms (LUTS). These risk factors include age, parity, nutritional status, family history of LUTS, and a history of consuming traditional and diuretic medicines. In this study, the majority of respondents were categorized as follows: age group ≤ 35 years (83.8%), multipara (56.8%), overweight (52.3%), had no family history of LUTS (97.3%), had no history of consuming traditional medicines (95.5%), and had not used diuretics (99.1%). Age over 35 years during pregnancy is considered a risk factor, as the risk of postpartum LUTS tends to increase with age[6]. This finding aligns with another study that demonstrates a connection between age and an increased risk of both microscopic and macroscopic trauma [7].

The majority of subjects in this study fall into the multipara category. Previous studies have highlighted the number of parity as an independent risk factor for the occurrence of Lower Urinary Tract Symptoms (LUTS) in postpartum subjects, irrespective of the delivery method used, be it vaginal or C-section[8]. In a separate study, it was observed that primipara subjects, particularly those who underwent vaginal delivery, experienced more voiding symptoms compared to multipara subjects.

This finding is attributed to the assumption that greater pelvic distension occurs in primipara subjects relative to multipara subjects, potentially leading to damage to the N. pudendum and subsequent complaints of LUTS.For subjects who underwent C-section delivery, multipara individuals were found to be at a higher risk of developing LUTS. This increased risk is associated with the accumulation of anatomic stress from the final trimester of pregnancy and previous deliveries [9].

Most of the subjects of this study are classified as overweight. Obesity is considered to act as the risk of postpartum LUTS in both vaginal delivery and SC. However, the latest studies found that BMI does not significantly relate to the incidence of LUTS in the postpartum period. In addition, another similar study found that the relationship between obesity and the incidence of LUTS in the postpartum period of the patients who undergoes C-section delivery method is not significantly related, even when risk factors such as age, nulliparity, perineal trauma, and the weight of the baby are controlled to minimize bias [4,6].

The data collection for this research was conducted on two occasions: first, 12 hours after the removal of the catheter on the first day postpartum, and second, during a follow-up visit on the seventh day postpartum. The choice of these time points was based on the assumption

that during the postpartum observation period in hospitals, discomfort such as Lower Urinary Tract Symptoms (LUTS) can be effectively monitored and managed. In contrast, on the seventh day, when patients are often at home and not under the continuous care of healthcare workers as in the hospital, it allows us to observe changes in LUTS prevalence.

This study identified differences in LUTS prevalence data between the two time points. Specifically, ten LUTS complaints decreased on the seventh day compared to the first day postpartum, while six complaints of LUTS increased. The increased complaints included bladder pain, insensible urinary incontinence (UI), hesitancy, urinary retention, dysuria, and the feeling of incomplete emptying.

A study involving 489 postpartum subjects that underwent the C-section method in China showed that LUTS was one of the most common complaints in the postpartum period. This study also showed symptoms that occurred are related to the C-section method of delivery (P <0.001), surgery time of more than 60 minutes (p = 0.006), or the use of postoperative analgesia (p = 0.001). LUTS recorded in the research may be caused by the hypotonic state of the vesica due to the decrease in intravesical pressure or decreased sensitivity of the distal part of the vesica [6].

Other studies also show C-section delivery method becomes one of the independent risk factors for the occurrence of LUTS in postpartum (ODD Ratio (OR) = 2.21; 95%CI = 1.10 - 4.41). Symptoms that were assessed and explained in these studies are frequency, urgency, nocturia, dysuria, urinary incontinence, voiding disorder, and straining. However, these study considers those symptoms to be physiological, and in most cases, improvements are reported as the postpartum period went by [4].

Another study provides a different perspective on the relationship between labor methods and the experience of Lower Urinary Tract Symptoms (LUTS). This study underscores the various types of damage that can occur in the urinary tract as a result of labor. The study found that both vaginal and C-section delivery methods carry a risk of complaints related to the urinary tract. Vaginal delivery is associated with long-term side effects on the urinary tract, whereas the C-section method of delivery is linked to fewer side effects. This difference may arise because urinary tract injuries during C-section procedures can be readily identified and addressed during the surgery [10].

Table 3 shows that the prevalence of LUTS on the first and seventh day was significantly different. Most complaints decreased on the seventh day. This result is in line with previous research which shows that LUTS is one of the changes in the pregnancy period and is caused by the pressure of the urinary tract organs as the uterus enlarges. The majority of subjects with symptoms of LUTS in the study reported improvements in the postpartum period [11].

Although the majority of symptoms decreased on the seventh day, several cases increased on the seventh day. These cases can be influenced by several factors such as patient subjectivity, comorbidity factors, history of surgery, and anatomical disorder of the urinary tract experienced by the subject [4,11–14] The history of previous vaginal delivery methods, young maternal age, and a history of gestational diabetes can also influence the progressivity of LUTS [13]. Therefore, it is essential to control these risk factors to rule out the possibility of research bias.

A specific study explains that the symptoms of LUTS experienced during the postpartum period start during pregnancy, especially from the final trimester. These complaints will then continue during the postpartum period with varying duration [14]. Previous studies also found similar findings where urinary vesica capacity increased during the gestational age of 12 weeks and progressed through 6-8 weeks postpartum. This capacity increase in vesica may cause complaints of urinary retention several days postpartum [7].

While the C-section delivery method is identified as an independent risk factor contributing to Lower Urinary Tract Symptoms (LUTS) in the postpartum period, it is also considered a protective factor against the persistence of LUTS during this period. The C-section delivery method results in minimal stress on the urinary tract in comparison to the vaginal method. In contrast, the vaginal delivery method, where babies pass through the birth canal, can stretch the pelvic floor muscles, thereby increasing the risk of LUTS due to injuries caused by this strain [6,7,9,11]. However, it is important to consider indications for C-section surgery, such as prolonged labor, macrosomia, and cephalopelvic disproportion, as they may affect the emergence of LUTS in the postpartum period. Therefore, it is crucial to take these factors into account when assessing the improvement of LUTS in the postpartum period

in subjects who undergo labor with the C-section method.

RESEARCH LIMITATIONS

Researchers did not control risk factors that might affect the severity of LUTS, and this may cause bias in the process of research. The number of research samples may not have been able to represent the LUTS population as a whole and has not been able to get rid of the subjective factors that may appear in this study. In this study, the researchers does not investigate between the LUTS prevalence and existing risk factors.

CONCLUSION

Based on the results obtained from this study, there is a significant difference in LUTS numbers on the first and seventh day of the postpartum period in which the majority of LUTS complaints in the postpartum SC method had decreased on the seventh day, except for six complaints that increased on the seventh day. This study found that the duration of the postpartum period affects the LUTS complaints experienced by postpartum in C-section patients.

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Case Report

Resolution of Ethical Conflicts between Medical Indications and Patient Preferences in Case of Unmarried Woman with Ovarian Cancer

Penyelesaian Konflik Etika antara Indikasi Medik dan Preferensi Pasien pada Kasus Perempuan yang belum Menikah dengan Kanker Ovarium

Taufik Suryadi[1,2], Putri Irmayani[3], Kulsum Kulsum[4]

[1]*Department of Forensic Medicine and Medicolegal*
[2]*Ethics and Medicolegal Consultant*
[3]*Department of Obstetric and Gynecology*
[4]*Department of Anesthesiology and Intensive Care*
Faculty of Medicine Universitas Syiah Kuala
Banda Aceh

Abstract

Objectives: To resolve ethical conflicts in medical decision making in unmarried patients with a diagnosis of ovarian cancer. The ethical issue in this case is the main operative management in cases of ovarian cancer, namely removal of the uterus and both ovaries even though the patient is not married and has never been pregnant. The opportunity for patients to get pregnant no longer exists, so there is an ethical conflict between medical indications and patient preferences.

Methods: This case report is about an unmarried woman 38-year with a diagnosis of ovarian cancer. This patient initially underwent right salfingoooophorectomy surgery. Anatomical pathology results found adenocarcinoma serosum ovarii. The patient underwent chemotherapy for 3 cycles. Then the patient was re-operated with a planned debulking interval laparotomy.

Discussion: From the aspect of patient indications, the results of combination treatment between surgery and chemotherapy have shown a marked increase in the survival rate of patients in five years. The choice of performing a debulking interval laparotomy is a difficult choice. The patient's preference to get pregnant will be difficult to accept, but it can be accommodated by improving the quality of life and paying attention to humanism, social and cultural aspects of its contextual features.

Conclusion: Clinical ethical considerations related to uterine removal in unmarried patients is a matter of debate. Clinical ethical theory namely quality of life, patient preferences, medical indications, and contextual features are beneficial in medical decision making.

Keywords: debulking intervals, ethical conflicts, medical indications, ovarian cancer, patient preferences.

Abstrak

Tujuan: *Untuk menyelesaikan konflik etik dalam pengambilan keputusan medik pada pasien yang belum menikah dengan diagnosis kanker ovarium. Isu etik pada kasus ini yaitu manajemen operatif utama pada kasus kanker ovarium yaitu pengangkatan uterus dan kedua ovarium padahal pasien belum menikah dan belum pernah hamil. Kesempatan untuk pasien untuk hamil tidak ada lagi sehingga terjadi pertentangan etik antara indikasi medik dengan preferensi pasien.*

Metode: *Laporan kasus ini tentang seorang pasien perempuan yang belum menikah, berusia 38 tahun dengan diagnose kanker ovarium. Pasien ini awalnya dilakukan operasi salfingoooforektomi kanan. Hasil patologi anatomi ditemukan adenokarsinoma serosum ovari. Pasien menjalani kemoterapi sebanyak 3 siklus. Kemudian pasien dilakukan operasi kembali yang direncanakan tindakan laparotomi interval debulking.*

Diskusi: *Dari aspek indikasi pasien, hasil pengobatan kombinasi antara pembedahan dan kemoterapi telah menunjukkan peningkatan survival rate yang nyata pada pasien dalam lima tahun. Pilihan melakukan tindakan laparotomi interval debulking merupakan pilihan sulit. Preferensi pasien untuk dapat hamil akan sulit dikabulkan, namun dapat diakomodir dengan peningkatan kualitas hidup dan memperhatikan aspek humanism, sosial dan kultural pada fitur kontekstualnya.*

Kesimpulan: *Pertimbangan etik klinik yang berhubungan dengan pengangkatan rahim pada pasien yang belum menikah merupakan masalah yang diperdebatkan. Teori etika klinis yaitu indikasi medis, preferensi, kualitas hidup dan fitur kontektual sangat membantu dalam pengambilan keputusan medis yang etis.*

Kata kunci: *indikasi medis, interval debulking, kanker ovarium, konflik etik, preferensi pasien.*

INTRODUCTION

The medical profession involves clinical skills and decision-making in services aimed at protecting and restoring human well-being. A doctor must make clinical judgments gained through practice, experience, knowledge, and ongoing critical analysis. Two-way communication is very important in the doctor-patient relationship.[1]

Important aspects of doctor-patient communication include developing doctor-patient interpersonal relationships, doctors listening to all patient problems holistically, doctors providing as much information as possible to patients, and making treatment management plans for patients. Good and effective doctor-patient communication increases patient confidence in doctors. It will indirectly affect the level of patient satisfaction and treatment outcomes, such as symptom improvement and adherence to medical treatment. Therefore, from a clinical standpoint, good and directed communication is the main capital of the doctor-patient relationship and can increase trust and service to patients effectively.[1,2]

In making clinical decisions, doctors are often faced with dilemma cases between the patient's medical problems and ethical decisions regarding the patient's condition. Therefore we need four main ethical principles, namely beneficence, nonmaleficence, autonomy, and justice in making medical decisions. In patient care situations, there is often a conflict between the ethical principles themselves, especially between the principles of beneficence and autonomy. Each of the four ethical principles must be considered a prima facie obligation that must be fulfilled.[3]

One of the dilemmas faced by doctors is decision making in cases of ovarian cancer in unmarried women. Ovarian cancer can occur at any age. Ovarian cancer is one of the leading causes of death in the United States. In 2015 there were an estimated 21,290 cases of ovarian cancer and 14,180 of them ended in death. The average survival rate of ovarian cancer patients is only around 30%, despite chemotherapy and surgery. This is because ovarian cancer itself is a "silent killer", resulting in a delay in diagnosis. Ovarian cancer has non-specific symptoms such as discomfort in the stomach, nausea, vomiting, urinary disorders, so it is often mistaken and is considered a dyspepsia problem.[4]

The National Cancer Institute reports that young patients have a mortality rate of 1.0 per 100,000. For patients over 50 years old, the mortality rate is 25.5 per 100,000.[5] Ovarian cancer can occur at any age. Ovarian cancer occurs 6%-11% in premenopausal age and 29%-35% in malignant postmenopausal age. Ovarian cancer remains the third most common gynecologic malignancy with the highest mortality rate in developed countries. Only 20% of ovarian cancers are diagnosed at an early stage if the disease is confined to the ovaries.[6,7]

In general, patients come with advanced stage conditions so that the mortality rate is higher (75%), where there has been metastasis to other organs such as the peritoneal cavity and even to more distant organs. Ovarian cancer metastases can be through direct spread from the ovaries or through the fallopian tubes to surrounding organs such as the large intestine or bladder, metastases can also occur when cancer cells are separated from the primary tumor. Tumor cells exfoliate in the peritoneal cavity and adhere to the peritoneal fluid, causing expansion in the abdominal cavity. Metastasis of this type is often suspected as ascites, especially in advanced ovarian cancer.[6,7]

In this case, the doctor is faced with a dilemma between carrying out actions according to medical indications based on the patient's diagnosis, namely ovarian cancer and the patient's preference for not having surgery because she is not yet married. The patient's hope to get pregnant in the future is very high, but it seems difficult to be granted so that the doctor must provide the best solution to overcome this dilemma. Consideration of clinical ethics by balancing quality of life, medical indications, contextual features and patient preferences can help resolve this dilemma.

In this case, a dilemmatic conflict will be discussed, namely an unmarried woman and diagnosed with ovarian cancer. The ethical issue in this case is the main operative management in cases of ovarian cancer, namely removal of the uterus and both ovaries with the patient's desire to remain pregnant.

CASE

This case report is about a female patient, unmarried. 38 years old who initially came with complaints of an enlarged stomach that had been experienced since 3 months before being admitted to the hospital. The patient claimed to

have regular menstrual cycles and denied pain during menstruation. There were no complaints of bleeding from the birth canal, there were no complaints of prolonged menstruation, complaint of smelly vaginal discharge were denied. From the physical examination, the general condition was good, compos mentis consciousness, blood pressure 120/70 mmHg, pulse 76 times per minute, body temperature 36.5 0C, breathing 18 times per minute, from general status examination, there was no anemia in the eyes or conjunctiva or sclera icteric, the abdomen does not appear enlarged, there is scar tissue from surgery, with no shifting dullness, no undulation, no tenderness. From the gynecological status, inspection found the vulva urethra is calm. Vaginal toucher examination cannot be done because the patient is not married. Rectal toucher examination found smooth rectal mucosa, tight anal sphincter tone, no bleeding, no palpable intraluminal mass. From the laboratory examination, it was found that hemoglobin 10,3 g/dl, hematokrit 32 %, leukosit 12000/mm3, trombosit 284000/mm3, blood sugar 92 mg/dL, Natrium 146 mEq/L, Kalium 3,9 mEq/L, Cl 106 mEq/L. Ca125: 44.9, SGOT/SGPT: 133/370, Albumin: 4.8. From these laboratory results, it can be concluded that there is an increase in the tumor marker ca 125 in patients.

An ultrasound examination was performed. From the results of ultrasound, it was found that the uterus was anteflexed with a size of 7x7x5 cm. The positive endometrial line is 11.7 mm thick. The left ovary is within normal limits, there is no mass picture. The right ovary is difficult to assess the post-laparotomy effect of right salpingoophorectomy. The patient has had a dextra salfingoooophorectomy surgery on January 1, 2021 previously with the result of anatomical pathology, namely adenocarcinoma serosum ovarii. Then the patient underwent chemotherapy for 3 cycles. Then the patient underwent surgery again. The patient was planned for a debulking interval laparotomy. There was an ethical conflict in the case of an unmarried female patient who was diagnosed with ovarian cancer. The ethical issue in this case is the main operative management in cases of ovarian cancer, namely removal of the uterus and both ovaries even though the patient is not married and has never been pregnant. The opportunity for patients to become pregnant no longer exists, resulting in an ethical conflict between medical indications and patient preferences.

DISCUSSION

In this case there is an ethical conflict, namely the patient is an unmarried woman and was diagnosed with ovarian cancer. The patient had had surgery to remove one ovary and the results of anatomical pathology examination were malignant. Then the patient underwent 3 cycles of chemotherapy and a second surgery was planned, namely interval debulking of the tumor, where the procedure included removal of the contralateral uterus and ovaries and resection of all visible tumor masses. In an effort to overcome this problem, an ethical dilemma solution is used based on the clinical ethics theory proposed by Jonsen and Siegler with systematic consideration of medical indications (including advantages and disadvantages of treatment), patient preferences (including autonomy or protection and patient capacity to choose), patient's quality of life (patient sees the expected outcome, prospective interventions from his life situation, and the impact of his future quality of life), contextual features (equity issues).[8] Clinical ethical decision making can be seen in Figure 1.

Medical Indication

Medical indications in patients can be done using the principles of beneficence and non-maleficence. The principle of beneficence means that therapy must provide the maximum benefit to the patient both medically and ethically, while non-maleficence means that it does not cause harm to the patient. Determination of medical indications is done by looking at the diagnosis and medical problems of the patient's disease, including answering questions such as: What about the patient's medical history? What is the diagnosis and prognosis of the patient's disease? What are the benefits of the treatment? What is the probability of success and failure of the therapy process? Are there other plans if this therapy doesn't work?[8]

The main management for early-stage epithelial ovarian cancer is surgical staging. Surgical staging measures in early-stage ovarian cancer include peritoneal washings, total abdominal hysterectomy, and salpingo-oophorectomy, inspection of all abdominal organs and peritoneal surfaces, biopsy of suspicious areas, namely the posterior cul-de-sac, paravesica, both pelvic walls and paracolic, omentectomy, bilateral paraaortic and pelvic

lymphadenectomy and appendectomy in cases of mucinous lesions. Meanwhile, for advanced ovarian cancer, cytoreductive surgery or tumor debulking is performed, namely resection of the entire tumor mass, both primary and metastatic.

Cytoreduction surgery for ovarian cancer usually includes total abdominal hysterectomy (TAH) or supracervical hysterectomy (SCH), bilateral salpingo-oophorectomy (SOB), omentectomy, and resection of any metastatic lesion.[9,10]
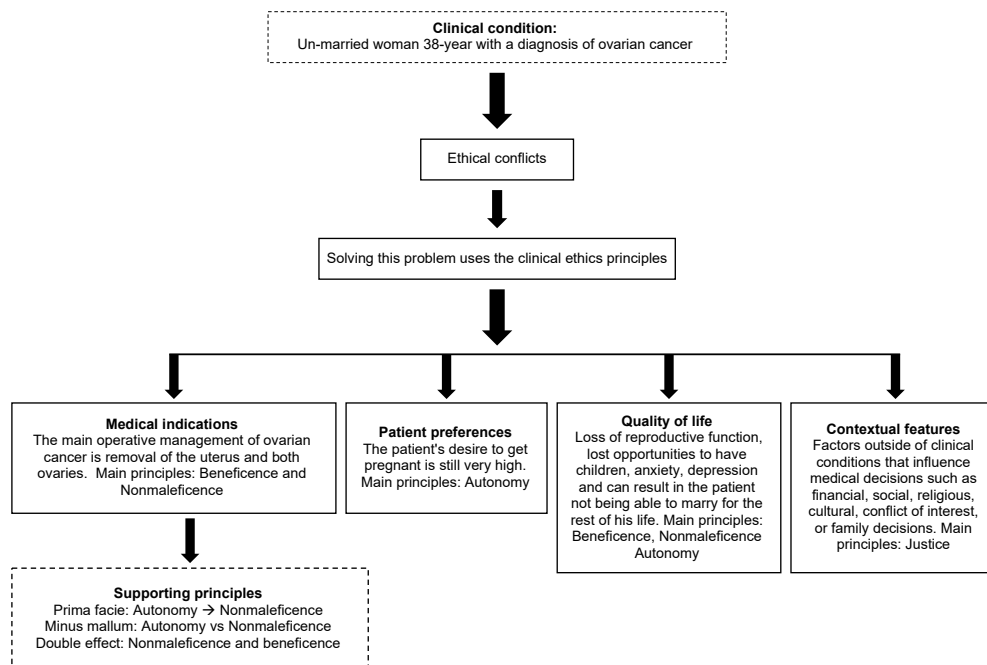

Figure 1. Schematic for solving ethical conflicts

It has been shown that patients with ovarian cancer can have atypical symptoms. The general public's knowledge of ovarian cancer is still low. In addition, the symptoms of ovarian cancer are often mistaken for symptoms of gastrointestinal disease. The survival of women with ovarian cancer is largely determined by stage women with stage I or II cancer have a five-year survival rate of 50%-90%. Meanwhile, the survival of women with advanced disease decreased to about 30%.[7,10,11]

The classification of ovarian cancer according to the International Federation of Gynecology and Obstetrics (FIGO) is described in table 1:[9,10]

Table 1. Ovarian Cancer Classification

Stadium	Disease conditions
	Stage I is limited to the ovaries or fallopian tubes
1A	The tumor is only in one ovary or fallopian tube, the tumor capsule is intact or not ruptured, there is no tumor growth on its surface, ascitic fluid or fluid flushing in the lining of the abdomen (peritoneum) no tumor cells
1B	Tumor confined to two ovaries or fallopian tubes, no tumor growth on their surface, no tumor cells in ascites or washings of the ovarian cavity
1C	Tumor confined to one or two ovaries with one of the following factors: IC1 tumor capsule ruptured due to surgery, IC2 tumor capsule ruptured before surgery or tumor growth on the surface of the ovary or fallopian tube, IC3 there are tumor cells in the ascitic fluid or in the peritoneal fluid rinses Stage II tumor in one or both ovaries or fallopian tubes with extension in the pelvic cavity
IIA	The tumor extends to the uterus and/or into the tubes
IIB	Tumor extends to other intraperitoneal pelvic organs Stage III tumor is present in one or both ovaries or fallopian tubes with extension of the tumor in the peritoneal cavity beyond the pelvis and/or regional lymph node metastases
IIIA	Stage IIIA1, retroperitoneal spread, IIIA1(i) metastases 10 mm, IIIA (ii) metastases > 10 mm, IIIA2 microscopic spread outside the pelvis
IIIB	Macroscopic spread outside the pelvis, the size of the injury spread 2 cm
IIIC	Macroscopic spread outside the pelvis, injury spread >2 cm and spread to lymph nodes. Stage IV spread beyond the peritoneal cavity
IV A	Pleural effusion with positive cytology, stage IVB: parenchymal metastases and metastases to extrabdominal organs.

Ovarian cancer patients have the lowest survival rate of all other cancers, which is 30-50% in the last five years. In comparison, breast cancer patients have a survival rate of more than 80 percent. In a retrospective survey it was found that 77% of ovarian cancer patients experienced abdominal symptoms, namely bloating, pain; 70% gastrointestinal symptoms, namely indigestion, constipation, and nausea; 58% of symptoms involving pain were abdominal pain, coitus pain, and back pain; 50% psychological symptoms namely fatigue, anorexia, and weight loss; 34% of urinary disorders, namely increased frequency of urination and difficulty holding urination (incontinence); and 26% of symptoms related to abnormal bleeding outside the menstrual cycle and a palpable mass in the abdomen.[7,12]

Debulking interval laparotomy or cytoreductive interval is the surgical option in advanced cancer. In principle, this operation is performed after chemotherapy. This procedure can be applied to the following situations; patients who underwent an initial exploratory laparotomy but were unable to remove the entire mass of the primary tumor due to adhesions, and patients who were deemed unsuitable for primary cytoreductive surgery due to unfavorable general conditions, such as disease comorbid or extensive disease metastases.10

The results of combination treatment between surgery and chemotherapy have shown a marked increase in the survival rate in patients over a period of five years, but death can still occur due to factors of metastatic lesions, non-adherence in chemotherapy discipline, and chemotherapy drug resistance. The use of chemotherapy is also limited because the dose-related toxicity of chemotherapy drugs can interfere with the patient's quality of life.[7,13]

Ethical aspects in clinical situations often lead to ethical dilemmas in the form of dilemmas between medical indications versus patient preferences, medical indications versus quality of life and medical indications versus contextual descriptions.8 In this case, there is an ethical conflict between medical indications vs patient preferences, namely:

Table 2. Ethical Conflicts between Medical Indications versus Patient Preferences

Medical indications	Patient preferences
Patients diagnosed with ovarian cancer. The treatment to be taken on the patient is the tumor debulking interval. The goal of treatment for patients is to reduce complaints caused by primary tumors or metastases. This treatment is expected to increase the survival rate of this patient. Patients are still required for regular clinical evaluation, laboratory and ultrasound examinations.	The patient is not married and wants to get pregnant someday. The patient is 38 years old and able to decide his own life matters. The patient has the right to make the best choice for her own body. The patient has been given an explanation of his illness, treatment options and side effects regarding the action taken. The patient has understood and is willing to sign the informed consent form. Patients can cooperate well for postoperative evaluation and follow-up chemotherapy.

Patient Preference

Preference is based on several options, namely whether the patient is mentally prepared and competent enough to receive a legal operation? Has the patient been informed about the benefits and dangers, does he or she understood it, and has he or she given informed consent? Are there any conditions that make the patient more likely to be disabled? Does the patient indicate something he or she prefers? Is the patient reluctant or unable to participate with the prescribed therapy? If so, ask the patient to explain why. Furthermore, does the patient's right to choose depend on the patient's religion and ethnicity?[8]

This approach to ovarian cancer can restore life expectancy in patients with this disease.[12] The Hopkins study found that in premenopausal women with a diagnosis of ovarian cancer, removal of both ovaries (oophorectomy) induces a sudden decrease in estrogen and androgens and general symptoms, and others such as hot flushes. Menopause can then cause vaginal wall atrophy, vaginal dryness, and increased local sensitivity to pain. These factors contribute to dyspareunia or pain during coitus. The fear that accompanies pain can also reduce sexual response. Decreased androgens can be associated with reduced sexual arousal. Chemotherapy can also cause side effects including fatigue, alopecia, and neuropathy, all of which can also negatively impact body image

and sexuality. Hopkins also stated that there are five factors that quite influence sexual function in ovarian cancer survivors, namely: disinterest in sex, physical disorders, not having a partner, fatigue, and partners who are not interested in having sex. The patient's desire to get pregnant is still very high. However, it is difficult for doctors to accept this considering the severity of the patient's clinical condition. National Ovarian Cancer Coalition , issues related to the quality of life of ovarian cancer patients include: [14,15]

Treatment-related side effects consisting of: Surgery-related side effects i.e. loss of fertility, menopause due to surgery, sexual worries, intestinal obstruction, and ostomy care. Side effects related to chemotherapy are side effects on the digestive system such as nausea, vomiting, loss of appetite, constipation, and diarrhea; peripheral neuropathy in the form of tingling and numbness; side effects on the brain i.e. being forgetful; hair loss; disorders of blood cell formation in the form of anemia and thrombocytopenia; and easily feel tired. Depression, anxiety, and distress. In some women with ovarian cancer, strategies for managing depression, anxiety, and distress are exercise, relaxation, going out and doing fun things.Financial problem can be a source of stress for women with ovarian cancer.[14,15]

The basic moral principles serve as an analytical framework which can then serve as guidelines for professional ethics, namely; [3,16-19] Respect for patient decisions (Autonomy). Adult patients have the choice to accept or refuse surgery. Even if the choice is not the best, the decision must be respected. The patient has the right to choose what can be done to his/her body. Norms of avoiding harm/harmness (Non-Maleficence). A doctor must also be aware of the dual effects of therapy, where a very good treatment can inadvertently cause harm to the patient's body. This means that any medical procedure can have consequences. The basic principle of medical ethics is to avoid things that can cause harm to patients and every health worker must be fully aware of this norm. The norm of giving the most benefits and causing the least harm (Beneficence). Each scenario should be evaluated based on the individuality of the patient. This condition implies that what is beneficial to one patient may not be beneficial to another. All health workers must understand that improving the patient's health is by doing the best in the situation according to the wishes of each patient. The norm of justice for the right of every individual to their fair and equitable health care and the risks involved (Justice). Moral principles that emphasize fairness and justice in behavior, do not discriminate against a patient based on ethnicity, race, culture, religion, level of wealth and occupation.

Quality of Life

Quality of life describes the patient's quality of life after treatment. How is the patient's condition now or in the future?, is the patient's next life still the same when compared to before treatment? What is the patient's chance of returning to quality of life, with or without therapy? Can the patient experience medical, emotional, or social problems as a result of the treatment? Are there biases that could cast doubt on the health care provider's assessment of a patient's quality of life? Is there a logical reason to continue treatment? Are there strategies for comfort and palliative care?[8]

Removal of the uterus in an unmarried patient has a major life impact. A woman will lose reproductive function, the opportunity to have children, anxiety, depressed and can result in the patient not being able to marry for the rest of her life. In this case, psychological and mental support is needed for the patient from friends, family and people closest to the patient. The theoretical model in ovarian cancer patients describes four domains of quality of life (QOL) including physical and symptom well-being, social, mental, and spiritual well-being. Physical nicely-being and signs and symptoms include bodily electricity/fatigue, sleep and relaxation, basic physical fitness, menstrual changes, pain/neuropathy, urge for food, and nausea/constipation. Social nicely-being includes a circle of relatives (family) pressures, roles and relationships, sexuality/fertility, isolation, budget, painting, social aid, and fear of future generative diagnosis. Mental nicely-being consists of management, anxiety, despair, happiness, worry of recurrence or metastasis, cognition/attention, difficulties with analysis or treatment, coping, appearance/self-concept, and value. In the end, the area of spiritual properly-being consists of wisdom from illness, religiosity, spiritual lifestyles, hope, uncertainty, and existence's motive/task.[20]

Several studies have stated that there is a relationship between decreased quality of life and ovarian cancer. The subgroup of women with ovarian cancer diagnosed as having a better threat of experiencing distress related to the

mental measurement. The researchers adviced for routine mental screening and monitoring, identify, and intervene in women who are at high risk for psychological distress due to cancer. Other studies have shown that women with ovarian cancer are at risk for mental problems due to their diagnosis. It is recommended to conduct early screening to overcome mental problems.[20]

In this condition, ethical considerations can be made with a prima facie approach by prioritizing the interests of the patient, namely surgical removal of the uterus and both ovaries so that the cancer does not spread to other body parts that can endanger the patient. In this case the doctor won the principle of nonmaleficence (preventing harm to the patient) over the patient's autonomy, even though in the end the patient had no chance of getting pregnant, or it could be the minus mallum approach by choosing the least bad thing, i.e. there is still life expectancy if an operation is performed with a better survival rate, it has a minimal risk compared to the patient dying without any medical procedure. Removal of the uterus in an unmarried patient is a bad way because it will injure the patient, the procedure certainly makes wounds on the patient's body, but the goal is good, namely the health and safety of the patient, this condition is called the double effect principle. The patient's family already understands this information and gives consent and accepts whatever will happen to the patient. [8,21]

Contextual Features

Medical decisions are not only decided by doctors and patients but also must consider other aspects such as socio-cultural, belief, religion, and finance. The related contextual features are: Are there any family problems that might influence the decision to choose treatment? Are there problems with the data sources (doctors and nurses) that might influence treatment selection decisions? Are there financial or other economic issues? Are there religious and cultural considerations? Are there limits to the patient's trust in the therapeutic management team? Is there a problem with resource allocation? How does the law affect treatment decisions? Is there clinical research or ongoing learning? Is there a conflict of interest in the health department in the decision making of an institution?[8] In this patient there was no conflict of interest in decision making. There are no family problems that affect treatment decision

making, there are no financial problems because the patient is covered by the Indonesia of Health Social Security Administration Agency *(Badan Penyelenggara Jaminan Sosial (BPJS) Kesehatan)* and there are no barriers to religious and cultural factors.

CONCLUSIONS

The patient underwent debulking interval laparotomy even though the patient was not married. This procedure is the main management of ovarian cancer. Clinical ethical considerations related to uterine removal in unmarried patients is a matter of debate. The principles of clinical ethics, namely contextual features, medical indications, quality of life and patient preferences are very helpful in making ethical clinical decisions. The patient has been given the best possible explanation of the procedure performed and agreed to it.

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Literature Review

Neurodevelopment and Fetal Growth in Fetuses with Congenital Heart Disease

Perkembangan Saraf dan Pertumbuhan Janin dengan Penyakit Jantung Bawaan

Adhi Pribadi

Division of Maternalfetal
Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Padjadjaran
Dr. Hasan Sadikin General Hospital
Bandung

Abstract

Objective: To determine mechanisms underlying fetal growth abnormalities, particularly intrauterine neurodevelopment, in congenital heart defects.

Method: Literature Review.

Results: Since intrauterine, smart mechanisms have ensured that blood flow to the central nervous system remains smooth to maintain Neurodevelopment. The mechanism fluctuates to keep oxygen flowing to the brain. Blood with the highest oxygen content should always be pumped to upper body and the head via the heart and the aorta. Aortic arch region contains three major blood vessels, a.Brachiocephalic, a.Carotid communis, and a.Subclavia that bleed the upper body and head, including the brain. So, blood flow from the left heart through the aortic arch is critical for fetal brain growth. If the heart cannot drain blood to the head, brain growth will be jeopardized because hypoxia will interfere with brain growth so will be influence to Neurodevelopment. Impaired blood flow can occur as early as intrauterine, particularly if the fetus has congenital heart disease. Blood flow in the Middle Cerebral Artery (MCA) can be used to measure blood flow in the fetus head. The pulsatility index value can be used to measure blood flow in the MCA, and another parameter is the cardioplacental ratio. There is a decrease in flow to the head in congenital heart disease, which results in a decrease in the Pulsatily index of the MCA and a decrease in the cardioplacental ratio.

Conclusions: Prolonged reduction in cardiac-derived blood flow leads to compromised neurodevelopment. Consequently, timely correction of postpartum heart defects becomes paramount to prevent protracted impairments in brain growth. Failing to address this promptly could also diminish the overall quality of life for children afflicted by congenital heart disease.

Keyword: cardioplacental ratio, cerebral media artery, congenital heart disease, fetal neurodevelopment.

Abstrak

Tujuan: Untuk menentukan mekanisme kelainan pertumbuhan janin terutama perkembangan saraf intrauterin pada cacat jantung bawaan.

Metode: Kajian Pustaka.

Hasil: Pada kehidupan intrauterin, mekanisme yang baik telah memastikan bahwa aliran darah ke sistem saraf pusat tetap lancar untuk mempertahankan perkembangan saraf. Mekanisme ini berfluktuasi untuk menjaga oksigen tetap mengalir ke otak. Darah dengan kandungan oksigen tertinggi harus selalu dipompa ke otak melalui jantung dan arteri utama ke kepala melalui a.Brachiocephalic, a.Carotid communis, dan a.Subclavia. Pada daerah arkus aorta terdapat tiga pembuluh darah utama yang memperdarahi tubuh bagian atas dan kepala, termasuk otak. Aliran darah ini dipompa melalui jantung kiri melalui arkus aorta. Bila jantung tidak dapat mengalirkan darah ke kepala, maka akan menyebabkan pertumbuhan otak terancam karena hipoksia akan mengganggu pertumbuhan otak, sehingga secara jangka panjang akan berpengaruh terhadap perkembangan saraf fetus. Gangguan aliran darah dapat terjadi sejak dini terutama jika janin memiliki penyakit jantung bawaan. Aliran darah di Arteri Serebri Media (MCA) dapat digunakan untuk mengukur aliran darah pada bagian kepala. Nilai indeks pulsatilitas dapat digunakan untuk mengukur aliran darah di MCA, dan parameter lain adalah rasio kardioplasental. Terdapat penurunan aliran ke kepala pada penyakit jantung bawaan, yang mengakibatkan penurunan indeks Pulsatily pada MCA serta terdapat penurunan rasio kardioplasental.

Kesimpulan: *Penurunan perkembangan saraf terjadi ketika aliran darah dari jantung berkurang secara kronis ke daerah kepala janin, sehingga bila terdapat kelainan jantung bawaan pasca persalinan harus diperbaiki segera agar penurunan pertumbuhan otak pada periode pascasalin tidak berlangsung terlalu lama. Bila hal ini terjadi akan menurunkan pula kualitas hidup anak dengan penyakit jantung bawaan.*

Kata kunci: *arteri serebri media, penyakit jantung bawaan, perkembangan saraf janin, rasio kardioplasenta.*

INTRODUCTION

The fetal brain is highly malleable and relies on environmental cues for proper development; therefore, an unsupportive environment can impede its progress.[1] Elevated intrauterine pressure has both short- and long-term impacts on fetal neurological development, with lasting consequences for mental health disorders throughout childhood and adulthood, as supported by existing empirical evidence.[2] The principal pathways implicated in programming brain development involve endocrine and inflammatory stress mediators.[3] These mediators respond to various intrauterine disorders and modify crucial signaling pathways essential for optimal brain development.[4]

In addition, the maintained blood flow to the head is very important. The flow towards the head in the intrauterine period is supplied mainly by the left heart, while the right heart predominantly pumps clean blood towards the rest of the body through ductus arteriosus. Failure of the left heart to pump blood towards the aortic arch results in a lack of blood supply and oxygen to the upper body and head. So if there is a heart defect in the fetus, especially those that affect the heart pump, it will have a bad effect on brain growth. Indirectly, if the fetal brain is not developed, it will affect fetal weight during intrauterine or the baby's weight during labor has a small for gestational age category (SGA).

There exist two potential mechanisms: Firstly, the brain development in infants with congenital heart defects (CHD) might diverge due to genetic or environmental influences. Secondly, both the heart and brain undergo simultaneous development within the human fetus, guided by a genetic pathway.[5] Disruptions in either of these pathways can lead to anomalous development of both organs, consequently giving rise to neurological developmental disorders.[6] Heart defects cause changes in blood flow, which affects the supply of oxygen and nutrients to the brain and, as a result, can interfere with normal brain development.[7]

The plasticity of the brain is very high, with the possibility of disruption in the event of hypoxia or when there is a relatively short period of hypoxemic state, which causes partial neuron loss and brain white matter damage.[8] Smooth brain injury, for example, can occur, and this can have a significant effect on certain system functions, so that postnatal abnormalities are highly dependent on which region experiences pathology.[9] Hypoxic brain injury may not affect survival rate and can survive until delivery, but brain development is not optimal and may even appear disturbed in subsequent developments.[10] This can be seen in autism syndrome, hyperactivity, lack of intelligence and other conditions.[11]

Mild and chronic placental insufficiency can result in long-term deficits in neuronal connectivity, affecting postnatal function, as seen in the auditory and visual systems.[12] Repeated acute inflammatory agent exposure causes diffuse white matter damage and, in some cases, periventricular necrosis.[13] As a result, the duration and severity of this prenatal disorder are long-term predictors of functional outcome.[14] Doppler examination of MCA can be used to detect the presence of disturbances in blood flow to the brain or systemic conditions that result in fetal hypoxia.[15]

The examination of the Middle Cerebral Artery involves assessment within the Willis circle (Figure 1A), followed by the identification of the MCA itself, and the placement of a sample volume at its proximal third (Figure 1B). A standard MCA Doppler spectral pattern displays minimal diastolic waves (Figure 1C), corresponding to a high Pulsatility Index (PI) value. Conversely, instances of chronic hypoxia, such as Fetal Growth Restriction, lead to an elevation in the peak of diastolic waves, resulting in a decrease in the PI value (Figure 1D).

The Doppler parameter analysis indicated that the Pulsatility Index (PI) of the Middle Cerebral Artery (MCA) exhibited lower values across all study groups, including cases of congenital heart defects (CHD) diagnosis.[16] When contrasting with healthy controls, fetuses diagnosed with left hypoplastic heart syndrome (HLHS) or heart anomalies linked with compromised brain oxygen supply demonstrated a diminished Pulsatility Index in the middle cerebral artery (MCA-PI).[17,18] Conversely, when comparing to HLHS, fetuses afflicted with right-sided obstructive lesions often displayed elevated MCA-PI values.[19] None of the studies on Doppler parameters in CHD fetuses found higher MCA when compared to healthy controls.[20] Very low MCA-PI levels begin in the second trimester and continue into the third trimester, and they tend to decline faster than expected for gestational age.[20,21]
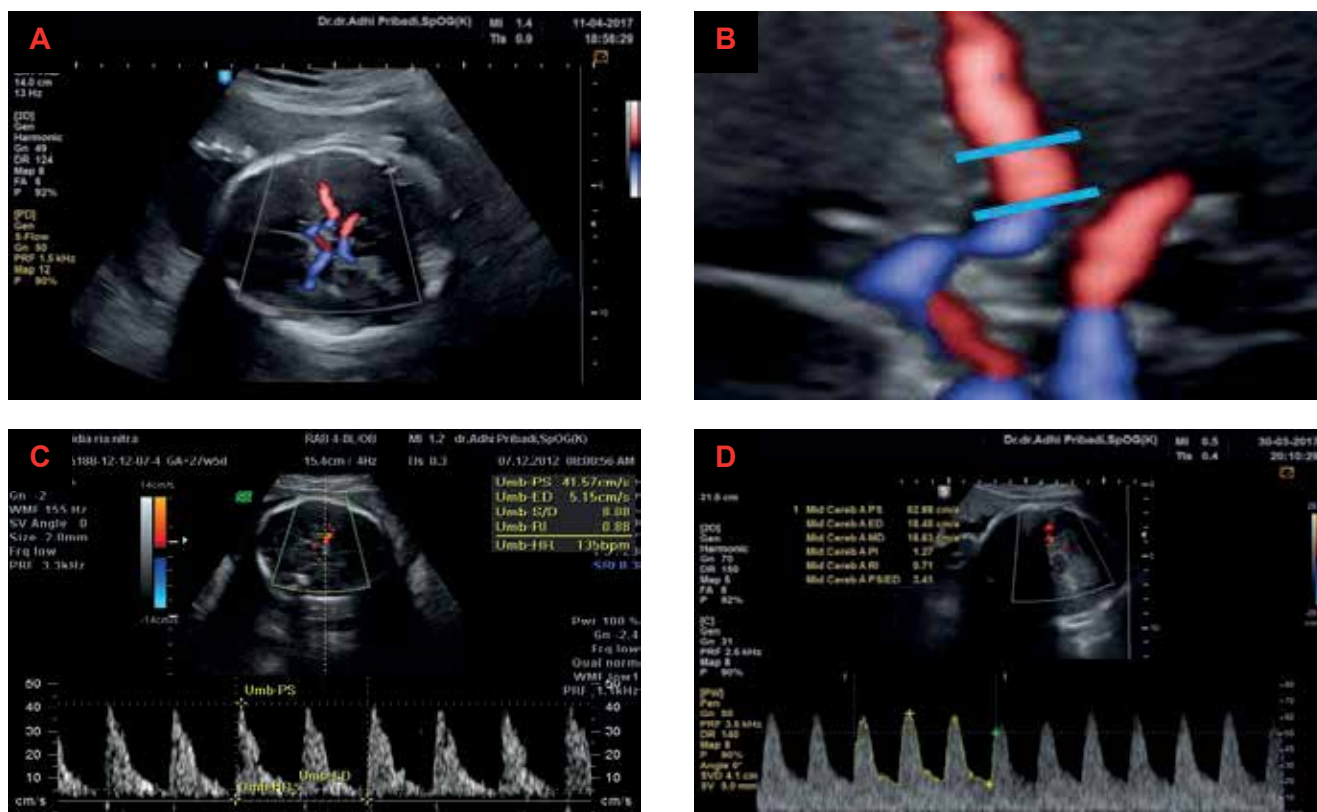
Figure 1. Middle Cerebri Artery (MCA). A.Circle of willis, B. Proximal one third to
place volume samples, C. Normal MCA, D. Increase end diastolic waves results in a decrease PI value

The CPR appears to be an important predictor of adverse pregnancy outcomes which has implications for assessing fetal well-being in women of small gestational age.[22] Calculated as a simple ratio of the middle cerebral artery pulsatility index (MCA-PI) and the umbilical artery pulsatility index (UA-PI).[23] This ratio is associated with placental insufficiency and adverse effects on the fetus, and it is almost certainly associated with postnatal neurological outcomes.[24] If there is a heart abnormality that affects head growth and overall fetal growth, it will affect CPR and neurodevelopmental as a whole.

METHODS

In this review, a search was conducted across five electronic databases—Scopus, Cochrane Library, Science Direct, PubMed, and Google Scholar. Data extraction was carried out from original articles written in English.

RESULTS

Study found childbirth with a SGA incidence of 26% in CHD cases.[25] Wallenstein's study found patients with a prenatal diagnosis of fetal CHD had a threefold increased risk of becoming fetal growth restriction (FGR); patients with isolated fetal CHD were twice as likely to develop FGR.[26] In the CHD subtypes associated with lower mean HC, these percentages ranged from simple transposition of the great arteries (3%) and Hypoplastic Left Heart Syndrom (8%) to higher in subgroups associated with lower placental weight, that is, in anomalous pulmonary vein return (13%), Tetralogy of fallot as much as 36%, and Ventricle Septal Defect as much 66%.[27] Fetal CHD is associated with uteroplacental dysfunction, secondary to maternal uteroplacental perfusion disorders resulting in hypoxemia and reduced fetal growth.[28] Below is shown (table 1) the results of the search for stunted growth events affected by the size of the fetal head (head circumference) with the results of SGA delivery. the variation in the incidence of stunted fetal growth in the incidence of CHD, which is in the range of 15.2% at the lowest to the highest as much as 26% of all CHD cases, which of course is influenced by the size of the fetal head. [25-31] The limitation of this study is that not all search results from articles found display the incidence of fetal growth restriction or SGA in pregnancy without CHD as the results of the study so comparisons cannot be made.

Table 1. Incidence of Small for Gestational Age (postpartum) in CHD

Method	CHD (N)	SGA (N/%)	Country	Reference No
Meta-analysis	1789	470/26	France	25
Retrospective Cohort study	175	28/16	US	26
Retrospective study	7569	1589/21	Danish	27
Retrospective Case control	153	37/24	UK	28
Retrospective	6863	1722/25.1	US	29
Retrospective	3395	516/15.2	US	30
Retrospective	303	56/18.5	Japan	31

Note: SGA: small for gestational age, CHD: congenital heart disease

DISCUSSION

When compared to a fetus with normal CPR, fetuses with abnormal CPR that is suitable for gestational age or has a late-onset small for gestational age (≥ 34 weeks of gestation) have a higher incidence of fetal distress in labor that requires emergency caesarean delivery, lower cord pH, and an increased level of admission to the intensive care unit.[32] Fetuses with early-onset small for gestational age (≤ 34 weeks of gestation) and abnormal CPR have a higher risk of worsening and are linked to the following; preterm birth, small for gestational age, increased cesarean section rates, an increase in Apgar score of less than 7 in 5 minutes, an increase in neonatal acidosis, an increase in intensive care, and an increase in perinatal death.[33] CPR also predicts adverse outcomes earlier than the biophysical, umbilical artery, or media cerebral artery profiles.[34,35] Finally, CPR should be considered as an assessment tool for fetuses undergoing third trimester ultrasound examination.[35]

Cerebroplacental ratio was also found to be lower in the majority of CHD fetuses.[36] Flow from the left heart through the aortic arc is critical for fetal brain growth because the arcus region contains three major blood vessels that bleed the upper body and head, including the brain.[37] The three blood vessels are; a.Inominata or a.Brachiocephalic, a.Left Carotid comunnis, and a. Left Subclavia (figure 2). If the flow into these three blood vessels is obstructed (particularly the carotid), there will be a lack of blood supply to the brain and a decrease in brain oxygenation (figure 3).[38] Long-term effects will include chronic hypoxia and widespread brain damage.[10] Types of heart defects that affect fetal brain development, especially when there are abnormalities in the left heart, for example, Hypoplastic left heart syndrom, Aortic stenosis or atresia, and aortic coarctasio. Decreased neurodevelopment due to inadequate blood flow to the head results in a lower HC,[27] which practically affects the growth chart in general, and makes it easier for the fetus to be included in the category of fetal growth restriction or SGA after delivery.

If blood flow to the brain decreases, resulting in hypoxia, the body will respond by dilating blood vessels and increasing blood flow to these organs, particularly the brain which will be reflected by changes in the appearance of MCA [39] The MCA pulsatility index, which tends to decrease in hypoxia to a certain point is said to be the brain sparring effect.[40] The description of the brain sparring effect in obstetrics occurs frequently in cases of intrauterine growth retardation, with the same principle (hypoxia) in the CHD state.[41]

The limitation of this study is that not all search results from articles found display the incidence of fetal growth restriction or SGA after delivery without CHD as the results of the study, so comparisons cannot be made. When looking at the incidence of FGR in the entire population ranges from 2.3% to 10.3%,[42] so that the overall incidence of FGR in CHD (table 1) is higher when compared to the general population.
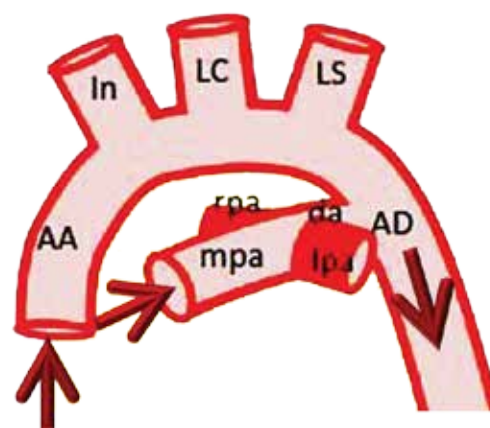

Figure 2. Normal flow in the aorta arch and ductus arteriosus. The amount of blood pumped from the right and left hearts is equal. AA:Ascendent Aorta, In:Inominate (Brachiocephalic), LC:Left Carotid, LS: Left Subclavia, mpa:main Pulmonary artery, rpa:right pulmonary artery, lpa:left pulmonary artery, da: ductus arteriosus,AD:Descendent Aorta.
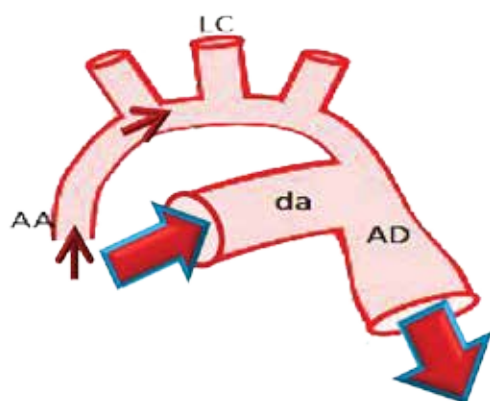
Figure 3. Abnormal flow in the aortic arch and ductus arteriosus. The amount of blood pumped from the right and left heart is anequal. Blood flow to the carotid artery decreases or less blood is pumped into the head area, while blood flow to the ductus arteriosus increases (does not flow into the head area directly to the entire body).AA: Ascendent aorta, LC: Left Carotid, da:ductus arteriosus, AD: Descendent Aorta.

CONCLUSIONS

In conclusion, the incidence of lower head circumference (HD) in CHD is higher when compared to the general population. This contributes to a rise in occurences of infants classified as small for gestational age (SGA). As a result, the prompt correction of postpartum heart defects becomes imperative.

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