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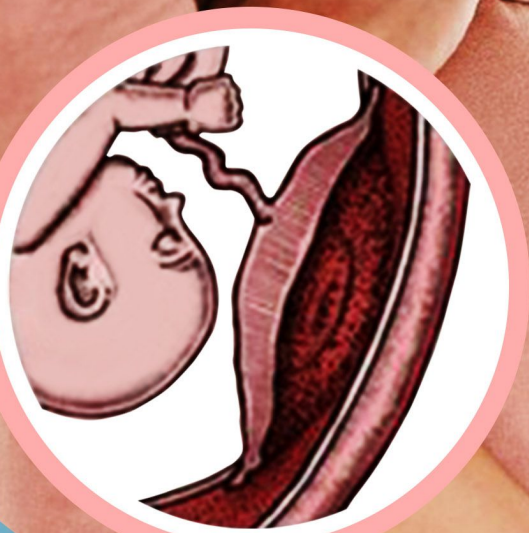
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Placenta Accreta



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Placenta Accrete Spectrum : Modern Obstetrics Nightmare

Yudianto Budi Saroyo

There is an emerging condition in modern obstetrics nowadays due to increase cases of placenta accrete spectrum (PAS). The condition has become an obstetrician major problem due to high maternal morbidity and mortality.¹⁻⁴ The increasing is about four-fold from 0.08% to 0.3% over the past decades.^{1,2,5} Thus, it is associated with complications such as massive bleeding, organ damage, blood transfusion, intensive care unit admission, and maternal/perinatal mortality.^{1,5}

The natural risk of placenta accrete spectrum remain unclear. Previous uterine surgery, specially caesarean delivery directly linked to increase PAS incidence.^{3,5,6} There was significant increasing in caesarean delivery within 2 decades, from less than 7% in 1990's to approximately 15% in 2010's, which above WHO recommendation for caesarean delivery.⁶

There has been changes in PAS perspective nowadays. The perspective changes from abnormal invasive of villi that invading to myometrium or until serosa layer, to decidual maldevelopment, when there is direct contact between chorionic villi towards myometrium with an absence of decidua. It is known associated with previous operative procedure such as in previous caesarean section, myomectomy or in uterine curettages. Thus, a proposed hypothesized that an accrete placenta occurred due to a maldevelopment of decidua, excessive trophoblastic invasion or a combination of both.² Additionally, the expression of growth, angiogenesis and invasion-related factors in trophoblast are the main factors causing accrete placenta.⁷

An early and accurate diagnosis of PAS is important during surgery preparation. An ultrasound at 11-14 weeks in highly recommended to be performed, especially when there is history of previous caesarean section, since the classical ultrasound signs of PAS appears in most of the affected women.⁵ Ultrasound examination in first trimester highly recommended to be performed in looking for Caesarean Scar Pregnancy (CSP) feature.^{1,5,6} An occurrence of CSP known as an early precursor of PAS.⁸⁻¹⁰ Another important thing is a confirmation of gestational week also helps the surgeon to decide time to deliver the baby. Therefore, antenatal diagnosis and preoperative preparation with multidisciplinary team approach are major consideration in reducing maternal and perinatal morbidity and mortality.^{5,6}

The principal management strategy in managing PAS is to prevent morbidity and mortality, including to prevent excessive bleeding and to minimize surgical complication, such as organ damage, requirement for blood transfusion and also intensive care unit admission.^{1,3,5,6,11} This can be achieved through an early and accurate diagnosis, definitive or conservative surgical methods and multidisciplinary team approach.

An accrete placenta spectrum has changed from a rare pathological condition to a serious obstetrical problems and there has not been best treatment option. There are some "notes" as our homework to be considered in accrete placenta management, such as : Well trained on awareness and an early detection on diagnosing an accrete placenta; A referral system on detecting and managing of accrete placenta need to be established, especially in remote are; An establish funding system; A guideline or professional recommendations; yet, a further research is still needed, especially how to prevent an occurrence of an accrete placenta.

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Research Article

Maternal and Perinatal Outcomes in Pregnancy Complicated with Pre- and Gestational Diabetes Mellitus

Hasil Maternal dan Perinatal pada Kehamilan dengan Komplikasi Diabetes Melitus Pra dan Gestasional

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Abstract

Objective: To analyze maternal and perinatal outcomes in pregnancies complicated by pre-gestational and gestational diabetes.

Methods: This is an analytical observational study with a cross-sectional design. We examined 57 women, 39 of pre-gestational diabetes mellitus (PGDM) women, and 19 had gestational diabetes mellitus (GDM). The data were analyzed using the chi-square and Fisher's exact test.

Results: There were no maternal deaths in either group. Pre-eclampsia was significantly higher in the PGDM group. Perinatal deaths and asphyxia were the same in both groups. Prematurity was higher in the PGDM group. Neonates of GDM women appeared to be heavier. Intrauterine fetal death (IUFD) rates were higher in the GDM group. Congenital anomalies were found in the GDM group.

Conclusion: There were differences in maternal and perinatal outcomes in both groups, namely pre-eclampsia and congenital anomaly.

Keywords: complication, congenital anomaly, diabetes mellitus gestational, pre-eclampsia.

Abstrak

Tujuan: Untuk menganalisis hasil ibu dan perinatal pada kehamilan dengan komplikasi diabetes pra-kehamilan dan kehamilan.

Metode: Penelitian ini merupakan penelitian observasional analitik dengan desain potong lintang. Kami memeriksa 57 perempuan, 39 perempuan diabetes mellitus pra-kehamilan (PGDM), dan 19 memiliki diabetes melitus gestasional (GDM). Data dianalisis menggunakan uji chi-square dan Fisher's exact.

Hasil: Tidak ada kematian ibu pada kedua kelompok. Pre-eclampsia secara signifikan lebih tinggi pada kelompok PGDM. Kematian perinatal dan asfiksia sama pada kedua kelompok. Prematuritas lebih tinggi pada kelompok PGDM. Neonatus perempuan GDM tampak lebih berat. Angka kematian janin intrauterin (IUFD) lebih tinggi pada kelompok GDM. Anomali kongenital ditemukan pada kelompok GDM.

Kesimpulan: Terdapat perbedaan luaran maternal dan perinatal pada kedua kelompok yaitu preeklamsia dan kelainan kongenital.

Kata kunci: diabetes mellitus, gestasional, komplikasi, kelainan kongenital, preeklamsia.

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INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disorder caused by either inadequate insulin production by the pancreas, insufficient insulin usage, or both.^{1,2} Diabetes diagnosed before pregnancy, defined as pre-gestational diabetes mellitus (PGDM), is either DM-type-1 or DM-type-2.³ Gestational diabetes mellitus (GDM) is a common metabolic complication in pregnancy, and glucose intolerance occurs in the second or third trimester.^{3,4}

In 2019, International Diabetes Federation reported that 1 out of 6 birth is affected by hyperglycemic pregnancy, and 84% of which is GDM. Southeast Asia has become the first region with the highest prevalence of GDM, 27%, followed by North America and the Caribbean, with 20.8%, and Europe, with 16.3%. Based on a 2013 study from The Society of Indonesian Endocrinology, Indonesia has a 1.9–3.6% prevalence of GDM.⁵

Diabetic pregnancy is closely related to pregnancy and labor complications in both mother and baby. Mothers with PGDM are associated with complication risks such as macrosomia, neonate asphyxia, preterm labor, congenital anomaly, and stillbirth. Those complications can also appear in women with GDM but are less frequent and less severe due to onset differences of hyperglycemic conditions.^{6,7}

There has been an increase in diabetic pregnancy cases globally. This study analyzed maternal and perinatal outcomes of PGDM and GDM pregnancies at Dr. Kariadi Hospital Semarang Indonesia by examining its short and long-term consequences for mothers or their offspring. This paper focuses on the different maternal and perinatal outcomes in pregnancies with PGDM and GDM, notably in Semarang, Indonesia. Even though many researchers had studied this topic, this paper shows findings that were slightly different from most hypotheses. Therefore, it contributes to existing literature and merits further discussion.

METHODS

This is an observational analytic study with a cross-sectional design to analyze the differences in maternal and perinatal outcomes of PGDM and GDM pregnancies in Dr. Kariadi Hospital Semarang. This study's subjects are mothers with PGDM and GDM pregnancies who gave birth in Dr. Kariadi Hospital Semarang in 2015–2019. The

secondary data came from their medical records. The Health Research Ethics Committee Faculty of Medicine Diponegoro University/Dr. Kariadi Hospital Semarang granted ethical approval of the study before it began (176/EC/KEPK/FK-UNDIP/VII/2020).

This study used the consecutive sampling method to collect medical records of obstetric patients at Dr. Kariadi Hospital Semarang who met the inclusion and exclusion criteria. Inclusion criteria were medical records of mothers with PGDM and GDM pregnancies who gave birth at Dr. Kariadi Hospital Semarang. Exclusion criteria in this study were medical records that were illegible, incomplete, or damaged.

Data obtained were then analyzed using the Statistical Product and Service Solution program, which includes univariate analysis to determine the frequency distribution of variables. Later, bivariate analysis was conducted to see the differences of maternal and perinatal outcomes in PGDM and GDM pregnancies using the chi-square test or Fisher's exact test as an alternative. The difference was considered significant if the p-value is <0.05.

RESULTS

The study began with 95 subjects, and 57 met the inclusion criteria. We divided the subjects into two groups, 38 in the PGDM group and 19 in the GDM group. Based on the medical record database, there were 95 pregnancies complicated with DM in 2015–2019. The incidence of PGDM and GDM generally increased every year, but GDM had a greater increase (Figure 1).

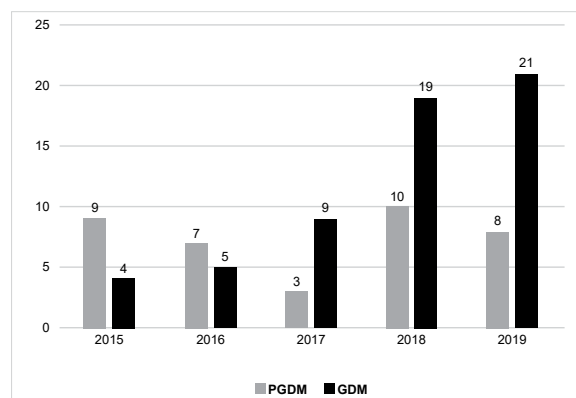


Figure 1. Subject Distribution at Dr. Kariadi Hospital Semarang in 2015–2019

Most patients had PGDM, which comprised 66.7% of the total sample, and 33.3% had GDM. Table 1 shows the subjects' characteristics and compares the two groups. Compared to the GDM group, the PGDM group had more mothers aged >35 years (52.6% vs. 10.5%; $p < 0.05$). Most of the pregnancies complicated by PGDM occurred in multiparous mothers (42.1%). Primiparous mothers had more cases of complications from GDM (47.4%) ($p > 0.05$). The study also shows that both PGDM and GDM mothers tend to deliver their babies by C-section, where GDM mothers

were more frequent ($p > 0.05$). Comorbidities such as hypertension and obesity were common in both groups ($p > 0.05$). As in drug of choice, insulin appeared to be the most used regimen in both groups, and PGDM mothers tended to use insulin more than GDM mothers (92.1% vs. 57.9%; $p < 0.05$). Babies born from PGDM mothers tend to have low birth weight (57.9%), preterm (63.2%), and APGAR scores of 7–10 (63.2%). However, in the GDM group, babies born tend to have normal birth weight (47.4%), preterm (68.4%), and APGAR score of 7–10 (68.4%) ($p > 0.05$).

Table 1. Comparison Demographic Data of Pre-Gestational Versus Gestational Diabetes Groups

Variable	PGDM (38)		GDM (19)		P-value
	n	%	n	%	
Age (years)					
20–35	18	47.4	17	89.5	0.002**
>35	20	52.6	2	10.5	
Parity					
Nulliparous	10	26.3	5	26.3	0.424‡
Primiparous	12	31.6	9	47.4	
Multiparous	16	42.1	5	26.3	
Delivery method					
Vaginal	12	31.6	3	15.8	0.202‡
CS	26	68.4	16	84.2	
Blood pressure					
Normal	13	34.2	7	36.8	0.844‡
Hypertension	25	65.8	12	63.2	
BMI					
Normal	4	10.5	0	0	0.315‡
Overweight	9	23.7	6	31.6	
Obese	25	65.8	13	68.4	
Anti-diabetic drugs					
Insulin	35	92.1	11	57.9	0.004‡*
Non insulin	3	7.9	8	42.1	
Childbirth weight					
LBW	22	57.9	7	36.8	0.298‡
Normal	13	34.2	9	47.4	
HBW	3	7.9	3	15.8	
Gestational age					
Preterm	25	65.8	12	63.2	0.844‡
Aterm	13	34.2	7	36.8	
APGAR score					
0–3	8	21.1	4	21.1	0.859‡
4–6	6	15.8	2	10.5	
7–10	24	63.2	13	68.4	

* Significant ($p < 0.05$); ‡ Pearson chi-square; † Fisher's exact.

There was no maternal mortality either in PGDM or GDM groups found (Table 2). Pre-eclampsia was more frequent in PGDM mothers than GDM mothers (65.7% vs. 36.8%; $p < 0.05$). A total of 12 cases of perinatal death were found in which both groups had the same incidence (21%; $p > 0.05$). Preterm birth was the most common perinatal outcome in both groups, in which babies from PGDM mothers were more likely to be preterm compared to the ones from GDM mothers (65.8%

vs. 63.2%; $p > 0.05$). Six macrosomic babies were born, mostly in the GDM group rather than the PGDM (15.8% vs. 7.9%; $p > 0.05$). Babies with mild asphyxia were more common in the GDM group, whereas babies with moderate asphyxia were more common in the PGDM group ($p > 0.05$). Ten out of twelve perinatal deaths caused by IUFD were more common in the GDM group (21.1 vs. 15.8%; $p > 0.05$). Three babies born with congenital anomalies were in the GDM

group (15.8%; $p < 0.05$). The analysis showed that the only significant differences in maternal and perinatal outcomes were pre-eclampsia and congenital anomalies ($p < 0.05$).

Table 2. Comparison Maternal and Perinatal Outcome Data of Pre-Gestational Versus Gestational Diabetes Groups

Variable	PGDM (38)		GDM (19)		P-value
	n	%	n	%	
Maternal outcome					
Maternal death	0	0	0	0	–
Pre-eclampsia	25	65.7	7	36.8	0.038 ^{**}
Perinatal outcome					
Perinatal death	8	21.1	4	21.1	0.625 [£]
Premature	25	65.8	12	63.2	0.844 [¥]
Macrosomia	3	7.9	3	15.8	0.313 [£]
Asphyxia					0.918 [£]
Mild	3	7.9	2	10.5	
Moderate	5	13.2	2	10.5	
Severe	0	0	0	0	
IUFD	6	15.8	4	21.1	0.440 [£]
Congenital anomaly	0	0	3	15.8	0.033 ^{£*}

* Significant ($p < 0.05$); [¥] Pearson chi-square; [£] Fisher's exact.

DISCUSSION

In this study, there was no maternal mortality in either group. In line with Alex Fong et al.'s findings, pre-eclampsia occurred more in the PGDM group than in the GDM group. This occurrence could be because of the prolonged exposure to hyperglycemia in the fetus in the PGDM group.^{8,9} Pre-eclampsia pathology remains a complex and elusive matter, but studies show that in patients with DM and increased insulin resistance can increase the incidence of hypertension in these patients. Also, it seems that diabetic pregnancy is associated with dysfunction and vascular disease, which is one of the basic pathophysiologies of pre-eclampsia.^{10,11}

Perinatal outcomes, including perinatal mortality, prematurity, macrosomia, asphyxia, and IUFD in pregnancies with PGDM and GDM, were not statistically significant. Similar to a study conducted in Sri Lanka, prematurity was more frequent in the PGDM group than in the GDM group, which was not statistically significant.¹² Another study found that preterm birth incidence increased 4-fold in mothers with diabetes and concluded they had poor glycemic control in the second trimester -2 is a risk factor for preterm labor, although there is no further explanation for this association. With various complications that occur, the health of the mother and baby is the most important thing, and early delivery can be a parameter in life management.¹³

In contrast to previous studies, in this study, macrosomia was more common in the GDM group. Meanwhile, Wahabi et al. reported that macrosomia incidence was more common in the PGDM group than in the GDM group.¹⁴ The difference in onset of diabetes in mothers can result in differences in perinatal outcomes where theory stated that the PGDM group has a higher risk for macrosomia than GDM. However, this study who reported more frequent macrosomia in the GDM group than in the PGDM.¹² Judging from the study sample distribution, the incidence of obesity was more common in the GDM group than PGDM, where obesity was associated with a 4–12-fold increase in the likelihood of macrosomia and influenced the study results.^{15–17}

Asphyxia had the same frequency in both groups, namely 21.1%. This finding contradicts previous studies where neonatal asphyxia was more common in the PGDM and GDM groups (24% vs. 8%).⁹ This will affect the fetus who was born in the form of neonatal asphyxia.¹⁸ The relatively high incidence of asphyxia in the GDM group could be related to the high incidence of macrosomia in the GDM group.

The incidence of perinatal mortality in this study was the same in both groups, namely 21.1%. Of the 12 causes of perinatal death, 10 were caused by IUFD and 2 by a stillbirth. IUFD cases were more common in the GDM group than in the PGDM group. This finding does not support where the incidence of IUFD was more prevalent in the PGDM group than in GDM.⁹

The exact cause of perinatal death is not fully explained. However, maternal factors such as pre-eclampsia, which is associated with diabetes, may also disturb the placental blood flow and fetal oxygenation resulting in IUFD. Also, the most common cause of IUFD in pregnancies with diabetes is a congenital anomaly. In this study, all congenital anomaly cases occurred in pregnancies with GDM.^{19,20}

CONCLUSIONS

There are differences in maternal and perinatal outcomes between pregnancies with PGDM and GDM: pre-eclampsia and congenital malformation. This study revealed several maternal and perinatal events in accordance with the hypothesis, but there were several differences. Suggestions for future researchers are further research on the differences in maternal and perinatal outcomes in pregnancies with PGDM and GDM with other outcomes and research on findings that were not following the hypothesis. Also, there is a need for research on the postpartum outcomes of diabetic pregnancies.

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Research Article

Dinoprostone Gel versus Intra-cervical Foley's Catheter for Pre-induction Cervical Ripening: An audit

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Abstract

Objective: to compare the efficacy and safety of the inexpensive mechanical method of induction Foley's catheter to the more established pharmacological agent Intracervical Dinoprostone (Prostaglandin E2) gel.

Methods: The present prospective randomised control study was carried out on 200 women with a term singleton pregnancy in cephalic presentation, with an unfavourable cervix and a valid indication for induction of labour. The patients were randomly allocated using the chit method to either Foley's catheter [group A, n=100] or PGE2 gel [group B, n=100]. Augmentation with oxytocin was done if required and labor was closely monitored till delivery and the perinatal outcome and maternal side effects was recorded. Quantitative variables were compared using unpaired t-test/Mann-Whitney Test and qualitative variables were compared using Chi-Square test /Fisher's exact test. Analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0

Result: The cesarean section rate did not show a significant difference between the Foley's group(18%) and PGE2 group(11%). The incidence of fetal distress, Meconium stained liquor and APGAR score <7 at 5 minutes was significantly with PGE2 as compared to group A. (P<.05). Incidence of hyperstimulation of uterus was reported in 6% women who received PGE2 as compared to none in Foley's group. The induction delivery interval did not show any significant difference between the two groups.

Conclusion: In women undergoing induction of labour at term in resource constraint set ups like ours, Foley catheter is a good alternative to the more established prostaglandin E2 gel, with good efficacy and better neonatal and maternal safety profile.

Keywords: catheters, cervical ripening, dinoprostone, labor, induced, prostaglandins.

Abstrak

Tujuan: untuk membandingkan kemanjuran dan keamanan metode mekanis induksi kateter Foley yang murah dengan gel agen farmakologi Intracervical Dinoprostone (Prostaglandin E2) yang lebih mapan.

Metode: Studi kontrol acak prospektif ini dilakukan pada 200 wanita dengan kehamilan tunggal cukup bulan dalam presentasi kepala, dengan serviks yang tidak baik dan indikasi yang valid untuk induksi persalinan. Para pasien secara acak dialokasikan menggunakan metode chit ke kateter Foley [grup A, n=100] atau gel PGE2 [grup B, n=100]. Augmentasi dengan oksitosin dilakukan jika diperlukan dan persalinan dimonitor secara ketat sampai melahirkan dan hasil perinatal serta efek samping maternal dicatat. Variabel kuantitatif dibandingkan menggunakan uji-t tidak berpasangan/Uji Mann-Whitney dan variabel kualitatif dibandingkan menggunakan uji Chi-Square/Fisher's tes eksak. Analisis dilakukan dengan menggunakan Statistical Package for Social Sciences (SPSS) versi 21.0

Hasil: Tingkat operasi caesar tidak menunjukkan perbedaan yang signifikan antara kelompok Foley (18%) dan kelompok PGE2 (11%). Insiden gawat janin, cairan bernoda Mekonium dan skor APGAR <7 pada 5 menit secara signifikan dengan PGE2 dibandingkan dengan kelompok A. (P<.05). Insiden hiperstimulasi uterus dilaporkan pada 6% wanita yang menerima PGE2 dibandingkan dengan tidak ada pada kelompok Foley. Interval pengiriman induksi tidak menunjukkan perbedaan yang signifikan antara kedua kelompok.

Kesimpulan: Pada wanita yang menjalani induksi persalinan cukup bulan dalam pengaturan kendala sumber daya seperti kami, kateter Foley adalah alternatif yang baik untuk gel prostaglandin E2 yang lebih mapan, dengan kemanjuran yang baik dan profil keselamatan ibu dan bayi yang lebih baik.

Kata kunci: kateter, pematangan serviks, dinoprostone, persalinan, diinduksi, prostaglandin

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INTRODUCTION

Induction of labor is indicated in many fetal and maternal indications in modern obstetrics. The frequency of labor induction in the United States was 31.4 percent in 2020, more than tripling since 1990 when it was 9.5 percent.¹ In developing countries like India the rates are generally lower, but in some settings, they can be as high as those observed in the United States.² The success of induction of labor is largely dependent on the state of the cervix. Hence, cervical ripening is a prerequisite for successful induction of labor and for lowering the cesarean section rate. Consensus is yet to be reached regarding the ideal method for cervical ripening. There are a variety of methods of cervical ripening available, which can be pharmacological or mechanical. Pharmacological agents used for cervical ripening include prostaglandins (PGE1 & PGE2). Intracervical PGE2 (Dinoprostone) gel is most commonly used in present day obstetric practice.³ Prostaglandins are derivatives of prostanoid acid and act as local hormones. They have direct effect on the production of procollagenase which is a precursor of collagenase, decreases collagen & increases hyaluronic acid which in turn softens the cervix and helps in cervical ripening, effacement and dilatation. While PGE2 reduces the likelihood of caesarean section compared with placebo, it increases the risk of uterine hyperstimulation with fetal heart changes.⁴ It is contraindicated in patients of asthma and those allergic to prostaglandins, is expensive and has to be refrigerated for storage.

Intracervical Foley's catheter and. Hygroscopic dilator (laminaria tent) are the commonly available mechanical methods available for cervical ripening. In the recent years there is a renewed interest in induction of labor using Foley's catheter mostly because of lesser side effects due to hyper stimulation of uterus seen with prostaglandins. Ripening of cervix may be achieved by introduction of trans-cervical Foley's catheter. It causes mechanical dilatation of cervix and stimulates endogenous release of prostaglandins by stripping the fetal membranes and release of lysosomes from decidual cell.

Foley's catheter is a cheap and easily available but under utilised method for cervical ripening with hardly any neonatal or maternal risks. Hence, the aim of this study is to increase the data for safety and efficacy of use of Foley's catheter for

preinduction cervical ripening, so that its use can be increased in resource constraint setups.

METHODS

The present prospective randomised comparative study was carried out on 200 pregnant women admitted to the labor room of Dr. BSA hospital between November 2017 to March 2019 for labor induction after a written consent. The study was approved by the ethical committee of our institute. Detailed history was taken and general physical & systematic and obstetric examination was done. Investigations were recorded. Inclusion criteria; >37 weeks period of gestation, singleton pregnancy, intact membranes, cephalic presentation, Valid indication of induction of labour like IUGR, oligohydramnios, postdatism, hypertensive disorder of pregnancy, Gestational diabetes mellitus and intra hepatic cholestasis of pregnancy, and bishop score less than 6. Exclusion criteria; scarred uterus, malpresentation, chorioamnionitis, antepartum hemorrhage, multiple pregnancies, and CPD or any other contraindication of vaginal delivery.

The patients were randomly allocated using the chit method to either Foley's catheter [group A, n=100] or PGE2 gel [group B, n=100].

Group A- After assessing FHR and Bishop score. Under all aseptic precautions Foleys catheter (No.16F) was inserted into endocervical canal extra amniotically. Tip of catheter was placed beyond internal cervical os. Bulb of catheter was inflated with 60 ml normal saline and downward tension was created by taping the catheter to the thigh. Fetal heart rate and uterine contraction were monitored every 2 hours. Bishop's score was measured after 12 hours or whenever Foley's catheter is expelled whichever was earlier. If required, augmentation with oxytocin was done.

Group B- After assessing FHR and bishop's score, 0.5mg PGE2 gel in 3 gm base (dinoprostone) was instilled intracervically. Thereafter, woman was instructed to lie in left lateral position for 30 min. FHR and uterine contraction was monitored after PGE2 gel instillation and Bishop's score was assessed after 6 hours. If Bishop's score was not favorable after 6 hours, repeat dose of PGE2 gel was instilled. Reassessment was done to see change in Bishop's score after 12 hours. Augmentation with oxytocin was done if required. Woman was followed up till delivery and perinatal outcome and maternal adverse effects were recorded.

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean \pm SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality is rejected then non parametric test was used. Statistical tests were applied as follows; quantitative variables were compared using unpaired t-test/Mann-Whitney Test (when the data sets were not normally

distributed) between the two groups, qualitative variables were compared using Chi-Square test /Fisher's exact test. A p value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0

RESULTS

Table 1. Comparison of Demographic Characteristics and Pre-induction Bishop Score between the Two Groups

Demographic Characteristic	Group		P-value
	A(n=100)	B(n=100)	
Age(Mean \pm SD	23.77 \pm 3.20	23.47 \pm 3.34	0.45
Primigravida (No & %)	71(71)	79(79)	0.19
Booked/Unbooked	69(69)	74(74)	0.43
Period of gestation	39.61 \pm 1.16	39.83 \pm 1.19 weeks	<0.05
Pre-induction Bishop	1.97 \pm .93	2.18 \pm 1.31	0.1

Demographic parameters and pre induction bishop score in the two groups were comparable as shown in Table 1.

Table 2. Comparison of Mode of Delivery between Groups

Mode of delivery	Group		Total	P-value
	A(n=100) (%)	B(n=100) (%)		
Forceps delivery	2 (2.00)	0 (0.00)	2 (1.00)	0.147
LSCS	11 (11.00)	18 (18.00)	29 (14.50)	
Vaginal	87 (87.00)	82 (82.00)	169 (84.50)	
Total	100 (100.00)	100 (100.00)	200 (100.00)	

No significant difference was seen in the mode of delivery between the two groups. ($P>.05$) Majority of patients in both the groups had vaginal delivery; 87% in group A and 82% in group B.

Table 3. Fetal and Neonatal Outcome Parameters in the Two Treatment Groups

	Group		Total	P-value
	A (n=100)	B (n=100)		
Fetal distress	92 (92.00)	85 (85.00)	177 (88.50)	0.018
Meconium stained liquor	7.56 \pm 0.9	7.25 \pm 1.11	7.4 \pm 1.02	0.030
APGAR at 1 minute <7	8 (8.00)	15 (15.00)	23 (11.50)	0.
APGAR at 5 minute <7	3 (3.00)	14 (14.00)	17 (8.50)	0.009
NICU admission	6 (6.00)	14 (14.00)	20 (10.00)	0.059

Incidence of fetal distress, Meconium stained liquor and APGAR score <7 at 5 minutes was significantly more in babies in group B as compared to group A. ($P<.05$)

Table 4. Obstetric Outcome Criteria for the Two Groups. Values are Given as n % or Mean \pm Standard Deviation

	Group		P-value
	A(n=100)	B(n=100)	
Need for augmentation	100 (100)	72 (72)	0.0008
Induction delivery interval in hrs	18.42 \pm 4.94	16.64 \pm 7.98	0.06
Hyperstimulation	0 (0.00)	6 (6.00)	0.029

In group A, all the patients needed augmentation whereas in group B, 72% of patients needed augmentation. Induction delivery time although longer in group A as compared to group B, the difference was not statistically significant.

DISCUSSION

In the present study, the primary outcome was caesarean section rate. The caesarean section rate was lesser in group A (18%) as compared to group B (11%) but the difference was not statistically significant. Majority of patients in both the groups had vaginal delivery; 87% in group A and 82% in group B. Maternal and neonatal outcomes were better in group A in our study. The incidence of fetal distress, Meconium stained liquor and APGAR score <7 at 5 minutes was significantly more in babies in group B as compared to group A. ($P < .05$) Incidence of hyperstimulation of uterus was reported in 6% women in group B as compared to none in group A. However, the need for augmentation with oxytocin was more in group A ($p = 0.00001$). The induction delivery interval group A was longer than B but the difference was not statistically significant.

In meta-analysis with 3,437 women where in 1,711 participants received Foley's catheter and 1,726 participants received prostaglandins.⁵ Both groups had a similar risk of cesarean section, vaginal delivery in 24 h or less, 5 min Apgar score less than 5, and arterial cord pH level less than 7.10. The Foley's group had a higher risk of oxytocin augmentation and the prostaglandins group had a higher risk of neonatal ICU admission.

In a systematic review including nine studies (1866 patients) both the double-balloon catheter and PGE2 agents were found to be comparable with regard to rate of caesarean section (RR 0.92; 95% CI 0.79, 1.07), vaginal delivery within 24 hours (RR 0.95; 95% CI 0.78, 1.16) and maternal adverse events, but the risk of excessive uterine activity (RR 10.02; 95% CI 3.99, 25.17) and need for neonatal intensive care

unit admissions (RR 1.31; 95% CI 1.01, 1.69) were significantly increased in women who received PGE2 agents.⁶

A randomized, comparative study found no significant difference in the side effects and caesarean section between the Foley's catheter and PGE2 group. The induction to delivery interval was 16.01 \pm 5.50 h in Foley's catheter group and 16.85 \pm 3.81 h in PGE2 ($p = 0.073$).⁷

In a comparative study on multiparous women⁸, the cesarean section rate was similar among the Foley group (9.5%), PGE2-CR group (9.6%; $P = 0.970$), and PGE2-gel group (11.8%; $P = 0.664$). Women in the Foley group had a significantly shorter ripening-to-delivery interval compared with women in the PGE2-CR group (16.2 \pm 9.2 hours vs. 27.0 \pm 14.8 hours; $P < 0.001$) and were more likely to deliver within 12 hours.

In a randomized control trial from Israel⁹, the time to active labor was significantly shorter in the Foley's group compared with the dinoprostone group, but required more oxytocin administration. The rate of vaginal delivery was the same in both the groups. A lower rate of cesarean section was found only in nulliparous women in the Foley's group. The neonatal outcome was favorable and similar in both groups.

In a comparative study from France on obese women,¹⁰ a double-balloon catheter was significantly associated with an efficient cervical ripening compared to vaginal dinoprostone (aOR 7.81, 95% CI 2.58-23.60). No difference was observed in cesarean section rate (39.1% in each group; $P = 0.96$) and in mean induction time to vaginal delivery (34.5h in the balloon group vs 36.5h in the dinoprostone group; $P = 0.53$). Maternal and neonatal outcomes were similar.

In a study comparing PGE2 insert vs Foley's catheter for labor induction, no significant difference was noted in the mode of delivery or induction delivery interval between the two groups. However, PGE2 insert was found to be associated with more cases of tachysystole and requirement of a second method of cervical ripening.¹¹

CONCLUSION

In our study there was no significant difference in the caesarean section rate and induction delivery interval in the two groups. The need for oxytocin augmentation was more in the Foley's group. Perinatal outcome was better and maternal adverse effect like hyperstimulation was less in the Foley's catheter group. In a developing country like India with limited resources, Foley's catheter may be advantageous for induction of labor as it is safer with regard to fetal outcome, which is advantageous in a resource constraint setting with higher patient load where continuous electronic fetal monitoring is not available. Foley's catheter has low cost and does not require special storage facility like PGE2 gel (which requires refrigeration).

LIMITATION

Larger sample size could have been analysed.

CONFLICT of INTEREST /FUNDING

None

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Research Article

The Anxiety Level and Premature Rupture of Membrane Incidence during COVID-19 Pandemic

Tingkat Kecemasan dan Kejadian Ketuban Pecah Dini pada Masa Pandemi COVID-19

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Abstract

Objective: To determine the association between anxiety level and premature rupture of membrane incidence during COVID-19 pandemic.

Methods: This study was a case-control study. The subjects of this study were patients giving birth at RSUD Dr. Moewardi Surakarta Hospital and UNS Sukoharjo Hospital in June - October 2021. Sampling was done by the purposive sampling technique on 70 samples. Data were analyzed using the chi-square test and logistic regression test.

Results: Characteristic data of the study samples found that most of the study samples was severe anxiety (40%). There was a significant association between the level of anxiety with PROM incident ($p = 0.00$), and pregnant women with severe anxiety had a risk of PROM of 3.761 times compared to pregnant women who were not anxious ($OR=3.761$). In multivariate analysis, it was found that the most influential variable on the incidence of premature rupture of membranes was the level of anxiety ($p=0.001$) compared to parity ($p=0.155$), employment status (0.193), and education level (0.576).

Conclusion: There was a significant association between anxiety level and premature rupture of membranes incidence during the COVID-19 pandemic, and there was an increased risk of premature rupture of membranes in pregnant women with severe anxiety levels during the COVID-19 pandemic.

Keywords: anxiety level, COVID-19 pandemic, premature rupture of membrane.

Abstrak

Tujuan: Mengetahui hubungan antara tingkat kecemasan dan kejadian ketuban pecah dini pada masa pandemi COVID-19.

Metode: Penelitian ini menggunakan pendekatan kasus kontrol. Subjek penelitian ini adalah pasien bersalin di RSUD Dr. Moewardi Surakarta dan RS UNS Sukoharjo pada bulan Juni hingga Oktober 2021. Pengambilan sampel dilakukan dengan menetapkan kriteria khusus pada 70 sampel. Data dianalisis dengan uji chi-square dan regresi logistik.

Hasil: Pada data karakteristik sampel penelitian ditemukan tingkat kecemasan terbanyak pada sampel penelitian adalah kecemasan berat (40%). Terdapat hubungan yang bermakna antara tingkat kecemasan pada ibu hamil dengan kejadian ketuban pecah dini pada masa pandemi COVID 19 ($p=0,00$) dan pada ibu dengan kecemasan berat memiliki risiko terjadinya ketuban pecah dini 3,761 kali dibandingkan ibu hamil yang tidak cemas ($OR=3,761$). Pada analisis multivariat didapatkan bahwa variabel yang paling berpengaruh terhadap kejadian ketuban pecah dini adalah tingkat kecemasan ($p=0,001$) dibandingkan dengan variabel paritas ($p=0,155$), status pekerjaan (0,193), dan tingkat pendidikan (0,576).

Kesimpulan: Terdapat hubungan yang signifikan antara tingkat kecemasan ibu hamil dan kejadian ketuban pecah dini di masa pandemi COVID-19 dan terdapat peningkatan risiko kejadian ketuban pecah dini pada ibu hamil dengan tingkat kecemasan berat pada masa pandemi COVID-19.

Kata kunci: ketuban pecah dini, pandemi COVID-19, tingkat kecemasan.

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INTRODUCTION

COVID-19 pandemic trigger anxiety for pregnant women. Several circumstances cause this anxiety, such as the fact that COVID-19 is a new disease, the fear of being infected with COVID-19, the implementation of restrictions on community activities (PPKM) policy that causes saturation, and much misinformation circulating about COVID-19^{1,2}. Anxiety is a condition that is quite common among pregnant women. Pregnant women report anxiety symptoms, such as excessive worry, nervousness, and agitation, in approximately 21 to 25% of cases³. According to an Italian study involving 100 pregnant women during COVID-19, 53% suffered severe psychological effects. About two-thirds of respondents experienced excessive anxieties⁴.

There are approximately 358,000 maternal deaths occurring worldwide every year, with 99% occurring in poor countries and 67% occurring in developing countries such as Indonesia⁵. Indonesia's Badan Pusat Statistik states there were 359 maternal deaths per 100,000 births, and 32 infant deaths per 1,000 births. Among infants who died within one month of age, 40% of cases experienced complications during delivery, including prolonged labour by 28%, rupture of amniotic fluid less than six hours before delivery by 14%, and excessive bleeding by 9%⁶. In Surakarta, the maternal mortality rate in 2018 was 41.61 per 100,000 births, and the infant mortality rate was 3.43 per thousand births, according to Dinas Kesehatan Kota Surakarta. In the 33 infant deaths, 19 infant deaths occurred in the neonatal period, and 14 deaths occurred in the post-neonatal period⁷.

PROM refers to the rupture of the amniotic membrane before the delivery process occurs. Approximately 5%-10% of PROM of all pregnancies, with 80% occurring at term⁸. PROM affects 19.53 % of pregnancy outcomes in China and 5%-7.6 % in Indonesia^{8,9}. The risk of morbidity and mortality will be more significant for the fetus and mother when preterm PROM occurs far from term¹⁰.

During the COVID-19 pandemic, pregnant women's mental health will be significantly affected. Many pregnant women have prenatal anxiety and depression¹¹. Anxiety disorders can be associated with HPA-axis hyperactivity, increasing cortisol levels, and triggering uterine contractions to cause PROM^{12,13}.

Based on the description above, pregnant women who are anxious are at a greater risk of experiencing premature rupture of membranes. Anxiety can increase uterine contractions, and one of the causes of premature rupture of membranes is increased uterine contractions. Therefore, this study was intended to examine and analyze the increased risk of premature rupture of membranes in pregnant women with severe anxiety levels during the COVID-19 pandemic.

METHODS

This study was a case-control study. The subjects of this study were all patients who gave birth at Dr. Moewardi Surakarta Hospital and UNS Sukoharjo Hospital in June – October 2021. Samples were collected by purposive sampling by distributing a modified PASS (Perinatal Anxiety Screening Scale) questionnaire that had passed the validation stage. The total population were 70 patients, divided into two groups: 35 patients with PROM and 35 patients without PROM.

The inclusion criteria were pregnant women with a desired pregnancy, pregnant women with intra-amniotic infection, aged over 20 years, and willing to be a research subject. The exclusion criteria were pregnant women with multiple pregnancies, polyhydramnios, and cervical incompetence. Data were analyzed using the chi-square test and logistic regression test. This study has been registered with the ethical clearance number 628/V/HREC/2021.

RESULTS

From the results of research conducted, there are several distributions of subjects. Data obtained from PROM and no PROM patients are 35 people (50%). The highest anxiety level experienced by the research sample was severe anxiety, which amounted to 38 people (40%). The highest parity of the research sample was nullipara, which amounted to 32 people (45.7%). In terms of employment status, 28 people (40%) did not work and 42 people (60%) worked. Most of the sample's education levels were graduated high school/vocational high school, which amounted to 39 people (55.7%).

Table 1. The Characteristics of Study Samples

Characteristic	Frequency	%
PROM Incident		
No PROM	35	50
PROM	35	50
Anxiety Level		
No Anxiety	24	34.3
Mild-moderate anxiety	18	25.7
Severe anxiety	38	40
Parity		
Nulliparous	32	45.7
Primiparous	18	25.7
Multiparous	20	28.6
Employment status		
Not work	28	40
Work	42	60
Education Level		
Elementary school	3	4.3
Junior high school	7	10
High school/vocational high school	39	55.7
University	21	30

Bivariate Analysis

The bivariate analysis used in this study was the chi-square test and the odds ratio. Based on Table 2, pregnant women who are not anxious are 19 people (79.17%) in non-PROM and 5 people (20.83%) in PROM. There are 6 people (17.65%) in non-PROM and 28 people (82.35%) in PROM in pregnant women with severe anxiety. There is a significant association between the level of anxiety with PROM incident ($p = 0.00$), and pregnant women with severe anxiety had a risk of PROM of 3.761 times compared to pregnant women who were not anxious.

Table 2. Results of Bivariate Analysis

Variable	PROM Incident		P-value	OR
	No PROM %	PROM %		
Anxiety Level				
No Anxiety	19 (79.17)	5 (20.83)	0.00	3.761
Mild-moderate anxiety	10 (55.6)	8 (44.4)		
Severe anxiety	6 (17.65)	28 (82.35)		
Parity				
Nulliparous	10 (31.25)	22 (68.75)	0.14	0.427
Primiparous	11 (61.1)	7 (38.9)		
Multiparous	14 (70)	6 (30)		
Employment Status				
Not work	16 (57.14)	12 (42.86)	0.329	1.614
Work	19 (45.23)	23 (54.77)		
Education Level				
Elementary school	3 (100)	0 (0.0)	0.007	1.367
Junior high school	6 (85.71)	1 (14.29)		
High school / vocational high school	13 (33.33)	26 (66.67)		
University	13 (61.9)	8 (38.1)		

In the parity variable, nulliparous pregnant women were 10 people (31.25%) in non-PROM and 22 people (68.75%) in PROM. There were 14 pregnant women who were multiparous (70%) in non-PROM and 6 (30%) in PROM. Parity did not have a significant association with PROM incidence ($p = 0.14$) and multiparous pregnant women had a 0.427 times risk of PROM compared to nulliparous pregnant women.

In the employment status variable, 16 pregnant women (57.14%) do not work in non-PROM and 12 pregnant women do not work (42.86%) in PROM. There were 19 people (45.23%) who worked in non-PROM and 23 people (54.77%) in PROM. Employment status did not have a significant association with PROM incidence ($p = 0.329$), and pregnant women who worked had a risk of developing PROM by 1.614 times compared to pregnant women who did not work.

In the education level variable, pregnant women who graduated from SMA/SMK were 13 people (33.33%) in non-PROM and 26 people (66.67%) at PROM. Pregnant women who graduated from university amounted to 13 people (61.9%) in non-PROM and 8 people (38.1%) in PROM. Education level had a significant association with PROM incidence ($p = 0.007$), and pregnant women who graduated from college had a risk of developing PROM by 1.367 times compared to pregnant women who graduated from elementary school.

Multivariate Analysis

Multivariate analysis in this study used a logistic regression test. Based on the results of Table 3, it was found that the variable that had a significant association with the incidence of PROM was the level of anxiety ($p = 0.001$), and pregnant women with severe anxiety levels had a risk of PROM incidence of 3.53 times compared to pregnant women who were not anxious. While the variables parity, employment status, and education level did not have a significant association with the incidence of PROM ($p > 0.05$).

Table 3. Results of Multivariate Analysis

Variable	OR (95% CI)	P-value
Anxiety Level	3.535 (1.698 – 7.358)	0.001
Parity	0.589 (0.284 – 1.222)	0.155
Employment Status	2,226 (0.668 – 7.418)	0.193
Education Level	0.795 (0.356 – 1.776)	0.576

DISCUSSION

According to the bivariate analysis in this study, anxiety level was significantly associated with PROM ($p = 0.00$), and pregnant women with severe anxiety were more likely to develop PROM by 3.761 times than pregnant women without anxiety. The results of this study were matched with research who examined 72 pregnant women and found that psychosocial stress was significantly associated with the incidence of PROM ($p = 0.018$)¹⁴. In addition, research by examining 40 pregnant women also found a significant association between anxiety levels and the incidence of PROM at Sultan Agung Islamic Hospital Semarang ($p = 0.00$)¹⁵.

Anxiety can trigger an increase in cortisol levels which affects the decrease in progesterone and stimulates the emergence of the hormone prostaglandin, which triggers uterine contractions to cause PROM^{12,13}. Some of the things that cause anxiety in pregnant women during the COVID-19 pandemic are the fact that COVID-19 is a new disease, fear of being infected with COVID-19 that can harm the fetus, government policies for PPKM that cause saturation, and much misinformation circulating about COVID -19^{1,2}.

Chronic anxiety is known as a risk factor for infection. Cortisol produced is usually anti-inflammatory and contains an immune response. However, if there is a chronic increase in cortisol, it can cause the immune system to become resistant and increase the production of

inflammatory cytokines, which further interfere with the immune response making it easier for infection to occur¹⁶. Intra-amniotic infection can occur directly or ascend from the vagina or cervix. Ascending bacteria from the vagina and cervix can spread to the uterus and amniotic fluid, causing inflammation and causing PROM¹⁷.

The bivariate analysis results showed that parity did not have a significant association with PROM incidence ($p = 0.14$), and multiparous pregnant women had a risk of PROM of 0.427 times compared to nulliparous pregnant women. These results were matched with research by examining 100 pregnant women, and the results obtained that parity does not have a significant association with the incidence of PROM ($p = 0.377$)¹⁸. In contrast to the research examining 249 pregnant women and the results obtained that parity has a significant association with PROM incidence ($p = 0.031$)¹⁹. Pregnant women with multiparous will be more at risk of PROM because there was a disturbance in uterine vascularization, causing the connective tissue of the amniotic membrane to be fragile and can rupture spontaneously²⁰.

In multiparous, the increased risk of PROM is due to the intrinsic weakening of the uterus, not an increase in uterine activity. Intrinsic weakening of the uterus results from a history of trauma to the cervix, previous vaginal delivery, cervical dilatation, and curettage¹⁹.

According to bivariate analysis, employment status was not associated with the incidence of PROM ($p = 0.329$). However, pregnant women who work have a PROM risk 1.614 times higher than pregnant women who do not work. Examining 1036 pregnant women, and the results showed that work did not have a significant association with PROM incidence ($p = 0.760$)²¹.

Examining 100 pregnant women, and it was found that work had a significant association with the incidence of PROM ($p = 0.023$). Pregnant women who work every day to the office is a heavy burden that must be carried out during pregnancy both physically and psychologically so that it can cause increased tension in the uterine muscles and affect the amniotic membranes to become weaker and break easily¹⁸.

Based on the bivariate analysis results, it was found that the level of education had a significant association with the incidence of PROM ($p = 0.007$). Examining 94 pregnant women, and it was found that the level of education had a significant association with the incidence of PROM ($p =$

0.007)²². However, it does not match the existing theory where the mother's level of education plays a role in seeking information about her pregnancy care and examination to increase the mother's knowledge about her pregnancy. The higher of mother's education, the mother will tend to have greater awareness to maintain health and pregnancy care, both regarding food, activities, hygiene, ANC, pregnancy risk factors, and the first action that must be taken related to danger signs pregnancy²³.

According to this study, pregnant women who graduated from college were 1.367% more likely to develop PROM than pregnant women who graduated from elementary school, contrary to the existing theory. This is due to the uneven distribution of data between pregnant women who graduated from elementary school, graduated from junior high school, graduated from high school/vocational school, and graduated from college.

Based on multivariate analysis, the variable associated with the incidence of PROM was anxiety level ($p = 0.001$), and pregnant women with severe anxiety had a 3.53 times greater risk of developing PROM than pregnant women without anxiety. Meanwhile, parity, employment status, and education level did not significantly affect the incidence of PROM ($p > 0.05$). As can be concluded from the study, the most influential variable was anxiety level.

CONCLUSIONS

There is a significant association between anxiety level and premature rupture of membranes incidence during the COVID-19 pandemic, and there is an increased risk of premature rupture of membranes in pregnant women with severe anxiety levels during the COVID-19 pandemic.

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Research Article

Mentzer and RDW Index in the Establishment of Iron Deficiency Anemia Diagnosis in the First Trimester of Pregnant Woman

Indeks Mentzer dan RDW dalam Diagnosis Anemia Defisiensi Besi pada Ibu Hamil Trimester Pertama

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Abstract

Objective: To determine the sensitivity and specificity of the Mentzer and RDW index to assist in the diagnosis of iron deficiency anemia in first trimester pregnant women at RSIA Asih.

Methods: This research was conducted by a cross-sectional method using the medical records of 100 samples of first trimester pregnant women with iron deficiency anemia by consecutive sampling and 100 samples of controls, which is also first trimester pregnant women with anemia. The data is then analyzed using Kolmogorov-Smirnov test and the independent-T test.

Result: This study showed a significant relationship between the Mentzer index and the RDW index in iron deficiency anemia patients and control with p value = 0.000. Calculated by the ROC curve, the cut-off of Mentzer and RDW indices were 18.33 (sensitivity 37%, specificity 36%) and 249.2 (sensitivity 36%, specificity 36%). Calculated by chi-square, the sensitivity and specificity values of the Mentzer index were 69% and 22% (literacy cut-off = 13), while the sensitivity and specificity values of the RDW index were 63% and 34% (literacy cut-off = 220).

Conclusion: Mentzer index and RDW index cannot be proposed as the main parameter to help the establishment of iron deficiency anemia diagnosis in first trimester pregnant women.

Keywords: anemia, iron deficiency, mentzer index, pregnant woman, RDW index.

Abstrak

Tujuan: Untuk mengetahui sensitivitas dan spesifitas dari Indeks Mentzer dan RDW untuk membantu penegakan diagnosis anemia defisiensi besi pada ibu hamil trimester pertama di RSIA Asih.

Metode: Penelitian ini dilakukan secara potong lintang dengan menggunakan rekam medis 100 sampel pasien ibu hamil trimester pertama dengan anemia defisiensi besi secara consecutive sampling dan 100 sampel kontrol, yakni ibu hamil trimester pertama dengan anemia. Data kemudian dianalisis dengan uji Kolmogorov-Smirnov dan uji statistik t tidak berpasangan.

Hasil: Penelitian ini menunjukkan adanya hubungan yang bermakna antara indeks Mentzer dan indeks RDWI pada pasien anemia defisiensi besi dan kontrol dengan nilai $p=0,000$. Dihitung dengan kurva ROC, cut-off indeks Mentzer dan RDW adalah 18,33 (sensitivitas 37%, spesifisitas 36%) dan 249,2 (sensitivitas 36%, spesifisitas 36%). Dihitung dengan chi-square, nilai sensitivitas dan spesifitas indeks Mentzer adalah 69% dan 22% (cut-off literasi = 13), sedangkan nilai sensitivitas dan spesifitas indeks RDW adalah 63% dan 34% (cut-off literasi = 220).

Kesimpulan: Indeks Mentzer dan indeks RDW tidak dapat diusulkan sebagai parameter utama dalam membantu penegakkan diagnosis anemia defisiensi besi pada ibu hamil trimester pertama.

Kata kunci: anemia, defisiensi besi, ibu hamil, indeks mentzer, indeks RDW.

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INTRODUCTION

A total of 48.9% of pregnant women in Indonesia experience anemia (Riskasdas, 2018) and based on data from the National Health Work Meeting (RAKERKESNAS) in 2019, the incidence of anemia is estimated to reach 13.6% of maternal deaths during pregnancy and childbirth.^{1,2}

The increasing needs of iron and lack of iron intake are the main causes of iron deficiency anemia in pregnancy. Anemia deficiency in pregnant women can increase maternal and perinatal mortality, as well as increasing the risk of low birth weight, premature birth, postpartum hemorrhage, and stunted psychomotor and neurocognitive development of infants. Early diagnosis of iron anemia deficiency is needed so that treatment can be given as early and as accurately as possible. Various erythrocyte indices are still being developed in order to obtain diagnostic parameters with the highest sensitivity and specificity values, the lowest cost, and the easiest calculation.³⁻⁵

Mentzer index and RDW index are screening tests to differentiate beta-thalassemia minor from hypochromic microcytic anemia, especially iron-deficiency anemia. Therefore, this study aimed to determine the sensitivity and specificity of the Mentzer Index and RDW to assist in the diagnosis of iron deficiency anemia in first trimester pregnant women at *RSIA Asih*.⁶⁻⁸

METHODS

This study is a retrospective cross-sectional study with a descriptive analytic approach. The sample in this study was taken by non-probability consecutive sampling, namely collecting medical records of first-trimester pregnant women with iron deficiency anemia from March 2018 - March 2020 at the ASIH Mother and Child Hospital, South Jakarta who met the inclusion and exclusion criteria of the study. The total samples that met the inclusion and exclusion criteria were 200 samples.

The inclusion criteria of this study were first-trimester pregnant women who were patients at ASIH Jakarta Mother and Child Hospital who had been diagnosed with iron deficiency anemia from the results of blood tests and clinically by obstetricians at ASIH Mother and Child Hospital Jakarta and had medical record results of routine hematological tests and ferritin levels. Exclusion criteria from this study were pregnant women

with chronic disease or infection and pregnant women who consumed drugs that could affect routine hematological values and ferritin.

The data in this study were statistically analyzed using the program Statistical Product and Service Solutions (SPSS) 26 with normality test Kolmogorov Smirnov. Then the parametric independent t test was carried out and the sensitivity and specificity test on both erythrocyte indices using chi-square and curve Receiver Operating Characteristics (ROC).

RESULTS

Table 1. Characteristics of Subject

Variable	Anemia	Control
	% (N)	% (N)
Maternal age (y o)		
≤19	1 (2)	0 (0)
20-29	28 (56)	28 (56)
30-39	19 (38)	20.5 (41)
≥40	2 (4)	1.5 (3)
Gestation age (weeks)		
≤4	2 (4)	0 (0)
5-8	11 (22)	18 (36)
9-12	37 (74)	32 (64)
Parity		
1	30 (60)	31.5 (63)
2	12.5 (25)	13 (26)
3	5.5 (11)	3.5 (7)
>3	2 (4)	2 (4)
Formal education		
High school	8.5 (17)	6.5 (13)
S1 Graduation	41.5 (83)	43.5 (87)
Occupation		
House wife	21 (42)	20.5 (41)
Civil service employee	5.5 (11)	9 (18)
Private employee	17 (34)	17.5 (35)
Entrepreneur	6.5 (13)	3 (6)
Total	50 (100)	50 (100)

Table 2. Mean, Standard Deviation and P-value of Mentzer and RDW Index

Indices	Mean	Std Deviation	p-value*	p-value**
Mentzer				
IDA	18.9	1.8	0.16	< 0.001
Control	17.7	1.8	0.2	
RDW				
IDA	263.4	35.1	0.143	< 0.001
Control	240.1	1.2	0.2	

* p-value of Kolmogorov-smirnov test; ** p-value of T Independent test.

Table 3. Chi-square Results of Mentzer and RWD Index

	According to Ferritin Level	
	IDA	Control
Mentzer index > 13 and Hb < 11	69	78
Mentzer index < 13 and Hb > 11	31	22
RWD index > 220 and Hb < 11	63	66
RWD index > 220 and Hb > 11	37	34

Table 4. Sensitivity, Spesificity and cut-off Results of Mentzer and RDW Index

Mentzer index						
	Sensitivity (%)	Spesificity (%)	Cut-off	Sensitivity (%)	Spesificity (%)	Cut-off
ROC Curve	37	36	18.33	36	36	249.2
Chi-square	69	22	13	63	34	220

DISCUSSION

The American Society for Reproductive Medicine states that the peak of the fertile period and the best egg quality for women is at the age of 20-30 years old, then it will decline after entering the age of 35 years.⁹ This is in accordance with the results of the study 200 samples studied which have an age range of 19-43 years, with the largest number of samples in the age range of 20-29 years (56%, N=56), both in the iron-deficiency anemia group and the control group. The prevalence of pregnant women with anemia during their reproductive years is still very high and women over 35 years of age have a twofold greater risk of developing iron-deficiency anemia and women under 20 years of age have a thirteen-fold greater risk of developing iron-deficiency anemia.^{10,11}

The more mature the pregnancy, the greater the risk of iron deficiency due to the increased need for the fetus¹². The first trimester of pregnancy iron requirements are reduced due to the cessation of menstruation, while iron requirements will increase dramatically in the second trimester due to expansion of blood volume and increased erythropoiesis. This is in accordance with the sample of this study where the gestational age of the most iron deficiency anemia is weeks 9-12 which is approaching the second trimester.¹³

Parity

In the results of this study, it was found that pregnant women with iron-deficiency anemia were primigravida. This result is similar with the theory and research who reported that primigravida pregnant women are more prone to anemia because of the frequent occurrence of hyperemesis gravidarum so that the food intake of pregnant women is reduced and nutrition is not fulfilled.^{14,15} However, this results seem to contradict to the results of who got a higher prevalence result in multigravida than primigravida.¹⁶

The results of this study indicate that pregnant women with S1 graduates are more

likely to experience iron deficiency anemia during pregnancy. These results are where most pregnant women who experience iron deficiency anemia are S1 graduates, but this study states that there is no significant relationship between education level and the incidence of anemia in pregnancy.¹¹ In contrast to the results where the most pregnant women who experience iron deficiency anemia are high school graduates because the mother's education level affects the incidence of iron deficiency anemia. If a mother gets higher education and knowledge, she will be able to choose nutritious foods to prevent anemia during pregnancy.¹²

Occupation

From this study, it was found that the majority of pregnant women with iron deficiency anemia were housewives. There is a significant relationship between maternal occupation and the incidence of anemia during pregnancy because mothers who do not work can be associated with a lower socioeconomic status which is known to be a risk factor for the incidence of anemia in pregnancy.¹⁷

Relationship between Mentzer Index and Pregnant Women with Iron Deficiency Anemia and Control

The principle of Mentzer index is to differentiate the etiology of hypochromic microcytic anemia, that is, between iron deficiency anemia and beta-thalassemia minor. Mentzer's theory is based on the understanding that in iron deficiency anemia, the bone marrow cannot produce adequate erythrocytes and produce smaller erythrocytes, which will result in low erythrocyte and MCV counts, also the quotient between MCV and RBC will be > 13. In contrast, in thalassemia where there is abnormality in globin synthesis, the number of erythrocytes produced is normal, but small in size and easily lysed. This results in a normal RBC but a low MCV, hence the MCV and RBC quotient will be < 13. Cut-off of 13 in Mentzer index is the result of several previous studies and is quite often used in daily practice.^{4,6}

The results of this study indicate that there is

a difference in the Mentzer index value between patients with iron deficiency anemia pregnant women and controls. The results of the statistical test with the independent T test also showed a significant relationship with the value of $p = 0.000$ ($\alpha = 0.05$; $p <$). Using the Mentzer cut-off from previous research and calculated using the test Chi-Square, obtained the sensitivity and specificity of Mentzer index are 69% and 22%. On Chi-square calculation, the researchers also included additional requirements in the form of Hb values due to differences in cut-off Hb anemia in RSIA Asih and WHO. RSIA Asih uses cut-off Hb <12 while WHO uses cut-off <11 .

In this study, the researcher also wants to find cut-off based on the sample obtained at RSIA Asih, therefore analysis was also carried out using the ROC curve, obtained the value of Area Under Curve (AUC) 31.5%, sensitivity 37% and specificity 36%. Score cut-off based on the Youden index is 18.33. These results are similar to the research conducted by Sari et al. which also got a sensitivity value of 60.5% and a specificity of 28.6% with a cut-off value of 10.7.¹⁸ The sensitivity and specificity values of the Mentzer index obtained in this study were significantly different when compared to the study which achieved a sensitivity and specificity value of $>85\%$.¹⁹ This is because, in previous studies, the samples used were patients with iron deficiency anemia and beta-thalassemia minor. This becomes important and critical to test the Mentzer index, remembering the principle of the Mentzer index itself, which has a fairly narrow scope of diagnosis, which can only diagnose both diseases. The control group used in this study were hypochromic microcytic anemia patients, but not iron deficiency anemia and beta-thalassemia minor.

Relationship between RDW Index and Pregnant Women with Iron Deficiency Anemia and Control

The principle of the RDW index is to distinguish the etiology of hypochromic microcytic anemia, namely between iron deficiency anemia and beta-thalassemia minor. Red Cell Distribution Width or RDW is a number that shows how varied the size and volume of human erythrocytes are. The RDW theory is based on the understanding that when there is iron deficiency, the erythropoiesis process will also be disrupted and the blood cells produced become smaller and paler so that in

the circulation there are normal and small-sized erythrocytes. This will have an impact on increasing RDW value because the size of red blood cells in the body is more varied. An increased RDW value is not only associated with iron deficiency but also deficiencies of other substances such as folic acid or B12. Cut-off The number used to differentiate between iron deficiency anemia and thalassemia is 220.^{7,8}

The results of this study indicate that there is a difference in the RDW index value between patients with iron deficiency anemia pregnant women and controls. The results of statistical tests with independent T-test also showed a significant relationship with $p < 0.001$ ($\alpha = 0.05$; $p < \alpha$). Using RDW index' cut-off from previous studies, and calculated using the test Chi-square, obtained sensitivity and specificity of 63% and 34%, respectively. On Chi-square calculation, the researchers also included additional requirements in the form of Hb values due to differences in cut-off Hb anemia in RSIA Asih and WHO. RSIA Asih uses cut-off Hb <12 while WHO uses cut-off <11 .

In this study, the researcher also wants to find cut-off based on the sample obtained at RSIA Asih, therefore an analysis was also carried out using the ROC curve, obtained the value of Area Under Curve (AUC) 32.6%, sensitivity 36% and specificity 36%. The cut-off score based on the Youden index is 249.2. The sensitivity and specificity values of the RDW index obtained in the study were significantly different when compared to the finding of which achieved sensitivity and specificity values $>80\%$.^{20,21}

This is because, in previous studies, the samples used were patients with iron deficiency anemia and beta-thalassemia minor. This becomes important and critical to test the RDW index, remembering the principle of the RDW index itself, which has a fairly narrow scope of diagnosis, which can only diagnose both diseases. The control group used in this study were hypochromic microcytic anemia patients, but not iron deficiency anemia and beta-thalassemia minor. This is what causes confusion in the RDW index value in the control group.

CONCLUSION

The general distribution of the population of first-trimester pregnant women who experience iron deficiency anemia at RSIA Asih is at most 20-29 years old, with a gestational age of 9-12 weeks, is in its first pregnancy, has the last bachelor's

education and is a housewife. According to the ROC curve analysis, the sensitivity of the Mentzer index was 1% higher than the RDW Index, while the specificity values for the two indexes were the same. According to chi-square analysis the sensitivity of the Mentzer index was higher but the specificity of the Mentzer index was lower than the RDW index.

From these results, it can be concluded that the Mentzer index and RDW index cannot be proposed as the main parameters in helping to diagnose iron-deficiency anemia in first-trimester pregnant women.

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Research Article

Menstrual Cycle Length and Dysmenorrhea in Female Adolescents Aged 9-18 Years

Panjang Siklus Menstruasi dan Dismenore pada Remaja Perempuan usia 9-18 tahun
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Abstract

Objective: To determine the relationship between menstrual cycle length and dysmenorrhea in female adolescents aged 9-18 years in Sang Timur Tomang School West Jakarta.

Methods: This study used a cross-sectional study approach to conduct observational analytic research. The study samples were female students aged 9-18 years in Sang Timur Tomang School. Study data were obtained through the Verbal Multidimensional Scoring System (VMSS) questionnaire in Indonesian. The Chi-square test of independence was used to determine the relationship between menstrual cycle length and dysmenorrhea.

Result: From a total of 137 respondents, 38% have abnormal menstrual cycle length. Eighty-two-point-seven percent of respondents who have abnormal menstrual cycle length experienced dysmenorrhea, and 17.3% of participants who have abnormal menstrual cycle length did not experience dysmenorrhea. Chi-square test results showed a significant relationship between menstrual cycle length and dysmenorrhea in female adolescents aged 9-18 years in Sang Timur Tomang School West Jakarta ($p = 0.005$).

Conclusion: There is a significant relationship between menstrual cycle length and dysmenorrhea in female adolescents aged 9-18 years in Sang Timur Tomang School West Jakarta.

Keywords: dysmenorrhea, female adolescents, menstrual cycle, menstrual cycle length.

Abstrak

Tujuan: Mengetahui hubungan panjang siklus menstruasi dengan dismenore pada remaja perempuan usia 9-18 tahun di Sekolah Sang Timur Tomang Jakarta Barat.

Metode: Penelitian ini menggunakan pendekatan potong lintang dengan melakukan penelitian observasional analitik. Sampel pada penelitian adalah siswi usia 9-18 tahun di Sekolah Sang Timur Tomang. Data penelitian diperoleh melalui kuesioner Verbal Multidimensional Scoring System (VMSS) dalam Bahasa Indonesia. Uji Chi-square digunakan untuk mengetahui hubungan antara panjang siklus menstruasi dengan dismenore.

Hasil: Dari total 137 responden, sebanyak 38% memiliki panjang siklus menstruasi abnormal. Delapan puluh dua koma tujuh persen responden yang memiliki panjang siklus menstruasi abnormal mengalami dismenore dan 17,3% responden yang memiliki panjang siklus menstruasi abnormal tidak mengalami dismenore. Hasil uji Chi-square menunjukkan adanya hubungan signifikan antara panjang siklus menstruasi dengan dismenore pada remaja perempuan usia 9-18 tahun di Sekolah Sang Timur Tomang Jakarta Barat ($p = 0,005$).

Kesimpulan: Terdapat hubungan bermakna antara panjang siklus menstruasi dengan dismenore pada remaja perempuan usia 9-18 tahun di Sekolah Sang Timur Tomang Jakarta Barat.

Kata kunci: dismenore, panjang siklus menstruasi, remaja perempuan, siklus menstruasi.

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INTRODUCTION

Menstruation is a natural phenomenon in women during their reproductive ages. During menstruation, women can experience pain in the area around the abdomen called dysmenorrhea.¹⁻³ Dysmenorrhea causes negative impacts on female students, specifically in decreased academic performance (88.3%) such as absenteeism, reduced participation and concentration during classes, and limitations in sports, study, and exams.² The prevalence of dysmenorrhea reaches 87.5% in Central Jakarta.⁴ Dysmenorrhea is more common in female adolescents aged 13-20 years (93.3%) compared to females aged 21-30 years and 31-44 years.⁵ Age at menarche is one of the risk factors of dysmenorrhea. A recent study has identified a secular trend of declining age at menarche in Indonesia, from 14.43 to 13.63 years over a decade.⁶

Female adolescents generally have abnormal menstrual cycle length during the first two years after menarche. Entering the third year after menarche, 60-80% of female adolescents will have a normal menstrual cycle length.⁷ Abnormal menstrual cycle length and dysmenorrhea are related in certain studies, but the findings are still controversial as its mechanism remains unknown.^{8,9} This study was undertaken to see a relationship between menstrual cycle length and dysmenorrhea in female adolescents aged 9-18 years in Sang Timur Tomang School West Jakarta.

METHODS

This study was a cross-sectional study utilizing an observational technique. All participants will be observed once, and the p-value will be searched to determine the hypothesis test results. The study samples were female students aged 9-18 years in Sang Timur Tomang School West Jakarta. The sampling method used in this study is the total sampling method. The researcher distributed the questionnaire in Google Form to all female students in the 4th to 12th grades at Sang Timur Tomang School. Samples are collected from all respondents who returned the questionnaire and met the inclusion and exclusion criteria. This study has received ethical approval by Atma Jaya Catholic University of Indonesia, Faculty of Medicine and Health Sciences number 01/05/KEP-FKIKUJ/2021, with a minimum of 97 respondents.

Data were collected in August 2021. Study data were obtained through the Verbal Multidimensional Scoring System (VMSS) questionnaire in Indonesian. Data were processed by the original SPSS Statistics 26 program. The relationship between independent and dependent variables was analyzed using the Chi-square test of independence (CI = 95%, α = 0.05%).

RESULTS

Table 1. Demographic Characteristics of Respondents

Characteristics	Frequency	(%)
Age (y o)		
9-11	28	20.4
12-14	22	16
15-18	87	63.6
Age at menarche (y o)		
< 12	74	54
12-15	63	46
Body mass index		
Underweight	5	3.6
Normal	99	72.3
Overweight	24	17.5
Obesity	9	6.6
Family history of dysmenorrhea		
Yes	89	65
No	48	35
Family history of reproductive disorders		
Yes	8	5.8
No	129	94.2
Gynecological age		
> 2	79	57.7
≤ 2	58	42.3

Interpretation: most respondents came from the 15-18 years age group, had age at menarche in < 12 years, had normal body mass index (BMI), had a family history of dysmenorrhea, did not have a family history of reproductive disorders, and had gynecological age > 2 years. The average respondents' age is 14.42 years, with the average age at menarche and gynecological age are 11.42 years and 3 years.

Table 2. Respondents' Characteristics of Menstrual Cycle Length and Dysmenorrhea

Characteristics	Frequency	%
Menstrual cycle length		
Normal	85	62
Abnormal		
< 24	29	21.2
> 38	23	16.8
Dysmenorrhea		
No	43	31.4
Yes	78	56.9
	2	11.7

Interpretation: from 137 respondents, 38% of respondents had abnormal menstrual cycle length, and 68.6% of respondents experienced dysmenorrhea.

Table 3. Bivariate Analysis Results for Relationship between Body Mass Index, Family History of Dysmenorrhea, and Abnormal Menstrual Cycle Length with Dysmenorrhea

Variable		Dysmenorrhea		Total (%)	P-value
		Yes (%)	No (%)		
Body mass index	Normal	66 (66.7)	33 (33.3)	99 (72.3)	0.428
	Abnormal	28 (73.7)	10 (26.3)	38 (27.7)	
Family history of dysmenorrhea	No	24 (50)	24 (50)	48 (35)	0.001
	Yes	70 (78.7)	19 (21.3)	89 (65)	
Menstrual cycle length	Normal	51 (60)	34 (40)	85 (62)	0.005
	Abnormal	43 (82.7)	9 (17.3)	52 (38)	

Interpretation: the results of the Chi-square test showed a significant relationship between family history of dysmenorrhea ($p = 0.001$) and menstrual cycle length with the presence of dysmenorrhea ($p = 0.005$).

Table 4. Bivariate Analysis Results for Relationship between Gynecological Age with Menstrual Cycle Length

Gynecological Age	Menstrual Cycle Length		Total (%)	P-value
	Normal (%)	Abnormal (%)		
> 2	55 (69.6)	24 (30.4)	79 (57.7)	0.033
≤ 2	30 (51.7)	28 (48.3)	58 (42.3)	
Total	85 (62)	52 (38)	137 (100)	

Interpretation: the results of the Chi-square test showed a significant relationship between gynecological age with menstrual cycle length ($p = 0.033$).

DISCUSSION

Menstruation is a physiological process in women that normally occurs every 24-38 days as a result of the absence of pregnancy. Women can experience discomfort and pain in the area around the abdomen during this period, called dysmenorrhea.^{1-3,10}

The prevalence of dysmenorrhea varies from 16-91% and reaches 87.5% in Central Jakarta.^{4,11} Dysmenorrhea and abnormal menstrual cycle length are more common in female adolescents, and the relationship between the two variables is still controversial.^{5,7-9} Age at menarche, body mass index (BMI), family history of dysmenorrhea, and gynecological age are risk factors for dysmenorrhea and menstrual cycle length.¹² The study identified a secular trend of declining age at menarche in Indonesia from 14.43 to 13.63 years over a decade.⁶

Demographic characteristics of respondents

Our study found that our respondents' average age at menarche is 11,42 years and 54% of our respondents experienced menarche at the age of < 12 years, which is considered early menarche. These results were consistent with previous studies about a secular trend of declining age at menarche and early menarche phenomenon in Indonesia.^{6,13} Urbanization, increased BMI, and sedentary lifestyle are the main factors. Physical activity can increase the

metabolism and excretion of the estrogen so that the concentration of endogenous estrogen decreases. Estrogen plays a role in females' puberty, which is marked by menarche. Decreased physical activity causes endogenous estrogen concentrations to increase, resulting in early menarche and precocious growth.^{14,15}

Lack of physical activity is closely related to increased BMI, which is also a risk factor for early menarche. Previous studies concluded that women with a high BMI were more likely to experience early menarche because of hyperandrogenism.^{14,15} Therefore, an increase in phospholipids and arachidonic acid in women with an excess BMI produces excess prostaglandins, which is causing dysmenorrhea.¹² Our study found that most respondents (72.3%) had normal BMI, and 33 out of 137 respondents (24,1%) had overweight and obese BMI. Of the total 33 respondents who had high BMI, 26 respondents (78.8%) experienced early menarche. Furthermore, there is no relationship between BMI with dysmenorrhea ($p = 0,428$), which is consistent with the previous study ($p = 0.636$).⁸

The bivariate analysis showed a significant relationship between family history of dysmenorrhea with dysmenorrhea ($p = 0.001$). Seventy out of 137 respondents (78.7%) who had a family history of dysmenorrhea also experienced dysmenorrhea. Consistent with the previous study, a girl who has a mother or sisters who experience dysmenorrhea is more likely to experience dysmenorrhea. Family history as a

risk factor includes genetics and the same daily lifestyle in the family.^{11,16,17}

Our study also identified the gynecological age of our respondents, which reflects the maturity of the function of the female reproductive organs. This is because our respondents were female adolescents aged 9-18 years. Most of them had just experienced menarche and had abnormal menstrual cycle length, so it's crucial to assess the reproductive organ function's maturity through gynecological age. Gynecological age indirectly strengthens the relationship between menstrual cycle length and dysmenorrhea in this study.^{7,18} We found that most respondents (57.7%) had a gynecological age > 2 years with an average of 3 years. Bivariate analysis showed that there is a strong relationship between gynecological age and menstrual cycle length ($p = 0.033$). Our findings indicate that respondents with gynecological age > 2 years also have normal menstrual cycle length. Generally, the menstrual cycle length of women with a gynecological age ≤ 2 years is abnormal. Entering the third year after menarche, 60-80% of women will have a normal menstrual cycle length because the HPO (hypothalamus-pituitary-ovarian) axis is gradually maturing.^{7,18}

Menstrual Cycle Length

Our study found that 52 respondents (38%) have an abnormal menstrual cycle length and 85 respondents (62%) have normal menstrual cycle length. Previous literature from The American College of Obstetricians and Gynecologists (ACOG) and a study identified that abnormal menstrual cycle is more common in female adolescents. As mentioned before, this phenomenon is caused by immaturity of the HPO axis that occurs during puberty. Even though the girl has experienced menarche, it does not mean that the HPO axis has fully developed. Therefore, the immaturity of HPO causes the length of the menstrual cycle to be shorter (< 24 days) or longer (> 38 days) than normal.^{7,18-20}

The neuroendocrine axis of a female's puberty takes time to reach its maturity. Puberty begins with the first release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which induces the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. During puberty, generally the feedback mechanism and the response of the ovarian follicle to hormonal stimulation are still

not sensitive. This causes the luteal phase of the ovarian cycle to be longer and the failure to form the pre-ovulatory follicles that (normally) should produce estrogen to provide positive feedback on GnRH, causing an LH surge and ovulation to occur. This failure causes ovulation not to occur, thereby inducing endometrial proliferation even without progesterone as a nutrient. In fact that the corpus luteum should produce progesterone after ovulation. Therefore, the occurrence of the anovulatory cycle causes abnormal menstrual cycle length in female adolescents. This phenomenon will improve with the continuous GnRH stimulation over time, which will make the ovarian follicles more sensitive.^{21,22}

Most respondents in this study (62%) had a normal menstrual cycle length. This finding is thought to be because most respondents are from the 15-18 years age group (Table 1), which is approaching late adolescence. This group has gynecological age > 2 years and a mature HPO axis, so they have a normal menstrual cycle length.^{20,22}

Dysmenorrhea based on VMSS

Our study found that most respondents (68.6%) experienced dysmenorrhea. This prevalence is lower which identified the prevalence of dysmenorrhea in female adolescents in Central Jakarta reached 87.5%. The difference in prevalence is due to the difference in the age range between the two studies. Involved female adolescents aged 11-22 years, which means the youngest age in our study is 2 years younger (9 years). In addition, 37 out of 137 respondents (27%) in this study had gynecological age ≤ 1 year. Considering that the emergence of dysmenorrhea occurred 6-12 months after menarche, so there is a possibility that dysmenorrhea in this group of respondents has not been detected, resulting in the lower prevalence of dysmenorrhea. On the other hand, the prevalence of dysmenorrhea in this study was higher than the prevalence of dysmenorrhea in Indonesia, which was 54.89%.⁴

In Nigeria identified that dysmenorrhea is more common in female adolescents, where the majority (93.3%) of female adolescents of their study experienced dysmenorrhea. These results support the fact that our respondents were female adolescents aged 9-18 years, and most respondents experienced dysmenorrhea.⁵

The Relationship between Menstrual Cycle Length and Dysmenorrhea

Bivariate analysis of the relationship between menstrual cycle length and dysmenorrhea showed that the p-value was 0.005 ($p < 0.05$). These findings indicate a significant relationship between menstrual cycle length and dysmenorrhea in this study. Female adolescents who have an abnormal menstrual cycle length are more likely to experience dysmenorrhea. Our results are consistent which concluded that there was a relationship between menstrual cycle length and dysmenorrhea. Their study involved 354 women and identified that women with menstrual cycle length > 35 days or longer than normal were more likely to experience dysmenorrhea.⁸ This conclusion is also supported which identified that women with menstrual cycle length > 29 days were more likely to experience dysmenorrhea.²³ Otherwise, our findings contradict the study which identified that there was no relationship between menstrual cycle length and dysmenorrhea.^{16,24}

Pathophysiology of dysmenorrhea begins with the degradation of the unfertilized corpus luteum into corpus albicans, resulting in the reduction of progesterone production. Then the low progesterone level causes the shedding of the endometrial wall and activation of the cyclooxygenase (COX) and lipooxygenase (LOX) pathways. These two pathways then produce prostaglandins ($\text{PGF}_{2\alpha}$, PGE_2), prostacyclin, thromboxane A_2 , and leukotrienes. These substances then cause the vasoconstriction of endometrial blood vessels, stimulate myometrial muscle contraction, and increase hypersensitivity to central and peripheral pain stimuli, resulting in recurrent dysmenorrhea.^{25,26}

A study identified that women with abnormal menstrual cycle length were more likely to experience anovulation and decreased progesterone secretion. The decrease in progesterone secretion leads to excessive activations of the COX and LOX pathways, resulting in the excessive production of prostaglandins, prostacyclins, A_2 thromboxane, and leukotrienes. The increased levels of these substances are associated with increased intensity of dysmenorrhea.^{27,28}

CONCLUSIONS

Based on the results of this study, it can be concluded that 68,6% of respondents experienced dysmenorrhea, and 32% of respondents had abnormal menstrual cycle length. There is a relationship between menstrual cycle length and dysmenorrhea in female adolescents aged 9–18 years in Sang Timur Tomang School West Jakarta.

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Research Article

Overview of S-RBD Antibody Levels After Covid-19 Vaccination in Premenopausal and Menopausal Women

Gambaran Kadar Antibodi S-RBD Pascavaksinasi COVID-19 pada Perempuan Premenopause dan Menopause

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Abstract

Objective: To determine the levels of S-RBD antibodies in premenopausal and postmenopausal women who received the COVID-19 vaccine.

Methods: This study involved 21 premenopausal and postmenopausal women who received two doses of CoronaVac at 28 days intervals. The duration of vaccination was 4-24 weeks. This study was conducted on May–October 2021 in Kendari City, Indonesia. Blood samples were taken at a health care facility and examined at the Prodia Clinical Laboratory. Participants were healthy women, willing to participate, and signed informed consent. Participants were excluded if they had a history of COVID-19, had taken antibiotics or immunomodulators in the last 24 hours, had a history of acute/chronic inflammatory disease and malignancy, were traumatized and received monoclonal antibody therapy.

Results: Participants were 52.95±7.61 years old. The duration of the second vaccination was 13.67±5.26 weeks. The lowest level of S-RBD antibody was menopause with vaccination duration ≤12 weeks (185.59±112.34 U/mL), and the highest was premenopause with vaccination duration >12 weeks (257.5±3.54 U/mL). The S-RBD antibody level in premenopausal women was higher than in menopausal women at the duration of vaccination ≤12 weeks (223.37±63.45 vs 185.59±112.34 U/mL) and >12 weeks (257.5±3.54 vs 225.55±91.14 U/mL). There was no significant difference in S-RBD antibody levels between two or more groups ($p>0.05$).

Conclusion: S-RBD antibody levels in postmenopausal women after receiving two doses of COVID-19 vaccine were lower than in premenopausal women, but the difference was not significant. S-RBD antibody levels in postmenopausal women increased with increasing duration of vaccine administration.

Keywords: COVID-19 vaccine, immune response, menopause, S-RBD antibody.

Abstrak

Tujuan: Mengetahui gambaran antibodi S-RBD pada perempuan premenopause dan menopause yang mendapat vaksin COVID-19.

Metode: Penelitian ini melibatkan 21 perempuan premenopause dan menopause yang telah melakukan vaksinasi sebanyak dua dosis (interval 28 hari) dengan CoronaVac dalam kurun waktu 4-24 minggu pasca vaksinasi. Penelitian telah dilaksanakan pada bulan Mei–Oktober 2021 di Kendari, Indonesia. Pengambilan sampel darah dilakukan di fasilitas pelayanan vaksinasi COVID-19 dan pemeriksaannya dilakukan di Laboratorium Klinik Prodia. Partisipan adalah perempuan yang sehat, bersedia ikut dan menandatangani informed consent. Partisipan akan dikeluarkan dari kelompok sampel bila memiliki riwayat COVID-19, mengkonsumsi antibiotik atau immunomodulator dalam 24 jam terakhir, memiliki riwayat penyakit inflamasi akut/kronik dan penyakit keganasan, dalam kondisi trauma, dan mendapat terapi antibodi monoklonal.

Hasil: Umur partisipan adalah 52,95±7,61 tahun. Durasi waktu vaksinasi kedua adalah 13,67±5,26 minggu. Kadar antibodi S-RBD yang terendah adalah kelompok menopause dengan durasi waktu vaksinasi ≤12 minggu (185,59±112,34 U/mL) dan yang tertinggi pada premenopause dengan durasi vaksinasi >12 minggu (257,5±3,54 U/mL). Kadar antibodi S-RBD pada premenopause dengan durasi vaksinasi ≤12 minggu lebih tinggi dibanding pada menopause (223,37±63,45 U/mL vs 185,59±112,34 U/mL). Kadar antibodi S-RBD pada premenopause dengan durasi vaksinasi >12 minggu lebih tinggi dibanding pada menopause (257,5±3,54 U/mL vs 225,55±91,14 U/mL). Tidak ada perbedaan yang signifikan kadar antibodi S-RBD antara dua atau lebih kelompok ($p>0,05$).

Kesimpulan: Kadar antibodi S-RBD perempuan menopause setelah mendapat dua dosis vaksin CoronaVac lebih rendah daripada premenopause, namun perbedaannya tidak signifikan. Kadar antibodi S-RBD pada perempuan menopause meningkat dengan bertambahnya durasi pemberian vaksin.

Kata kunci: antibodi S-RBD, menopause, respon imunitas, vaksin COVID-19.

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INTRODUCTION

The government struggles to deal with the COVID-19 pandemic by realizing herd immunity through vaccination.¹ Research with simulation studies shows the controlled spread of SARS-CoV-2 achieved when a large proportion of the population has been vaccinated (70–80%).²

The elderly have a higher risk of suffering severe conditions and mortality caused by COVID-19.³ In a previous study, elderly patients (>65 years) experienced more severe cases of COVID-19 and have a higher mortality rate possibility than survivability.⁴ Of all COVID-19 cases in Indonesia, 11.8% of cases and 46.7% of mortality are the elderly.⁵ Therefore, the elderly are prioritized to receive the COVID-19 vaccine.⁶

The mechanism of the COVID-19 immune response has not been fully understood and is under investigation. The correlation of estradiol with a decrease in vaccine-induced immunity was found during influenza vaccination for women.⁷ However, another study showed antibody response of post-menopausal women who received hormone therapy was similar to that of those who did not.^{8,9}

Quantitative tests for anti-SARS-CoV-2 antibodies could determine the specific antibody response to the vaccine and individual antibody levels and monitor antibody responses.¹⁰ Neutralization test is the gold standard for detecting specific immunity.¹¹ Some standard examinations require a level-3 biosafety laboratory which is difficult to find in developing countries.¹² A substitute assay for the neutralization test is a specific antibody against the Receptor Binding Domain (RBD) of the SARS-CoV-2 virus. The reason is most of the neutralizing antibodies bind to RBD. Each Coronavirus species has a different Sub-unit of RBD due to their bonds with a different receptor. Thus, they are specific.¹³

Today, many researchers investigate COVID-19 to find out various aspects of this virus, including vaccination and the impacts. This study aimed to determine the SRBD antibodies levels in premenopausal and menopausal women after receiving the COVID-19 vaccine. The results of this research are expected to be information for evaluating the COVID-19 vaccine effectiveness.

METHODS

It was a cross-sectional study conducted on May – October 2021 in Kendari City, Indonesia.

Blood samples were taken at the vaccination service facility and examined at the Prodia Clinical Laboratory. Participants were premenopausal and postmenopausal women who had received 2 doses of CoronaVac with an interval of 28 days. The duration of vaccination was 6–24 weeks. Inclusion criteria were healthy, willing to participate, and signed the informed consent. Exclusion criteria were having a history of COVID-19, taking antibiotics or immunomodulators in the last 24 hours, having a history of acute/chronic inflammatory disease and malignancy, traumatic conditions, and receiving monoclonal antibody therapy.

This study used Anti-SARS-CoV-2 S (Roche) reagent, ECLIA method, RBD anti-agent, sensitivity percentage of 98.8%, and sensitivity percentage of 100%. The researchers collected venous blood samples. The plasma or serum of the samples was separated with the centrifugation technique. The applied angular speed was 12.000 rpm within 5 minutes. Plasma or serum was transferred into several 200 L tubes and immediately checked the samples. If it is not possible, so the samples were stored in a freezer at a temperature of 2–8 °C for a maximum of 14 days. Approximately 12–20 µL samples were incubated for 9 minutes with recombinant-specific SARS-CoV-2-S-RBD antigen and ruthenium-labeled recombinant-specific SARS-CoV-2-S-RBD antigen to form a sandwich complex. Add streptavidin-coated microparticles, and a second incubation was carried out. The complex would become a solid phase that reacted with biotin and streptavidin. The reagent mixture was put into a microplate which was magnetically trapped on the surface of the electrode. The unbound substance was rinsed through the washing process. Induction of chemiluminescent emission is carried out by providing an electric current that is measured by a photomultiplier. The results are measured automatically using software by comparing the electrochemiluminescent signal obtained from the sample reaction with the calibration cutoff value signal. The displayed number will describe the antibody titer.

Univariate analysis was carried out to determine the characteristics of the participants and the distribution of the observed variables. Data analysis used SPSS to assess differences with the Kruskal-Wallis test.

This research has received ethical approval from the Health Research Ethics Commission, Faculty of Medicine, Halu Oleo University, number

120/UN29.17.1.3/ETIK/2021.

RESULTS

This report includes 21 participants whose age is 52.95 ± 7.61 years. The second vaccination interval was 13.67 ± 5.26 weeks. The characteristics of the participants are shown in table 1.

Table 1. Characteristics of Participants

Characteristics	n	%
Education		
Middle	5	23.8
High	16	76.2
Occupation		
Housewife	5	23.8
Employess	16	76.2
Parity		
≤ 2	6	28.6
> 2	15	71.4
Age (years)		
≤ 55	10	47.6
> 55	11	52.4

Table 1 shows that the majority of participants are highly educated (76.2%), are employees (76.2%), and have parity > 2 (71.4%).

Table 2. Mean, Standard Deviation, Minimum and Maximum Values of S-RBD Antibody Levels based on the Duration of Vaccination

Variabel	S-RBD antibody levels (U/mL)				
The duration of vaccination	Minimum	Maximum	Mean	SD	P-value
Premenopause					
(weeks)					
≤ 12	150.1	260.0	223.37	63.45	.855*
> 12	255.0	260.0	257.50	3.54	.686*
Menopause					
(weeks)					
≤ 12	9.42	260.0	185.59	112.34	.962*
> 12	18.82	260.0	225.55	91.14	.444*

Table 2 presents descriptive analysis, namely the minimum, maximum, mean, standard deviation, and normality values of the data distribution in each group. The lowest levels of S-RBD antibodies were menopause with vaccination duration 12 weeks (185.59 ± 112.34 U/mL), and the highest was premenopause with vaccination duration > 12 weeks (257.5 ± 3.54 U/mL).

At the duration of vaccination 12 weeks, the mean S-RBD antibody levels in premenopause were higher than in menopause (223.37 ± 63.45 U/mL vs 185.59 ± 112.34 U/mL). S-RBD antibody levels at vaccination duration > 12 weeks also found that premenopause was higher than

menopause (257.5 ± 3.54 U/mL vs 225.55 ± 91.14 U/mL).

The Shapiro-Wilk normality test showed that the data was not normally distributed ($p < 0.05$) so that the Kruskal-Wallis difference test was continued. There was no significant difference in S-RBD antibody levels between two or more groups ($p > 0.05$).

DISCUSSION

This study aims to describe the SRBD antibody levels in premenopausal and postmenopausal women who received two doses of the COVID-19 vaccine. Receptor Binding Domain (RBD) is an important target for antiviral compounds and antibodies that can be evaluated post-vaccination.¹⁴ This study showed that there was a difference in S-RBD antibody levels between premenopause and menopause but it was not statistically significant. Menopausal women have a good COVID-19 vaccine-induced immune response. They had lower immunity responses due to COVID-19 vaccine induction than premenopause women.

These findings are in line with Wu et al. that reported in their clinical test that CoronaVac could be properly tolerated and was immunogenic for healthy adults aged older than 60 years old. Responses of neutralizer antibodies on the population toward SARS-CoV-2 did not decrease.¹⁵ Estradiol affects modulated immune cells, namely B cell activation and production of neutralizing antibodies, including S-RBD.^{16,17} In addition, some factors influence the immune response to vaccines, namely intrinsic factors (age, sex, genetic, comorbid), extrinsic factors, lifestyle, nutrition, environment, vaccine administration, and vaccine factors.¹⁸

These results indicate differences in SRBD antibody levels between pre-menopause and menopause based on the duration of vaccination. Statistically, it is not significant. The highest amount of SRBD antibody titer was found on participants with > 12 weeks of vaccination, both in premenopausal and menopausal women. The findings showed menopausal women, after receiving twice doses of vaccine, could improve their antibodies. The same findings were similar with premenopausal women. Thus, menopausal women could take vaccination schedules as younger women did.

It is in line with the study who found that two doses of vaccination with CoronaVac were able

to induce a humoral response in people older than 60 years old. Patients with comorbidity tended to have lower immune responses toward vaccine and infection. These matters resulted in higher vaccination doses or vaccination schedule changes for this group.¹⁹

A study in China found anti-spike antibody responses in health care workers aged 60 years (n=24) after the first dose was relatively low (37.5%). their immunogenicity could reach the level of people aged between 18-59 years old after receiving the second dose (95.7%).¹¹ A study in Chili on CoronaVac found the seroconversion level for people aged 60 years old with a percentage of 18.1% after 14 days of first vaccine administration. Then, the percentage turned into 100% after the second dose received after 28 days.²⁰ The findings were similar to this study, although this is preliminary research. We found an increased antibody titer during <12 weeks after the second dose. This finding would be a consideration to provide vaccination for the susceptible group.

The RBD subunit is an epitope that produces neutralizing antibodies specific to Spike (S) protein.²¹ In this study, participants had varying levels of S-RBD antibodies. Research in identifying the correlation between neutralizing antibodies and CD4+ T cells against S protein found an important role for CD4+ T cell activation in collaborating the activity of B cells and T cells against SARS-CoV-2.²¹ Titer levels of antibodies that are protective against SARS-CoV-2 are still unknown. Memory T cells and B cells triggered by the inactivated vaccine are expected to play an important role in protection against infection by SARS-CoV-2.²²

In this study, some participants have S-RBD antibody titers below <250 U/mL. It could be caused by the low immunogenicity of the inactivated vaccine if compared to the SARS-CoV-2 vaccine using other methods due to the multivalence of antigens from the inactivated vaccine or the decrease in the number of B cells and memory cells due to aging.^{23,24}

CONCLUSION

Based on the results of this study, we conclude that after vaccination, postmenopausal women have lower levels of S-RBD antibodies than premenopausal women. However, the difference is not significant. S-RBD antibody levels in postmenopausal women increased with the

duration of vaccine administration. Two doses of CoronaVac can induce excellent immunity in postmenopausal women, both in terms of and timing of repeated dosing.

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CONFLICT of INTERESTS

The authors declare that there is no conflict of interest.

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Research Article

Preoperative Platelet-Lymphocyte Ratio as a Prognostic Factor of Epithelial Ovarian Cancer

Rasio Trombosit-Limfosit Pra Operasi sebagai Faktor Prognostik Epitel Kanker ovarium

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Abstract

Objective: To determine whether platelet-lymphocyte ratio can be a prognostic factor for epithelial ovarian cancer.

Methods: This study was a retrospective cohort with analytical design, conducted in the Department of Obstetrics and Gynecology of Prof. Dr. R.D. Kandou Manado General Hospital from January – November 2020. The subjects were all patients with epithelial ovarian cancer who met the inclusion and exclusion criteria. Data analysis was conducted with Chi-square test.

Results: 35 subjects were included in this study. Most subjects were 40-50 years and had a platelet-lymphocyte ratio of above 200. The mean platelet-lymphocyte ratio of the subjects with epithelial ovarian cancer was 244.663 ± 130.0234 . Chi-square test showed a significant association between platelet-lymphocyte ratio and the ovarian cancer relapse ($\chi^2 = 14.464$ $p = 0.000$) with $RR=4.0$

Conclusion: There was a significant difference between platelet-lymphocyte ratio and the ovarian cancer relapse.

Keywords: epithelial ovarian cancer, inflammatory marker, platelet-lymphocyte ratio, prognosis.

Abstrak

Tujuan: Untuk mengetahui apakah nilai rasio platelet limfosit dapat menjadi faktor prognostik kanker ovarium epitel.

Metode: Penelitian ini merupakan kohort retrospektif dengan desain analitik di Departemen Obstetri dan Ginekologi RSUP Prof Dr. R.D. Kandou Manado dari Januari – November 2020. Subyek penelitian adalah seluruh pasien dengan kanker ovarium epitel yang memenuhi kriteria inklusi dan eksklusi. Analisa data dilakukan dengan uji Chi-square.

Hasil: Sebanyak 35 pasien diikutsertakan dalam penelitian ini. Mayoritas subyek berusia 40-50 tahun dan mayoritas memiliki rasio platelet limfosit diatas 200. Rerata rasio platelet limfosit pada subyek dengan kanker ovarium adalah 244.663 ± 130.0234 . Uji Chi-square menunjukkan bahwa terdapat hubungan bermakna antara rasio platelet limfosit dengan kekambuhan keganasan ovarium ($\chi^2 = 14,464$ $p = 0,000$) dengan $RR=4.0$

Kesimpulan: Terdapat hubungan bermakna antara rasio platelet limfosit dengan kekambuhan keganasan ovarium.

Kata kunci: kanker ovarium epitel, penanda inflamasi, prognosis, rasio platelet limfosit.

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INTRODUCTION

Epithelial ovarian cancer accounts for 3% of all women cancers worldwide, and ranks third among the most common gynecologic cancers worldwide.¹ Primary cytoreductive surgery, followed by adjuvant chemotherapy, is still the gold standard of epithelial ovarian cancer.² As an advances and development of surgical and chemotherapy techniques, but the prognosis is still poor with a 40% 5-year survival rate. It is due to late stage of detection.³

The understanding of biomolecular properties could predict the patient outcome, many prognostic factors have been investigated especially regarding angiogenesis. Recently, several factors in angiogenesis of epithelial ovarian cancer are inflammatory markers or blood cells, have been studied. An increase in absolute platelet and lymphocyte counts or the platelet-lymphocyte ratio (PLR) has been reported and investigated as a prognostic factor in epithelial ovarian cancer. Furthermore, poor prognosis is found on elevated inflammatory markers in epithelial ovarian cancer patients.^{4,5}

Several studies stated that an increased of PLR is associated with poor clinical and pathological features of cancer.^{4,5} In epithelial ovarian cancer, preoperative thrombocytosis was associated with advanced or inoperable stages.⁶ Several studies used PLR for a study of various type of cancer, namely colorectal, gastric, pancreatic, lung and epithelial ovarian cancers, to improve the prognostic function of platelets.⁷ The limited study on PLR on epithelial ovarian cancer which limits its role as a prognostic factor, whereas another parameter, namely neutrophil-lymphocyte ratio, had been related with it.^{4,5} Meta-analysis in 2014 from various types of cancer, shown that PLR was associated with advanced disease and poor survival from two studies on epithelial ovarian cancer.^{4,5,7}

Due to this lack of study in Manado, so this study was done to evaluate the relationship of platelet-lymphocyte ratio as a prognostic factor of epithelial ovarian cancer on disease free survival (DFS), especially at Prof. DR. R. D. Kandou Central General Hospital, Manado.

METHODS

This study was a retrospective cohort study of epithelial ovarian cancer women confirmed by histopathology, conducted at the Department

of Obstetrics and Gynecology Prof. DR. R. D. Kandou Central General Hospital, from January to November 2020. The sample was collected from medical record. This study was accepted by ethical clearance of Prof. DR. R. D. Kandou Central General Hospital, Manado.

All epithelial ovarian cancer women confirmed by histopatological examination, without any other patologic disease at the same time, without any disease which influence the platelet-lymphocyte ratio significantly (heart valve, autoimmune, blood abnormality disease), with a complete preoperative full blood count preoperative and operation report, and done a treatment at oncology department Prof. DR. R. D. Kandou Central General Hospital for one year, were met the inclusion criteria. Patients willing to participate in this study were asked to sign an informed consent. The exclusion criteria were unfollowed patient in the study period, uncomplete medical record, died due to Covid-19, and not willing to participate in the study. The number of participants were all of the epithelial ovarian cancer medical record at 2020 at Prof. DR. R. D. Kandou Central General Hospital, Manado.

The dependent variable was disease free survival (DFS) of epithelial ovarian cancer. The DFS was the length of survival without a signs or symptoms of the disease after a complete of primary treatment in one year, categorized by relapse and not relapse. The independent variables was platelet-lymphocyte ratio. The platelet-lymphocyte ratio was an absolute platelet count divided by absolute lymphocyte count, and the ratio was grouped by <200 and >200.

Data of platelet-lymphocyte ratio obtained and were collected, processed and analyzed using SPSS software 23rd version. The relationship of platelet-lymphocyte ratio and prognostic factor of DFS was assessed using chi-square test. The survival rate of ovarian cancer based on platelet-lymphocyte ratio was using risk estimation. The significance was used $p < 0.05$.

RESULTS

This study was conducted on 35 women with an epithelial ovarian cancer who met the inclusion and exclusion criteria and signed an informed consent for this study. The characteristics of the study subjects were shown in Table 1.

Table 1. Characteristics of Study Subjects

Characteristic	N	%
Age (years)		
< 40	7	20
40 – 50	15	42.9
> 50		37.1
Platelet-to-Lymphocyte Ratio (PLR)	13	
< 200	13	37.1
> 200	22	62.9
Menopausal Status		
Yes	14	40
No	21	60

Ovarian cancer incidence was more likely found on age of 40-50 years old (42.9%), then 50 years old (37.1%). The mean age of ovarian cancer was 47.57 years old. The platelet-lymphocyte ratio more than 200 was found on 21 ovarian cancer women (60.0%) than 14 (40.0%) women less than 200. The menopausal status from 35 subjects shown that 40% was menopause and the rest was not.

Table 2. The Relationship of Platelet-Lymphocyte Ratio Prognostic Factor and Disease-Free Survival

	Relapse		χ^2*	RR	P-value
	Yes	No			
Platelet-to-Lymphocyte Ratio (PLR)			14.464	4.0	0.000
≥200 (n=21)	18	3			
< 200 (n=14)	3	11			

*using chi-square

In 21 epithelial ovarian cancer women with a PLR ≥ 200 , 18 women had a relapse. In epithelial ovarian cancer women with PLR < 200 , 3 women had a relapse and 11 women did not. The chi-square test showed that there was a significant relationship between PLR and ovarian cancer relapse ($\chi^2 = 14,464$ p = 0.000) with RR=4.0.

Table 3 showed a distribution of PLR in ovarian cancer. The mean PLR in ovarian cancer women in this study was 244.663 ± 130.0234 .

Table 3. Mean Distribution of Platelet-to-Lymphocyte Ratio in Ovarian Cancer

Ovarian Cancer (n=35)	
Platelet-to-Lymphocyte Ratio (PLR)	
Mean	244.663
Median	223.655
Std Deviation	130.0234
Minimum	73.23
Maximum	812.08

DISCUSSION

The study was conducted on women with epithelial ovarian cancer. The age of 40-50 years old (42.9%) were the most common, followed by over 50 years old (37.1%). The mean age was 47.57 years old.

Epithelial ovarian cancer increased at the age of 40-49 years, then leveled off at the age of 50-59 years and decreased above the age of 60 years.⁸ Based on data from Cancer Research UK, the average age of Caucasian women diagnosed with ovarian cancer is 63 years. Shen et al., in China reported that the mean age of epithelial ovarian cancer was 53 years (range, 17-79 years old), which is 10 years earlier than Caucasians.⁹

The PLR > 200 was found in 22 ovarian cancer women (62.9%) and < 200 was found in 13 women (37.1%) from this study. The PLR can be used as a predictive factor in various types of cancer. It plays an important role in the pathogenesis of the systemic inflammatory response and also associated with the prognosis of cancer.¹⁰ Platelet counts increase due to the release of inflammatory mediators which stimulate megakaryocytes to produce more platelets. A PLR > 200 has a significant association with a poor survival in advanced-stage cancer.⁴ The advantage of using this ratio was affordable and easy to examine.¹⁰

From the 35 women, 40% were menopause, in this study. The incidence of epithelial ovarian carcinoma increases after menopause. Several epidemiological studies report that 30% of ovarian neoplasms occurring in postmenopausal patients are malignant, and only 7% of malignant ovarian neoplasms occurring before menopause.⁸

Two main theories have been proposed to explain the association between epithelial ovarian cancer risk and menopause, namely the persistent ovulation hypothesis and the gonadotropin stimulation theory. During the reproductive phase, the epithelial surface of the ovary will be injured due to the physiological process of ovulation. The wound will occur continuously, and the cell proliferation will heal the ovarian epithelium during the post-ovulatory phase. However, the mutation of proliferation leads to the formation of tumors. There is an increase in gonadotropin levels due to reduced ovarian follicles. Which causes an inflammatory response in the ovaries and will lead to tumor formation on the epithelial surface of ovarian cells.⁸

In 21 epithelial ovarian cancer women with a PLR > 200 , 18 women had a relapse. The epithelial

ovarian cancer women with a PLR <200 shown that 3 women had a relapse and 11 women did not. The chi-square test showed that there was a significant relationship between PLR and Ovarian Cancer Relapse ($\chi^2 = 14.464$ $p = 0.000$) with RR=4.0. The results of this study indicate a relationship between PLR with the relapse of ovarian cancer.

Tumor cells and the immune system interact in a complex manner. The immune system inhibits tumorigenesis, but promote inflammation through angiogenesis and immune cell evasion.¹¹ The tumor microenvironment activity is characterized by the presence of inflammatory markers such as platelets, lymphocytes and neutrophils.¹² Inflammation is crucial for tumor progression.¹³ Leukocytes and platelets are secreted in large amounts due to inflammatory mediators such as cytokines and chemokines. Elevated PLR, NLR, and CRP are a sign of an increase inflammation due to the tumor itself or the host response.¹⁴

Inflammation plays a role in carcinogenesis and cancer progression. It contributes to the cancer capability by maintaining proliferation, angiogenesis, activation of the epithelial-to-mesenchymal transition, invasion, metastasis, and inhibitor of cancer cells death.¹⁵ It is required in both early and late stages of tumorigenesis, as a result of a natural and adaptive immune response for eliminating cancer cells. However, cancer cells can escape from it and continue to grow. Chronic inflammation is a developmental risk factor. Several studies examine the relationship of cytokines and chemokines to cancer cells. In ovarian cancer, cytokines regulate the proliferation and survival of cancer cells.¹¹ Inflammation in ovarian cancer can be used as a predictor of its prognosis and response to therapy.¹⁶

The inflammatory response of neutrophil, lymphocytes, and platelets are an important factor in the tumorigenesis pathway. Platelet counts increase due to platelet-derived growth factor, platelet factor 4, transforming growth factor β , vascular endothelial growth factor and thrombospondin, for attachment of several cell types, including the surface epithelium of the ovary. In addition, its production in bone marrow stimulated by cytokines such as interleukin 6, TNF- α , and growth factors influenced by cancer cells, causing thrombocytosis.¹⁷ Thrombocytosis in cancer is associated with poor survival.¹⁸

Platelets recruited by tumor cells can be used

by cancer cells as a catalyst for the acceleration of tumor growth, angiogenesis, and metastasis processes. When the tumor volume exceeds a certain size (>1-2mm³), the tumor begins to produce a new vascularization (angiogenesis) through the surrounding blood vessels, as a source of nutrients and oxygen for the tumor cells for survival and growth. Pro-angiogenic factors facilitate the process of angiogenesis by increasing vascular growth, vasodilatation, and increasing blood supply, which in turn accelerates tumor growth and metastasis.¹⁹

An increase in platelet count and a high PLR are indicators of poor prognosis in a several types of cancer.^{12,20} Ovarian cancer women undergone a surgery, the PLR >300 had a poorer prognosis.²¹ A meta-analysis showed that a high PLR before treatment had an overall survival and progression-free survival shorter. Patients with ovarian cancer had a higher PLR than benign ovarian masses.²²

Previous clinical studies reported that an increase of NLR, PLR, neutrophil count, or platelet count was associated with poor clinical characteristics such as a high risk of relapse, aggressive tumor biology, and higher tumor progression in various types of cancer. A high PLR and CRP were associated with lower overall survival and DFS. The advantage of using inflammatory markers in ovarian cancer is easily obtained, inexpensive, and non-invasive using a laboratory data.¹⁴

The meta-analysis in 1250 ovarian cancer women reported that a higher PLR was strongly associated with lower overall survival, with a hazard ratio of 1.63. In addition, a high PLR has a lower progression free survival than a low PLR.²² The PLR was a superior prognostic factor over the neutrophil ratio or other markers of the inflammatory response in the epithelial ovarian cancer women.²³

However, the mechanism underlying the increase of PLR on ovarian cancer is not fully understood. It is associated by an increase of systemic inflammatory response. The lymphocyte count decreased due to the antitumor immune response, as a favorable condition for the tumor microenvironment.²²

A reduced number of lymphocytes is an indicator of a reduced immune response, and correlated with a higher mortality in ovarian cancer than the control group or benign disease.²² Lymphocytes kill cancer cells, inhibit the proliferation and migration of tumor cells.¹⁸

A low absolute lymphocyte count reduces the efficacy of therapy and the prognosis of ovarian cancer originating from epithelial, connective, or lymphoid tissue.¹⁵ A high lymphocyte count and type 1 lymphocyte infiltration in tumor tissue are associated with a better prognosis in ovarian, colon, lung, and breast cancer. A low lymphocyte levels causes a weaken immune response to tumors.²²

The other factors affect the prognosis of ovarian cancer are cancer pathology, molecular genetic factors, and cancer stage. Ovarian tumors are a heterogeneous, with a varied outcome. The heterogeneity of these tumors is characterized by its biological and molecular profile. In addition, the platelet counts can be influence not only by cancer cells but also the occurrence of acute or chronic infections or other inflammatory diseases and smoking habits.^{19,24,25}

CONCLUSION

There was a significant relationship between platelet-lymphocyte ratio with a relapse of ovarian cancer, higher with ratio platelet-lymphocyte more than 200. There should be a further cohort study with a more sample and different prognostic parameter.

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Research Article

Effect Knowledge and Attitude with Behaviour of HPV Vaccination in Women of Reproductive Age***Pengaruh Pengetahuan dan Sikap dengan Perilaku Vaksinasi HPV pada Wanita Usia Reproduksi*****Budi Darmawan, Bismarck J. Laihad, Frank M. M. Wagey**

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Abstract

Objection: To observe the association between knowledge and attitude towards HPV vaccination with the behavior towards HPV vaccination on reproductive woman in Indonesia.

Methods: We conducted observational analytic study with cross-sectional design. The study was conducted in obstetric and gynecologic outpatient clinic in Prof. Dr. R. D. Kandou General Hospital, Manado Indonesia through July and August 2021. Reproductively active woman were included as the subject. Univariate and bivariate analysis were conducted in this study.

Results: We included 364 reproductive woman. The majority of the subject were 20-35 year-old woman (50.8%) and were married (61.3%). The majority of the subject (72.8%) have received information about HPV vaccination. We found significant association between knowledge and attitude with the OR of 5.57 ($p=0.00$). Knowledge and attitude showed significant association with eagerness towards HPV vaccination. However, knowledge and behavior did not show any significant association towards HPV vaccination behavior.

Conclusion: There is a significant association between knowledge and attitude of HPV vaccination with eagerness toward HPV vaccination in reproductive women in Indonesia.

Keywords: behavior, HPV vaccination, knowledge, reproductive women.

Abstrak

Tujuan: Untuk mengetahui hubungan pengetahuan dan sikap terhadap perilaku vaksinasi HPV pada perempuan usia reproduktif di RSUP Prof. DR. R. D. Kandou, Manado.

Metode: Penelitian ini merupakan penelitian analitik observasional dengan pengambilan subjek potong lintang. Penelitian dilakukan di unit pelayanan bagian Obstetri dan Ginekologi RSUP Prof. Dr. R. D. Kandou Manado pada Juli-Agustus 2021. Subjek penelitian merupakan perempuan usia reproduktif yang bersedia untuk mengikuti penelitian ini. Analisis data akan dilakukan secara univariat dan bivariat serta dilaporkan pada penelitian ini.

Hasil: Penelitian ini mencakup 364 perempuan dengan usia produktif. Mayoritas subjek merupakan perempuan dengan usia 20-35 tahun (50,8%) dan sudah menikah (61,3%). Mayoritas subjek (72,8%) pernah mendapatkan informasi vaksinasi HPV sebelumnya. Hubungan antara pengetahuan dan sikap terhadap vaksinasi menunjukkan hasil yang signifikan ($p=0,00$) dengan OR 5,57. Pengetahuan dan sikap juga menunjukkan hubungan yang signifikan dengan kesediaan vaksin ($p<0,05$). Pengetahuan dan sikap tidak menunjukkan hubungan yang bermakna terhadap perilaku vaksin ($p>0,05$).

Kesimpulan: Terdapat hubungan yang bermakna antara pengetahuan dan sikap dengan perilaku keinginan vaksinasi HPV pada perempuan usia reproduktif.

Kata kunci: pengetahuan, perempuan usia reproduktif, sikap, Vaksinasi HPV.

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INTRODUCTION

Cervical cancer causes approximately 300,000 deaths in women annually. New cases of cervical cancer is recorded to be half a million cases annually. Cervical cancer is a major problem since 90% of women with cervical cancer live in the low-middle-income countries with limited screening and HPV vaccination programs. The treatment of cervical cancer depends on the diagnosis and staging; therefore, screening and diagnosis is crucial in reducing the mortality and morbidity rate of cervical cancer.

Cervical cancer is the fourth most common cancer in women and is still a huge problem in the medical world. The mortality rate in low-income and developing countries is 18 times higher than in the developed countries. Almost all of cervical cancer cases is caused by the *human papillomavirus* (HPV) with a high-risk cervical cancer subtype. In the developed countries, proper preventive measures with screening and HPV vaccination have effectively reduced the incidence rate; however, developing countries are still struggling to implement preventive methods evenly. This makes preventive methods of cervical cancer in patients important to be developed and studied.¹

Human papillomavirus or HPV is a member of the *Papillomaviridae* family, which is a non-enveloped DNA viral family. HPV has approximately 216 subtypes, which are generally classified into low-risk, moderate-, and high-risk types. The low- and moderate-risk types have a low potential in causing malignant transformation, while the high-risk types, particularly type 16 and 18, have a high risk in causing malignancy. Both types are responsible for 70% of cervical cancer cases globally.²⁻⁵

WHO also stated that doubts about vaccine are one of the 10 biggest threat of health to the world, which highlights the importance of vaccine in preventing various morbidity and mortality, especially in cases of cervical cancer.^{6,7}

Despite the efficacy of HPV vaccine, there are important problems regarding the application in the society. HPV vaccination is target population is still suboptimal. According to studies in several countries, especially developing countries, HPV vaccination behavior in preventing cervical cancer is still low. One of the study in West Kenya stated that only 9.4% of people received HPV vaccination.⁸

From these studies, it can be concluded that

although the first or second generation of HPV vaccine is proven to be effective in preventing cervical cancer and has minimum side effects, there are still many obstacles in the behavior of the people. The knowledge and attitude factors are essential to be studied to conduct a wide and effective HPV vaccination, thus, reducing the incidence of cervical cancer. Therefore, we conducted a study regarding the association of knowledge and attitude with behaviour of HPV vaccination in women of reproductive age who presented to the Department of Obstetrics and Gynecology RSUP Prof. DR. R. D. Kandou, Manado.

METHODS

This study was an observational analytic with cross-sectional design, conducted in every Obstetrics and Gynecology services in RSUP Prof. Dr. R. D. Kandou Manado from July – August 2021. The sample in this study included women of reproductive age who visited the Department of Obstetrics and Gynecology of RSUP Prof. Dr. R. D. Kandou during the study period and met the inclusion criteria.

The inclusion criteria included women aged 15-49 years old who visited the Department of Obstetrics and Gynecology of RSUP Prof. Dr. R. D. Kandou, in a healthy condition and fully conscious, and are willing to participate in the study. The exclusion criteria included women who refused to participate in the study, were sick, had difficulty speaking or were not fully conscious, not part of the health workers at RSUP Prof. Dr. R. D. Kandou Manado, and patients with suspected COVID-19 based on symptoms and examination.

Data were obtained using questionnaires. The knowledge and attitude variables were assessed based on the median result of the questionnaire. Vaccination behaviour variable was assessed by collecting data on whether the patient was vaccinated for HPV or not. Data were analyzed with chi-square and Fisher exact using the SPSS program. All subjects have signed the informed consent, and the study has been approved by the Ethics Committee of RSUP Prof. Dr. R. D. Kandou Manado.

RESULTS

A total of 364 women who presented to the Department of Obstetrics and Gynecology RSUP Prof. Dr. R. D. Kandou Manado were included

in the study. Most subjects (50.8%) were 20-35 years old.

Table 1. Characteristic of the Study Subjects

Characteristic	Cases	
	N (364)	%
Age		
<20	53	14.6
20-35	185	50.8
>35	126	35.6
Education Level		
Had never attended school	6	1.6
Elementary	18	4.9
Junior High	51	14
Senior High	199	54.7
Diploma/Undergraduate	89	24.5
Postgraduate	1	0.3
Occupation		
Student	91	25
Not working	134	36.8
Working	139	38.2
Marital Status		
Unmarried	135	37.1
Married	223	61.3
Widowed	6	1.6
Family Income (rupiah)		
< 2.000.000	204	56
2.000.000 – 5.000.000	119	32.7
> 5.000.000	41	11.3
Have Heard Informations about HPV Vaccination		
Yes	265	72.8
No	99	27.2
Have Heard Informations about Cervical Cancer Screening		
Yes	129	64.6
No	235	35.4

The median score for the knowledge variable was 76, while the score for attitude variable was 80. The analysis of association between knowledge and the willingness to vaccinate and vaccine behaviour showed a significant association between knowledge and willingness to vaccinate with a p value of <0.05 OR 5.75. The association between knowledge and vaccine behaviour showed non-statistically significant result, with a p-value of >0.05.

Table 2. The association between knowledge and willingness to vaccinate

Variable	Willingness to vaccinate		P-value	OR (CI 95%)
	Good	Poor		
Knowledge			0.000	5.75 (3.5-9.3)
- Good	178 (83.1)	36 (16.8)		
- Poor	67 (31.3)	78 (36.4)		
Total	245 (68.2)	114 (31.7)		

*Analysis with chi-square and expected count <5 less than 20%.

Table 3. The association between knowledge and vaccine behaviour

Variable	Vaccine behavior		P-value	OR (CI 95%)
	Good	Poor		
Knowledge			0.652	2.71 (0.3-24.4)
- Good	4 (1.8)	214 (100)		
- Poor	1(0.4)	145 (67.7)		
Total	5 (1.3)	359 (100)		

*Analysis with Fisher exact and expected count <5 less than 20%.

The association between attitude and willingness to vaccinate was shown to have a significant association with a p-value of <0.05 and OR 17.6, indicating that good attitude increases the likelihood of willingness to vaccinate of 17 times higher than subjects with poor attitude.

Table 4. The association between attitude and willingness to vaccinate

Variable	Willingness to vaccinate		P-value	OR (CI 95%)
	Good	Poor		
Knowledge			0.000	17.6 (9.3-33.3)
- Good	170 (79.4)	13 (6)		
- Poor	75 (35)	101 (47.1)		
Total	245 (68.2)	114 (31.7)		

* Analysis with chi-square and expected count <5 less than 20%.

Table 5. The association between attitude and vaccine behaviour

Variable	Vaccine behaviour		P-value	OR (CI 95%)
	Good	Poor		
Knowledge			0.061	2.32
- Good	5 (2.3)	183 (85.5)		
- Poor	0 (0)	176 (82.2)		
Total	5 (1.3)	359 (100)		

* Analysis with Fisher exact and expected count <5 less than 20%.

DISCUSSION

In this study, 364 women in reproductive age who presented to the Department of Obstetrics and Gynecology of RSUP Prof Dr R D Kandou Manado were included. Most subjects were women aged 20-35 years (50.8%), followed by women aged >35 years (35.6%). The age distribution in this study is considered appropriate considering the high incidence of cervical cancer in women aged 30-49 years. The consideration of age was also adjusted with the timing of HPV vaccination, which is recommended for adult women. The guideline by CDC stated that HPV vaccine can be administered in adult women aged 27-45 years with a clinician's consideration if the patient has not received adequate HPV

vaccination during their youth.⁹ This result showed that most subjects in this study were candidates for HPV vaccination in adult and might reflect the population. In the educational level, most subjects had an educational level of high school or undergraduate/diploma, accounting for over 80%. The educational level might affect knowledge and attitude toward HPV vaccination, which is the outcome of this study. Previous studies have shown an association of lower education with awareness of HPV infection.¹⁰ Previous studies regarding knowledge level in HPV vaccination also showed similar educational level of the subjects as in this study.¹¹ In this study, the educational level of most subjects were considered quite high with high school or diploma/undergraduate. This is expected to provide a fairly good knowledge level regarding HPV infections or vaccinations.

This study showed a 5.7 times increase in willingness to vaccinate in subjects with good knowledge level compared to poor level. The association between knowledge and HPV vaccination behaviour was not statistically significant. However, the result showed a 2.7 times increase in HPV vaccine behaviour in subjects with good knowledge level compared to poor knowledge level. The non-significant result in this study might be due to the small study sample in the group who had received vaccination in this study. Only five subjects (1.37%) in this study who have received HPV vaccination. Previous studies showed similar result with very low vaccination rate in the population, particularly in developing countries.¹¹ This finding might be due to the low knowledge level of the population in those countries regarding cervical cancer and HPV vaccination. Other studies have shown that the low HPV vaccination rate might be due to confusing age recommendation and unclear vaccination schedule, leading to patients' reluctance in counseling and receiving HPV vaccination.^{12,13} This finding showed the importance of knowledge and education from the health workers in promoting HPV vaccination to the society.

The association between attitude and willingness to vaccinate showed a statistically significant result. The OR in this study showed a 17 times increase of willingness to vaccinate in subjects with good attitude compared to subjects with poor attitude. In contrast, the association between attitude and HPV vaccine behaviour was not statistically significant ($p > 0.05$). However,

the OR showed increased vaccine behaviour in subjects with good attitude. The non-significant result might be due to the low number of study sample. There was no subject who have received vaccination and have a poor attitude, which caused a higher risk of bias in the analysis. Previous studies showed that positive attitude towards HPV vaccination might affect the willingness to vaccinate in women.¹⁴

The analysis result of this study showed an imbalance between the willingness to vaccinate and vaccination behaviour of the study subjects. The imbalance between willingness to vaccinate and behaviour might be due to the limited access for adult population to obtain HPV vaccines. Furthermore, the vaccination criteria for women of a certain age might also be the cause of such low vaccination rate in this study population. Currently, HPV vaccination program has been ongoing for children in the fifth and sixth grade of elementary school for free. However, HPV vaccination is young adult and adult populations is still scarce. Therefore, more efforts to increase education and information regarding HPV vaccination in the adult population are needed in Indonesia to increase the knowledge and willingness of women of reproductive age in receiving HPV vaccines as an effort to prevent cervical cancer.

CONCLUSION

Based on this study, it can be concluded that there is no significant association between knowledge and attitude of women of reproductive age with HPV vaccination behaviour, there is a significant association between knowledge and attitude of women of reproductive age with willingness to vaccinate.

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Case Report

Thanatophoric Skeletal Dysplasia Type 2: Diagnostic and Management Dilemmas

Displasia Skeletal Tanatoforik Type 2: Dilema dalam Diagnosis dan Manajemen

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Abstract

Objective: To report a rare case of thanatophoric skeletal dysplasia type 2 that we diagnosed during prenatal period; and to provide further review of dilemmas in diagnostic methods and management, based on appropriate literatures and guidelines available.

Methods: Case report

Case: A 33-year old primigravida women was diagnosed with pre-term pregnancy (24th weeks of gestation) and intra-uterine singleton live fetus with thanatophoric skeletal dysplasia type 2 via ultrasonography. Pregnancy termination via elected caesarean section at 26th weeks of gestation was performed per the patient request after considering the fetus's lethality. A female neonate was born weighing 980 grams with frontal bossing (Head Circumference: 26 cm), lower set of ears, hypertelorism, bilateral exophthalmos, short neck, rhizomelic short extremities, and narrow thorax (Thorax Circumference: 17 cm). The newborn was immediately transferred to NICU for post-natal management and observation. The newborn is in stable condition for the first several hours; nevertheless, significant destabilization occurred afterwards and the newborn deceased approximately 10 hours after birth due to cardiorespiratory failure. No further invasive resuscitative efforts and post-mortem examinations were performed on the parent's request.

Conclusion: Thanatophoric dysplasia is primarily diagnosed using ultrasonography, which has a high detection rate for both diagnosis and prognostications. Even though, There has been a dilemma in performing molecular diagnostic testing, prediction of recurrence risk in future pregnancies can be assessed with its use. Although still remains a challenge in ethical and medicolegal grounds; proper management requires holistic considerations of maternal, fetal, and perinatal aspects.

Keywords: Thanatophoric, Skeletal Dysplasia, FGFR3 mutation.

Abstrak

Tujuan: Melaporkan suatu kasus langka displasia skeletal tanatoforik tipe 2 yang kami diagnosa dalam periode perinatal; serta memberikan ulasan lanjut mengenai dilema dalam metode diagnostik dan manajemen, berdasarkan literatur dan pedoman ilmiah yang tersedia.

Metode: Laporan Kasus.

Kasus: Seorang perempuan primigravida berusia 33 tahun di diagnosa dengan kehamilan pre-term (24 minggu gestasi), janin tunggal hidup intrauterin dengan displasia skeletal tanatoforik tipe 2 via ultrasonografi. Terminasi kehamilan dengan Sectio Caesarea dilakukan atas permintaan pasien setelah mempertimbangkan letalitas janin. Lahir bayi perempuan berat 980 gram, dengan 'frontal bossing' (lingkar kepala: 26 cm), kedua telinga rendah, hipertelorisme, eksoftalmos bilateral, leher pendek, ekstremitas pendek rizomelik, dan rongga dada kecil (lingkar dada: 17 cm). Bayi segera dipindahkan ke NICU untuk manajemen paska-natal dan observasi. Kondisi bayi stabil selama beberapa jam pertama; namun, ketidakstabilan yang signifikan terjadi setelah itu dan bayi dinyatakan meninggal 10 jam paska kelahiran dikarenakan kegagalan kardiorespirasi. Bayi tidak dilakukan tindakan resusitasi invasif dan pemeriksaan paska kematian atas permintaan pasien.

Kesimpulan: Displasia tanatoforik dapat di diagnosa secara primer menggunakan pemeriksaan ultrasonografi (US) dengan tingkat deteksi diagnosis dan prognosis yang tinggi. Meskipun pemeriksaan diagnostik molekular masih menjadi dilema, pemeriksaan ini dapat memprediksi resiko rekurensi pada kehamilan selanjutnya. Walaupun masih merupakan suatu tantangan dalam segi etika dan medikolegal; manajemen ideal perlu mempertimbangkan secara holistik seluruh aspek yang mencakup: ibu, janin, dan paska kelahiran.

Kata kunci: Tatanoforik, Displasia Skeletal, Mutasi FGFR3.

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INTRODUCTION

Thanatophoric Skeletal Dysplasia (TD) is a type of lethal skeletal dysplasia disorders, which typically involves underdeveloped formation and growth of long bones; and limitation in lung growth.¹ The term first described by Maroteaux et al. 1967, based on the Greek term 'thanatophoric' or 'deathbringing'.² TD is considered as a rare disorder with an overall incidence of 1 in 20,000 to 1 in 60,000 births; however, it is also considered as the most common lethal skeletal dysplasia, contributing to approximately 29% of all lethal skeletal dysplasia cases.³ The incidence of TD varies between congenital autosomal dominant inheritance (20% cases) and sporadic incidence (80% cases); both involve mutations in fibroblast growth factor receptor gene 3 (FGFR3). This further classifies TD into two distinct types: the more common variant of TD type 1, which is usually caused by missense, no-stop codon, or insertion variant mutations; and the less common variant of TD type 2, which is usually caused by single pathogenic variant mutation.^{4,5} Although it is considered rare, dilemmas arise in determining proper diagnostic methods and managements. Since early prenatal recognition of the disorder will promote proper management planning; therefore we considered discussions regarding this matter necessary to raise awareness of medical personnel specifically working in the field of obstetrics and gynecology. In this paper, we reported a case of pre-term fetus with prenatal sonographic findings consistent with TD type 2 in our obstetrics and gynecology out patient department.

CASE REPORT

A 33-year old primigravida women (G1A0) on her 24th week of gestation visited our out patient department for a follow up prenatal check-up. The patient had five consecutive previous prenatal check-ups performed once each month in our clinic. The first and latest prenatal check-ups were performed on her 6th and 19th week of gestations respectively with no major fetal anatomic abnormalities discovered during previous visitations. Previous laboratory examinations; which include routine blood examination, urine dipstick, hepatitis B surface antigen (HbsAg), anti-syphilis (VDRL) and anti-HIV; were within normal limits. She recalled having tetanus toxoid injection once during her first prenatal check-up

visit. The patient had routinely consumed folic acid and ferrous sulfate medications; and no other medications are consumed or used. The patient has been married for a year; she was a non-smoker, non-alcoholic, and has no history of drug abuse. She has neither personal nor family history of congenital abnormalities, diabetes, hypertension, and other diseases.

General physical, vital signs, and obstetrics examinations of the patient were unremarkable. Transabdominal 2D ultrasonography with real time 4D rendering performed by a maternal-fetal specialist; revealed a singleton intrauterine pregnancy with fetal heart rate of 135 beats per minute (M-Mode) and fetal movement was unremarkable. Fetal biometry was equivalent to 24⁺⁵ weeks of gestation with EFW of 766 +/- 112 grams. Neurological cranial sonography revealed megalencephaly (BPD: 79.4 mm and HC: 262.3 mm) with the appearance of cloverleaf skull, enlarged temporal lobe, hypertelorism, and slight low nasal bridge [Figure 1]. Short extremities with rhizomelic pattern were also observed (FL: 35.9 mm). Thoracic sonography revealed visible small narrow bell/barrel shaped chest cavity (TC: 164.7 mm, AC: 211.1 mm, TC/AC: 0.78, FL/AC: 0.17) with heart to chest diameter > 0.5, which further signified pulmonary hypoplasia [Figure 2]. Normal placental structure was observed along the anterior wall of the uterus with no polyhydramnios (AFI: 146 mm). In general, sonographic impressions was suggestive of thanatophoric skeletal dysplasia type 2.



Figure 1. (A) 2D Transabdominal Ultrasound of fetal head (Axial View) at 24⁺⁵ weeks' gestation revealed megalencephaly and temporal lobe enlargement (BPD: 79.4 mm and HC: 262.3 mm, both values > 97.5th percentile of Hadlock Standard) with cloverleaf skull, (B) 4D Real Time Sonographic Rendering (from Mid-Sagittal View) revealed frontal bossing (white asterisk), hypertelorism and slight low nasal bridge (blue triangle).

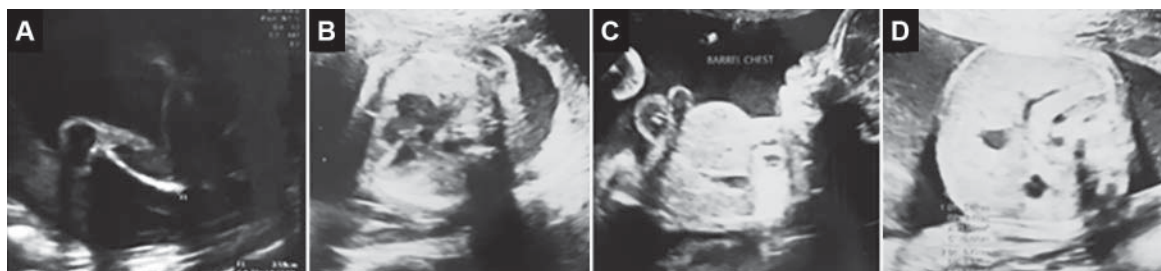


Figure 2. (A) 2D Transabdominal Ultrasound revealed short extremities with rhizomelic pattern (FL: 35.9 mm, < 2.5th percentile of Hadlock Standard), (B) (C) Thorax at the level of four chamber view (Axial View) and (Mid-Sagittal View) respectively revealed small narrow bell/barrel chest cavity (TC: 164.7 mm, which is slightly < 50th percentile and visible heart:thorax > 0.5) which signifies pulmonary hypoplasia, (D) Abdominal Circumference (AC) measured: 211.1 mm (< 50th percentile of Hadlock Standard); hence, calculated TC:AC of 0.78 (< 0.8) and FL:AC of 0.17 (close to < 0.16) which also signifies pulmonary hypoplasia.

The case was considered lethal for the fetus; henceforth, termination of pregnancy was advised after further consultation with a maternal-fetal specialist, in which the patient agreed. The labor was then terminated via lower uterine segment caesarean section at the gestational age of 26th weeks on behalf of the patient's request. The patient's pre-operative blood examination revealed B positive blood group with blood count and infection marker results confirmed uneventful. The perinatology department was informed about the situation and parents were given proper counselling regarding the child's poor prognosis and potential post-natal management. The newborn was a 980 grams female. Head examination revealed frontal bossing (head circumference: 26 cm), lower set of ears, hypertelorism, bilateral exophthalmos, and short neck. Upper and lower extremities examination revealed visibly slight short proximal extremities (rhizomelia). Chest examination revealed slightly narrow thorax (thorax circumference: 17 cm) [Figure 3]. Placenta and umbilical cord appearances were normal. Post-operative course of the mother was uneventful.



Figure 3. General appearance of the newborn revealed frontal bossing, lower set of ears, hypertelorism, bilateral exophthalmos, short neck and slight short proximal extremities.

The newborn was immediately transferred to the neonatal intensive care unit (NICU) for further monitoring due to suspected lethality of the skeletal dysplasia with mild asphyxia and respiratory distress after birth (APGAR score: 7/8). At birth, the newborn was peripherally cyanotic, heart rate and respiratory rate above 100 bpm and 60 bpm respectively, cry when stimulated with flexed arms and legs; however, the condition improved after proper neonatal management was given. The newborn was given oxygen supplementation via nasal cannule with 1L/minute flow rate, and oral-gastric tube (OGT) was also installed to reduce the risk of aspiration. The newborn's condition remained stable for the first seven hours after birth; nevertheless, significant reduction in heart rate, respiratory rate and oxygen saturation occurred simultaneously afterwards. Despite the best efforts provided by the perinatology team to re-stabilize the condition, the newborn continually worsened; and unfortunately deceased approximately 10 hours after birth due to cardiorespiratory failure. No further invasive resuscitative efforts and post-mortem examinations were performed on the parent's request.

DISCUSSION

Thanatophoric skeletal dysplasia (TD) is a part of lethal skeletal dysplasia cluster of conditions typically involving abnormal bone formation and growth in long bones of the extremities and the ribs, which consequently lead to limitation in lung growth contributing to its lethality.¹ The term first described by Maroteaux et al. 1967, based on the Greek term '*thanatophoric*' or 'deathbringing', which emphasizes the high mortality of such affected infants within the first few hours after birth.² The most recent nosology and classification of genetic skeletal disorders

9th ed. 2015 classified skeletal dysplasia into 436 disorders divided into 42 distinct groups with a total number of 364 genes involved.⁶ The overall prevalence of skeletal dysplasia is approximately 3 in 10,000 births, in which approximately half is considered lethal; and contributed to approximately 9 in 1,000 cases of perinatal deaths, in which 23% are stillbirths and 32% do not survive within the first week of life. TD is considered as the most common lethal skeletal dysplasia, contributing to approximately 29% of all lethal cases (1 in 20,000 to 1 in 60,000 births).¹⁻³ There has been three cases reported in Indonesia.^{2,7,8}

The etiopathology of TD varies between congenital autosomal dominant inheritance in minority of cases and sporadically 'de novo' new mutations in majority of cases; both involve mutations in fibroblast growth factor receptor gene 3 (FGFR3). This further classifies TD into two distinct types: (1) Type 1 (80% of cases), the more common variant of TD usually caused by missense, no-stop codon, or insertion variant mutations of R248C and Y373C in FGFR3 gene; and (2) Type 2 (20% of cases), the less common variant of TD usually caused by single pathogenic variant mutation of K650E in FGFR3 gene.^{4,5}

Diagnostic Dilemma

The diagnosis of TD can be established by initial prenatal evaluation using ultrasonography (US) and/or molecular diagnostic testing; and postnatal/termination evaluation. Prenatal diagnosis of TD with ultrasonography (US) is considered as the primary method of evaluation in order to narrow the differential diagnosis of skeletal dysplasia, hence specific confirmatory molecular testing can be performed afterwards; and to predict lethality, which affects management planning. Sonographic impressions of TD varies between short extremities seen as mild straight rhizomelic (proximal) with flared metaphyses and cloverleaf skull seen in TD type 2; and severe micromelic (proximal and distal) with bowed 'telephone receiver' shaped proximal bones of extremities with frontal bossing, midface hypoplasia and no cloverleaf head deformity seen in TD type 1.^{4,9}

Fetal head and spine are both compulsory anatomic regions to be screened in a routine sonographic examination; therefore, craniofacial and neurological anomalies, which is commonly associated with skeletal dysplasia, can be

included or excluded. Fetal head sonographic examination of patients with TD Type 2 in axial plane view may typically revealed cloverleaf skull, which is due to premature closure of the coronal and lambdoid sutures, accompanied with megalencephaly (abnormally enlarged brain) and enlarged temporal lobes. Our case presented impressions of cloverleaf skull accompanied with megalencephaly and temporal lobe enlargement, shown by measured biparietal diameter (BPD) of 79.4 mm and head circumference (HC) of 262.3 mm, in which both values > 97.5th percentile according to Hadlock Standard. Mid-sagittal plane view with real time 4D rendering may revealed frontal bossing, hypertelorism, and slightly low nasal bridge suggestive of midface hypoplasia, just as presented in our case **[Figure 1]**.^{4,9}

The fetal femur is one of the proximal long bones routinely examined during the second trimester sonographic evaluation; severe short femur below the 5th percentile or two standard deviation for the gestational age is typically a defining characteristic of skeletal dysplasia specifically in TD; our case presented a straight rhizomelic short extremities with average bilateral femur length (FL) of 35.9 mm, which is below 2.5th percentile for the gestational age according to Hadlock standard **[Figure 2]**. Severe short femur warrants complete examination of all the long bones of extremities, ribs and vertebrae; not only to confirm the diagnosis of TD, but also to exclude other differential diagnosis such as: homozygous achondroplasia (typically characterized by 'trident hand' formation and both parents are typically affected), and asphyxiating thoracic dysplasia ('Jeune Syndrome', typically characterized by polydactyly, slightly short extremities and normal vertebrae).^{4,9} Mild short femur above 5th percentile for gestational age otherwise requires serial examinations in order to exclude non-skeletal dysplasia conditions such as: false measurements, constitutional short extremities, fetal growth restrictions (FGR), or aneuploidy (Trisomy 21 or Down Syndrome).¹⁰

Lethality prediction in skeletal dysplasia with ultrasonography is considered a crucial step in prenatal diagnosis, since half of skeletal dysplasia is considered lethal, which therefore affects prognosis and post-partum management in planning necessary airway and ventilation support for the newborn.³ This highlights one important aspect of skeletal dysplasia, in which management requires multi-disciplinary

collaborations between obstetrician, geneticist, perinatologists, paramedics and other medical fields necessary. Skeletal dysplasia lethality is attributed to pulmonary hypoplasia with several sonographic parameters, which includes: (1) thoracic circumference/TC at the level of four chamber heart view measured < 2.5th percentile for the gestational age¹¹, (2) thoracic to abdominal circumference ratio (TC:AC) < 0.8¹¹, (3) heart to chest circumference ratio > 0.5¹¹, (4) small bell/barrel shaped chest cavity^{4,11}, and (5) femur length to abdominal circumference ratio (FL:AC) < 0.16, especially in the presence of polyhydramnios.¹²

Our case presented a fetus with sonographic measured thoracic circumference (TC) of 164.7 mm, this parameter may not be significant since its slightly below the 50th percentile for the gestational age according to Lian et al. 2021 chart.^{11,13} However, our case also displayed other parameters of pulmonary hypoplasia; such as TC:AC of 0.78 (< 0.8 cut-off mentioned) and FL:AC of 0.17 without the presence of polyhydramnios (close to the 0.16 cut-off mentioned with amniotic fluid index/AFI of 146 mm, which is still within normal limits of 5 - 250 mm), while taking into account the measured AC of 211.1 mm (below 50th percentile for gestational age according to Hadlock standard).^{11,12} Other parameters which support the lethal characteristic of our skeletal dysplasia case include visible heart to chest circumference ratio > 0.5 and small narrow bell/barrel shaped chest **[Figure 2]**. All sonographic impressions acquired from our case is suggestive of thanatophoric skeletal dysplasia type 2, which is considered lethal with poor prognosis.^{4,11}

Molecular diagnostic testing and referral for genetic counseling in order to confirm specific skeletal dysplasia and predict prognostications, has been a dilemma in patients with an ongoing pregnancy affected with a 'de novo' (sporadic) skeletal dysplasia disorder, and in patients with prior pregnancy affected with a new dominant skeletal dysplasia disorder. This in part due to the fact that: (1) DNA analysis can be a lengthy process; (2) a failure or negative result to identify a specific mutation doesn't change prognostications based on sonographic findings; (3) mutations in the same gene can cause different forms of skeletal dysplasia and the opposite applied and (4) high cost for examination. Likewise, most common methods used to obtain fetal DNA for sampling are considered invasive and highly associated with miscarriage, such methods include: chorionic

villus sampling (CVS) performed transcervical (11th -14th weeks of gestation) or transabdominal (after 11th weeks of gestation), and amniocentesis performed transabdominally (after 15th weeks of gestation); however, circulating cell-free DNA (CF-DNA) in maternal blood has recently been developed as a non-invasive fetal DNA sampling method. Prenatal diagnosis of skeletal dysplasia with ultrasonography (US) has a high detection rate; nevertheless, molecular diagnostic testing in affected fetus with parental history of skeletal dysplasia is proven useful for determining prenatal or preimplantation risk of recurrence and lethality in future pregnancies rather than for prognostication in current affected pregnancy.¹⁴

Fetal DNA sample is compared with both parental leucocyte DNA samples. In TD cases, if mutated FGFR3 pathogenic variant can be detected in fetal DNA sample but not in parental leucocyte DNA samples, then the occurrence is more likely to be 'de novo' or inherited from parents with somatic and/or germline mosaicism; risk of recurrence in 'de novo' cases are presumably low, but slightly higher than in general population due to possibilities of parental mosaicism. The fetus described in our case is suspected as an example of 'de novo' thanatophoric skeletal dysplasia (TD) type 2, since both parents has recalled no history of congenital anatomic anomalies and sporadic TD accounts for majority of all cases as previously mentioned. Nonetheless, due to cost-effectivity measures with assumed high lethality within the first few hours of life and presumably low risk of recurrence in future pregnancies; after further discussion with the patients, they decided to postpone molecular diagnostic testing for the next pregnancies to come.^{3,4}

Management Dilemma

After lethal skeletal dysplasia specifically TD type 2 is diagnosed and prognosis is predicted, management planning is the next fundamental step. Effective doctor-patient communication must be maintained in order to communicate the difficult news, expressing empathy and give mental support. All necessary information concerning the diagnosis, prognosis, pregnancy management and postnatal management should be explained in a simple language; hence the parents can make informed decision. The recently published practice consensus of diagnosis and delivery of skeletal dysplasia published by Savarirayan et al. 2018 in American

Journal of Obstetrics and Gynecology (AJOG), summarizes management planning into three tiers: (1) Maternal: assessment for cephalopelvic disproportion and/or preterm labor risk and polyhydramnios in order to plan mode of delivery; (2) Fetal: serial assessment of malpresentation, lung volume, and/or fetal stress testing for termination consideration if necessary; and (3) Perinatal: establishment of intensive postnatal care, clinical and radiographic assessment, and post-mortem evaluation in terminated pregnancy. The consensus also recommends for referral to centers with appropriate facilities and maternal-fetal medicine specialists for diagnosis confirmation, further management and advice; if prenatal diagnosis of TD is suspected.¹⁵

One persistent challenge in management of pregnancy with lethal fetus based on both ethical and medicolegal ground is pregnancy termination consideration. Indonesian Society of Obstetrics and Gynecology (POGI)'s Good Practice Guideline, which has been cemented by Indonesian presidential decree (*Peraturan Pemerintah no. 61, tahun 2014*); settled that pregnancy termination with medical indication (therapeutic abortion) can be performed through proper counselling and informed consent of the patient. Medical indications, which includes both fetal (lethal congenital anomalies) and maternal life-threatening indications; must be re-evaluated by a medical committee of at least two experts.^{16,17} What remains a challenging dilemma is to decide the best period for pregnancy termination, since there is not a single recommended or agreed time frame between different practitioners and the decision is mostly dependent on the patient. A few studies have proven that approximately 90% of practitioners agreed to discuss or offer late termination of pregnancy (after 21⁺⁶ weeks of gestation) for the patient, in contrast to approximately 70% of practitioners who agreed to discuss delivery near term or when spontaneous labor or maternal compromise arises; patient's judgement remains a major factor in final decision making in medically legal abortion countries.^{18,19} Patient's mindset in culture, religion, and past personal experiences affected their decision making.²⁰

In our case, the patient had been referred to the maternal-fetal specialist and multidisciplinary discussion with the patient was conducted; pregnancy termination was considered and offered to the patient due to the fetus's lethality and presumed low survivability, the patient

agreed and requested for the termination to be conducted via caesarean section. The newborn was immediately monitored in neonatal intensive unit with stabilized condition for several hours; the condition suddenly worsened afterwards and deceased shortly afterwards due to cardiorespiratory failure.¹⁵

CONCLUSION

Thanatophoric skeletal dysplasia (TD) is a disorder involving abnormal bone formation and growth in long bones with lung growth limitation, which is considered lethal. TD cases are considered rare with overall incidence of 1 in 20,000 to 1 in 50,000 births, however, it is considered as the most common lethal skeletal dysplasia contributing to approximately 29% of all lethal cases. Most fetus with TD do not survive in utero and in some cases do not survive the first week of life. The etiopathology of TD varies between sporadic in most cases and congenital, which further classified into two types. The prenatal diagnosis of TD is primarily established using ultrasonography (US), which has a high detection rate for both diagnosis and prognostications. Even though, There has been a dilemma in performing molecular diagnostic testing, prediction of recurrence risk in future pregnancies can be assessed with its use. Although still remains a challenge in ethical and medicolegal grounds; proper management requires holistic considerations of maternal, fetal, and perinatal aspects.

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Literature Review

Factors Influencing Word-of-Mouth Behaviour at Outpatient Department

Faktor yang Berperan pada Perilaku Word-of-Mouth pada Pelayanan Rawat Jalan

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Abstract

Objective: To determine the factors that influence the word-of-mouth behavior of patients seeking treatment at YPK Mandiri Hospital, Jakarta.

Methods: This study uses a quantitative approach. Data were obtained using online questionnaire distributed to patients receiving outpatient treatment at YPK Mandiri Hospital from July – September 2021. A convenience sampling technique was used in this study. Data analysis was performed using the Partial Least Square-Structural Equation Modelling (PLS-SEM) approach using SmartPLS software.

Results: There were 162 respondents obtained in this study, most of them (96.3%) consisted of female with the highest age group being 26-30 years (40.1%). The factors studied were doctor's expertise, doctor's communication, nursing, ancillary, and administration services, hospital reputation, and the physical structure and facilities of the hospital. Results showed that doctor's expertise, doctor's communication, hospital reputation, and physical structure and hospital facilities affect word-of-mouth behavior with standardized path coefficient of 0.199, 0.204, 0.339, and 0.212; as well as p-values of 0.044, 0.046, 0.00, and 0.008, respectively. Meanwhile nursing, administration, and support services is not supported with standardized path coefficient of 0.054 and p-value of 0.469, which indicated that it does not affect word-of-mouth behavior.

Conclusion: Doctor's communication, hospital reputation, and the physical structure and facilities of the hospital are related to word-of-mouth behavior. On the other hand, nursing, ancillary, and administrative services are not related to word-of-mouth behavior.

Keywords: ancillary services, doctor communication, doctor expertise, hospital physical structure, hospital reputation, word-of-mouth.

Abstrak

Tujuan: Untuk mengetahui faktor yang memengaruhi perilaku word-of-mouth pasien yang berobat di RS YPK Mandiri, Jakarta.

Metode: Penelitian ini menggunakan pendekatan kuantitatif. Data diperoleh dengan menggunakan kuesioner online yang dibagikan kepada pasien rawat jalan di RS YPK Mandiri periode Juli – September 2021. Teknik convenience sampling digunakan dalam penelitian ini. Analisis data dilakukan dengan pendekatan Partial Least Square-Structural Equation Modeling (PLS-SEM) menggunakan software SmartPLS.

Hasil: Responden yang diperoleh dalam penelitian ini adalah sebanyak 162 subjek, sebagian besar (96,3%) berjenis kelamin perempuan dengan kelompok usia terbanyak adalah 26-30 tahun (40,1%). Faktor yang diteliti adalah expertise dokter, komunikasi dokter, pelayanan keperawatan, penunjang, dan administrasi, reputasi rumah sakit, dan struktur fisik dan kelengkapan rumah sakit. Hasil penelitian menunjukkan bahwa expertise dokter, komunikasi dokter, reputasi rumah sakit, serta struktur fisik dan kelengkapan rumah sakit berpengaruh terhadap perilaku word-of-mouth dengan standardized path coefficient 0,199, 0,204, 0,339, dan 0,212; serta nilai p masing-masing 0,044, 0,046, 0,00, dan 0,008. Sementara itu pelayanan keperawatan, administrasi, dan penunjang tidak didukung dengan standardized path coefficient 0,054 dan p-value 0,469 yang mengindikasikan bahwa faktor tersebut tidak berpengaruh terhadap perilaku word-of-mouth.

Kesimpulan: Expertise dokter, komunikasi dokter, reputasi rumah sakit, dan struktur fisik dan kelengkapan rumah sakit berpengaruh terhadap perilaku word-of-mouth. Pelayanan keperawatan, penunjang, dan administrasi tidak berpengaruh terhadap perilaku word-of-mouth.

Kata kunci: expertise dokter, komunikasi dokter, pelayanan penunjang, reputasi rumah sakit, struktur fisik rumah sakit, word-of-mouth.

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INTRODUCTION

By efforts done to improve or develop a business, the role of marketing in advertising products is very important. With increased sales, a service can progress and develop further. Therefore, various ways were carried out to increase marketing to increase the number of customers. One way to increase sales that are widely known today is through word of mouth (WOM).^{1,2} Word of mouth is one of the methods that play a vital role in marketing a product, whether goods or services.¹ As the name implies, this method is carried out by passing information directly from people to people, where this circulating information can be in a negative or positive connotation and is and promoted to the public's circle.³

The role of word of mouth has become a prominent activity in our daily life, where we will instinctively come to a trusted workshop recommended by a friend, or try a restaurant recommended by our family. This is a common occurrence because when a person intends to try something new, they will seek information about the said new thing, and often from people they trust or are closest to. The same thing happens when a patient attempts to choose the doctor they want to visit. Often, they seek opinions from people around them for alternative options. A study has also stated that 70% of people in America rely on the advice of those around them while choosing a doctor for treatment.⁴

In the health industry, WOM behavior is influenced by the level of patient satisfaction, which comes from various factors including the quality of the doctors working in the hospital, the quality of the equipment used, the doctor's communication skills, the reputation of the hospital, and so on.^{5,6} So far, various existing studies have been carried out by the experts of the general hospital setting, and on this occasion, the researcher intends to replicate similar research in the setting of a mother and child hospital, in Jakarta.

YPK Mandiri Hospital is one of the maternal and child hospitals that has been established since 1960. Most of the patients at YPK Mandiri Hospital choose to seek treatment at this hospital due to recommendations from their parents or relatives and friends. In this case, word-of-mouth behavior plays a major role in efforts for service marketing at YPK Mandiri Hospital. In this regard, it is very important to be able to

convince customers or patients to carry out this word-of-mouth behavior. On this occasion, the researcher wants to find out more about the factors that influence word-of-mouth behavior at YPK Mandiri Hospital patients.

Literature Review and Hypotheses

Relation between Doctor's Expertise and Word of Mouth Behavior

Prior study has found that doctors' expertise was directly influenced by patient satisfaction⁶. A similar result was found in another study where a doctor's expertise could increase patient satisfaction, and decrease malpractice claims⁷. This finding could be explained because with the increase in doctors' expertise, so will the ability to handle a case, hence decreasing complaints felt by patients. This phenomenon will result in increased patient satisfaction. Likewise, with the increase in expertise, the incidence of unwanted cases will quickly decrease, which in turn will decrease malpractice claims by doctors. Patients' satisfaction will then influence word-of-mouth behavior. According to this theory, the first hypothesis that we can propose is: H₁: Doctor's expertise affects word-of-mouth behavior.

Relation between Doctors' Communication Skills and Word-of-Mouth Behavior

Previous study has stated that the interaction or communication between doctors and their patients has a crucial role in determining the level of patients' satisfaction⁸.

This also sometimes instigates a suggestive effect on patients' adherence to treatment, giving positive effects on increasing recovery rate. Similarly, another study found that doctors' interpersonal communication skills were shown to increase patients' satisfaction rate towards hospitals' or doctors' services⁹. The quality of provided communication often was evaluated on allocated time by doctors for *visits*, delivering clear explanations about diagnosis, and planning on treatment. Increasing satisfaction will then imply word-of-mouth behavior among patients. Based on the data above, the second proposed theory is:

H₂: Doctor's Communication Skill affects word-of-mouth behavior

Relation between nursing, ancillary, and administration services with Word-of-Mouth Behavior

The quality and adequacy of a service are often judged by the level of patient satisfaction.

Another thing that was also found to affect satisfaction was nursing, administration, and ancillary services. Nursing has a major role in providing emotional and psychological support to patients and their families in various conditions, for example supporting patients when receiving their diagnosis, and ensuring the best service is provided to patients. Nursing parties are also expected to have professional knowledge and behavior and can provide informational, emotional, and practical support.¹⁰

In addition to nursing support, other supports in health facilities also affect the level of patient satisfaction, such as professional and trained customer service facilities, quick and clear administrative processes, and so on.⁸ Based on data stated above, we composed our third hypothesis as follows:

H₃: Nursing, ancillary, and administration services affects Word-of-Mouth Behavior
Relation between Hospital Reputation and Word-of-Mouth behavior

Nowadays it is easy for patients to find out about the reputation of the hospital and the doctors where the patient will seek treatment. This is also supported by the increasing number of competing health facilities, both private and public. Good service quality of a hospital enhances the good reputation of the hospital, and a good reputation will increase patient satisfaction and help to assure patients' loyalty to the health facility.⁵

The identical theory was stated in a preceding research¹¹, where they found that a good reputation of a health facility increases patient confidence and also a sense of security (from the possibility of mismanagement / medication); resulting in increased patient satisfaction and also WOM behavior. Based on data provided above, we concluded our fourth hypothesis as follows:

H₄: Hospital Reputation affects Word of Mouth behavior

Relation between Physical Structures and Facilities of Hospital with Word-of-Mouth Behavior

Prior studies found that the physical structures of hospitals could influence the level of patients' satisfaction¹². A good room layout can facilitate patient activities in health facilities, thereby increasing the patient's level of comfort. Another study has also found that good decoration or display quality also played a role in patient satisfaction.¹³ However, it is still the quality of the service itself that most influences their

satisfaction.

In a previous research, similar findings has also been stated, where the quality of the room affects patient satisfaction, and hence supports a health facility to be memorable and exceptional in the eyes of the patient¹. Based on the data above, we constructed the fifth hypothesis as follows:

H₅: The physical structure and facilities of the hospital affects word-of-mouth behavior

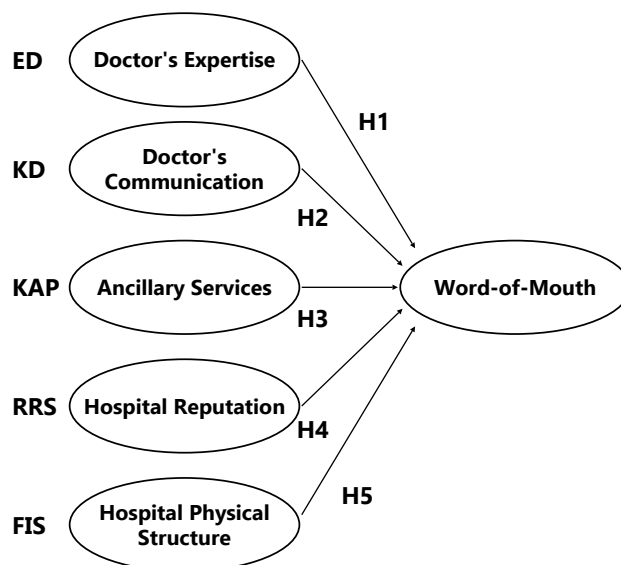


Figure 1. Study Model^{2, 5, 6, 10, 13}

METHODS

The purpose of this study was to determine the factors that influence the word-of-mouth behavior of patients seeking treatment at YPK Mandiri Hospital, Jakarta. This study has 5 independent variables, namely: doctor's expertise, doctor's communication, nursing, axillary, and administrative services, hospital reputation, and hospital physical structure and facilities. The dependent variable in this study was the patient's word-of-mouth behavior.

The method used in this study is a quantitative approach. Data collection was taken using a questionnaire instrument that was filled out by outpatients online in Google Form after the patient was treated. The target population in this study were patients receiving outpatient treatment at YPK Mandiri Hospital, Jakarta, during the period July – September 2021. Sampling was done using the convenience sampling technique. The number of samples was calculated and determined to be 160 samples.

The measurement instrument used in this study is a Likert scale which produced interval

data: strongly agree, agree, neutral, disagree, and strongly disagree. Questions in the questionnaire were adapted from research¹⁴ Statistical analysis was performed using Partial Least Square-Structural Equation Modelling (PLS-SEM) with SmartPLS software.

Respondent’s Profile

There were 162 respondents obtained in this study. In Table 1, the profile of the respondents is presented. Most of them (96.3%) are female. The highest age group was 26-30 years (40.1%) followed by 31-35 years (33.3%). The most visited specialists were obstetrics and gynecology (77.1%) followed by pediatricians (14.2%).

Table 1. Respondents’ Profile

Statement	Frequency	(%)
Gender		
Male	6	3.7
Female	156	96.3
Age Group (y o)		
< 20	5	3.1
21-20	17	10.5
26-30	65	40.1
31-35	54	33.3
≥35	21	13
Visited Specialist		
Pediatrics	23	14.2
Andrology-Urology	4	2.5
Obstetrics and Gynecology	125	77.1
Internal Medicine	10	6.2

Source: Results of Data Processing

Table 2. Evaluation of Measurement Model¹⁴

Construct	Item	Outer Loading
Doctor’s Expertise (AVE=0.825, CR=0.934)		
ED1	Doctors have the expertise (skills) in their field	0.920
ED2	Doctors are capable to make an accurate diagnosis	0.901
ED3	Doctors are capable to give adequate therapy or treatment	0.904
Doctor’s Communication Skill (AVE=0.812, CR= 0.945)		
KD1	Doctors have a good communication style	0.903
KD2	Doctors can give clear explanations about my disease/condition	0.900
KD3	Doctors pay attention and listen to my complaints	0.896
KD4	I find it easy to communicate with doctors	0.905
Nursing, Ancillary, and Administration sServices (AVE=0.650, CR=0.881)		
KAP1	I feel comfortable with this hospital’s registration service	0.754
KAP2	I feel comfortable with this hospital’s nursing service	0.796
KAP3	I feel comfortable with this hospital’s cashier service	0.820
KAP4	I feel comfortable with this hospital’s pharmacy service	0.852
Hospital’s Reputation (AVE=0.533, CR=0.818)		
RRS1	The reputation of the hospital affects my choice of place of treatment	0.720
RRS2	The number of hospital patients affects my choice of place of treatment	0.594
RR33	The hospital’s treatment outcomes affect my choice of place of treatment	0.857
RRS4	Social media activity (Google Search, Instagram, Website, etc.) affects my choice of place of treatment	0.725

Evaluation of Measurement Model

Evaluation of the measurement model is a test used to assess the validity and reliability of the model. Tests of convergent validity, discriminant validity, and composite reliability were applied in this study. The criteria for convergent validity are loading factor >0.7; average variance extracted (AVE) >0.5, and the discriminant validity must meet the Fornell-Larcker criteria, that is the square root value of the AVE must be greater than the correlation value between variables.¹⁵ The same explanation about the ideal limit of loading factor and AVE¹⁶, that is the value of outer loading between 0.4 to 0.7 is still accepted as long as the AVE value is > 0.5. In this study, a reliability test was conducted using the composite reliability method. If the minimum composite reliability value is above 0.7, then the data is said to be reliable.¹⁷

Hospital's Physical Structures and Facilities (AVE=0.520, CR=0.808)

FIS1	I feel comfortable with the waiting room in this hospital	0.804
FIS2	The ancillary facilities (such as laboratories, radiology, pharmacy) of this hospital are sufficient for my needs	0.804
FIS3	The structure (layout) of the hospital building affects my comfort	0.726
FIS4	The address (location) of the hospital affects my choice of place of treatment	0.510

Word-of-Mouth Behavior (AVE=0.582, CR=0.846)

WOM1	I tell about my treatment experience to relatives/friends	0.808
WOM2	I review/post/tell stories about treatment experiences on my social media (Instagram, Facebook, Twitter, etc.)	0.642
WOM3	I will recommend this hospital to my friends for treatment	0.845
WOM4	I will recommend my doctor to my friends for treatment	0.740

Annotation: AVE=average variance of extracted; CR=composite reliability

Source: Results of Data Processing

The results of the convergent validity test are shown in Table 2, which shows the AVE value of all variables > 0.5, and the outer loading results for convergent validity range from 0.510 to 0.920. The results of the composite reliability test ranged from 0.808 to 0.934. Discriminant validity test has also met the Fornell-Larcker criteria. Thus, the overall results of the measurement model evaluation test have met the predetermined criteria.

Evaluation of Structural Model

In the evaluation of the structural model, the test starts from measuring multicollinearity to find out the relationship between existing independent constructs and the possibility of collinearity. The multicollinearity test was carried out by observing the results of the Variance Inflation Factor (VIF) to detect the presence of collinearity in the independent construct. Hair et al. 16 stated the VIF value must be below 5. If the VIF value exceeds 5, it can be said that the research model has multicollinearity issues. In Table 4 it can be concluded that there are no multicollinearity issues detected in the construct.

Table 4. Collinearity Evaluation

	Word-of-Mouth Behavior
Doctor's Expertise	1.667
Doctor's Communication Skills	1.635
Nursing, Administrative, and Axillary Services	2.180
Hospital's Reputation	1.805
Physical Structures and Facilities of Hospital	2.495

Source: Results of Data Processing

Other than tests conducted for the VIF value, an R-Square test was performed on the structural model. R-Square will describe the extent to which the independent construct describes the

dependent construct. The R-Square test on the word-of-mouth behavior variable is 0.565, which means that the word-of-mouth behavior can be explained by the previous variable by 56.5%.

Hypothesis testing in this study was carried out by looking at the path coefficients by looking at the parameter coefficient values, p-values, and t-statistical significance. P-value and t-statistics appear to indicate the support of a hypothesis. A hypothesis can be said to be significant if the t-statistic value is > 1.65 with a significance level of 5% and p-value <0.05 by considering the direction of the path coefficient.

The hypothesis test shows that hypotheses H1, H2, H4, and H5 are supported, that is doctor's expertise, doctor's communication, hospital reputation, and physical structure and hospital facilities affect word-of-mouth behavior with standardized path coefficient of 0.199, 0.204, 0.339, and 0.212; as well as p-values of 0.044, 0.046, 0.00, and 0.008, respectively. Meanwhile hypothesis H3 is not supported with standardized path coefficient of 0.054 and p-value of 0.469, which indicated that nursing, administration, and support services do not affect word-of-mouth behavior.

DISCUSSION

The result of testing the first hypothesis is that doctor's expertise affects word-of-mouth behavior, hence the results are supported. This is supported by stated that with the increase in the expertise of a doctor, the ability to handle a case will also increase, resulting in a quick decrease of complaints felt by the patients and therefore leading to patient satisfaction.^{6,7,18}

The result of testing the second hypothesis is that doctor's communication affects word-of-mouth behavior, hence the results are supported.

This result is also supported by previous research^{8,9} In contrast to the competence and expertise of doctors which are standardized nationally, the communication skills of each doctor are different and thus become one of the distinguishing factors between doctors. Communication skills played a vital role in the success of medical practice and factors affecting patient satisfaction, adherence, and treatment outcomes¹⁹. Communication skills are also related to the allocation of time given to listening to complaints and answering patients' questions.

The result of testing the third hypothesis is that nursing, administrative, and supporting services affect word-of-mouth behavior, hence the results are not supported. Previous research¹⁰ found that nursing services were related to patient satisfaction, and stated that supporting facilities were also related to patient satisfaction.²⁰ This hypothesis was not supported in our study. One of the reasons underlying these findings is the brief interaction between nurses and patients during outpatient services. Other research stated that nursing and support services play a role in word-of-mouth behavior, especially in emergency and inpatient services.²¹

The result of testing the fourth hypothesis is that hospital reputation affects word-of-mouth behavior, hence the results are supported. This finding is supported by previous research.^{5,11} A hospital with a good reputation will increase patient loyalty to the hospital, and similarly, in our study, it also affects word-of-mouth behavior.

The result of testing the fifth hypothesis is that the physical structure and facilities of the hospital affect word-of-mouth behavior, hence the results are supported. A similar result has been found in a previous study. The physical structure and equipment of the hospital in this study included the comfort of the waiting room, the completeness of the hospital facilities, the structure of the building (layout), and the location of the hospital. Patients will feel more comfortable and satisfied in a one-stop service hospital, meaning that all their needs can be met at the hospital, canceling the obligation to visit other diagnostic facilities or additional procedures outside. The layout, floor plan, and location of the hospital also have to be considered to facilitate the flow of patients for treatment and create a comfortable environment while waiting.^{12,13}

CONCLUSION

Based on the results of data analysis in this study, it can be concluded that doctor's expertise, doctor's communication skills, hospital's reputation, as well as hospital's physical structure and facilities affects patients' *word-of-mouth behavior* at YPK Mandiri Hospital RS, Jakarta. On the other hand, it was also concluded that nursing, *ancillary, and administration services* have no effects on patients' word-of-mouth behavior at YPK Mandiri Hospital RS, Jakarta.

Limitations and Suggestions for Further Research

This study was conducted on patients receiving outpatient treatment at YPK Mandiri Hospital and covered the entire cluster of outpatient services. Therefore, the variables analyzed in this study cannot be generalized to all hospital service units. Suggestions for further studies are researching patient satisfaction with delivery, inpatient service satisfaction, and patient satisfaction in each medical service cluster.

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