

Editorial**Covid-19 and Pregnancy****Yudianto B. Saroyo**

It has been a year since Covid-19 (coronavirus disease of 2019) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) firstly reported in Wuhan, China.¹ This infection indiscriminately affect from neonate until the elderly, and pregnant women also inevitable. Since March 2020, WHO has already declared this situation as a pandemic.² Covid-19 contagion can transmit into two methods, close contact from infected people, the droplet dispersion into the mouth, eye, nose, or airway tract until the alveoli, touch from a specific object that contains the virus then the person sweep the mouth, nose or the eye.³ The virus is single-stranded RNA with 4 structural proteins, S (spike), E (envelope), N (nucleocapsid), and M (membrane). A crucial point in the pathogenesis is the binding between S protein to the ACE 2 receptor in the pneumocyte at alveoli. Subsequently, endocytosis happens and virus RNA is released and replication takes place inside the cell. Eventually, the new virus will be released and it will infect another cell. And it will provoke some immunologic reaction inside alveoli and in blood circulation.⁴

Then, how about in pregnant women? The maternal immune system more susceptible to Covid-19 infection due to in these conditions undergo decrease of lymphocyte, NGK2A inhibitor receptor, and increase of ACE2, IL-9, IL-10, and IP-10 receptors.⁵ Like another maternal infection, the first thing in mind is there any vertical transmission to the fetus? The scientific report already stated that vertical transmission to the fetus is low, around 3.2% in third-trimester mother with Covid-19 infection, without an adverse event to the neonate.⁶ Beside of ACE2 receptor in the placenta, N and S proteins is highly expressed in the placenta in confirmed case mother.⁷ Thus far, Covid-19 infection does not correlate with the neonatal poor outcome but somehow isolates the mother from the baby have an important role to cut off the transmission.⁸ However, Covid-19 is related to an increased risk of preterm labor and fetal distress.⁹ It is still controversy in the delivery method with Covid-19 infection. Until now, no recommendation for the best method for delivery concerning better outcome for the mother and also prevention vertical transmission. The delivery method selection should consider the availability of health care providers, hospital facility, spatial room of care, procurement of personal protective equipment (PPE), ability to implement, human resources, and exposure risk of infection. It will influence the physician who took care of the patient, to determine the suitable method of delivery for each patient. Rooming-in can be performed in Covid-19, the transmission risk to the baby is low, and no risk discrepancy SARS-CoV-2 infection in rooming-in baby and not rooming-in.¹⁰ No evidence that the virus is discovered in the breastmilk. Breastmilk gives important nutrition for the baby. Nevertheless, in this pandemic era, the Indonesian Pediatric Association recommends a discussion and decision in conjunction with healthcare, mother, and family. The recommendation contraception in mother after delivery is long-acting reversible contraceptive (LARC) method and can be given right after delivery like intrauterine device or implant. In the patient with Covid-19 with hormonal contraception, some of these drugs have such drug interactions. It will affect the favipiravir clearance, baricitinib and sarilumab will decrease the level and activity of hormonal contraception, while lopinavir/ritonavir will increase hormonal contraception in blood. No data regarding in concomitant with remdesivir use. Meanwhile, tocilizumab has no interaction with hormonal contraception.¹¹ Another issue is regarding maternal vaccination. Some pharmaceutical companies have already performed research on the Covid-19 vaccine. So far, just one vaccine has been published phase 3 trial from BNT162b2 mRNA with protection claim until 95%.¹² Unfortunately, this study has not proven the efficacy in pregnant women. The vaccination program in pregnant women is not only to give protection or prevention to the mother but also to prevent congenital infection and neonatal infection.¹³ It is very interesting to await in the future months, whether the vaccine can protect not only the general adult population but also pregnant women and the neonate.

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Research Article

Clinical Profile of Pregnant Women with COVID-19 Hospitalized in Regional Referral Hospital

Profil Ibu Hamil dengan COVID-19 yang Dirawat di Rumah Sakit Rujukan

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Abstract

Objective: To determine the clinical profile of pregnant women with COVID-19 who hospitalized in a referral hospital.

Methods: This was a descriptive study conducted on pregnant women with COVID-19 who were hospitalized at Regional Hospital of Bau-Bau and Bahteramas Hospital in Southeast Sulawesi from May to July 2020. The confirmation of COVID-19 was based on RT-PCR. Data including characteristics, clinical profile, laboratory test, imaging, management, and outcomes.

Results: There were 41 pregnant women with COVID-19 and no maternal death cases. Maternal age was approximately 19 to 39 years, had middle education levels, and was a housewife. Most of them did not know their closed contacts, had no comorbidities, and referrals from other hospitals. They were 3rd-trimester and hospitalized with complaints related to pregnancy. Only 3 cases had complaints related to COVID-19, namely fever and cough. The majority of laboratory tests were leucocytosis. Chest X-ray shows bronchopneumonia, pneumonia, and normal imaging. Obstetrics management was performed according to the condition of the mother and fetus, including dilatation and curretage vaginal delivery, cesarean section, and curettage. The treatment was using broad-spectrum antibiotics and antiviral. Adverse pregnancy outcome were miscarriage, fetal distress, LBW, and asphyxia.

Conclusions: Pregnant women with COVID-19 have mild or asymptomatic symptoms, hospitalized with complaints related to their pregnancy, and treatment according to the condition of the mother and fetus. There are no maternal complications, while fetal complications are not clear.

Keywords: COVID-19, pregnant women, referral hospital.

Abstrak

Tujuan: Mengetahui gambaran klinis ibu hamil dengan COVID-19 yang masuk di rumah sakit rujukan COVID-19.

Metode: Penelitian ini bersifat deskriptif yang dilakukan pada ibu hamil dengan COVID-19 yang dirawat di rumah sakit rujukan di Sulawesi Tenggara, yaitu RSUD Bau-Bau dan RSU Bahteramas di Kendari, pada bulan Mei sampai Juli 2020. Konfirmasi positif COVID-19 berdasarkan hasil pemeriksaan RT-PCR. Data berupa karakteristik, gambaran klinis, pemeriksaan penunjang, penatalaksanaan, dan luaran.

Hasil: Terdapat 41 ibu hamil dengan COVID-19 dan tidak ada kasus kematian ibu. Usia ibu berkisar 19-39 tahun, tingkat pendidikan menengah, dan sebagai ibu rumah tangga. Sebagian besar kasus pada trimester-3, tidak tahu memiliki kontak erat, tidak memiliki komorbid, dan rujukan dari RS lain. Sebagian besar dirawat dengan keluhan terkait kehamilannya dan hanya 3 kasus dengan keluhan terkait COVID-19, yaitu demam dan batuk. Pemeriksaan laboratorium menunjukkan leukositosis. Gambaran foto toraks menunjukkan bronkopneumonia, pneumonia, dan normal. Tindakan obstetri dilakukan atas indikasi ibu dan janin, yaitu persalinan normal, seksio sesarea, dan kuretase. Terapi yang digunakan adalah antibiotik spektrum luas dan antivirus. Komplikasi pada janin/bayi berupa abortus, gawat janin, BBLR, dan asfiksia.

Kesimpulan: Ibu hamil dengan COVID-19 memiliki gejala ringan atau asimtomatik, dirawat dengan keluhan terkait kehamilannya, dan dilakukan tindakan obstetri sesuai dengan indikasi ibu dan janin. Tidak ada komplikasi pada ibu, sedangkan komplikasi pada bayi belum jelas.

Kata kunci: COVID-19, ibu hamil, rumah sakit rujukan.

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INTRODUCTION

Corona virus Disease 2019 (COVID-19) is a new disease in humans.¹ Increasing the number of COVID-19 cases in Indonesia is taking quickly.² Currently, the spread of COVID-19 has reached all provinces in Indonesia, with an increasing number of cases and/or deaths.³

Coronaviruses are a large family of viruses that cause illness with mild to severe symptoms. Most at risk of contracting this disease are people who have close contact with COVID-19 patients, including those who treat COVID-19 patients. Several groups susceptible to being infected with COVID-19 are the elderly, children, and pregnant women.^{1,2}

Pandemic has affected political, social, economic, public welfare, and culture in Indonesia, including affect anxiety in pregnant women.^{3,4} Knowledge about COVID-19 infection in pregnancy and the fetus is still limited, and there are no recommendations issued by the World Health Organization (WHO) for handling pregnant women with COVID-19. It is suspected that pregnant women with co-morbid have a higher risk of experiencing COVID-19 with severe symptoms, morbidity, and mortality compared to the general population. The fetal side effect of preterm delivery is also unclear whether it related to infection in the mother.³

Therefore, this study aims to evaluate the pregnant women with COVID-19 who hospitalized in regional referral hospitals. This data can provide information to physicians about differences and variations in the clinical profile of pregnant women with COVID-19.

METHODS

This was a descriptive study conducted on pregnant women with COVID-19 who admitted to referral hospitals in Southeast Sulawesi, Regional Hospital of Bau-Bau and Bahteramas Hospital, from May to July 2020. Positive confirmation of COVID-19 based on the real-time reverse transcription-polymerase chain reaction (RT-PCR) assay, which was the current gold standard for detecting SARS-CoV-2 from respiratory specimens in suspected COVID-19 patients.

The inclusion criteria were pregnant women who confirmed positive for COVID-19 and had complete data. The data were filled in and reported by their doctor, including characteristics, clinical features, laboratory tests, imaging, management, and outcomes of maternal and infant. The characteristics of respondents comprised age, education, occupation, gravida, gestational age, history of close contact with COVID-19 patients, co-morbid, and referral. The clinical features including symptoms and signs related to pregnancy and related to COVID-19. The laboratory tests comprise hemoglobin levels, leucocytes, and platelets count. Imaging was performed with a chest X-ray. Management comprised treatment and drug administration. The infant outcome includes birth weight and the complication of the baby.

Statistical analysis used SPSS for windows Version-23 and was presented as frequency and percentage. The ethical clearance had approved by the Health Ethics Commission of Halu Oleo University.

RESULTS

There were 41 pregnant women who were confirmed positive for COVID-19 who admitted at referral hospitals. There was no maternal death case. All cases had good maternal outcome. There were 35 babies, 5 cases without outcome babies, and one case with a good intrauterine fetal. The characteristics of pregnant women showed in Table-1.

Table 1. Sociodemographic and Obstetrics Characteristics.

Variable	Total		Condition of the Fetus/Baby			
			Good		Asphyxia	
	n	%	n	%	n	%
Age						
< 20	2	4.9	2	4.9	0	0
21-25	6	14.6	4	9.8	2	4.9
26-30	14	34.1	11	26.8	3	7.3
31-35	10	24.4	5	12.2	2	4.9
> 35	9	22.0	7	17.1	0	0
Education level						
Low	3	7.3	0	0	1	2.4
Middle	23	56.1	18	43.9	4	9.8
High	15	36.6	11	26.8	2	4.9
Occupation						
Housewife	29	70.7	19	46.3	6	14.6
Employees	10	24.4	8	19.5	1	2.4
Self employees	2	4.9	2	4.9	0	0
Gravida						
Primigravida	12	29.3	9	22.0	2	4.9
Multigravida	29	70.7	20	48.8	5	12.2
Gestational Age						
Trimester-1	5	12.2	0	0	0	0
Trimester-2	0	0	1	2.4	0	0
Trimester-3	36	87.8	28	68.3	7	17.1
Close Contact						
Yes	2	4.9	1	2.4	0	0
Unknown	39	95.1	25	68.3	7	17.1
Co-morbid						
Hypertension	1	2.4	1	2.4	0	0
None	40	97.6	25	68.3	7	17.1
Referral						
Primary health centre	11	26.8	8	19.5	2	4.9
Other hospital	18	43.9	12	29.3	3	7.3
Doctor's clinic	4	9.8	4	9.8	0	0
Without a reference	8	19.5	5	12.2	5	4.9

Table 1 showed that the range of women ages was 19 to 39 years, and the majority was 26-30 years (34.1%). Most pregnant women were middle education levels (56.1%) and work as housewives (70.7%).

The COVID-19 cases were distributed in primigravida (29.3%) and multigravida (70.7%). Most of them were in the 3rd trimester (87.8%). Most pregnant women did not know the history of close contact, only 2 cases with close contact. Most of them were without comorbid, only 1 case with hypertension as comorbid. Most pregnant women have a referral from other hospitals (43.9%), primary health centers (26.8%), and doctor's clinic (9.8%). However, there were 19.5% cases without a reference.

Table 2. Clinical Features, Laboratory Test, and Imaging

Variable	Total		Condition of the Fetus/Baby			
			Good		Asphyxia	
	n	%	n	%	n	%
Complaints related to pregnancy						
Contractions	25	61.0	20	48.8	5	12.2
Leakage of fluid from the vagina	3	.3	2	4.9	0	0
Bleeding	5	12.2	1	2.4	0	0
None	8	19.5	6	14.6	2	4.9
Complaints related to COVID-19						
Fever	3	7.3	2	4.9	1	2.4
Cough	3	7.3	2	4.9	1	2.4
Dispneu	0	0	0	0	0	0
Haemoglobin levels						
<8	5	12.2	3	7.3	2	4.9
8-10	10	24.4	8	19.5	2	4.9
>10	26	63.4	18	43.9	3	7.3
Leukocyte						
<10	11	26.8	7	17.1	2	4.9
10-15	30	73.2	15	36.6	3	7.3
Platelets count						
Normal	41	100.0	29	70.7	7	17.1
Abnormal	0	0	0	0	0	0
Chest X-ray						
Pneumonia	2	4.9	1	2.4	1	2.4
Bronchopneumonia	1	2.4	0	0	1	2.4
Normal	1	2.4	1	2.4	0	0

Most of the complaints of pregnant women with COVID-19 were related to their pregnancy, including labor (68.3%) and bleeding (12.2%). However, there were 19.5% of cases had no complaints. Pregnant women with symptoms of COVID-19 were only 3 cases. They experienced fever, malaise, myalgia, and cough. There was none experienced shortness of breath.

Laboratory tests showed that most hemoglobin levels were > 10 g% (63.4%), had leukocytosis (73.2%), and the platelet count was normal in all cases. There were 4 cases with chest X-ray, comprise pneumonia (4.9%), bronchopneumonia (2.9%), and normal (2.9%).

Table 3. Management and Infant Outcomes

Variable	Total		Condition of the Fetus/Baby			
			Good		Asphyxia	
	n	%	n	%	n	%
Treatment						
Dilatation and Curettage	5	12.5	0	0	0	0
Vaginal delivery	19	47.5	14	34.1	5	12.2
Caesarean section	16	40.0	14	34.1	2	4.9
Drug administration						
Antibiotic	36	87.8	27	65.9	5	12.2
Anti virus	5	12.2	2	4.9	2	4.9
Birth weight						
<2500	3	8.6	1	2.4	2	4.9
2500-4000	29	82.8	25	61.0	4	9.8
>4000	3	8.6	2	4.9	1	2.4
Complication of infant						
Misscarirage	5	12.2	0	0	0	0
Fetal distress	2	4.9	0	0	2	4.9
Low birth weight	3	7.3	1	2.4	2	4.9
Asphyxia	7	17.1	0	0	7	17.1

Treatment was based on the indications of the mother and the fetus comprises dilatation and curettage(12.5%), vaginal delivery (47.5%), cesarean section (40.0%), and curettage (12.5%). Therapy in this study was using broad-spectrum antibiotics (87.8%) and anti-virus (12.2%). There were no maternal complications. Most of the birth weight was 2500-4000 (82.8%). The complications in the fetus were misscarirage (12.2%), fetal distress (4.9%), LBW (7.3%), and asphyxia (17.1%).

DISCUSSION

There was no death case of pregnant women with positive COVID-19 in this study. A study in the elderly found the number of death cases was 23%.⁵ This was increasing evidence that some COVID-19 patients have mild symptoms. However, the absence of symptoms can make it difficult for detecting an asymptomatic infection.⁶ About 80% of COVID-19 infections are mild or asymptomatic; 15% severe, require supplemental oxygen; and 5% critical, requiring mechanical ventilation.¹ Outcomes of maternal with COVID-19 appear to be better than SARS and MERS. The case fatality rate for COVID-19, SARS, and MERS was 0%, 18%, and 25%, respectively. The most common causes of death in SARS and MERS were progressive respiratory failure and severe sepsis.⁷⁻⁹

Positive cases of COVID-19 in this study were found in all gravida and most of them in the third

trimester. This was similar to other studies which found that most pregnant women contracted COVID-19 in the third trimester.⁷ Almost all cases did not know the history of close contact with COVID-19 patients. They were diagnosed on admission with a rapid test followed by RT-PCR of an oropharyngeal swab. They were hospitalized with complaints related to their pregnancy and had referral letters from other hospitals, primary health centers, and doctors' clinics. Some of them had not a referral letter. It must be attention, that we must implement health protocols to prevent transmission because people without symptoms have the potential to transmit the virus. The COVID-19 can transmit through coughing/sneezing droplets. Most at risk of contracting this disease were people who have close contact with COVID-19 patients, including those caring for COVID-19 patients.^{1,2}

Fever, malaise, myalgia, and cough were symptoms of COVID-19 found in this study. There were no pregnant women who experienced shortness of breath. The clinical signs and symptoms of COVID-19 in most cases were fever, and some cases have difficulty breathing.² About 50% of elderly patients hospitalized with COVID-19 showed the classic symptoms of COVID-19, including fever, cough, and shortness of breath.⁵ Fever and cough were most symptoms of COVID-19 in both elderly and non-elderly patients.¹⁰ Changes in the immune and cardiorespiratory systems during pregnancy affected the susceptibility of pregnant women to severe infections and hypoxic disorders.¹¹

In this study, we found leukocytosis and platelet counts were normal, different from other studies that found leucocytosis, lymphopenia, and thrombocytopenia.⁷ The chest X-ray was pneumonia, bronchopneumonia, and normal. In most cases, the chest X-rays show pneumonia infiltrate in both lungs.² Chest imaging can help diagnose COVID-19, but do not replace molecular confirmation of COVID-19. Chest imaging is nonspecific and appears similar in pregnancy.^{8,12}

Treatment of pregnant women with COVID-19 in this study based on maternal and fetal indications, including curettage, vaginal delivery, and cesarean section. Obstetric and clinical factors were to determine the decision of therapy. There is no conclusive evidence of vertical transmission, so vaginal delivery did not contraindicate in patients with COVID-19.¹² In emergency conditions, the cesarean section is carried out with caution, using complete

personal protective equipment and in the room with negative pressure ventilation.^{7,13}

Broad-spectrum antibiotics and anti-viruses were given to the patients in this study. A recent study has identified remdesivir and chloroquine as strong candidate drugs to treat COVID-19.¹⁴ Remdesivir is a new widely acting nucleotide antiviral drug that inhibits the in vitro replication of SARS-CoV-2 and related coronaviruses, including the novel coronavirus 2019-nCoV.¹⁵ Its use appears to be safe in pregnant women and phase 3 trials testing the efficacy of COVID-19 are currently underway in the United States and China. In a study with SARS patients, all patients were given broad-spectrum antibiotics, beta-lactams, and macrolide or fluoroquinolone.⁸

There were no maternal complications in this study. Abortions, fetal distress, LBW, and asphyxia were found, but it is not clear whether this is a complication of COVID-19 infection. SARS during pregnancy is associated with high incidences of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction. There is no evidence of SARS infection among newborns to these mothers.⁸ There is no data that the increased risk of abortion associated with COVID-19 and it is also unclear whether COVID-19 infection can pass the transplacental route to the baby.³

CONCLUSION

Based on the results, we conclude that pregnant women with COVID-19 have mild or asymptomatic symptoms, hospitalized with signs and symptoms related to their pregnancy, and the management performed according to the mother and fetus indications. There are no maternal complications, and complications of the baby are not clear. Further research needs to be done with larger sample size and more complete variables.

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Research Article

Serum Nephtrin Levels in Severe Preeclampsia: A Cross-Sectional Study

Kadar Nephtrin Serum pada Preeklamsia Berat: Sebuah Studi Potong Lintang

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Abstract

Objective: To determine differences in serum nephtrin levels in severe preeclampsia compared to normal pregnancy and also its correlation with systolic and diastolic blood pressure and proteinuria.

Methods: This study is an analytical observational with cross sectional study. The observation group consisted of severe preeclampsia (n= 30) and normal pregnancy group as a control (n= 30). Both groups measured systolic and diastolic blood pressure, proteinuria and serum nephtrin using the Human NPHN (Nephtrin) ELISA Kit. Statistical test were performed with Mann-Whitney test and the Spearman's rank test. A value of $p < 0.05$ was considered significant. The study was conducted in the Obstetric Clinic Inward and Laboratorium Department of Clinical Pathology Dr. Hasan Sadikin General Hospital/Faculty of Medicine Universitas Padjadjaran on March–May 2019.

Results: Levels of serum nephtrin in the severe preeclampsia group were significantly higher than in normal pregnancies (6.4 ng/mL vs 4.2 ng/mL; $p = 0.014$). There is a positive weak correlation but statistically significant between serum nephtrin with systolic blood pressure ($r = 0.36$; $p = 0.02$) but not significant to diastolic blood pressure ($r = 0.3$; $p = 0.05$). There is no significant correlation was found between serum nephtrin levels and proteinuria ($r = 0.18$; $p = 0.54$).

Conclusions: Levels of serum nephtrin in the severe preeclampsia group were significantly higher than in normal pregnancies and there is a correlation between serum nephtrin with systolic blood pressure.

Keywords: blood pressure, proteinuria, serum nephtrin, podocyte, severe preeclampsia.

Abstrak

Tujuan: Untuk mengetahui perbedaan kadar nephtrin serum pada preeklamsia berat dibandingkan dengan kehamilan normal dan juga hubungannya dengan tekanan darah sistolik dan diastolik serta proteinuria.

Metode: Penelitian ini bersifat analitik observasional dengan pendekatan potong silang. Kelompok pengamatan terdiri dari kelompok preeklamsia berat (n= 30) dan kelompok kehamilan normal sebagai kontrol (n= 30). Pada kedua kelompok dilakukan pengukuran tekanan darah sistolik dan diastolik, proteinuria serta pengukuran kadar nephtrin serum menggunakan Human NPHN (Nephtrin) ELISA Kit. Uji statistik dilakukan dengan uji Mann-Whitney dan uji rank Spearman. Nilai $p < 0,05$ dianggap bermakna. Penelitian dilakukan di ruang perawatan obstetri FKUP/RSHS dan Laboratorium Patologi Klinik FKUP/RSHS pada bulan Maret–Mei 2019.

Hasil: Rerata kadar nephtrin serum pada kelompok preeklamsia berat lebih tinggi secara bermakna dibandingkan kehamilan normal (6,4 ng/mL vs 4,2 ng/mL; $p = 0,014$). Terdapat korelasi positif dengan derajat lemah namun bermakna secara statistik antara nephtrin serum dengan tekanan darah sistolik ($r = 0,36$; $p = 0,02$) namun tidak signifikan terhadap tekanan darah diastolik ($r = 0,3$; $p = 0,05$). Tidak ditemukan korelasi yang bermakna antara kadar nephtrin serum dengan proteinuria ($r = 0,18$; $p = 0,54$).

Kesimpulan: Kadar nephtrin serum pada kelompok preeklamsia berat lebih tinggi dibandingkan kehamilan normal dan terdapat korelasi antara nephtrin serum dengan tekanan darah sistolik.

Kata kunci: nephtrin serum, podosit, preeklamsia berat, proteinuria, tekanan darah.

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INTRODUCTION

Severe preeclampsia (SP) is a major cause of maternal and perinatal morbidity and mortality. In the world, severe preeclampsia occurs around 5-8%.¹⁻³ SP according to ACOG is if any of the following symptoms are found: increased systolic ≥ 160 mmHg, diastolic ≥ 110 mmHg; thrombocytopenia ($<100,000$ / mL); elevated liver enzymes (> 2 times), right upper abdominal pain or epigastric pain; serum creatinine > 1.1 mg/dL; pulmo edema; cerebral or visual impairment. Proteinuria in SP if the levels was 300 mg or more which obtained with urine 24 hours or +1 by dipstick, but proteinuria is not an examination to diagnose SP.⁴ The incidence of SP and the complications is still quite high. This is because of the pathophysiology of preeclampsia is still unclear although many studies on the pathophysiology of preeclampsia have been carried out, including endothelial damage.^{2, 5, 6} Other pathophysiology was known is angiogenic imbalance, sFlt-1 and sEng which causes endothelial and podocyte damage and causing proteinuria. Vascular endothelial growth factor (VEGF) blockers are known to induce endothelin-1 (ET-1) causing podocyte damage.^{2, 7-9} Vasoconstriction also causes neurohormonal system disorders including activation of the renin angiotensin aldosterone system (RAAS) known as ET-1.^{2, 10, 11} RAAS plays an important role in the regulation of BP and electrolyte balance as well as work on the kidney system.

Endothelial damage causes vasoconstriction and hypoxia resulting in systemic organ malfunction, one of it is in the kidneys.^{2, 12-14} Glomerular endotheliosis occurs in the kidney with thrombotic microangiopathy characterized by endothelial glomerular swelling and capillary lumen occlusion so that glomerular volume increases with severity and there is proteinuria which can cause chronic kidney failure or end stage renal disease (ESRD).^{1, 12, 15} This happened in glomerular podocytes consisting of podocin, synaptopodin, podocalyxin and nephrin which play a role in maintaining the integrity of the glomerular barrier protein slit diaphragm.^{2, 12, 16, 17}

Nephrin can be damaged in certain disease, including congenital nephrotic syndrome of the Finnish type (NPHS1), minimal change disease (MCD), membranous glomerulopathy, focal segmental glomerulosclerosis (FSGS), and nephropathic arthritis.^{12, 18-20} Nephrinuria is the result of glomerular slit diaphragm damage that

occurs in SP, related to the severity of proteinuria, also correlates with serum creatinine, illustrating renal function in SP.

Dipstick proteinuria is a semiquantitative examination which is a rough estimate to assess urine concentration, influenced by the amount of urine produced when taking urine samples. This can cause false negatives or false positives. Serum nephrin levels are known to be higher than urine nephrin, that the protein composition in the urine is different from the plasma protein composition. Plasma protein contains $\pm 60\%$ urine protein, while urine protein is only about 20%.²¹ The difference is influenced by gestational age, the more gestational age so the serum nephrin levels will decrease. Nephrin can be detected before proteinuria occurs and the clinical appearance of severe preeclampsia appears, therefore nephrin is used as a marker of subclinical kidney damage.

^{3, 12, 18-20, 22}

METHODS

This research is an analytical observational with cross sectional study. The observation group consisted of SP ($n= 30$) and normal pregnancy group as a control ($n= 30$). Both groups measured systolic and diastolic BP, proteinuria and serum nephrin using the Human NPHN (Nephrin) ELISA Kit. Research subjects were taken used consecutive sampling to inclusion criteria. Statistical test were performed with Mann-Whitney and the Spearman's rank test. A value of $p<0.05$ was considered significant. The study was conducted in the Obstetric Clinic Inward and Laboratorium Department of Clinical Pathology Dr. Hasan Sadikin General Hospital/ Faculty of Medicine Universitas Padjadjaran on March–May 2019. Analysis and data processing carried out by the researcher and statistic supervisor. This is done manually and computerized by using the software program Statistical Product and Service Solution (SPSS) for Windows version 25.0.

RESULTS

After conducting a study using a cross sectional study with consecutive sampling in each of the 30 patients in the severe preeclampsia group and the normal group with gestational ages over 20 weeks to 34 weeks who met the inclusion criteria in the Obstetrics and Gynecology Section of the Faculty of Medicine Unpad/Hasan Sadikin Hospital Bandung. The characteristics of the subjects are presented in Table 1.

DISCUSSION

Table 1. Characteristics of the Subjects

Characteristic	Group		P-value
	SP (n=30)	SP (n=30)	
Age(years old)			
<24	9 (30)	7(23)	0.788
25-29	19 (63)	20 (67)	
30-34	2 (7)	3 (10)	
Average (SD)	2.7 (3.6)	25.8 (2.9)	
Range	20-34	20-30	
Gestational age (week)			
20-28	2 (7)	2 (7)	1.0
29-34	28 (93)	28 (93)	
Nutritional status (BMI)			
Normal	1 (3)	11 (37)	0.002
Overweight	1 (3)	3 (10)	
Obesity	28 (94)	16(53)	
Average (SD)	30.6 (4.8)	25.4 (3.7)	
Range	21.6-44.4	20.3-32.4	

*) chi-square

Table 2. Blood Pressure Research Subjects

Characteristic	Group	
	SP (n=30)	SP (n=30)
Systolic (mmHg)		
Average (SD)	170.3 (15.0)	109.3 (10.8)
Range	160 – 230	80 – 120
Diastolic (mmHg)		
Average (SD)	106.0 (8.9)	72.7 (6.4)
Range	100 – 130	60 – 80

Table 3. Comparison of Serum Nephtrin Levels in Severe Preeclampsia and Normal Pregnancy

Serum Nephtrin (ng/mL)	Group		P-value
	SP (n=30)	SP (n=30)	
Average (SD)	6.4 (3.64)	4.2 (1.89)	0.014
Median	5.4	4.1	
Range	1.7 – 14.8	0.8 – 7.5	

*) Mann-Whitney test

Table 4. Correlation of Nephtrin Serum Rates with Proteins and Blood Pressure

Correlation Nephtrin Serum with	SP		Normal	
	r	P-value	r	P-value
Proteinuria 24 hours	-0.05	0.41	-	-
Dipstick	0.18	0.54	0.68	0.01
Systolic	0.36	0.02	0.02	0.91
Diastolic	0.30	0.05	0.23	0.22

r= Spearman's rank correlation coefficient

Table 1 presents data on the characteristics of pregnancy with SP and normal pregnancy, it shows that the maternal age and gestational age of the two groups did not show a significant difference ($p > 0.05$). The most SP occurred in maternal age 25-29 years as 19 patients (63%) and 29-34 weeks gestation (early onset) as 28 cases (93%). In this study, the calculation of BMI by obtaining the patient's weight during examination (most of them did not know their weight before pregnancy) so that nutritional status was obesity as 28 patients (94%) in SP group and 16 patients (53%) in normal group. In table 2 shows the systolic of the SP group was 170.3 mmHg with a range of 160-230 mmHg and the diastolic was averaged 100-130 mmHg with range of 106.0 mmHg.

Based on table 3 Comparison of Serum Nephtrin Levels in SP and Normal Pregnancy, the results showed in SP mean serum nephtrin levels are 6.4 ng/mL and in normal pregnancies 4.2 ng/mL. In the normal group the serum nephtrin levels were 0.895 ng/mL and in the SP group the serum nephtrin levels were 4.285 ng/mL with p values < 0.001 (significant). It's also found significant differences in serum nephtrin levels in severe preeclampsia (7.1 ng/mL) compared to the normal group (3.9 ng/mL).^{3, 12} So it concluded that serum nephtrin levels which is higher in the SP group than normal group.

From table 4, the relationship between nephtrin levels with 24-hours proteinuria levels in SP showed the $r = -0.05$ with $p = 0.41$ ($p > 0.05$) which was not significant. The result was same with examination using protein dipstick, $p > 0.05$ which means not significant ($r = 0.18$ and $p = 0.54$).

This might be caused that proteinuria in SP is transient. Dipstick proteinuria is also a semiquantitative examination which is a rough estimate for assessing urine concentration, influenced by the amount of urine produced when taking urine samples so that the accuracy of urine collection must also be considered. Nephtrinuria levels do not depend on serum nephtrin levels so it is proven that nephtrinuria concentrations do not originate from the systemic circulation.¹² As evidenced by Son et al, serum nephtrin is found to be five times higher than urine. In addition it is also known that the composition of protein in the urine is different from the composition of plasma proteins. Plasma protein contains \pm

60% protein while urine protein is only about 20%. This is also conducted by Jung et al, found that serum nephtrin levels increased at 21-28 weeks gestational age with serum nephtrin levels 145.64 ng/mL compared to 29-40 weeks gestation (100.60 ng/mL), whereas for urinary nephtrin levels at 21-28 weeks gestation urinary nephtrin levels are 0.23 ng/mL and at 29-40 weeks gestation with urinary nephtrin levels 2.11 ng/mL. So it can be concluded that at SP serum nephtrin levels decrease along with increases gestational age and will increase during postpartum. This is contrary to urinary nephtrin levels, increase along the gestational age and decreases during postpartum.^{21, 23}

The relationship between serum nephtrin levels with BP, obtained a weak and significant correlation with systolic with $r = 0.36$ and $p = 0.02$ ($p < 0.05$) whereas at diastolic obtained a weak correlation with $r = 0.30$ but not significant with $p = 0.05$ ($p > 0.05$). In this study, isolated systolic hypertension may occur so that a significant correlation exists only in systolic blood pressure. This occurs at a young age with risk factors for obesity and occurs in peripheral blood vessels rather than central. The pathophysiologic mechanisms include the involvement of aging factors, increased arterial stiffness, increased endothelial damage, elastin calcification, increased sympathetic activity, and increased RAAS activity. Age, atherosclerosis progression, and arterial elastin build up will increase deposits of calcium and arterial collagen. Decreased elastic arteries and this ability to adjust will reduce the ratio of lumen to artery walls and increase arterial stiffness. This change mainly occurs in large arteries and aorta. Other studies have also shown that an increase in systolic blood pressure induces inflammation that causes endothelial dysfunction, vasoconstriction and thickening of the intima tunica and arterial media. Stiffness in the left ventricle and hypertrophy occur due to efforts to maintain a balanced cardiac output due to increased afterload. The results of ventricular remodeling reduce filling during diastolic and disturb diastolic relaxation. This stiffness causes an increase in systolic blood pressure and a decrease in diastolic.²⁴

CONCLUSION

Levels of serum nephtrin in the severe preeclampsia group were significantly higher than in normal pregnancies and there is a positive weak

correlation but statistically significant between serum nephtrin with systolic blood pressure but not significant to diastolic blood pressure. There is no significant correlation was found between serum nephtrin levels and proteinuria.

SUGGESTION

Further research needs to be done on nephtrinuria and proteinuria or serum nephtrin with serum creatinine and the grouping of gestational age is not limited to early onset preeclampsia but also on late onset preeclampsia and also grouped if there are other complications such as Hellp Syndrome and others.

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Research Article

Glycated Albumin as an Outcome Predictor in Pregnant Women with Diabetes Mellitus

Glycated Albumin sebagai Prediksi Hasil pada Perempuan Hamil dengan Diabetes Melitus

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Abstract

Objective: To determine the correlation between Glycated Albumin concentrations with the outcome of pregnant women with Type 2 Diabetes Mellitus in Zainoel Abidin Hospital, Banda Aceh.

Methods: This was an observational correlational study using a cross-sectional design. Subjects include pregnant women with a history of Type 2 Diabetes Mellitus who are examined for serum GA levels using colorimetric enzymatic methods and the outcomes will be assessed during pregnancy. Data analysis was performed using the ETA test and Receiver Operating Characteristic (ROC) curve.

Results: A total of 29 subjects with a mean age of 33.25 years had normal maternal outcome and those with a mean age of 34.92 years had abnormal maternal outcome. Statistically there was a significant correlation between GA levels and the maternal outcome of pregnant women with Type 2 Diabetes Mellitus ($p = 0.009$) with a moderate degree of negative correlation ($r = 0.477$). The GA cut-off for pregnancy outcome is 16.77% with a sensitivity and specificity of 76% and 75% respectively.

Conclusions: Examination of GA concentration can be used as a predictor to assess maternal outcomes during pregnancy with moderate correlation and a cutoff point of 16.77%.

Keywords: diabetes mellitus, glycated albumin, maternal outcome, pregnancy.

Abstrak

Tujuan: Untuk mengetahui korelasi kadar Glycated Albumin terhadap outcome pada ibu hamil yang menderita diabetes melitus tipe I dan untuk mengetahui berapa kadar Glycated Albumin yang dapat memberikan hasil buruk pada ibu hamil yang menderita diabetes melitus tipe II di RSUD dr. Zainoel Abidin Banda Aceh.

Metode: Penelitian ini merupakan studi korelatif observasional menggunakan desain potong lintang. Perempuan hamil dengan riwayat DM2 akan diperiksa kadar GA serum menggunakan metode enzimatik kolorimetri serta akan dinilai outcome selama kehamilan. Analisis data dilakukan menggunakan uji Eta dan kurva Receiver Operating Characteristic (ROC) dengan tingkat kepercayaan 95%.

Hasil: Sebanyak 29 subjek dengan rerata usia 33,25 tahun (hasil normal) dan 34,92 tahun (hasil kelainan). Secara statistik terdapat korelasi yang bermakna antara kadar GA dan outcome ibu penderita DM2 ($p = 0,009$) dengan derajat korelasi sedang ($r = 0,477$) dengan arah korelasi negatif. Titik potong GA terhadap outcome kehamilan adalah 16,77% dengan sensitivitas dan spesifitas secara berurutan 76% dan 75%.

Kesimpulan: Pemeriksaan GA dapat dijadikan sebagai prediktor untuk menilai outcome ibu selama kehamilan dengan tingkat korelasi sedang dan titik potong 16,77%.

Kata kunci: diabetes melitus, glikasi albumin, hamil, luaran ibu.

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INTRODUCTION

Type 2 diabetes is characterized by hyperglycemia and results from a combination of insulin resistance, inadequate insulin secretion, and excessive or inappropriate glucagon secretion. Uncontrolled type 2 diabetes is associated with various microvascular, macrovascular and neuropathic complications. Unlike patients with type 1 diabetes mellitus, patients with type 2 are not completely dependent on insulin for life. Diabetes mellitus is a chronic disease that requires long-term medical attention in order to prevent complications which may occur.¹

The prevalence of diabetes is increasing worldwide. The International Diabetes Federation predicts that the number of people living with diabetes will increase from 366 million in 2011 to 552 million in 2030.² The top ten countries with leading incidences of diabetes today include India, China, the United States, Indonesia, Japan, Pakistan, Russia, Brazil, Italy and Bangladesh. The biggest increase in diabetes will occur in Africa over the next 20 years. About 80% of people in Africa with diabetes are undiagnosed and many cases occur at the age of 30 to 60 years with high mortality rates.¹

Optimal control of blood sugar levels in the first and second trimesters of pregnancy is important to prevent complications in both the mother and fetus. The American Diabetes Association and the UK National Institute for Health and Care Excellence encourages proper glycemic control for women with type 1 diabetes during early pregnancy (recommended HbA1c levels <48 mmol / mol [$<6.5\%$]).³ Maternal influences due to diabetes can be subdivided during pregnancy, labor and puerperium. During pregnancy, diabetes can cause abortion, preeclampsia, polyhydramnios, premature labor and increased risk of pelvic head disproportion and malpresentation. During labor, diabetic complications include prolonged labor due to macrosomia, shoulder dystocia, increased risk for operation, rupture of the birth canal and postpartum hemorrhage. During puerperium, puerperal sepsis caused by immunocompromised conditions in pregnant women with diabetes may occur and can increase maternal morbidity. Effects of diabetes on the fetus include Fetus intrauterine death of the fetus, Macrosomia, late pulmonary maturation, birth trauma, growth retardation, congenital malformation, and increased neonatal mortality.

Optimal maintenance of blood glucose levels is known to be associated with decreased complications in diabetes mellitus. In 2010 the American Diabetes Association (ADA) included HbA1c levels in the diagnostic criteria of Diabetes and recommend that HbA1C examination should be performed to control diabetic complications.⁴⁻⁶ It has recently been reported that there are biomarkers that are more sensitive than HbA1C to indicate diabetes, namely Glycated Albumin (GA). Glycated Albumin was declared 10 times more sensitive than HbA1C in a study which examined a group of diabetics before and after undergoing diabetes therapy. The aim of this research is to find out whether glycated albumin levels is correlated with maternal outcome in pregnant women suffering from type II diabetes mellitus at the Regional General Hospital (RSUD) Dr. Zainoel Abidin Banda Aceh.

METHODS

This was a cross sectional design. The aim of this study is to determine the correlation between Glycated Albumin levels and the maternal outcome of pregnant women with Type 2 Diabetes. This research was conducted in the delivery suite of the Dr. Zainoel Abidin (RSUZA) General Hospital Banda Aceh from 4th January 2019 to 4th January 2020. Laboratory tests for Glycated Albumin levels were conducted at the Prodia Laboratory in Banda Aceh.

Inclusion criteria include a diagnosis of Diabetes Type 2 in pregnant women aged between 18 to 39 years old which is confirmed by an Internal Medicine Specialist. Exclusion criteria include: twin pregnancies, consumption of medication which affect pregnancies (for example, drugs which cause abortion and disruption of fetal organ development), pregnant women with congenital heart defects, autoimmune disease, malnutrition and placental and uterine abnormalities.

Blood specimens for examination of Glycated Albumin levels were taken from mediana cubital vein. About 3 ml was inserted into a serum separator tube and sent to the Banda Aceh Prodia Laboratory. Glycated albumin levels were assessed using colorimetric enzymatic method. The diagnosis of Diabetes Type 2 is made by an Internal Medicine Specialist. All data collected are analysed further using the ETA test and Receiver Operating Characteristic (ROC) curve.

RESULTS

There were 29 pregnant women suffering from type 2 diabetes mellitus who fulfilled the subject inclusion criteria. General characteristics of respondents and its respective maternal outcome are as follows:

Table 1. General Characteristics of Respondents and its Respective Maternal Outcome

Variable	Maternal Outcome	
	Normal (n=5)	Abnormal (n=24)
Age of Mother (years)	36 ± 3.16	34.42 ± 4.12
Gestational Age (weeks)	38.4 ± 0.89	29.25 ± 10.13
Body Mass Index (Kg/m ²)	29.82 ± 1.18	30.23 ± 4.52
Fasting Blood Glucose Concentration (mg/dL)	99.6 ± 19.55	164.88 ± 70.01
2 hours Post Prandial Blood Glucose Levels (mg/dL)	143 ± 32.57	236.08 ± 92.73
HbA1C Concentrations (%)	6.02 ± 0.24	8.22 ± 1.58
Gestational		
G1	0	3 (12.5)
G2	2 (40)	4 (16.7)
G3	1 (20)	8 (33.3)
G4	0	5 (20.8)
G5	2 (40)	2 (8.3)
G6	0	1 (4.2)
Parity		
P0	0	3 (12.5)
P1	2 (40)	8 (33.3)
P2	1 (20)	7 (29.2)
P3	1 (20)	4 (16.7)
P4	1 (20)	2 (8.3)
Abortus		
A0	4 (80)	16 (66.7)
A1	1 (20)	5 (20.8)
A2	0	2 (8.3)
A3	0	1 (4.2)
Diagnosis upon first visitation		
Incomplete Abortion	0	3 (12.5)
Severe Preeclampsia	0	8 (33.3)
Normal Delivery	5 (100)	0
Preterm Labour	0	2 (8.3)
Complete Abortion	0	1 (4.2)
IUGR	0	2 (8.3)
Macrosomia	0	4 (16.7)
Threatened Premature Labour	0	2 (8.3)
Missed Abortion	0	1 (4.2)

The distribution of parity and diagnosis are presented in the table above. The group with normal outcomes is dominated by the parity G1 and G5, P1 and A0, while the group with abnormalities is dominated by G3P1A0. Most groups of pregnant women with abnormalities had a diagnosis of severe preeclampsia (33.3%) and macrosomia (16.7%) and also Preterm Labor, IUGR and premature labor with an incidence percentage of 8.3% each.

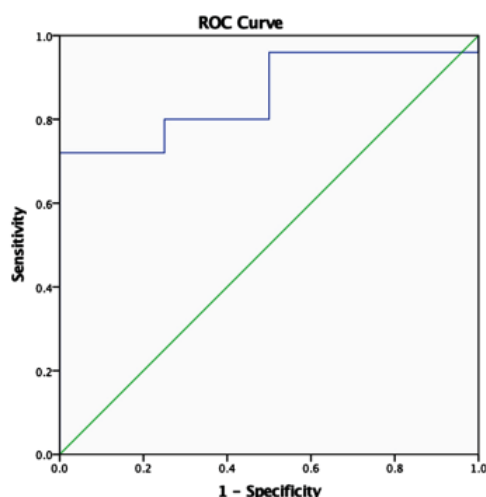


Figure 1. ROC Curve showing the correlation between Glycated Albumin and Maternal Outcome

The diagram above shows the Receiver Operating Characteristic (ROC) curve which shows the Area Under Curve (AUC) of 0.860. Based on these values it can be concluded that GA examination can be used as a predictor of pregnancy outcome in women suffering from type II DM with a discrimination rate of 86%. Furthermore, by using the coordinate of the curve, the GA intersection point is statistically 16.77%. The sensitivity and specificity values of the cut points are 76% and 75% respectively.

Table 2. Analysis of the Correlation of Study Variables

Glycated Albumin	Mean (Min – Max)	R*	P-value
Normal	12.54 (7.2 – 16.67)	-0.477	0.009
Abnormal	20.56 (7.1 – 38.2)		

Based on the ETA correlative test results above, it can be concluded that there is a correlation between glycated albumin levels and the outcome of mothers suffering from type II diabetes with a significance level of 0.009. Correlation coefficient values between the two variables indicate medium strength with a value of $R = 0.477$ with a negative correlation.

DISCUSSION

Infants of diabetic mothers generally experience various complications related to fetal hyperinsulinemia induced by maternal hyperinsulinemia. In the first trimester, maternal hyperinsulinemia can cause hyperinsulinemia embryopathy which can cause major disability and spontaneous abortion. Furthermore, in

the second and third trimesters, maternal hyperinsulinemia can cause fetal hyperglycemia, hyperinsulinemia, myocardial hypertrophy, delay of pulmonary maturation and macrosomia.⁷

At present the gold standard for checking glucose levels is by measuring the levels of glycated hemoglobin (HbA1C). This examination provides information of varying blood glucose levels during the last 2 to 3 months. However, HbA1C levels are as dependent on the abnormal life span of erythrocytes as they are with iron deficiency anemia. Pregnant women with diabetes mellitus or gestational diabetes mellitus often have iron deficiency anemia, making the HbA1C examination inaccurate.^{8,9}

In general, maternal outcomes can be divided into three, namely during pregnancy, labor and puerperium. Outcome during pregnancy can be in the form of abortion, preeclampsia, polyhydramnios, preterm labor. During labor in the form of prolonged labor due to a large baby, shoulder dystocia, ruptured birth canal and postpartum hemorrhage. Puerperal sepsis caused by immunocompromised conditions in pregnant women with diabetes can increase maternal morbidity. Furthermore, negative effects which may occur to the fetus include IUFD, macrosomia, late lung maturation, birth trauma, growth retardation, congenital malformation, and increased neonatal mortality.⁴

The condition of hyperglycemia in the fetus occurs when the maternal pancreatic insulin response is inadequate, this manifests as a recurring postprandial hyperglycemic episode. This postprandial episode is a major cause of rapid growth in the fetus. Maternal and fetal blood glucose levels are accompanied by episodic fetal hyperinsulinemia. Fetal hyperinsulinemia causes an increase in the storage of excess nutrients, causing macrosomia. Energy expenditure associated with the conversion of excess glucose into fat causes depletion of fetal oxygen levels. These episodes of fetal hypoxia are accompanied by increased adrenal catecholamines, which cause hypertension, cardiac remodeling and hypertrophy, erythropoietin stimulation, red blood cell hyperplasia, and increased hematocrit concentration. Polycythaemia occurs in 5-10% of newborns of diabetic mothers. High hematocrit values in neonates cause vascular sludging, poor circulation, and postnatal hyperbilirubinemia.¹⁰

Adverse effects due to abnormal maternal metabolism in offspring have also been observed. Glucose intolerance and higher serum

insulin levels are more common in children of diabetic mothers. Several literature supports the relationship between intrauterine exposure with diabetic mothers and the risk of metabolic syndrome later in life. Metabolic syndromes in childhood include obesity, hypertension, dyslipidemia, and glucose intolerance. Fetuses of diabetic women born with a large age for gestation appear to be at greatest risk.¹¹

Children born to mothers with diabetes exhibit higher levels of cardiac biomarkers for endothelial damage, as well as higher levels of leptin, BMI, waist circumference, and systolic blood pressure. This relationship remained significant even in pregnant women with a previously normal BMI.⁷

Diabetes management during pregnancy with continuous glucose monitoring (CGM) can reduce maternal hyperglycemia and macrosomia.¹² Maintaining normal blood glucose levels has been known to reduce the risk of maternal and neonatal complications during pregnancy. Referring to the study, monitoring of glucose levels using appropriate modalities is needed to improve neonatal and maternal outcomes during pregnancy and childbirth. A multicenter study concluded that GA examination is more superior for diabetes management during pregnancy than HbA1C.¹³

Glycated albumin (GA) is a ketoamine formed from albumin and glucose binded by non-enzymatic oxidation reaction, it is considered as an index of glycemic control that is not influenced by abnormalities in hemoglobin metabolism. Glycated albumin is able to monitor the administration of diabetes therapy and also anticipate earlier complications of DM. GA is not affected by albumin concentration because GA calculates the ratio of total serum albumin.¹²

However, before carrying out a GA examination on pregnant women, several factors which can affect serum albumin need to be considered. Serum GA levels are influenced by several factors associated with albumin regulation regardless of diabetes status such as thyroid dysfunction and cirrhosis. For example, thyroid hormone is known to play a role in albumin catabolism. Serum GA levels are positively correlated with serum TSH and negatively correlated to free T3 and T4. In addition, GA levels are also influenced by age and nutritional status.

Recent studies have reported the effectiveness of examining glycated albumin (GA) as a marker (biomarker) of glucose control in pregnant women. Compared to HbA1C, GA describes

blood glucose levels with a shorter duration of 2 to 3 weeks. GA is not affected by the life span of erythrocytes like HbA1C, so it is very useful during pregnancy.¹⁴ In addition to acting as a control of blood glucose levels, this study proves the correlation between GA levels on pregnancy outcomes in women suffering from type 2 diabetes mellitus.

Similar to this study, Sugawara et al in 2016 reported that GA examination served as a predictor of fetal complications during pregnancy. With a GA cutoff of 15.8% in the study, it was known that various neonatal complications such as hyperglycemia, respiratory distress, hypocalcemia, myocardial hypertrophy and macrosomia were identified.¹⁵ However, the GA cutoff point obtained from this study which predicts maternal pregnancy outcomes with DMT2 was found greater than 16.7%.

CONCLUSION

Our study concludes that examination of Glycated Albumin concentration can be used as a predictor to assess maternal outcomes during pregnancy with a moderate correlation level and a cutoff point of 16.77%.

SUGGESTION

Hopefully, this research can inspire more researchers to conduct more studies which reaffirm the importance of Glycated Albumin as a screening modality and its ability to predict maternal outcome in pregnant women with Type 2 Diabetes Mellitus.

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Research Article

Increased Levels of Umbilical Cord Blood Interleukin-6 (IL-6) and Serum C-Reactive Protein (CRP) in Premature Infants of Vitamin D Deficient Mothers

Peningkatan Kadar Interleukin-6 (IL-6) Darah Tali Pusat dan Serum C-Reactive Protein (CRP) pada Bayi Prematur dari Ibu dengan Defisiensi Vitamin D

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Abstract

Objective: Increased levels of inflammatory factors in newborns are often associated with lower maternal vitamin D levels. This study aimed to find out the relationship between maternal and umbilical cord vitamin D serum levels on umbilical cord Interleukin-6 (IL-6) and serum C-Reactive Protein (CRP) levels in premature infants.

Methods: The study was an observational analytic, cross-sectional design in mothers who underwent preterm birth at 28-34 weeks' gestation due to premature rupture of membranes (PROM) and their infants at Dr. Cipto Mangunkusumo General Hospital (RSCM), Jakarta and Persahabatan General Hospital, Jakarta, from January 2017 to August 2018. Levels of serum vitamin D of the maternal and umbilical cord, umbilical cord IL-6 and serum CRP in premature infants were recorded. Vitamin D level was divided into deficiency (<10 ng/mL), insufficiency (10-29 ng/mL), and normal (≥ 30 ng/mL) groups. The relationship of vitamin D levels with IL-6 and CRP was carried out using Kruskal Wallis test.

Results: A total of 70 subjects met the research criteria. Umbilical cord IL-6 and serum CRP levels in premature infants of vitamin D deficient mothers were higher (20.31 pg/mL and 0.50 mg/L) compared to insufficient (3.34 pg/mL and 0.45 mg/L) and normal mothers (3.29 pg/mL and 0.30 mg/L), although not statistically significant (IL-6 $p = 0.665$, CRP $p = 0.89$). Referring to the umbilical cord blood vitamin D levels, the results were different and not as expected, in which the umbilical cord IL-6 and serum CRP levels of preterm infants in the deficiency (3.76 pg/mL and 0.35 mg/L) and insufficiency (3.37 pg/mL and 0.40 mg/L) groups were lower (IL-6) and not different (CRP) than the normal group (9.41 pg/mL and 0.40 mg/L).

Conclusions: There were tendency for an increase in umbilical cord IL-6 and serum CRP level in premature infants of Vitamin D deficient mother although these were not statistically significant. Based on the levels of vitamin D umbilical cord blood, the CRP levels in the serum of premature infants were not different, while the IL-6 levels in the deficiency and insufficiency group were lower than in the normal group.

Keywords: CRP, IL-6, maternal vitamin D, umbilical cord vitamin D.

Abstrak

Tujuan: Peningkatan kadar faktor inflamasi pada bayi baru lahir sering dikaitkan dengan rendahnya kadar vitamin D ibu. Penelitian ini bertujuan untuk mengetahui hubungan kadar serum vitamin D ibu dan tali pusat, dengan kadar IL-6 tali pusat dan serum C-Reactive Protein (CRP) bayi prematur.

Metode: Studi observasional analitik dengan desain potong lintang pada subjek ibu yang mengalami kelahiran prematur di usia 28-34 minggu kehamilan disebabkan ketuban pecah dan bayi yang dilahirkannya, di Rumah Sakit Umum Pusat Nasional dr. Cipto Mangunkusumo (RSCM) dan Rumah Sakit Umum Pusat Persahabatan, Jakarta, pada bulan Januari 2017 sampai Agustus 2018. Variabel data adalah kadar serum vitamin D ibu dan tali pusat, kadar serum IL-6 tali pusat dan kadar CRP darah bayi. Kadar vitamin D (25(OH)D) dibagi menjadi defisiensi (<10 ng/mL), insufisiensi (10-29 ng/mL) dan normal (≥ 30 ng/mL) dan dicari hubungannya dengan kadar IL-6 tali pusat dan serum CRP bayi prematur, menggunakan uji Kruskal Wallis.

Hasil: Sebanyak 70 subjek telah memenuhi kriteria penelitian. Kadar IL-6 tali pusat dan serum CRP bayi prematur dari kelompok ibu defisiensi vitamin D (20,31 pg/ml dan 0,50 mg/L) lebih tinggi dibandingkan kelompok ibu insufisiensi vitamin D (3,34 pg/mL dan 0,45 mg/L) maupun kelompok ibu normal vitamin D (3,29 pg/mL dan 0,30 mg/L) tetapi perbedaan tersebut tidak bermakna (IL-6 $p = 0,665$ dan CRP $p = 0,899$). Mengacu pada kadar vitamin D darah tali pusat didapatkan hasil yang berbeda dan tidak sesuai harapan, dimana tali pusat IL-6 dan serum CRP bayi prematur mengalami defisiensi (3,76 pg / mL dan 0,35 mg / L) dan insufisiensi. (3,37 pg / mL dan 0,40 mg / L) kelompok lebih rendah (IL-6) dan tidak berbeda (CRP) dibandingkan kelompok normal (9,41 pg / mL dan 0,40 mg / L).

Kesimpulan: Didapat kecenderungan peningkatan kadar IL-6 darah tali pusat dan serum CRP bayi prematur dari ibu dengan defisiensi kadar vitamin D walaupun secara statistik tidak signifikan. Berdasarkan kelompok vitamin D darah tali pusat, kadar CRP serum bayi prematur tidak berbeda, sedangkan kadar IL-6 pada kelompok defisiensi dan insufisiensi lebih rendah dibandingkan pada kelompok normal.

Kata kunci: CRP, IL-6, vitamin D ibu, vitamin D tali pusat.

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INTRODUCTION

Preterm birth is one of the most prominent causes of perinatal death and long term morbidity.^{1,2} Several complications in form of growth retardation, airway problems, and digestive tract disorders are significantly higher in premature infants.³ Epidemiologically, prevalence of preterm birth differs in every country, ranging from 5-18% of live births. Prevention of premature birth is one of the global priority in medical fields until today.²

The main causes of preterm birth are still a matter of debate. One of the theories states that inflammatory mediator activation would excite myometrium and induce contraction.⁴ Previous study has shown that increase in inflammatory cytokines such as IL-6 and IL-8 was noted in pregnant women experiencing preterm birth.⁴ However, most of the cases remain to be idiopathic, raising a hypothesis of subclinical response to an inflammation on mother and fetus.⁵

Premature Rupture of Membranes (PROM) is associated with subclinical intrauterine infection in preterm birth. Chorioamnionitis as a complication of PROM would increase the level of proinflammatory cytokines in amniotic fluid, umbilical cord, and maternal serum. Those proinflammatory cytokines would circulate in maternal blood circulation, inducing the synthesis of C-reactive protein (CRP) in hepatocyte and leukocyte in bone marrow.⁵

Synthesis of proinflammatory cytokines is strongly associated with immune response in the body. One of the contributing factors in modulating immune response is nutrition, one of which is vitamin D (*25-dihydroxyvitamin D3*). Vitamin D in pregnancy in its active form *1,25-dihydroxyvitamin D3* [*1,25(OH)₂D₃*] would affect innate response immune through trophoblast, lowering inflammation and oxidative stress marker.⁶ It would also induce cathelicidin in various tissues to reduce bacterial infection, including in the placenta.⁶ Lower level of maternal vitamin D has been reported to stimulate acute phase response, increasing CRP, hemostatic factors, and proinflammatory concentration in both mothers and newborns.⁷

Vitamin D also plays a role in regulating the adaptive immune response. Vitamin D in the umbilical cord is correlated with antimicrobial substance production and inflammatory response induced by Toll Like Receptor (TLR). Escalation in

vitamin D level would modulate and decrease the level of TLR 2, TLR 4, and TLR 9, thus decrease the secretion of IL-6 as one of the inflammatory markers in circulation.^{8,9}

METHODS

This was a cross-sectional study determined to the relationship of serum maternal and umbilical cord vitamin D levels on umbilical cord IL-6 and serum CRP levels in premature infants. It was performed on August 2019 to July 2020, at RSCM and Persahabatan General Hospital, Jakarta, Indonesia.

Subjects were pregnant mothers at 28–34 weeks of gestation undergoing preterm birth preceded by PROM and their premature infants. Infants with birth weight >2.500 grams, having lethal congenital defects, stillbirth, or having intrauterine infection were excluded from the study. Pregnant women with systemic disease such as diabetes, thyroid disease, vascular disease, chronic hypertension, and liver disease were also excluded from the study. Maternal peripheral blood samples of 5 cc were taken at delivery to check levels of vitamin D. Five cc of umbilical cord blood was taken to check the levels of 25(OH)D and IL-6. Vitamin D serum levels were examined in the form of 25(OH)D, measured by the HPLC-MS (High-Performance Liquid Chromatography Mass Spectrometer) method. Serum IL-6 levels were measured using the ELISA method (Enzyme-Linked Immunosorbent Assay). Serum CRP was collected within 48 hours of the infant's life and examined using an immunoturbidimetric CRP assay. Subjects were taken by consecutive sampling method.

The ethical clearance was approved by the Research Ethics Committee Faculty of Medicine, Universitas Indonesia and Persahabatan Hospital Ethics Committee with ethical clearance number with number KET 798/UN2.F1/ETIK/PPM.00.02/2019 and LB.02.01/1.4.6/343/2019. All patients who were included in this study had given their informed consent prior to their inclusion in the study.

Collected data were then analyzed using SPSS for Macintosh ver. 20. Sociodemographic characteristics of subjects were analyzed descriptively. Vitamin D levels were categorized as deficiency (<10 ng/mL), insufficiency (10–29 ng/mL), and normal (≥30 ng/mL). The data was then analyzed for its relationship with umbilical cord IL-6 and serum CRP premature infants levels used Kruskal Wallis test.

RESULTS

During the period, a total of 70 subjects met the inclusion criteria and had been further analyzed. The sociodemographic characteristics of the subjects are shown in table 1.

Table 1. Sociodemographic and Clinical Characteristics of Subjects

Characteristics	n = 70
Maternal age (years)	30.39 ± 6.74
< 35	45 (64.3)
≥ 35	25 (35.7)
Education	
≤ High school	54 (77.1)
> High school	16 (22.9)
Occupation	
Employee	18 (25.7)
Housewife	52 (74.3)
Parity	
1st	32 (45.7)
2nd	13 (18.6)
Multiple	25 (35.7)
Gestational age (weeks)	31.59 ± 1.97
28 – 31+6	33 (47.1)
32 – 34+6	37 (52.9)

PROM duration (days)

1 – 3	55 (78.6)
4 – 6	10 (14.3)
> 7	5 (7.1)
Birth weight (gram)	1753.29 ± 369.87
1000 – 1500	18 (25.7)
1501 – 2000	35 (50.0)
2001 – 2500	17 (24.3)

Data distribution of serum 25(OH)D, IL-6 and CRP levels can be seen in table 2. Relationship between 25(OH)D level with inflammatory markers can be found in Table 3 (maternal) and Table 4 (umbilical cords).

Table 2. Data Distribution of Serum 25(OH)D, Interleukin-6 and C-Reactive Protein

Laboratorium Parameters	Median (min – max)
25(OH) D maternal serum (ng/mL)	23.07 (3.32 – 68.53)
25(OH) D umbilical cord (ng/mL)	13.05 (2.25 – 53.35)
IL-6 umbilical cord (pg/mL)	3.42 (0.45 – 35.72)
CRP infant (mg/L)	0.40 (0.02 – 35)

Table 3. Relationship between Maternal 25(OH)D, Interleukin-6 and C-Reactive Protein

Markers	Maternal 25(OH)D (ng/mL)			P-value
	Normal (n=22)	Insufficiency (n=42)	Deficiency (n=6)	
IL-6 umbilical cord (pg/mL)	3.29 (0.63 – 35.72)	3.34 (0.45 – 35.14)	20.31 (1.12 – 33.40)	0.665
CRP infants (mg/L)	0.30 (0.10 – 3.00)	0.45 (0.02 – 35.00)	0.50 (0.10 – 6.40)	0.899

Table 4. Relationship between Umbilical Cord 25(OH)D, Interleukin-6 and C-Reactive Protein

Markers	Umbilical cord 25(OH)D (ng/mL)			P-value
	Normal (n=9)	Insufficiency (n=41)	Deficiency (n=20)	
IL-6 (pg/mL)	9.41 (1.26 – 32.97)	3.37 (0.45 – 35.72)	3.76 (1.08 – 35.02)	0.758
CRP (mg/L)	0.40 (0.10 – 2.50)	0.40 (0.02 – 10.30)	0.35 (0.03 – 35.00)	0.815

DISCUSSION

This study found that maternal vitamin D or 25(OH)D levels generally showed insufficiency with a median of 23.07 (3.32–68.53) ng/mL. These results were similar to that of many studies that found vitamin D levels in pregnant women were generally insufficient. This study also found that the median umbilical cord 25(OH)D level was 13.05 (2.25–53.35) ng/mL. Study with large subjects, showed a median umbilical cord vitamin

D 39.43 nmol/l or equal to 15.8 ng/mL, similar with the result of this study where umbilical cord 25(OH)D levels were insufficient.¹⁰

Based on review articles and previous studies, it was stated that vitamin D plays a role in inhibiting the production of the cytokine IL-6. Low vitamin D levels may not reduce the release of inflammatory cytokines. In this study, it was found that there was a tendency for umbilical cord IL-6 and infant CRP serum levels to be higher in the group of vitamin D deficient mothers. This difference

was seen, especially in IL-6 levels. However, the difference in levels of umbilical cord IL-6 and infant CRP serum based on maternal vitamin D category was not statistically significant.

In one study reported comparisons of maternal serum vitamin D, serum CRP and IL-6 levels taken at 72 hours of life in infants without and with early clinical onset sepsis.¹¹ The levels of maternal vitamin D were 36.047 ± 1.243 ng/mL vs 22.3 ± 5.047 ng/mL, CRP levels were 5.1 ± 3.6 mg/dL vs 14.78 ± 9.3 mg/dL, and IL-6 levels were 24.71 ± 35.46 pg/mL vs 198.074 ± 59.58 pg/mL, respectively. It appears that at higher maternal vitamin D levels, CRP and IL-6 levels were found to be lower.¹¹ This is similar to the results in this study, where at higher maternal vitamin D levels, the infant's CRP and IL-6 umbilical cord levels were lower, in addition to different IL-6 sample origins.

This study found that at maternal general insufficient 25(OH)D levels of 23.07 (3.32–68.53) ng/mL, serum umbilical cord IL-6 levels showed a median of 3.42 (0.45–35.72) pg/mL. In one study in China regarding vitamin D and serum IL-6 as risk factors for tubal infertility, it was found that at a insufficient 25(OH)D level of 19.4 ng/mL (15.8–22.7 ng/mL), the serum IL-6 levels was 5.3 (4–7.5) pg/mL.¹² At first glance the results look similar. We have not been able to compare the results with previous studies with the same sample, so differences in sample types should be a concern.

At insufficient levels of 25(OH)D, in this study and other study¹¹, it were found that serum CRP levels were 0.40 (0.02–35) mg/L and 6.71 (SD = 3.07) mg/L. The different results may be due to differences in sample types, our study used serum CRP taken within 48 hours of the infant's life whereas another study¹¹ used umbilical cord CRP samples.

Several studies with similar variables but in different specimens may be able to compare the association of vitamin D with inflammatory factors. One study reported a significant negative correlation between maternal serum vitamin D and CRP levels in infants with early-onset sepsis ($r = -0.75$, $p < 0.001$).¹³ A significant negative correlation was also found between neonatal vitamin D and IL-6 levels taken at 72 hours of infant life with early-onset sepsis ($r = -0.923$, $p < 0.001$).¹¹ Another study in healthy women aged 25 to 82 years reported that there appears to be a slight trend toward an inverse association between 25(OH)D levels and serum IL-6 ($p = 0.0909$).¹⁴ These results indicated that the higher

the maternal vitamin D levels, the lower the IL-6 and CRP levels are expected.

Other studies have shown different results on the association of vitamin D with serum IL-6 and CRP. There was no significant association between serum vitamin D and CRP levels in asymptomatic adults.¹⁵ There was no significant difference in serum IL-6 levels with vitamin D levels by category in patients with rheumatoid arthritis.¹⁶

In contrast to maternal vitamin D, unexpected results were obtained for umbilical cord vitamin D. The infant's high umbilical cord IL-6 and CRP levels were seen at normal vitamin D levels. Based on the theory, the better the vitamin D level, it is expected that IL-6 and CRP levels will tend to decrease. The imbalance in the number of umbilical cord vitamin D samples based on the level category, may affect the statistical results and be one of the weaknesses of this study. Future studies with larger and balance samples will likely be able to reach theoretically and clinically relevant conclusions.

CONCLUSION

There were tendency for an increase in umbilical cord IL-6 and serum CRP level in premature infants of Vitamin D deficient mother although these were not statistically significant. Based on the levels of vitamin D umbilical cord blood, the CRP levels in the serum of premature infants were not different, while the IL-6 levels in the deficiency and insufficiency group were lower than in the normal group.

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CONFLICT of INTEREST

Authors declare that there is no conflict of interest in this study.

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Research Article

The Role of Intrapartum Ultrasound to Predict Outcome of Delivery

Penggunaan Ultrasonografi Intrapartum untuk Memprediksi Luaran Persalinan

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Abstract

Objective: To predict outcome of delivery by using ultrasound measurements consisting angle of progression, and head perineum distance.

Methods: Sixty two parturients assigned in cohort prospective study. Ultrasound examination begin with identifying the cephalic position by placement of transducer on suprapubic region. The angle of progression is obtained trans-labially, head perineum distance and cervical dilation trans-perineally. Ultrasound findings of Nuchal cord, caput, moulding, occiput posterior position then compared with conventional findings. Labour is observed, outcomes are grouped into vaginal delivery and cesarean section.

Results: Thirty-six women went for vaginal delivery, 26 underwent cesarean section. Independent T-test showed significant differences of the angle of progression (121.11° vs 88.85°) and head perineum distance (5.15 cm vs 7.26 cm) between the two groups. Linear regression test found a negative correlation on how the angle of progression affecting head perineum distance p-value <0.05 , R^2 0.684, (r) - 0.827. Cervical dilation measurements both ultrasound and digital examination were assessed with the Bland-Altman reliability test with level of agreement (-1.0 cm) - (1.2 cm). Receiver Operating Characteristic curve showed cut-off value $>101^\circ$ angle of progression predicts vaginal delivery, area under curve 0.902 and positive likelihood ratio 4.4. Kappa reliability testing for nuchal cord, caput, moulding, and occiput posterior are 0.919, 0.938, 0.384, 0.681 respectively.

Conclusions: Intrapartum ultrasound able to predict the outcome of delivery, digital examination of cervical dilation is the mainstay of measurement. Ultrasound able to rule out the presence of nuchal cord, caput, and occiput posterior.

Keywords: angle of progression, head perineum distance, intrapartum ultrasound.

Abstrak

Tujuan: Mengetahui besar sudut penurunan kepala dan jarak kepala ke perineum dengan ultrasonografi intrapartum dalam memprediksi luaran persalinan.

Metode: Enampuluh dua ibu bersalin dilakukan pemeriksaan ultrasonografi intrapartum. Identifikasi posisi kepala dengan meletakkan transduser di suprapubik, sudut penurunan kepala secara translabial, jarak kepala ke perineum dan nilai dilatasi serviks secara transperineal. Lilitan tali pusat, kaput, molase, dan oksiput posterior pada temuan ultrasonografi dibandingkan dengan hasil pemeriksaan konvensional. Observasi persalinan dilakukan, di kelompokkan untuk persalinan pervaginam dan seksio sesarea.

Hasil: Didapatkan 36 persalinan pervaginam dan 26 seksio sesarea. Uji - t secara signifikan berbeda, nilai sudut penurunan kepala ($121,11^\circ$ vs $88,85^\circ$), jarak kepala ke perineum (5,15 cm vs 7,26 cm) pada kedua kelompok. Uji regresi linier sudut penurunan kepala dan pengaruhnya terhadap jarak kepala ke perineum berkorelasi negatif p <0.05 , R^2 0.684, (r) - 0.827. Batas kesepakatan nilai dilatasi serviks kedua metode diuji dengan uji reliabilitas Bland-Altman dengan batas kesepakatan sebesar (-1.0) cm - (1.2) cm. Sudut penurunan kepala memprediksi persalinan pervaginam sebesar $>101^\circ$, uji diagnostik dengan kurva Receiver Operating Characteristic didapatkan area dibawah kurva 0.902, rasio kemungkinan positif 4,4. Uji reliabilitas Kappa lilitan tali pusat, kaput, molase, dan oksiput posterior berturut-turut (k) = 0.919, 0.938, 0.384, dan 0.681.

Kesimpulan: Penggunaan ultrasonografi intrapartum dapat memprediksi luaran persalinan, pemeriksaan dalam tetap menjadi pemeriksaan utama dalam menilai dilatasi serviks, ultrasonografi mampu mendeteksi lilitan tali pusat, kaput, dan posisi oksiput posterior.

Kata kunci: Jarak kepala ke perineum, sudut penurunan kepala, Ultrasonografi intrapartum.

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INTRODUCTION

Progression and outcome of labour are assessed through conventional methods comprise history taking and physical examination. The pelvic digital examination usually performs to gather useful information of cervical dilation, head position, and descent of presenting part through pelvis with Station or Hodge plane. Labour dystocia with presence of caput succedaneum and severe moulding make digital examination to determine head descent and denominator position are proven difficult¹. Intrapartum ultrasound compared with conventional method provides objective value with several anatomic landmarks related to labour progression².

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) released guideline states that several parameters through sonographic imaging can be achieved during labour to determine station and head position. Producing an ultrasound image consisting Angle of Progression/Angle of Descent (AOP), Head Perineum Distance (HPD), Fetal Head Direction, Midline Angle (MLA), Progression Distance (PD), and Head Symphysis Distance (HSD) provide useful values and prediction models on how labour will progress³. Each of these techniques aid in identifying anatomical landmarks and increase the success rate of operative vaginal delivery^{4,5}. Intrapartum ultrasound can aid preemptive measure to foresee labour dystocia requiring further intervention⁶.

Pelvic digital examination remains as the main choice to assess progression of labour in labour and delivery unit. This study aims to verify the value of angle of progression and head perineum distance predict the future outcome of labour. Cervical dilation, denominator position, caput succedaneum and moulding will be compared between ultrasound and digital examination findings. The presence of nuchal cord during ultrasound examination will also be compared soon after delivery.

METHODS

This study was performed from May 2019 – January 2020. Samples were gathered at RSUD Besuki, Situbondo, East Java. It uses cohort prospective model with the consecutive sampling method. The inclusion criteria are women who in the 1st stage of labour, singleton pregnancy, cephalic presentation, agreed on

informed consent. Meanwhile, those whose sexual transmitted disease and other blood born disease prove to be positive are excluded from this study.

We begin the examination by having the midwife to perform a routine pelvic digital examination to obtain cervical dilation, head position, and to rule out the presence of caput succedaneum and moulding. Soon after it is followed by series of ultrasonographic examinations operated by Obstetrician using GE LOGIQ C5 Premium in the obstetric emergency ward and Mindray DC-N3I in the delivery ward.

Placing of the transducer in the transverse plane in suprapubic region will achieve imaging of fetal orbits opposite to its occiput and transthalamic plane with choroid plexuses toward occiput⁷⁻¹⁵ (Figure 1). Then in the same region placing the transducer in sagittal plane will achieve an image of fetal vertebrae long axis and the posterior nuchal region relates to fetal occiput¹⁶.

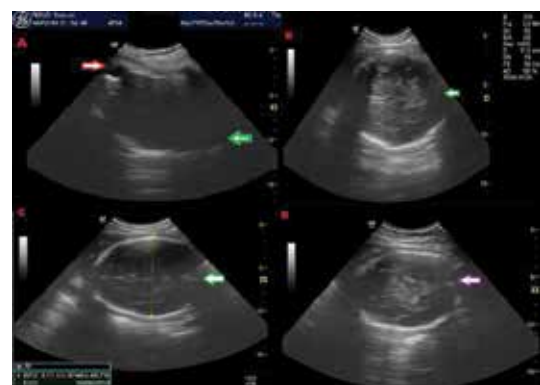


Figure 1. Fetal orbit (red arrow) opposite to fetal occiput. A.OP 4:00 (green arrow). B&C. Transthalamic plane LOT 9:00,D. LOA 2:30

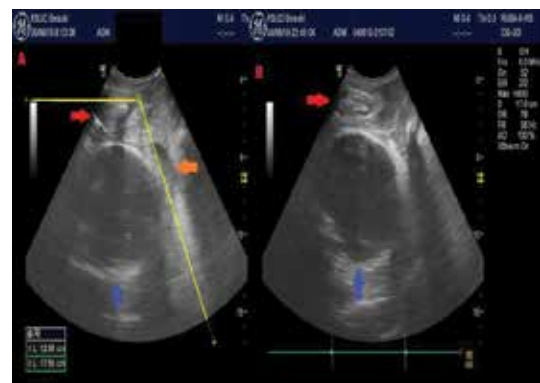


Figure 2. A. AOP 110°. Pubic Symphysis (red arrow), fetal head (blue arrow), forewaters (orange arrow).

Additional *colour flow Doppler* in the same plane will visualized cord vessels to raise nuchal cord suspicion. Divot sign can also be identified in B-Mode imaging as a result of nuchal cord entanglement pressure on fetal skin^{17,18}. ISUOG guideline stated that fetal occiput to be illustrated as a clock direction.

To obtain angle of progression, placement of the transducer should be in sagittal plane translabially. Anatomic landmarks are used in this plane which are pubic symphysis and outer edge of fetal skull. Imaginary lines are drawn from pubic symphysis long axis through the point of infrapubic then ends at the outer edge of fetal skull^{19,20} (**Figure 2**). The presence of caput and moulding can also be identified in this plane^{21,22}.

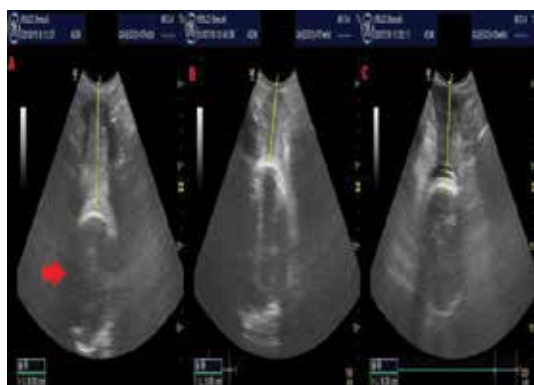


Figure 3. HPD **A.** 8 cm, **B.** 5.06 cm, dan **C.** 6.36 cm.

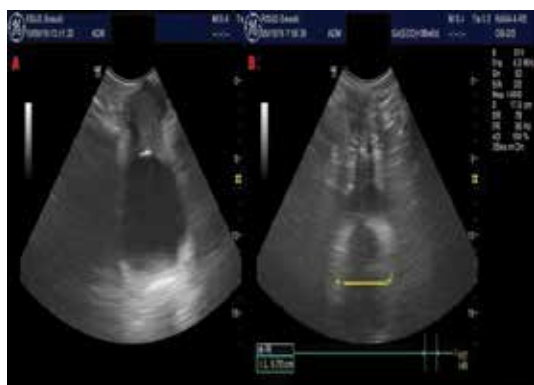


Figure 4. Cervical Dilation **B.** 5.73 cm cervical dilation.

Head perineum distance then achieved by placing the transducer transperineally with transverse plane. Slight pressure is applied to display perineal skin edge and the outer edge of fetal skull. The measurement between two callipers are then recorded^{23,24} (**Figure 3**).

In the same plane, slight angling to upward pressure manoeuvre will expect that the sound beam to produce an image of dilating external

cervical os, transverse diameter between the two calipers in the projected area are then recorded^{25,26} (**Figure 4**).

Samples are observed and grouped into vaginal delivery and cesarean section group. Statistical analysis then performed, Independent T-test is used to compare the angle of progression and head perineum distance between two groups. Linear regression with Pearson correlation then used to find the influence between the angle of progression and head perineum distance. All numerical data are processed through the Kolmogorov-Smirnov normality test. Inter-rater reliability test Kappa is used for comparing nuchal cord, caput succedaneum, moulding, and denominator position between ultrasound and conventional method. Bland-Altman reliability testing is also used to find the level of agreement between cervical dilation based on ultrasound finding compared with digital examination. Level of agreement not exceeding 0.5 cm are set as the threshold. Area Under Curve (AUC) on Receiver Operating Characteristics (ROC) curve will be used as diagnostic testing on how well angle of progression and head premium distance predict the outcome of labour. All statistical analyses were performed with IBM SPSS Statistics 23.

RESULTS

Samples Characteristic

Table 1. Gravity and Outcome of Parturients.

Variable	Mode of Delivery		Total
	Vaginal	Cesarean	
Primigravid	14	18	32
Multigravid	22	8	30
Outcome	36	26	62

From labour observation 36 labouring mother successfully deliver vaginally, and 26 underwent cesarean delivery. Most of labouring mother presenting in this study are primigravid.

Table 2. Distribution of Minimal, Maximal and Mean Values among Samples.

Characteristics	Value		
	Minimal	Maximal	Mean
AOP	59°	165°	107°
HPD	1.03 cm	10.7 cm	6.0 cm
CDUS	0.0 cm	10.8 cm	5.4 cm
CDPE	0 cm	10 cm	5.3 cm
Birth Weight	2100 gr	4050 gr	3115 gr
Gestational Age	34 weeks	43 weeks	38 weeks
Maternal Age	17 years old	39 years old	25 years old

From all samples, the value of each characteristic can be described. the angle of progression 59° being the smallest angle and 165° is the largest angle, with an average of 107° . Head perineum distance found to be 1.03 cm being the smallest and 10.7 cm being the largest distance. Ultrasound (CDUS) and conventional cervical dilation (CDPE) values obtained a minimum value of 0 cm, a

maximum value of 10.8 cm on ultrasonography and 10 cm on conventional examination, with no significant difference of mean between the two measurements (One sample T-test p 0.139). Birth weight average is 3115 gr, the smallest 2100 gr, and the largest 4050 gr. The youngest age of mothers in this study is 17 years old and the oldest being 39 years old.

Table 3. Independent T-test.

Variable	T-Test		Outcome		P-value
	Cesarean	Vaginal	Cesarean	Vaginal	
Angle of progression	26	36	88.85°	121.11°	0.001
Head perineum distance	26	36	7.26 cm	5.15 cm	0.001

Independent T-test Shows significant difference of angle of progression and head perineum distance values between vaginal and cesarean group.

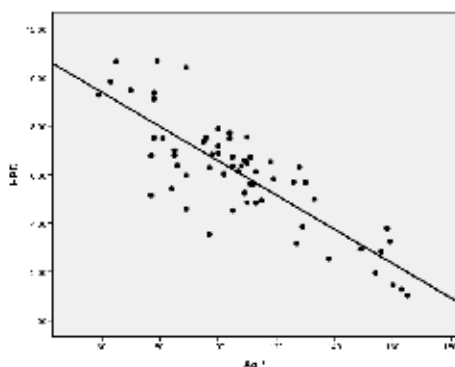


Chart 1. Linear regression scatter plot.

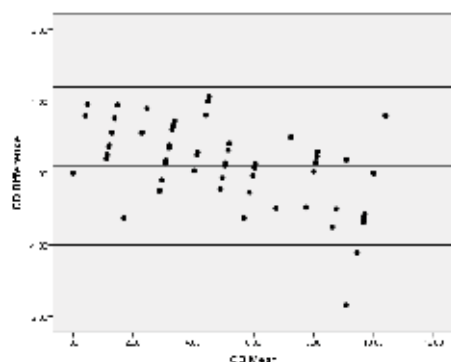


Chart 2. Bland-Altman scatter plot.

Scatter plot showing a negative correlation on how AOP affecting HPD. p value 0.001 with R^2 0.684 meaning that 68.4% HPD data variation are affected by AOP in this regression model, Pearson correlation p value <0.05 ($r = -0.827$) (**Chart 1**).

Bland Altman scatter plot showing a mean difference and level of agreement between the two measurements (middle line). Although there is no significant difference between cervical dilation value obtained from pelvic exam and ultrasonography, the level of agreement between the two disagree, with mean difference 0.1 cm (SD 0.56), upper limit of agreement 1.2 cm and lower limit of agreement -1.0 cm. This equation proves that cervical dilation value measured from ultrasonography will be between 1.2 cm more and 1 cm less compared with pelvic examination. Thus the 0.5 cm threshold for limit of agreement does not meet. CD (Cervical Dilation), SD (Standard Deviation) (**Chart 2**).

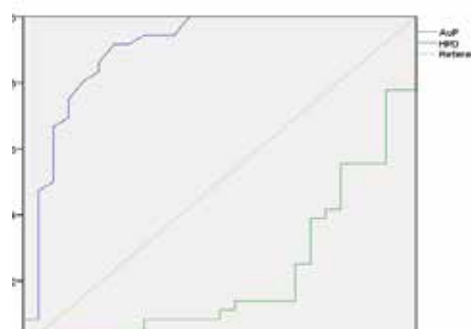


Chart 3. ROC Curve.

ROC (Receiver Operating Characteristics) curve showing how intrapartum ultrasound predicting outcome of labor. AOP proven to be better predictor of labor outcome compared to HPD. With AUC (Area Under Curve) 0.902 (90.2%) for AOP compared to HPD 0.213 (21.3%). According to the curve from 62 samples value of AOP greater than 101° predicts vaginal delivery. This proven to be true in our study as 86% of laboring women in $>101^\circ$ group deliver vaginally, only 14% of

them are assigned for cesarean. From 101° cut off value, this model has 86.1% sensitivity and positive predictive value, 80.7% specificity and negative predictive value, 4.4 positive likelihood ratio and 0.1 negative likelihood ratio. Thus concludes angle of progression greater than 101° is 4.4 times likely to result in vaginal delivery with 83.8% accuracy (**Chart 3**).

Kappa coefficient to predict accuracy between ultrasound and conventional method on assessing nuchal cord, caput succedaneum, moulding, and occiput position are $k = 0.919, 0.938, 0.384, 0.681$ respectively. It shows that nuchal cord, caput, and occiput position are acceptable in both method in contrast with molding it appears ultrasound is more reliable.

DISCUSSION

Our findings in this research are supported with the previous result from other similar studies. Determined the cut off value in angle of progression $>110^\circ$ (OR 3.1 & ROC/AUC 72%) and head perineum distance <4 cm (OR 4.9 & ROC/AUC 81%) as predictive to vaginal delivery outcome.²⁷ Were able to predict vaginal delivery during 1st stage of labour dystocia with angle of progression $<100^\circ$ (76% ROC/AUC) and head perineum distance >5 cm (81% ROC/AUC) increase the chance of cesarean section.²⁸ Determined the predictive value of vaginal delivery are with angle of progression $>105^\circ$ (87.7% ROC/AUC) and head perineum distance <4 cm (86.5% ROC/AUC)²⁹.

Meta-analysis showed that cervical dilation value through sonographic imaging compared with digital examination had good agreement based on Pearson's correlation test and linear regression.³⁰ This differs with our findings as our Bland Altman reliability testing show no level of agreement, which exceeds 0.5 cm. A review found that ultrasonography is superior compared with conventional method in to distinct every denominator positions and we find so in our research.^{31,32}

CONCLUSION

Intrapartum ultrasound predicts labour outcome, angle of progression is good parameter to predict the success of vaginal delivery. Nuchal cord, caput succedaneum, moulding, head position can be identified with intrapartum ultrasound. Cervical dilation obtained from ultrasound does not have agreement with digital examination.

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Research Article

High-Sensitivity Cardiac Troponin I Level and Left Ventricular Diastolic Dysfunction on Severe Preeclampsia

Kadar High Sensitivity Cardiac Troponin I dan Disfungsi Diastolik Ventrikel Kiri pada Preeklamsia Berat

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Abstract

Objective: To know the relationship between high-sensitivity cardiac Troponin I (hscTnI) level with left ventricular dysfunction on severe preeclampsia.

Methods: An observational analytics study with a cross-sectional approach of ten pregnant women with severe preeclampsia who underwent delivery or termination pregnancy and then performed a transthoracic echocardiography examination and serum levels of hscTnI.

Results: There is a significant relationship between hscTnI levels and left ventricular diastolic dysfunction ($p < 0.05$)

Conclusions: These findings of this study have significant implications that severe preeclampsia is associated with heart remodelling and significant change in cardiac function especially left ventricular dilatation and elevation of hscTnI. Early identification and intervention may ameliorate subsequent cardiovascular disease so this requires regular and close follow-up of this target group.

Keywords: high-sensitivity cardiac Troponin I, left ventricular diastolic dysfunction, severe preeclampsia.

Abstrak

Tujuan: Untuk mengetahui hubungan antara kadar high-sensitivity cardiac Troponin I (hscTnI) dengan disfungsi ventrikel kiri pada preeklamsia berat.

Metode: Studi observasional dengan pendekatan potong lintang terhadap sepuluh ibu hamil dengan preeklamsia berat yang menjalani persalinan atau terminasi kehamilan kemudian dilakukan pemeriksaan ekokardiografi dan kadar hscTnI serum.

Hasil: Ada hubungan yang bermakna antara kadar hscTnI dengan disfungsi diastolik ventrikel kiri ($p < 0,05$).

Kesimpulan: Temuan penelitian awal ini memiliki implikasi yang signifikan bahwa preeklamsia berat berhubungan dengan remodeling jantung dan perubahan signifikan pada fungsi jantung terutama dilatasi ventrikel kiri disertai peningkatan kadar hscTnI. Identifikasi dan intervensi dini dapat memperbaiki perjalanan penyakit kardiovaskular sehingga diperlukan pengawasan lanjut pada kelompok pasien ini.

Kata kunci: disfungsi diastolik ventrikel, high-sensitivity cardiac troponin I, jantung sensitivitas tinggi, kiri, preeklamsia berat

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INTRODUCTION

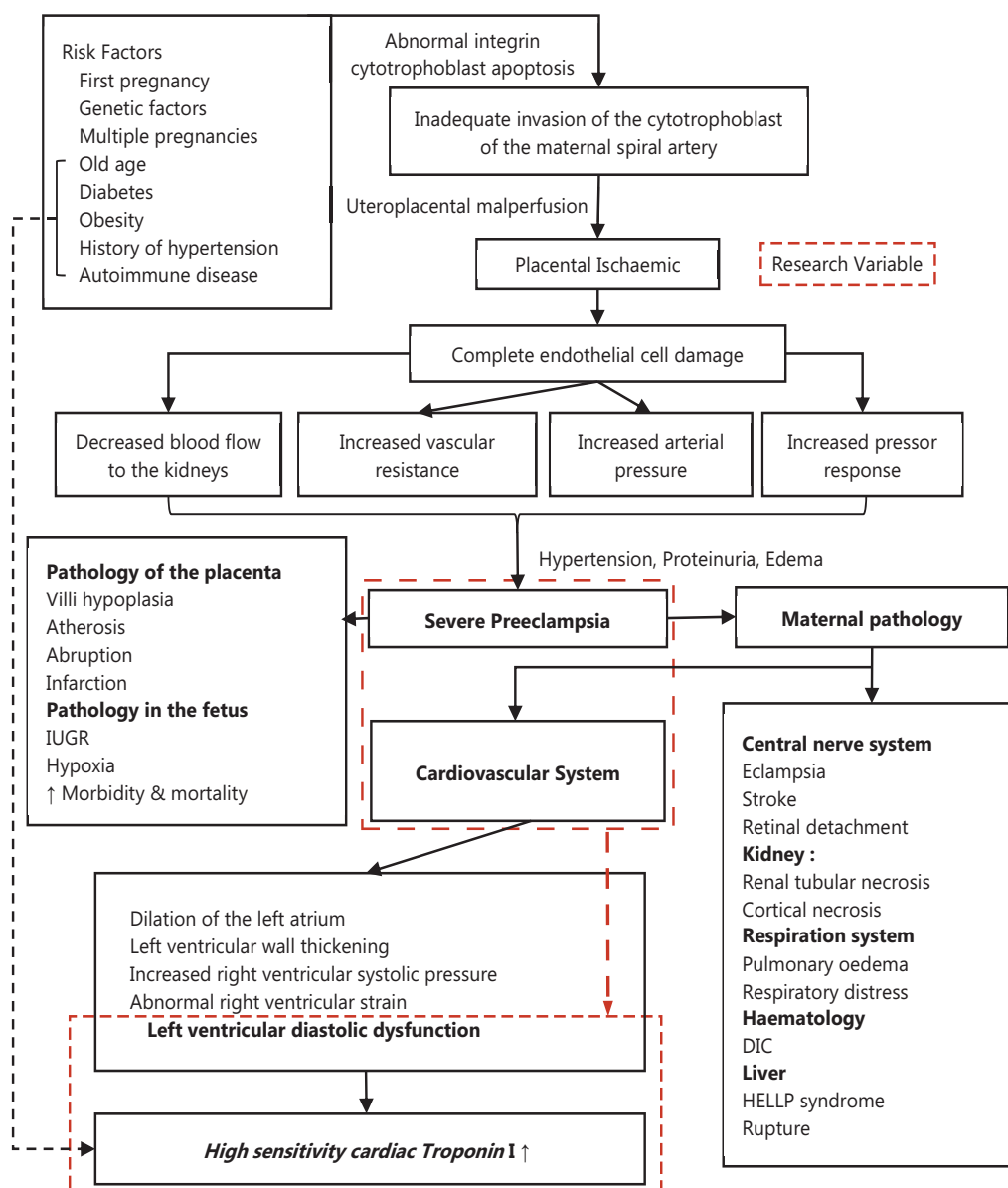
Preeclampsia is one of the leading causes of maternal and fetal death in developing countries. The pathogenesis of preeclampsia is not fully understood. The main causative factor is thought to be poor uteroplacental circulation caused by inadequate remodelling of the spiral arteries at between 8 and 18 weeks of gestation.¹ The result of this poor placentation process is placental hypoperfusion and oxidative stress. Maternal signs and symptoms result from concomitant endothelial dysfunction and vascular inflammation. Endothelial cells in the uteroplacental circulation that undergo hypoperfusion will release free radicals and fat peroxides.^{1,2}

Cardiovascular function and hemodynamics undergo significant changes during pregnancy, especially at delivery until one week postpartum there is a maximal cardiac change in morphology. The main change that occurs during pregnancy is an increase in cardiac output. These changes are associated with an increase in heart rate and blood volume, as well as a decrease in systemic vascular resistance during pregnancy. Conversely, preeclampsia is associated with decreased intravascular volume and increased arteriolar vasospasm leading to decreased cardiac output and increased systemic vascular resistance. In preeclampsia, there will be an excessive activity of the sympathetic system so that it will decrease blood reserves in the splanchnic organs causing increased venous return. This increase increases inferior vena cava diameter and left atrial volume so that patients with preeclampsia increase the risk of developing heart failure.³⁻⁵ Decreased stroke volume, diastolic dysfunction, and left ventricular remodelling were most common in severe preeclampsia.⁶ Research on the complications of preeclampsia in the incidence of heart failure has been investigated by several centres in Indonesia. Fifteen per cent of pregnant patients with heart failure at Kariadi General Hospital Semarang is caused by preeclampsia.⁷

Determining the presence of damage to the heart is an important factor for the evaluation of a patient with preeclampsia and plays an important role in the management and determination of the patient's prognosis. Cardiac biomarkers can be used for early identification of potential heart problems, one of which is troponin. The Troponin complex plays an important role in the regulation of the contraction of the skeletal and cardiac muscles. The complex consists of 3 subunits, namely Troponin T, Troponin I and Troponin C. Troponin I and T are both typical for the heart, however cardiac Troponin I is expressed exclusively in the heart muscle in contrast to cardiac Troponin T which may still be expressed by diseased skeletal muscle. Cardiac Troponin I reflect cardiac remodelling and can be used as a predictor of patients with heart failure. The level increases in response to myocardial damage and is one of the most specific and sensitive markers of ischemic or non-ischemic myocardial damage.⁸⁻¹⁰ However, several other studies suggest that there is no association between increased cardiac Troponin I and preeclampsia.¹¹⁻¹³

Recent advances in testing technology have resulted in increased sensitivity, now being able to calculate troponin levels with a high degree of precision at very low plasma concentrations. High sensitivity cardiac Troponin I (hs-cTnI) can detect troponin in more than 50% of the reference normal population and can identify patients above or below the 99th percentile with optimal accuracy.^{10,14} This study aimed to assess the relationship between hs-cTnI levels and left ventricular diastolic dysfunction in patients with severe preeclampsia obtained from echocardiographic examinations.

FRAMEWORK



METHODS

This research was conducted in the Department of Maternal-Fetal Medicine and Department of Cardiology Vascular Medicine, Dr. Kariadi General Hospital, Semarang. The inclusion criteria were patients with severe preeclampsia according to the 2016 PNPk Preeclampsia criteria with single pregnancy and delivery/termination at this hospital. The exclusion was made if there was a history of Diabetes mellitus, chronic hypertension, previous heart disease (congenital, acquired, cardiomyopathy and arrhythmias), chronic kidney disease, and receiving inotropic drugs and methylethylergometrine maleate. Study subjects were selected using consecutive sampling.

Observational analytic, Cross-sectional research was done in severe preeclampsia women who underwent echocardiography to assess the left ventricular diastolic dysfunction and measured hscTnI levels. Ten pregnant women were included in this study. The study was approved by the Ethical Committee of the Medical Faculty of Universitas Diponegoro and Dr. Kariadi General Hospital.

Patients with severe preeclampsia who met the inclusion and exclusion criteria were tested for transthoracic echocardiography (TTE), including 2-dimensional images, M-mode, color doppler, and tissue doppler by Cardiologists who served in the echocardiography diagnostic room. Echocardiography is performed a maximum of

48 hours after delivery. Echocardiography results obtained were then determined the presence of diastolic dysfunction according to the guidelines and recommendations of the American Society of Echocardiography.¹⁵ Blood samples were taken on the same day the patient was examined for echocardiography and then frozen and sent to the laboratory, serum hscTnI was measured by the ARCHITECT STAT (Abbott) immunoassay kit, then analyzed for the presence of left ventricular dysfunction.

SPSS software was used for statistical analysis. A comparison between groups was analyzed with an independent t-test. Data with abnormal distribution were analyzed using the Mann-

Whitney U test. Non-parametric data were analyzed using Fisher's Exact test. A value of $p < 0.05$ was considered significant.

RESULTS

At the end of the study, 10 subjects with severe preeclampsia were obtained and valid for analysis. The mean age was 30 ± 6 years and advanced maternal age (≥ 35 years) was observed in 30%. Fifty per cent of cases occur when gestational age is less than 34 weeks (early-onset severe preeclampsia). Cesarean section accounted for 60% of deliveries. The average weight of a baby born was 2107 ± 559 grams.

Table 1. Bivariate Test for the Relationship between Several Factors and Left Ventricular Diastolic function

Variable	Normal function		Diastolic dysfunction		P-value
	Mean (SD)	N (%)	Mean (SD)	N (%)	
Age (years)	31 (3)		29 (9)		0.635 [¥]
< 35		4 (40)		3 (30)	
≥ 35		1 (10)		2 (20)	
Gestational age (weeks)	35 (2)		34 (2)		0.544 [¥]
Early-onset (< 34)		2 (20)		3 (30)	
Late-onset (≥ 34)		3 (30)		2 (20)	
Systolic blood pressure (mmHg)	168 (8)		170 (17)		0.841 [*]
Diastolic blood pressure (mmHg)	97 (8)		98 (13)		0.841
Body mass index (kg/m ²)	34.3 (2.4)		30.6 (3.4)		0.090 [¥]
< 30		0 (0)		3 (30)	
≥ 30		5 (50)		2 (20)	
Glomerular filtration rate (GFR)	132 (17)		122 (17)		0.310 [*]
Mode of delivery					
Vaginal delivery		2 (30)		2 (20)	1.000 ^Σ
Cesarean section		3 (30)		3 (30)	
Parity	1 (1)		1 (1)		1.000 [*]
Nulliparity		0 (0)		2 (20)	
Primiparity		4 (40)		0 (0)	
Multiparity		1 (10)		3 (30)	
Birth weight (grams)	2382 (612)		1832 (493)		0.158 [¥]
< 2500		3 (30)		4 (40)	
≥ 2500		2 (20)		1 (10)	

¥: Independent t-test, *: Mann-Whitney U test, Σ: Fisher's Exact test, significant if $p < 0.05$

Based on table 1, age, gestational age, systolic and diastolic blood pressure, body mass index (BMI), glomerular filtration rate, mode of delivery, parity, and birth weight were not associated with left ventricular diastolic dysfunction ($p > 0.05$).

Table 2. Relationship of High Sensitivity Cardiac Troponin I Levels with Left Ventricular Diastolic Dysfunction

Left Ventricular diastolic function	high sensitivity cardiac Troponin I (Mean \pm SD)	P-value	PR (CI 95%)
Normal function	3.50 \pm 0.18	0.047 [*]	6 (1.4 – 11.8)
Dysfunction	9.50 \pm 2.11		

*: Independent t-test, significant if $p < 0.05$

The Shapiro-Wilk normality test was used to determine the distribution of hscTnI level data. From the normality test, the data distribution of hscTnI levels was normal so that the Independent T-Test was carried out between the hscTnI level and left ventricular diastolic dysfunction and obtained $p = 0.047$ ($p < 0.05$). Based on the above results, there is a significant relationship between hscTnI levels and left ventricular diastolic dysfunction.

DISCUSSION

Our study was conducted to determine the relationship between hscTnI levels and left ventricular diastolic dysfunction in patients with severe preeclampsia. Increased cardiac troponin I level in preeclampsia, as examined in this study, suggests the possibility that preeclampsia may have a deleterious effect on heart cells in pregnant women with preeclamptic conditions. Preeclampsia is associated with impaired vascular reactivity, hemodynamic index, and left ventricular function. Thus, left ventricular remodelling abnormalities as seen in some patients with preeclampsia can lead to left ventricular hypertrophy. Left ventricular involvement in preeclampsia is thought to cause cardiac ischemia, which can result in changes in several biomarkers of heart function.¹⁶ This study is consistent with the study of Morton et al. which measured hscTnI levels in 40 asymptomatic preeclamptic women results showed that hscTnI levels increased by 25% of the sample. Echocardiographic studies that were also carried out showed the presence of diastolic dysfunction in about 20% of women with preeclampsia.¹⁴ This is also following the study who compared hscTnI levels in normal pregnancy and preeclampsia and its relationship with impaired left ventricular function at the cellular level.¹⁰

Serum cardiac troponin is a specific and sensitive biomarker of cardiac injury that can detect even minor cardiac injury. Elevated cardiac troponin I after delivery could indicate myocardial injury during the delivery, significant rise in the early postpartum period. Preeclampsia induces the release of antiangiogenic factors, which impair vascular endothelial function in the placental and maternal circulation. These changes could lead to myocardial injury due to microcirculatory disorders in addition to hypertension's effects.³ Transient damage of this myocyte with or without pathological cardiac remodelling occurred even

in normal pregnant women postpartum because of cardiovascular maladaptation to the volume-overloaded state at term.¹⁷

Limitations of this study included small study size, absence of control group of normotensive pregnancy, and the measurement of hscTnI on only one occasion. HscTnI assays also more prone than sensitive assays to analytical problems because small differences can be of such importance.¹⁴

CONCLUSION

These findings of this study have significant implications that severe preeclampsia is associated with heart remodelling and significant change in cardiac function especially left ventricular dilatation and elevation of cardiovascular biomarkers (hscTnI). Early identification and intervention may ameliorate subsequent cardiovascular disease so this requires regular and close follow-up of this target group.

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Research Article

Identification of Bacteria on Postcesarean Section Patient's Wound Operation

Identifikasi Bakteri pada Luka Operasi Pasien Pascaseksio Sesarea

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Abstract

Objective: To determine the type of bacteria in post-cesarean surgical patient wounds obtained through the patient's surgical wound swab in the Ward Obstetrics and Gynecology RSUD Ulin Banjarmasin in the period August-October 2019.

Methods: This study was a descriptive study with a cross-sectional approach. A total of 36 samples were taken using a purposive sampling method, but only 32 bacterial isolates were obtained. Samples in the form of clean operating wound contaminated post-cesarean patients were planted on growth media and identified microscopically to be further classified based on responses to biochemical tests.

Results: Descriptive analysis shows that there are three types of bacteria, namely *Staphylococcus aureus* as much as 59.3%, *Staphylococcus epidermidis* as much as 25.0%, and *Escherichia coli* as much as 15.6%.

Conclusions: Obtained 3 types of bacteria in the results of surgical wound swab in post-cesarean section patients who were hospitalized in the Ward and Obstetrics Hospital of Ulin Hospital Banjarmasin, namely *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli*.

Keywords: cesarean section, contaminant bacteria, surgery wound swab.

Abstrak

Tujuan: Mengetahui gambaran jenis bakteri pada luka operasi pasien pascaseksio sesarea yang didapat melalui swab luka operasi pasien di Bangsal Kandungan dan Kebidanan RSUD Ulin Banjarmasin dalam periode Agustus-Oktober 2019.

Metode: Penelitian ini merupakan studi deksriptif dengan pendekatan potong lintang. Sebanyak 36 sampel diambil menggunakan metode purposive sampling, tetapi hanya didapatkan 32 isolat bakteri. Sampel swab luka operasi bersih terkontaminasi pasien paska seksio sesarea ditanam pada media pertumbuhan dan diidentifikasi secara mikroskopis untuk selanjutnya diklasifikasikan berdasarkan respon terhadap uji biokimia.

Hasil: Analisis secara deksriptif menunjukkan bahwa terdapat tiga jenis bakteri, yaitu *Staphylococcus aureus* sebanyak 59,3%, *Staphylococcus epidermidis* sebanyak 25,0%, dan *Escherichia coli* sebanyak 15,6%.

Kesimpulan: Didapatkan 3 jenis bakteri pada hasil swab luka operasi pasien pascaseksio sesarea yang dirawat inap di Bangsal Kandungan dan Kebidanan RSUD Ulin Banjarmasin, yaitu *Staphylococcus aureus*, *Staphylococcus epidermidis*, dan *Escherichia coli*.

Kata kunci: seksio sesarea, bakteri kontaminan, swab luka operasi.

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INTRODUCTION

Patient safety is a global issue of global concern, because of the flow of information technology globalization, public knowledge about health service indicators is increasing. One indicator of patient safety related to medical measures is Surgical Injury Infection (ILO) which is a major complication experienced by inpatients. The ILO is an infection originating from nosocomial

bacterial contaminants in the Hospital up to 30 days after surgery and is included in the third most commonly reported nosocomial infection for 14-16% of all infections in hospitalized patients in the Hospital.

Based on WHO data through the World Alliance for Patient Safety 2005 reported that the ILO occurs in 2-5% of the 27 million patients who operate each year.^{1,2} Percentage of incidence of surgical wound infections based on research

results from the Indonesian Infection Control Association and RSPI Prof. Dr., Suliati Saroso Jakarta was 18.9% in 2003, then at the Department of Surgery Dr. Cipto Mangunkusumo Hospital (RSCM) was 10% of the total patients after adult abdominal surgery, Dr. Pringadi Medan in 2006 amounted to 12%, RSUP Dr. Sardjito in 2007 was 5.9%, and in Adam Malik General Hospital Medan in 2010 it was 5.6%.³

One of the most common surgical procedures that can cause the ILO is cesarean section. This surgery aims to give birth to the fetus by opening the abdominal wall and uterus.³ Surgical action and several other factors affect the skin's defence against bacterial contaminants that can cause infection in the former trauma or injury. Internal risk factors of mothers who contribute to infection of postoperative surgical wound infections are a history of obesity, choriamnionitis, and diabetes mellitus. Whereas external factors stem from airborne bacterial contaminants in the inpatient ward of the hospital ward, prophylactic antibiotic administration, duration of surgery, and long term monitoring of post-operative wound care.^{1,2}

According to data at the RSUD Ulin and Gynecology Installation during 2018, there were only 362 patients undergoing cesarean section and the increase in the number of cesarean delivery methods was directly proportional to the increase in post-operative ILO events.⁴ The results of approving bacterial wound swabs for the most common surgical wound infections were *Pseudomonas* sp. In addition, other bacteria, such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Acinetobacter* sp., *Klebsiella* sp., and *Proteus* sp.^{5,6}

The correct cesarean section is to follow accurate medical indications and is a life-saving procedure for mother and fetus. However, on the one hand, providing safe and timely cesarean section remains a major challenge in countries with high maternal mortality rates; increased nosocomial infection. Therefore, this review is justified as needed to study knowledge about the frequency of complications of childbirth-related to labour with cesarean section without clinical indication to assist in counselling pregnant women regarding the advantages and disadvantages of this type of procedure compared to spontaneous vaginal delivery. Thus, with the increase in labour with cesarean section in several regions in Indonesia accompanied by infectious complications, especially in Banjarmasin City Hospital, South Kalimantan, further research

is needed regarding the identification of the type of bacterial contaminants for the surgical wound in postcesarean patients with sampling in hospitalized patients. inpatient in the obstetrics and gynecology ward of RSUD Ulin Banjarmasin starting from the August-October 2019 period.

METHODS

The method used in this study is descriptive, with a cross-sectional approach that is identifying bacteria from swab samples in post-cesarean surgical wounds for post-cesarean hospitalized patients in the Wards and Obstetrics Ward of RSUD Ulin Banjarmasin in the August October 2019 period. The population of this study were all post hospitalized post-cesarean in Midwives of RSUD Ulin Banjarmasin in the August-October 2019 period. as well as meeting the inclusion criteria as research subjects.

Patients are willing to be the subject of research by signing informed consent. The sampling technique is purposive sampling that matches the inclusion criteria, where all subjects who come and meet the selection criteria are included in the study until the number of required subjects is met. The number of samples taken was 36 samples. The inclusion criteria in this study were patients with post-cesarean section surgery who were treated 3x24 hours in the obstetrical and midwifery ward of Ulin Hospital Banjarmasin and were willing to participate in the study.

For sampling was to use sterile cotton swabs and rubbed on the patient's surgical scar area. After that the results of sampling were put into Bouillon media and the test tube is closed using cotton and aluminium foil. Then the sample is placed in an ice flask and taken to a laboratory for examination of bacterial identification. Sampling was done once. Isolation of the specimen is done by applying the specimen to the nutrient to tilt as a hatchery medium and incubated at 37oC for 24 hours, the growing bacterial colonies are counted and followed by bacterial identification. To identify bacteria microscopically against bacterial colonies that grow on blood agar and Mac Conkey media through Gram staining then look at the bacterial structure using a microscope with an objective magnification of 100 X. On the results of bacterial culture, Gram-positive bacteria will be purple and Gram-negative bacteria will be red. Furthermore, for Gram-positive bacteria the catalase test, mannitol test, and novobiocin test will be carried out, while for Gram-negative

bacteria a biochemical test will be carried out by placing the culture material on the test tube. Biochomia test consists of Citrate, SIM (Sulfite Indol Motility), KIA (Kliger Iron Agar), and LIA (Lysine Iron Agar).

The data obtained were collected through recording the results of bacterial identification in the wounds of patients after cesarean section based on microscopic examination and biochemical tests then tabulated and the percentage calculated.

RESULTS

Research on the identification of bacteria in surgical wounds of post-cesarean section patients in the Gynecology and Obstetric Ward of RSUD Ulin Banjarmasin was conducted in the period August-October 2019. This study used 36 samples of post-cesarean surgical wound swabs for post-cesarean section patients, but only 32 bacterial isolates were obtained.

Table 1. Table of Results of Bacterial Examination in Postoperative Patient Injuries in Caesarean in the Gynecology and Obstetric Ward of RSUD Ulin Banjarmasin.

Type of Bacteria	Amount	%
Staphylococcus aureus	19	59.4
Staphylococcus epidermidis	8	25
Escherichia coli	5	15.6
Total	32	100

DISCUSSION

These results are not much different from previous studies in the General Surgery Ward of RSUD Ulin Banjarmasin in 2013 that the bacteria that cause ILO in hospitalized patients is *Staphylococcus aureus* (56%), *Staphylococcus epidermidis* (23%), *Streptococcus* sp. (5%), and *Pseudomonas aeruginosa* (16%).⁷ Results of research conducted at Dr. H. Abdoel Moeloek Bandar Lampung Hospital in 2016 based on the results of the surgical wound swab of the patient suspect the infection is *Klebsiella* sp. (26.7%), *Staphylococcus epidermidis* (16.7%), *Pseudomonas aeruginosa* (13.3%), *Staphylococcus saprophyticus* (13.3%), *Staphylococcus aureus* (10%), *Proteus Vulgaris* (3.3%), *Enterobacter* sp. (3.3%), and *Streptococcus* sp. (3.3%). While the bacteria that cause ILO in the most midwifery care rooms are *Pseudomonas* sp. (25%), *Escherichia coli* (19.44%), *Klebsiella* sp. (16.67%), and *Staphylococcus epidermidis* (13.89%).⁸ Research results at the Rajah Muthaiah Hospital in India in

2010, said that the most common contaminant bacteria causing surgical site infections are *Staphylococcus aureus* and *Escherichia coli*.⁹ Based on data from the National Healthcare Safety Network at the Centers for Disease Control and Prevention (2013), reported that the most common types of bacteria were *Staphylococcus aureus*, *Enterococcus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus* sp., and *Klebsiella pneumoniae*.¹⁰

Operation in the womb and midwifery is a type of operation that is often performed in addition to other operations. The most common type of obstetric and obstetric surgery is cesarean section and the second most is hysterectomy.¹¹ The two surgeries are somewhat different from other types of surgical operations because of the different operating fields in the abdominal cavity and the high risk of being contaminated by bacteria from the digestive tract, such as *Escherichia coli*.

At the post-cesarean ILO there are 2 categories of problems that increase the risk of the ILO in patients operating wounds, namely mechanical factors (wound infection, obesity, intra-abdominal distension, cough) and metabolic factors (uncontrolled diabetes, corticosteroid use, anaemia, hypoalbuminemia, malnutrition). ILO is the condition of opening part or all layers of abdominal incision. ILO can be divided into incomplete or partial and complete surgical wound infections. ILO is complete when only covering the skin tissue or underlying tissue, whereas infection of a complete surgical wound if the fascial and peritoneal tissue is also exposed.¹¹

The types of bacteria in the surgical wound of post-cesarean patients examined in this study affect the recovery rate of patients post-surgery and medical personnel who are in this section. The discovery of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli* in postcesarean patients who are already hospitalized in the Wards and Obstetrics Ward of RSUD Ulin Banjarmasin are influenced by two factors, namely originating from autoinfection (endogenous, self-infection) is a bacterium that is already present in the Ward of Obstetrics and Obstetrics at RSUD Ulin Banjarmasin influenced by two factors, namely originating from autoinfection (endogenous, self-infection). Exogenous (cross-infection) infection comes from the hospital environment such as operating room air, inpatient air, unsterile equipment, and hospital staff who are less implementing aseptic

and antiseptic behaviour.

To avoid nosocomial infections, every operating room will be used must be sterilized before the air and as a standard number of germs in the operating room air is about 10 CFU / m³, so that the number of germs greater than 10 can potentially cause nosocomial surgery wound infections. Besides that, inpatient air in the hospital ward, especially the obstetric and midwifery section of RSUD Ulin Banjarmasin, should be well ventilated, air in and out freely, the floor is swept and mopped daily, and the bedsheets are changed every day. Sterile equipment and officers who work aseptically, such as the sterility of all equipment used both in the operating room, inpatient room, washing hands, wearing gloves, and wearing masks, are very important in preventing nosocomial infections such as the ILO. Also not less important is that the bacteria that cause the ILO are generally resistant to antibiotics so it is difficult to be eliminated, this is possible because in the hospital environment very much is used antibiotics to treat infectious diseases, so that bacteria are often exposed to antibiotics and this condition causes mutations in genes make bacteria commonly used antibiotic resistance.¹²

CONCLUSIONS

Based on research conducted, obtained 3 types of bacteria in the results of surgical wound swab in post-cesarean section patients who were hospitalized in the Ward and Obstetrics RSUD Ulin Banjarmasin, namely *Staphylococcus aureus* as much as 59.4%, *Staphylococcus epidermidis* as much as 25.0%, *Escherichia coli* as much as 15.6%.

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Research Article

Role of C-Reactive Protein, Erythrocyte Sedimentation Rate, Progesterone and Estradiol Hormone Levels in First Trimester Threatened Abortion

Peran C-Reactive Protein, Laju Endap Darah, Progesteron dan Estradiol pada Abortus Imminens Trimester Pertama

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Abstract

Objective: To assess correlation of High sensitivity C-Reactive Protein (Hs-CRP), erythrocyte sedimentation rate (ESR), progesterone and estradiol levels in the first trimester threatened abortion incidence in Dr. Zainoel Abidin Hospital, Banda Aceh.

Methods: Case control design used in this study divided threatened abortion into a case group and normal pregnancy into a control group with a total of 20 subjects for each group. This research was conducted in the Emergency Room and Obstetric Ward of Dr. Zainoel Abidin hospital Banda Aceh in 2019. Eta correlation test was conducted to find out the link between variables towards threatened abortion with 95% confidence level followed by the Receiver Operating Curve (ROC) analysis to find out the cut off points.

Results: Progesterone levels (14.76 ng/mL), estradiol (427.61 pg/mL), Hs-CRP (2.57 mg/L) and ESR (28.75 mm/hour) case group were lower compared to the control group. Incidence of threatened abortion correlates to progesterone and estradiol with the correlation strength respectively -0.838 and -0.416.

Conclusions: Progesterone and estradiol correlate negatively with first-trimester abortion incidence. Evaluation of these two hormones levels is useful for diagnostic purposes and screening of threatened abortion with a cut point of progesterone 23.03 ng/mL and estradiol 468.8 pg/mL.

Keywords: C-Reactive Protein, erythrocyte sedimentation rate, estradiol, progesterone, threatened abortion

Abstrak

Tujuan: Penelitian ini bertujuan untuk menilai korelasi antara kadar High sensitivity C-Reactive Protein (Hs-CRP), Laju Endap Darah (LED), progesteron dan estradiol terhadap kejadian abortus imminens pada trimester pertama di RSUD Dr. Zainoel Abidin Banda Aceh.

Metode: Desain kasus kontrol digunakan dalam penelitian ini dimana kejadian abortus imminens menjadi kelompok kasus dan kehamilan normal menjadi kelompok kontrol dengan jumlah masing-masing kelompok sebanyak 20 sampel. Penelitian ini dilakukan di Instalasi Gawat Darurat dan ruang rawat Obstetri Rumah Sakit Umum Dr. Zainoel Abidin (RSUDZA) Banda Aceh pada tahun 2019. Uji korelasi Eta digunakan untuk mengetahui korelasi antar variabel terhadap abortus imminens dengan tingkat kepercayaan 95% dilanjutkan dengan analisis Receiver Operating Curve (ROC) untuk menentukan titik potong.

Hasil: Kadar progesteron (14,76 ng/mL), estradiol (427,61 pg/mL), Hs-CRP (2,57 mg/L) dan LED (28,75 mm/jam) kelompok kasus lebih rendah dibandingkan kelompok kontrol. Kejadian abortus imminens berkorelasi terhadap progesteron dan estradiol dengan kekuatan korelasi (R) secara berurutan -0,838 dan -0,416.

Kesimpulan: Progesteron dan estradiol berkorelasi negatif terhadap kejadian abortus imminens pada trimester pertama kehamilan. Evaluasi kadar kedua hormon tersebut bermanfaat untuk kepentingan diagnostik dan penapisan abortus imminens dengan titik potong progesteron 23,03 ng/mL dan estradiol 468,8 pg/mL.

Kata kunci: abortus imminens, C-Reactive Protein, estradiol, laju endap darah, progesteron.

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INTRODUCTION

Abortion is known as a common complication during pregnancy. Abortion not only can cause morbidity but also has impacts towards social, psychological and overall quality of life. In 20% of cases, abortion is able to cause stress conditions. The cause of abortion has always been a question for couples who experience it. In general, abortion is caused by abnormalities in the results of conception or by maternal factors which cause pregnancy to not continue. Abortion is generally caused by various chromosomal abnormalities such as trisomy, monosomy and polypodia, which predicted to occur occur in 60% of cases.¹ In addition, various other factors such as chronic diseases, obesity, alcohol consumption, the consumption of certain drugs, infections and hormonal disorders are reported to increase the incidence of first-trimester abortion.^{2,4}

Inflammatory processes which trigger early abortion allows the development of inflammatory biomarkers in predicting pregnancy failure. Using acute and chronic inflammatory parameters has been recommended lately as in the increased activity of fibrinogen and plasma globulin which shows that inflammation can be seen with an increase in erythrocyte sedimentation rate (ESR). The use of other biomarkers that also has a fairly good correlation with ESR is C-Reactive Protein (CRP), which is a parameter that has been widely used to help establish an early diagnosis and treatment of an inflammatory process and also infection. Elevating the levels of CRP has been known to show a risk of endothelial thrombosis that causes complications of pregnancy failure. Other research also reports some genotypes in CRP is significantly correlated with abortion and higher CRP findings during acute chorioamnionitis that play an important part in pathological abortion during early pregnancy.^{5,6}

The involvement of the endocrine system during the pregnancy process is vital in maintaining an adequate uterine environment. The progesterone hormone helps protect the environment through secretory changes stimulation for implantation and suppressing the myometrial contractility also increasing the nitric oxide synthesis regulation in the endometrium to suppress the adverse pro-inflammatory cytokine response. Progesterone is also considered to play an important part in carrying out immunomodulating mechanisms in pregnancy that will facilitate different allogenic responses

to trophoblast cells. Trophoblastic invasion of maternal spiral arteries will occur without interference with progesterone. The occurrence of vascular remodelling triggered by adequate trophoblast cells invasion can produce a good uteroplacental circulation, which by facilitating high blood flow with a low resistance system. This will then result in a good placentation process.^{7,8}

Besides progesterone, estrogen is also important during ovulation and pregnancy. Estrogen increases slowly during pregnancy with the final product being estradiol. Related to the recurrent pregnancy loss (RPL) case study, estradiol together with FSH was significantly increase. When evaluating the occurrence of spontaneous abortion in obese women, it shows that estradiol levels that are high significantly increase spontaneous abortion risk. The correlation that was also reported was the mechanism of increasing levels of prostaglandin (PGF2) as an effect of increasing concentrations of estrogen receptors (nucleus and cytosol estradiol prematurely with oxytocin) which can trigger spontaneous abortion in pregnant women.⁹ The purpose of this study was to evaluate changes in biomarkers in C-Reactive Protein levels, erythrocyte sedimentation rate (ESR), progesterone and estradiol in early pregnancy and their correlation to the threatened abortion incidence.

METHODS

This research is a correlative observational study with a case control design. This research was conducted at the Obstetric Emergency Installation and Obstetric Ward of the General Hospital Dr. Zainoel Abidin (RSUDZA) Banda Aceh during 2019.

Our inclusion criteria include first-trimester pregnant women aged 20-35 years old who are experiencing threatened abortion (case group) and without threatened abortion (control group). In our study, the exclusion criteria were patients with a history of autoimmune chronic disease, chronic infection (Tuberculosis), endocrinological metabolic disorders, coronary heart disease, haematological or malignant abnormalities, multiple pregnancies, extrauterine pregnancy, mole hydatidiform, hormonal therapy or progesterone supplementation, anatomical abnormalities of reproduction and BMI = 30 kg/m². The amount of the subjects in this research was determined based on the formula of an

unpaired numerical analytic study and obtained a sample of each group to be 20 samples.

Blood specimens for the examination of High sensitivity C-Reactive Protein (Hs-CRP) levels, erythrocyte sedimentation rate (ESR), progesterone and estradiol were taken and sent to Prodia Laboratory Banda Aceh. All data collected were analysed further using the ETA test and Receiver Operating Characteristic (ROC) curve.

RESULTS

Based on collected data at the Emergency Obstetric Installation and Obstetric Ward of the General Hospital dr. Zainoel Abidin during the research period, the data obtained as many as 40 pregnant women with and without threatened abortion. In the following table, data on the characteristics of our study is shown.

Table 1. Sample Characteristics Data

Characteristics	Threatened Abortion n = 20	Non-Threatened Abortion n = 20
Age (year)*	29.2 ± 4.26	28.2 ± 3.65
Education		
Elementary School	1 (5)	0
Middle School	2 (10)	1 (5)
High School	7 (35)	7 (35)
Diploma	4 (20)	5 (25)
Bachelor	5 (20)	7 (35)
Master	1 (5)	0

Table 2. Correlation Analysis of Serum Progesterone, Estradiol, Erythrocyte Sedimentation Rates (ESR) and Hs-CRP with Threatened Abortion

	Average (Min – Max)		R*	P-value
	Threatened Abortion	Non-Threatened Abortion		
Progesterone	14.76 (2.8 – 23.40)	37.46 (21.6 – 53.38)	- 0.838	< 0.001
Estradiol	427.61 (101.9 – 1080)	771.07 (154 – 1676.5)	- 0.416	0.008
ESR	28.75 (14 – 44)	33 (22 – 44)	- 0.254	0.114
Hs-CRP	2.57 (0.3 – 4.8)	3.92 (2.8 – 5)	- 0.293	0.066

Table 2 presents the results of the correlation test of progesterone, estradiol, Erythrocyte Sedimentation Rates (ESR) and Hs-CRP with threatened abortion. Based on the Eta test results, both progesterone and estradiol levels between the two groups showed a negative correlation with strong and moderate correlation, respectively. Our results show no significant correlation in the levels of ESR and Hs-CRP between the two groups ($p > 0.05$).

Occupation

Occupied	8 (40)	6 (30)
Unemployment	12 (60)	14 (70)

Age of gestation (week)

< 8	4 (20)	10 (50)
8-12	16 (80)	10 (50)

Parity

Nulliparous	7 (35)	8 (40)
Multiparous	13 (65)	12 (60)

Observation

Spontaneous Abortion	9 (45)	2 (10)
No spontaneous abortion	11 (55)	18 (90)

Based on age, it is found that the abortion group was 1 year younger than the non-threatened abortion group. The highest number of threatened abortion groups was high school graduates (35%), while the highest number of non-threatened abortion groups were high school and undergraduate graduates with the same percentage of 35%. Eighty per cent of the group with threatened abortion was with 8-12 weeks gestation. The two groups of threatened abortion and non-threatened abortion were multiparous in the order of 13 and 12 respectively. The incidence of spontaneous abortion based on observations was 9 people in the threatened abortion group and 2 people in the non-threatened abortion group.

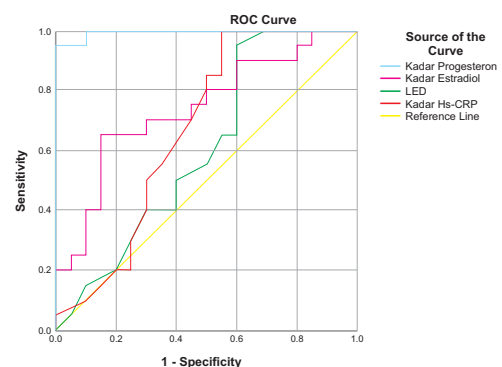


Figure 1. ROC curve of Progesterone, Estradiol, ESR and Hs-CRP levels for Threatened Abortion

Table 3. Interpretation of Area Under the Curve (AUC) Results

Variable	Area	P-value
Progesterone	0.995	< 0.001
Estradiol	0.740	0.009
Erythrocyte sedimentation rate	0.606	0.25
Hs-CRP	0.669	0.068

Figure 1 shows the ROC curve of progesterone, estradiol, ESR and Hs-CRP levels against threatened abortion with Area Under the Curve (AUC) as presented in Table 3. Based on the table, it is known that progesterone shows a higher level of discrimination compared to estradiol with percentages respectively of 99.5% and 74%.

Table 4. Progesterone and Estradiol Diagnostic Significance Values toward Threatened Abortion

Variable	Intersection	Sensitivity	Specification
Progesterone (g/L)	23.03	95	95
Estradiol (pg/mL)	468.8	70	70

The diagnostic significance of progesterone and estradiol for threatened abortion is presented in table 4 above. Progesterone levels 23.03 showed the best sensitivity and specificity values of 95% and estradiol levels of 468.8 showed the best sensitivity and specificity with a value of 70% threatened abortion predictors in the first trimester of pregnancy.

DISCUSSION

Based on the data obtained from this study, found that Hs-CRP levels in the group of threatened abortion patients were lower than those with non-threatened abortion group with average levels of 1.57 mg/L and 3.92 mg/L, respectively. One study reported that the expression of IL-10, IL-6, TNF- α and TNF-R1 was lower in women who is experiencing threatened abortion compared to normal pregnancies. In this regard, pro-inflammatory cytokine secretions such as IL-1, IL-6 and endothelin-1 are induced by CRP.¹⁰ This causes disruption of trophoblastic protein synthesis and uteroplacental inflammation in the area of implantation and placentation in the first-trimester pregnancy. The study also reported that serum Hs-CRP levels also decreased in pregnancy with threatened abortion.¹¹

Referring to the results of this study, there was a difference in Hs-CRP levels of 2.35 mg/L between the two groups. However, it was statistically concluded that Hs-CRP levels between the two

groups did not have a significant correlation ($p=0.066$). The same thing was also reported where the Hs-CRP examination did not provide information in the management of threatened abortion.¹¹ Another study also concluded that Hs-CRP did not contribute as a predictor of complications in the early phases of pregnancy.¹²

However, the role of CRP in pregnancy has not shown consistent results. The study reported concluded that an abnormal CRP response in the first trimester of pregnancy indicates a disruption in fetomaternal relationships and is associated with the incidence of abortion. They also concluded that CRP testing could be a predictor or even a screening modality in some cases that would carry out an immunotherapy program.¹³

Elevated CRP levels in early pregnancy are not known with certainty. The main stimulant that produces CRP is IL-6 which is produced by macrophages and active monocytes. Macrophages are the main leukocyte in the decidual cells early in pregnancy. Its existence is undoubtedly a major component of interaction between the trophoblast and the maternal immune system. Increased function in producing IL-6 is believed to be the cause of increased CRP.^{13, 14}

Another parameter that becomes the evaluation variable in this study is ESR. The average values of ESR in the groups with and without threatened abortion were 28.75 and 33 mm/hour, respectively. The difference between the two values does not indicate a difference that is significant statistically ($p=0.144$). Referring to the normal levels of ESR in the first trimester of pregnancy (4-57 mm/hour), the levels shown in this research are still in the normal range. Normal ESR levels will decrease in the second trimester (7-47 mm/hour) and will increase again in the third trimester (13-70 mm/hour).¹⁵ A study conducted by Khazal and Zangana of 300 normal pregnant women concluded that ESR had increased during pregnancy and their levels were influenced by haemoglobin concentration and gestational age.¹⁶

ESR is an inexpensive and simple examination modality for evaluating inflammation and acute phase responses. This examination was first discovered in 1897, but only in 1981 this examination began to be used for scientific purposes by Robert Fahraeus who first used it for the tests on pregnancy. The value of ESR will increase by 0.85 mm/hour every 5 years due to increased levels of fibrinogen or the incidence of

asymptomatic disease in the elderly.^{17, 18}

The ESR examination reflects the erythrocyte aggregation measured in a vertical tube with an internal diameter of 2.5 mm for 1 hour without any vibration at room temperature. Erythrocyte aggregation is influenced by erythrocyte cell surface shape and friction that occurs between erythrocytes. An extreme increase in ESR > 100 mm/hour is associated with serious illnesses such as collagen disease in blood vessels, tumours with metastases or severe infections. Other conditions such as anaemia, macrocytosis, increased molecular weight of protein in the blood, hemodilution, hypercholesterolemia, nephrotic syndrome, severe liver disease, thyroiditis and pregnancy are the causes of increased ESR. ESR was lower in the condition of hypofibrinogenemia, hypogammaglobulinemia, polycythemia, microcytosis, hemolytic anaemia, hemoglobinopathy, heart failure, allergic diseases and the consumption of anti-inflammatory drugs that can reduce ESR levels. ESR examination can modality for evaluating inflammation and acute responses and can be used as an alternative to other more expensive new examinations such as CRP.¹⁷

In this study, progesterone levels were found to be lower than those without abortion with a difference of 22.7 ng/mL. Statistically, progesterone levels are negatively correlated with the occurrence of abortion in the first trimester, with a strong correlation strength. A negative correlation means that with higher levels of progesterone, the risk of threatened abortion occurrence is lowered. Conversely, lower levels of progesterone in the first trimester of pregnancy will increase the risk of abortion. The same thing was reported study evaluating fetal viability in the first trimester of pregnancy when it was concluded that progesterone levels were higher in viable pregnancies by a difference of 13.31 ng/mL when compared to non-viable pregnancies group.¹⁹

Progesterone is an important hormone in the process of implantation, viability and maintaining pregnancy. Low progesterone levels is used as an accurate predictor of threatened abortion even in conditions where other accompanying conditions cause luteal insufficiencies such as genetic disorders or immunological anomalies, infections of the genital tract, uterine malformations, diabetes and Cushing's syndrome. One study reports that progesterone levels < 14 ng/mL were used as predictors of non-viable pregnancy.^{20, 21}

The cut-off point for the levels of serum progesterone as a predictor for the occurrence of abortion was 11 ng/mL.²²

In contrast to these two studies, the cut-off point for progesterone levels as a predictor of first trimester threatened abortion is higher at 23.03 ng/mL. Progesterone is a hormone which is essential in the reproductive process. This hormone secretion influences the changes in the uterus and has an important role in the success of the embryo implantation process. Progesterone also modulates the mother's immune response in preventing embryo rejection and suppressing uterine contractions.²³

Progesterone stimulates Th2 cytokine secretion and Th1 suppresses the maternal immunological system in preventing fetal rejection. Some studies report that progesterone supplementation can reduce the occurrence of abortion with a history of previous abortion. Progesterone and steroids similar to them (progestagens) are useful for preventing abortion and increasing the ratio of embryo implantation in pregnancy programs.²³

This study proves that the assessment of estradiol levels is a predictor of threatened abortion and shows moderate correlation strength ($r=0.416$). Estradiol levels are negatively correlated to the occurrence of threatened abortion, where the lower the level of estradiol, the greater the possibility for threatened abortion. Estradiol levels of 468.8 pg/mL were used as cut off points for threatened abortion predictors with a sensitivity and specificity of 70%. Another study reported the same thing as this study, where the levels of estradiol in patients with non-viable pregnancies were lower than viable pregnancies with a difference of 307.9 pg/mL. The difference in estradiol levels in the study was not much different from this study in the amount of 343.46 pg/mL. Then further concluded that a combination of progesterone, estradiol and hCG examination could be a predictor of pregnancy viability with an accuracy of 90.9%.¹⁹

Various factors influence the incidence of threatened abortion, including embryonic chromosome abnormalities, environmental and immune factors and maternal endocrine dysfunction.²⁴ Regarding the endocrine system, interactions between the mother and the fetus are strongly influenced by reproductive hormones (sex steroids) including estradiol (E2) which is also reported as a predictor in several cases of first-trimester abortion. Therefore, recommended abortion therapy is in the form of total rest (total

bed rest), luteal support and supplementation of a combination of progesterone and estradiol.^{25, 26}

Other than the importance of diagnosis, a comprehensive analysis of reproductive hormones is useful for evaluating the metabolism of reproductive which is generally influenced by 3 factors in the form of genetics, lifestyle and diet, also the environment. Because of these considerations, developing a comprehensive reproductive hormone analysis modality without invasive procedures will benefit the patient and clinical interests. Deficiency of dehydroepiandrosterone (DHEA) levels in urine will reduce estrogen activity in women with threatened abortion.²⁶

Estrogen has an important role in normal pregnancy. The increasing of hormone estrogen occurs gradually during pregnancy which increases blood vessel formation and nutrient transfer and supports fetal growth. Any changes in hemostasis that occur on these hormones will have an impact on pregnancy. Low estrogen levels are found in threatened abortion patients and giving estrogen is one of the modalities to save pregnancy in these women. A study reports that hormone-HCG and estrogen are closely related to the incidence of threatened abortion.²⁷ Similar to this study, estradiol levels in women with threatened abortion were lower than those without threatened abortion with an average level of 427.61 pg/mL.

CONCLUSION

C-Reactive Protein and Erythrocyte sedimentation rate do not correlate with the incidence of the first trimester threatened abortion. Progesterone and estradiol negatively correlated with the incidence of the first trimester threatened abortion. Evaluation of these two hormones levels is useful for diagnostic purposes and screening of threatened abortion with a cut point of progesterone 23.03 ng/mL and estradiol 468.8 pg/mL.

SUGGESTION

Further research needs to be done with more research subjects in order to evaluate ESR with similar haematological profiles subjects (matching) and to comprehensively analyze changes in reproductive hormones in cases of threatened abortion.

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Research Article

Role of Lifestyle Modification through Dietary Changes to Endometrial Receptivity on Infertility Women and Obesity with Polycystic Ovary Syndrome

Peran Perubahan Gaya Hidup melalui Perubahan Pola Diet terhadap Reseptivitas Endometrium Perempuan Infertil dan Obesitas dengan Sindrom Ovarium Polikistik

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Abstract

Objective: To investigate the effect of lifestyle modification on endometrial receptivity of obese women with polycystic ovary syndrome using ultrasonography.

Methods: This observational study was conducted at Dr. Cipto Mangunkusumo General Hospital Jakarta from August 2019 to May 2020. A total of 14 subjects were participated in this study. The subjects were advised to get nutrition counseling by nutritionist and then followed up the endometrial profiles for 6 months by ultrasonography.

Results: A total 19 subjects were received nutrition counseling by Clinical nutritionist, but then, only 14 subjects were evaluated the endometrial study by Ultrasonography. There were several significant result between before and after treatment some subjects such as calories, body weight, body mass index, waist circumference ($p < 0.05$) and type of the endometrial vascular zone, endometrium volume, and vascular flow index by ultrasonography ($p < 0.05$). In this study, no significant results have been found on the correlation between dietary changes and changes in endometrial receptivity profiles.

Conclusions: No significant correlation was observed between changes in anthropometrics and daily calorie intake with changes in endometrial vascular zones.

Keywords: endometrial receptivity, obese, polycystic ovary syndrome, ultrasonography.

Abstrak

Tujuan: Untuk mengetahui pengaruh modifikasi gaya hidup pada reseptivitas endometrium perempuan obesitas dengan sindrom ovarium polikistik menggunakan ultrasonografi.

Metode: Penelitian observasional ini dilakukan di Rumah Sakit Umum Cipto Mangunkusumo Jakarta dari Agustus 2019 hingga Mei 2020. Sebanyak 14 subjek berpartisipasi dalam penelitian ini. Semua subyek disarankan untuk mendapatkan konseling gizi oleh ahli gizi dan dilakukan observasi profil endometrium selama 6 bulan dengan ultrasonografi.

Hasil: Sebanyak 19 subjek menerima konseling gizi oleh ahli gizi klinis, tetapi kemudian, hanya 14 subjek yang dievaluasi profil endometrium dengan Ultrasonografi. Ada beberapa hasil yang signifikan antara sebelum dan sesudah perawatan beberapa subjek seperti kalori, berat badan, indeks massa tubuh, lingkar pinggang ($p < 0,05$) dan tipe zona vaskular endometrium, volume endometrium, dan indeks aliran vaskular dengan ultrasonografi ($p < 0,05$). Dalam penelitian ini, tidak ditemukan hasil yang signifikan pada korelasi antara perubahan pola makan dan perubahan dalam profil reseptivitas endometrium.

Kesimpulan: Tidak ada korelasi yang signifikan antara perubahan antropometrik dan asupan kalori harian dengan perubahan zona vaskular endometrium.

Kata kunci: endometrium, obesitas, reseptivitas, sindrom ovarium polikistik, ultrasonografi.

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INTRODUCTION

Polycystic Ovary Syndrome was the most (85%) form of ovulation disorders that causes type II infertility according to World Health Organization and being one of the most common endocrinopathies and affects 5% to 10% of childbearing age women.^{1, 2} Obesity exacerbates the condition due to increased androgen levels so responsible to occur the symptom of polycystic ovary syndrome such as chronic anovulation.³ At Dr. Cipto Mangunkusumo General Hospital, about 73% of obesity has been observed among polycystic ovary syndrome women.⁴

Obesity and Polycystic Ovary Syndrome (PCOS) have an impact on the capacity of the endometrium to accept the results of conception.⁵ Therefore, nowadays endometrial receptivity is being considered as one determinate factor responsible for infertility treatment. A study conducted in 2010 concluded that pregnancy rates for clomiphene citrate users were only 12.2%, but lifestyle modification, succeed to increase the pregnancy rate of PCOS patients up to 20%.⁶

Examination of endometrial receptivity by the biopsy endometrial dating method done by Noyes since 1950 until now has a weakness, due to it's traumatic clinical procedures carried out during period of embryo implantation. So that this procedure does not become a standard of endometrial receptivity examination.^{7, 8} Then ultrasonography has replaced as an important role in the evaluation and treatment of endometrial receptivity in infertility patients because it is expected to be more efficient, cost-effective and a traumatic clinical proceeding procedures.⁹

treatment on endometrial receptivity using ultrasonography. Therefore this study emphasizes the effect of lifestyle modification trough dietary changes on endometrial receptivity of obese women with PCOS using ultrasonography.

METHODS

This was a prospective longitudinal observational study that investigated at the effect of diet controlled by clinical nutritionist in infertile women with PCOS on changes in endometrial vascular zone. This study was conducted at Yasmin Clinic Dr. Cipto Mangunkusumo General Hospital Jakarta from August 2019 to May 2020. Women in reproductive age (20–35 years) women with PCOS, suffered of primer or secondary infertility,

obesity according to Asia Pacific WHO criteria we included in this study.

The subject received clinical nutrition interventions by clinical nutritionist once a week in first control, and then once every two weeks until once a month. Every subject that has given intervention also did clinical anthropometrics and daily intake measurement. The subjects also performed ultrasound examination at the first control and then evaluated again in the third month and/or in the sixth month in between 19 to 21 day of menstrual cycle after check the progesterone level. The subjects that become pregnant were considered as intension to treat subject and still included in the study results. This study was approved by ethical committee of Faculty of Medicine, Universitas Indonesia number 596/UN2.F1/ETIK/PPM.00.02/2019.

RESULTS

A total 32 subjects who were willing to participate and meet the inclusion and exclusion criteria were recruited. After the initial ultrasound examination process, subjects were immediately educated about the importance of changing lifestyles in the form of diets and direct physical activity by nutritionist. But, at the end of study there were only 14 subjects that completed the study and 18 subjects were drop out. Baseline characteristics of 14 subjects that had been completed the study can be seen on Table 1.

Table 1. Baseline Characteristics of Subjects

Variable	N (%)	Mean ± SD
Age (year)		30 ± 2.75
Domicile		
Bogor	5 (35.7)	
Bekasi	3 (21.4)	
Tangerang	1 (7.1)	
Cikarang	1 (7.1)	
Jakarta	4 (28.6)	
Education		
High School	2 (14.3)	
University degree	12 (85.7)	
Infertility		
Primer	10 (72)	
Secondary	4 (28)	
Length of Married (years)		4.86 ± 2.21
History of menstrual cycle		
Irregular	2 (14.3)	
Oligomenorhea	10 (71.4)	
Secondary amenorrhea	2 (14.3)	
Occupation		
Housewife	4 (28.6)	
General employees	6 (42.9)	
State employees	1 (7.1)	
Business woman	3 (21.4)	
Body mass index (kg/m ²)		30.0 ± 3.4
Body weight (kg)		75.2 ± 11.9
Height (cm)		156.5 ± 3.5
Waist size (cm)		98.5 ± 10.0

In all subjects both in the ovulatory and anovulatory cycles group, a significant ratio ($p = 0.001$) was obtained between the daily calorie intake before and after receiving medical therapy by a clinical nutrition specialist. All subjects were able to decrease by an average of 374.6 calories until the end of the study. Overall, there was also a significant comparison ($p = 0.008$) in body weight before and after receiving medical therapy by a clinical nutrition specialist, although it did not show statistical significance in each group. The mean weight loss in the group that had an ovulatory cycle was greater than the anovulatory one which was 4 kg compared to 1.8 kg.

Overall there was also a significant difference ($p = 0.036$) on the Body Mass Index before and after receiving medical therapy by a clinical nutrition specialist, although it did not show statistical significance in each group. In the group of subjects who experienced ovulatory cycles, the mean decrease in waist size was 6.7 cm until completed the study compared to the average decrease in waist size in the group of subjects who experienced anovulatory cycle, the mean decrease in waist size was 5 cm. As can be seen on table 2.

Table 2. Calorie Intake and Clinical Anthropometry, According to Clinical Nutrition Intervention in 14 Subjects

		Ovulatory Cycle (n=6)			Anovulatory Cycle (n=8)			Comparison between the ovulation and anovulation Cycle			Total (n=14)		
	Unit	Pre	Post	P-value	Pre	Post	P-value	Ovulatory	Anovulatory	P-value	Pre	Post	P-value
Calorie*	Calorie	1755.7 (± 353.8)	1409.6 (± 479.6)	0.014	1494.7 (± 278.1)	1099 (± 225.7)	0.029	346.1	395.7	0,391	1606.6 (± 328.2)	1232 (± 375.9)	0.001
Weight*	Kg	70.9 (± 10.9)	66.9 (± 9.1)	0.050	78.5 (± 12.35)	76.7 (± 10.9)	0.100	4.04	1.83	0,050	75.2 (± 11.9)	72.5 ± 11.0	0.008
BMI*	Kg/m ²	28.5 (± 1.5)	27.1 (± 1.6)	0.073	31.2 (± 4.0)	30.9 (± 3.6)	0.392	1.34	0.33	0,016	30.0 (± 3.4)	29.3 (± 3.4)	0.036
Waist Size*	cm	95.7 (± 10.8)	89.0 (± 12.3)	0.036	100.7 (± 9.4)	95.7 (± 9.3)	0.069	6.62	5.00	0,872	98.5 (± 10.0)	92.8 (± 10.8)	0.004

Note. Normal Distribution, ** Abnormal Distribution

In the ultrasound profile of endometrial vascular zone type, groups experiencing ovulatory cycles found significant differences ($p = 0.026$) from vascular zones 1 to 3 compared to groups undergoing anovulatory cycles. In all subjects both in the ovulatory cycle group and the anovulatory cycle group there was an increase

in endometrial volume and an increase in the Vascular Flow Index which were all statistically significant ($p < 0.05$). There has not been a statistically significant increase in the flow index of subjects who have received medical therapy by a clinical nutrition specialist. As can be seen on table 3.

Table 3. Ultrasound Picture of Endometrial Receptivity after Clinical Nutrition Intervention in 14 Subjects.

		Ovulatory Cycle (n=6)			Anovulatory Cycle (n=8)			Total (n=14)**		
	Unit	Pre	Post	P-value	Pre	Post	P-value	Pre	Post	P-value
Type ZV**		1 (1-3)	3 (1-4)	0.026	1 (1-2)	2 (1-4)	0.066	1 (1-3)	3 (1-3)	0.005
VE*	cm ³	1.67 (± 1.03)	3.44 (± 1.34)	0.025	1.80 (± 1.23)	3.82 (± 2.01)	0.039	0.033 (0 – 1.88)	0.747 (0 – 10.94)	0.002
FI*	%	1.67 (± 1.03)	3.44 (± 1.34)	0.173	19.75 (± 13.47)	16.90 (± 11.16)	0.199	21.7 (0 – 34.17)	21.2 (0 – 31.12)	0.695
VFI**	%	0.02 (0 – 1.88)	2.87 (0 – 5.33)	0.028	0.067 (0 – 0.91)	0.694 (0 – 10.94)	0.028	0.033 (0 – 1.88)	0.747 (0 – 10.94)	0.002

Note. Normal Distribution, ** Abnormal Distribution

In this study, the Spearmans method obtained a positive correlation ($r > 1$) between changes in body weight, body mass index and waist circumference of 14 subjects who received medical therapy by a clinical nutrition specialist with changes in endometrial vascular zones,

although not statistically significant (although not statistically significant ($p > 0.05$). While the correlation between changes in calories with changes in endometrial Vascular Zone in this study is negatively correlated ($r < 1$). As can be seen on table 4 and figure 1.

Table 4. Effects of Lifestyle Changes on Endometrial Vascular Zone in 14 Subjects

Variable Factor	VZ		EV		FI		VFI	
	P-value	r	P-value	r	P-value	r	P-value	r
Weight	0.774	0.084	0.982	-0.007	0.325	-0.284	0.313	0.291
BMI	0.646	0.135	0.875	0.046	0.343	-0.274	0.166	0.392
Waist Size	0.191	0.372	0.731	0.101	0.940	-0.022	0.413	0.238
Calories	0.768	-0.087	0.281	-0.310	0.736	-0.099	0.994	0.002

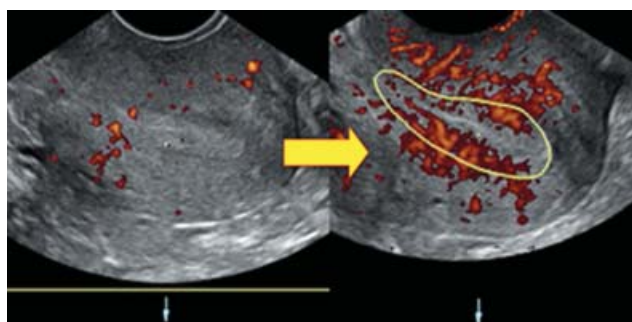


Figure 1. Example of Vascular Zone before and after receive clinical nutrition interventions

DISCUSSION

According to our analysis this is due to the difficulty of changing patients perceptions that lifestyle changes in the form of diet and exercise are first-line management of PCOS treatment, most subjects want to get drugs or actions immediately without any lifestyle changes. This opinion has been refuted in a study that the pregnancy rate of Clomiphene citrate users was only 12.2% while another case with lifestyle changes from the study can increase the pregnancy rate of PCOS patients to 20%.⁶

Seventy one point four percent of the subjects were workers / self-employed so that it became an obstacle to arrange the time to come to the RSCM. Likewise, in 28.6% of the subjects who, although they were a housewife, still found it difficult to regulate their diet and exercise because they were not used to it in their daily lives, especially during this covid-19 era that demanded for people stay at home more and not have activities outside the house. This is correlate with a study revealed that the incidence of obesity is closely related to various physical activities that can be done, the fatter a woman will be lazy to move and do physical activities.¹⁰ Other studies revealed that with increasing time to watch television the physical activity will be

reduced will further increase the occurrence of obesity.¹¹ Another study conducted in Mexico states that the lack of relaxing time to regular exercise is the key to increasing rates of obesity among career women.¹²

All subjects in this study also did physical activity in the form of footsteps that were monitored through a mobile phone application and regular light exercise weekly and managed to achieve a pregnancy rate of 21.4% (3 subjects). This is in line with research who have concluded that by reducing the diet 500 Calories / day consisting of 50-60% carbohydrates, 25-30% fat, 15-20% protein accompanied by risk-free activities such as climbing stairs, relaxing walks, for at least 30 minutes 3 to 5 times a week for 6 months can increase pregnancy rates by 20%.⁶

The coefficient (r) is the closest to 1 in the correlation between decreasing waist size and increasing endometrial vascular zone. This is consistent with statement from WHO that the increasing waist circumference is associated with higher visceral obesity which can increase the occurrence of metabolic syndromes such as insulin resistance.¹³ In accordance with a review conducted by Schulte about insulin resistance which is wrong one cause of worsening in endometrial receptivity in PCOS obese patients due to the effects of accumulation of free fatty acids (FFA) resulting from visceral fat.⁵

There has not been found any significant correlation between changes in body weight, body mass index and waist circumference and daily calorie intake with changes in endometrial vascular zones due to high loss to follow-up rates and uncontrolled daily caloric intake for each subject, even in some subjects there are actually increased daily calorie intake because of this. However, in general there were significant differences in the endometrial receptivity of

subjects who had received medical therapy by clinical nutrition specialists as evidenced by the p value <0.05 on the vascular zone type, endometrial volume and Vascular Flow Index values for all subjects. An increase in median vascular zone type 1 to 3 according to Sonal research can increase pregnancy rates from 8.3% to 33.8%. Increasing endometrial volume in a group of subjects undergoing an ovulation cycle from 1.67 to 3.44 cm³ can increase pregnancy rates to 47%. The increase in the percentage of Vascular Flow Index from 0.02 to 2.87% in the group of subjects with ovulation cycle also according in the same year was able to increase the pregnancy rate to 41.4%.¹⁴

A total 14 subjects at the beginning of the study had obtained clomiphene citrate as standard management of PCOS. However, in this study until the end of the study of 14 patients only 3 subjects were assessed for their endometrial receptivity because of the value of progesterone >10 ng / ml, the remaining 3 more patients were confirmed pregnant so that a total of 6 patients were considered to be ovulating according, regarding progesterone levels ≥ 10 ng / ml in the middle luteal phase can be a marker of ovulation in normal women.¹⁵ The review said that 75 - 80% of patients with PCOS will ovulate after the use of Klomifen citrate, but in this study the percentage of ovulation was 42%.¹⁶ Possible causes of clomiphene citrate failure are obesity, insulin resistance and hyperandrogen which besides requiring clomiphene citrate must also lose weight by 5-10% in the form of lifestyle changes. The possibility in these subjects that the progesterone value is still low is because it is still in the late proliferation phase or early ovulation phase so there has not been an increase in progesterone levels. Therefore, in the future these subjects still have to wait for ovulation if they want to assess their endometrial receptivity, even if we look at the current ultrasound picture of endometrium, we can also see improvements in the endometrium.

The limitation of this study is the still high loss to follow up rate (56%) which is probably due to the difficulty of changing lifestyles without a strong desire from the subjects involved in the study. Another possibility is the lack of the process of taking research subjects where the patients taken in this study were not purely patients who went to RSCM but were invited patients through social media that are located far away from the RSCM so that it becomes an obstacle to follow the control

process by the clinical nutrition department. In addition, this study is still observational in nature, so there is no uniformity in the level of obesity or metabolic syndrome in each subject, as well as the amount of daily calorie intake and the type of daily physical activity on each subject so as to make different results on each subject of research.

CONCLUSION

No significant correlation was found between changes in body weight, body mass index and waist circumference and daily calorie intake with changes in endometrial vascular zones due to high loss to follow-up rates and uncontrolled daily caloric intake for each subject. However, in general there were significant differences in the endometrial receptivity of subjects who had received medical therapy by clinical nutrition specialists.

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AVAILABILITY of DATA and MATERIAL

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT of INTERESTS

None to declare.

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Research Article

Postradiotherapy Outcome on Cervical Cancer Stage IIIB Patients with and without Paraaortic Lymph Nodes Enlargement

Hasil Pascaradioterapi pada Pasien Kanker Serviks Stadium IIIB dengan dan tanpa Pembesaran Nodus Paraaorta

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Abstract

Objective: To determine whether there are differences in clinical response after radiotherapy and 1 year survival in patients with advanced cervical cancer with and without enlargement of PALN.

Methods: An observational analytic study using a retrospective cohort method was done using consecutive sampling. The subjects of this study were all women with a primary diagnosis of stages IIB to IVB cervical cancer who came to the gynecological oncology clinic of Dr. Cipto Mangunkusumo National General Hospital and underwent MRI examination before undergoing treatment in January 2016 to May 2017.

Results: Among 76 subjects studied, there were 4 (5.1%) subjects who had enlarged PALN. There were no significant differences between the enlargement status of PALN and age ($p = 0.829$), age of first sexual intercourse ($p = 0.33$), parity ($p = 0.642$), mass diameter ($p = 0.777$). Patients with PALN enlargement have 2.13 times risk of having negative radiotherapy outcome ($p = 0.02$, OR 2.13, CI95% 1.12 – 4.07). There was no difference in 1-year survival between patients with and without enlargement of PALN (median 201 vs. 293, $p = 0.072$).

Conclusions: Patients with PALN enlargement have increased risk of having negative radiotherapy outcome ($p < 0.05$). There were no differences in 1 year survival between patients with advanced cervical cancer with enlargement PALN.

Keywords: cervical cancer, lymph node enlargement, paraaortic, radiotherapy.

Abstrak

Tujuan: Mengetahui adakah perbedaan respon klinis pascaradioterapi dan kesintasan 1 tahun pada pasien kanker serviks stadium lanjut dengan pembesaran KGB paraaorta dibandingkan tanpa pembesaran KGB paraaorta.

Metode: Penelitian ini merupakan penelitian analitik observasional dengan menggunakan metode kohort retrospektif. Pengambilan sampel dilakukan dengan cara pengambilan sampel berturut-turut. Subyek penelitian ini adalah semua perempuan dengan diagnosis primer kanker serviks stadium IIB hingga IVB yang datang ke poliklinik Onkologi Ginekologi RSUPN Dr. Cipto Mangunkusumo dan menjalani pemeriksaan MRI sebelum dilakukan terapi pada bulan Januari 2016 hingga Mei 2017.

Hasil: Dari 76 subjek yang diteliti, didapatkan sebanyak 4 (5,1%) subyek yang mengalami pembesaran KGB paraaorta. Tidak didapatkan perbedaan yang bermakna antara status pembesaran KGB paraaorta dan usia ($p = 0,829$), usia hubungan seksual pertama ($p = 0,333$), paritas ($p = 0,642$), dan diameter massa ($p = 0,777$). Pasien dengan pembesaran KGB paraaorta memiliki risiko 2,13 kali lipat ($p = 0,02$, OR 2,13, IK95% 1,12-4,07) memiliki risiko respon terapi negatif. Tidak terdapat perbedaan kesintasan 1 tahun antara pembesaran KGB paraaorta dan tidak (median 201 vs. 293, $p = 0,072$).

Kesimpulan: Pasien dengan pembesaran KGB paraaorta memiliki risiko lebih tinggi mengalami respon radioterapi negatif. ($p < 0,05$). Tidak terdapat kesintasan 1 tahun antara pasien kanker serviks stadium lanjut dengan dan tanpa pembesaran KGB.

Kata kunci: kanker serviks, paraaorta, pembesaran KGB, radioterapi.

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INTRODUCTION

Cervical cancer is the third leading cause of morbidity and mortality in women worldwide¹⁻³. GLOBOCAN survey results in 2018 showed that 569,847 women diagnosed with cervical cancer with new cases with a mortality rate of 311,365 worldwide². The Ministry of Health of the Republic of Indonesia estimates that the incidence of cervical cancer is 100 / 100,000 women per year and ranks second in the ranking of cancer cases in Indonesian women.³ Previous study data in 2007 stated that 75% of gynecological cancers originated from the cervix, and more than 50% of which were diagnosed with advanced stage³. This data shows that cervical cancer needs to be highlighted as one of the female main causes of fatalities in Indonesia⁴.

Determination of staging in cervical cancer is very important because it is very influential, not only on its management but also on the patient's prognosis^{5,6}. Life expectancy will decrease as the stage increases of which cervical cancer is diagnosed. The development of medical technology in recent decades, especially imaging technology, created a paradigm of imaging technology as a vital part of cancer management. In 2018, FIGO had revised its guidelines of cervical cancer, recommending imaging modalities as an additional examination to further guide clinician in diagnosis and treatment choice^{7,8}.

Along with time advancement and the development of various medical diagnostic tools, there are some addition of new categories in the FIGO scoring system, namely in stage 3C which is now separated into 3C1 and 3C2. Stage 3C states that metastasis has occurred to pelvic and/or paraaortic lymph nodes, whereas at stage 3C1 there is only pelvic metastasis and stage 3C2 metastasis has occurred to the paraaortic lymph nodes⁸. In patients without metastasis to lymph nodes, the 5-year overall survival rate (5-YSR) is about 85-90%. However, when metastases to lymph nodes are obtained, 5-YSR decreases between 20-75%.⁸

Although it is known that enlargement of paraaortic lymph nodes has a worse effect on patient outcomes, there has never been a study in Indonesia on how worse the effects exerted on the radiotherapy response and overall survival. Therefore, this study seeks to provide an overview of the effect of paraaortic enlarged lymph nodes on the success of therapy and patient survival.

METHODS

Analytic observational research with retrospective cohort method was done in Gynecologic Oncology clinic in National General Hospital Dr. Cipto Mangunkusumo, Jakarta, Indonesia on March 2018 to June 2019. The study population were women diagnosed with primary cervical cancer stage IIIB to IVB, undergoing magnetic resonance imaging (MRI) before and after treatment, and completed treatment with radiotherapy. Patients with another malignancy or having incomplete medical record were excluded in this study.

Consecutive sampling method was done in this study. Patients were then divided into paraaortic lymph node (PALN) enlargement group and control group. PALN enlargement was determined using MRI and examined by radiology consultant. Baseline characteristics were then analyzed and compared. Bivariate analysis between subjects' characteristics and was done. Survival analysis using Kaplan-Meier was done to all subjects and overall survival between study groups were compared. Ethical clearance was issued from health research and ethical committee in Faculty of Medicine, Universitas Indonesia.

RESULTS

During the time of the study, a total of 118 subjects were recruited. However, 39 patients met the exclusion criteria and were excluded from the study. Among 79 patients included in this study, 1 patient did not come for follow up after treatment. Among 78 subjects of this study, 4 patients was known to have PALN enlargement, while 74 patients did not have PALN enlargement. Baseline characteristics of subjects can be found on Table 1.

Table 1. Baseline Characteristics of Subjects

Characteristics	N = 78
Age	50.51 (8.493)
First sexual intercourse age	
< 20	44 (56.4)
> 20	34 (43.6)
Parity	3 (0 -8)
Mass diameter	5.25 (1.9 – 15.0)
Mass differentiation	
Good	19 (24.4)
Poor	59 (73.6)
PALN enlargement status	
Positive	4 (5.1)
Negative	74 (94.9)
Radiotherapy response	
Positive	49 (62.8)
Negative	29 (37.2)
Survival time (days)	242 (18 – 1.460)

In order to determine the differences between study groups, bivariate analysis between groups was done. Result of bivariate analysis in this study can be found in Table 2.

Table 2. Result of Bivariate Analysis

Variables	Study groups		P-value	RR	CI 95%
	PALN (+) (n = 4)	PALN (-) (n = 74)			
Age	51.50 (12.3)	50.46 (8.35)	0.829		
First sexual intercourse age (years)			0.333	0.43	0.08-2.37
< 20	1 (25)	43 (58.1)			
> 20	3 (75)	31 (41.9)			
Parity	3 (3 – 4)	3 (0 – 8)	0.643		
Mass diameter	5.0 (3.9 – 6.6)	5.35 (1.9 – 15)	0.777		
Mass differentiation					
Good	4 (100)	55 (74.3)	< 0.0001	3.89	2.64-5.74
Poor	0	19 (25.7)			
PALN enlargement status					
Positive	3 (75)	26 (35.1)	0.02	2.13	1.12-4.07
Negative	1 (25)	48 (64.9)			

In order to compare overall survival rate of patients, 1 year survival analysis using Kaplan-Meier was done in this study. The Kaplan-Meier graph for this study can be found on figure 1.

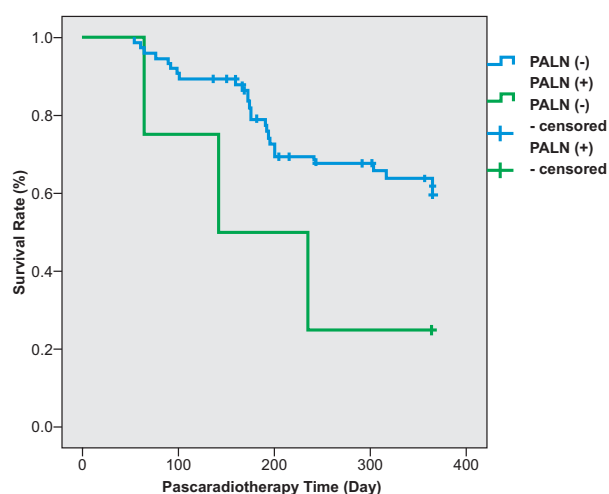


Figure 1. Kaplan-Meier Graph between Study Groups

It was known from the Kaplan Meier analysis that the median survival days for PALN enlargement group was 201 days, while median survival days for PALN negative group was 293 days. However, the result was not statistically significant ($p = 0.072$).

DISCUSSION

In this study, 78 research subjects fitting the inclusion and exclusion criteria of the study were successfully followed up until the end of the study period. On these subjects, the average age was

50.51 years (standard deviation 8.493 years). The mean age obtained in this study is higher than the average age of diagnosis of cervical cancer in both developed countries such as the United States (47 years) and in developing countries such as South Africa (40-49 years old). Previous studies have shown that older women tend to be diagnosed with more advanced cervical cancer while also having a higher mortality rate than younger patients.^{9,10}

Cancer differentiation was generally poor in the study subjects (73.6%). The result is reasonable considering the inclusion criteria in this study were patients who have been diagnosed with advanced cervical cancer, thus having worse differentiation. However, the percentage of poor differentiation patient is higher than a similar study conducted in cervical cancer patients with paraaortic lymph node involvement in 2015 in Belgium which had 33% subjects having poor mass differentiation.¹¹ Another study in Korea only had 1% research subjects who had poor cancer differentiation.¹² In enlarged paraaortic lymph nodes group, it was found that 100% subjects had poor mass differentiation ($p < 0.001$, $RR = 3.89$ CI95% 2.65-4.07).

In this study, only 4 people (5.1%) of 76 study subjects experienced enlargement of the paraaortic lymph nodes. In the analysis between paraaortic lymph node enlargement and radiotherapy response, a significant relationship was found ($p = 0.02$, $RR = 2.13$, CI95% 1.12 - 4.07). In addition, the median survival of 1 year

for subjects with enlargement of the paraaortic lymph nodes was 201 days, while 1 year survival for subjects without enlarged lymph nodes was 293 days. The P value was 0.072, meaning that there were no statistically significant differences of survival rate between the study groups. Although data obtained was not statistically significant, the median survival of patients obtained was judged to be clinically meaningful. In a previous study conducted specifically on cervical cancer patients with enlarged paraaortic lymph nodes in 2001, it was found that the estimated survival at 2 years was 46% and 4 years survival was 29%.¹³

Various factors influence the survival of cervical cancer patients with lymph node involvement. Some risk factors beyond lymph node involvement that have been proven to affect survival are ethnicity, tumor size, treatment performed, age, and nutritional status.³ A large amount of attempts have been made to improve overall survival in cervical cancer patients with enlarged paraaortic lymph nodes. Previous study assessed that the survival of cervical cancer patients with enlarged paraaortic lymph nodes that carried out radiotherapy extension until the paraaortic lymph nodes is similar compared to patients undergoing standard radiotherapy, despite having a much lower incidence of distant metastasis¹⁴. Another attempt to perform paraaortic lymphadenectomy before chemoradiotherapy in late cervical cancer is considered effective to improve survival only in patients who have not had an enlarged paraaortic lymph node. However, it has little to no difference in patients with enlarged paraaortic lymph nodes¹⁵.

CONCLUSIONS

Patients with PALN enlargement have increased risk of having negative radiotherapy outcome ($p < 0.05$). There were no differences in 1 year survival between patients with advanced cervical cancer with enlargement PALN.

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Case Report**Uterine Fibroid in Breast Cancer Patients receiving Tamoxifen Therapy*****Mioma Uteri pada Penderita Kanker Payudara dengan Terapi Tamoksifen*****Rismawati, Fahriatni, Hasanuddin**

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Abstract

Objective: Selective estrogen receptor modulators (SERMs) such as tamoxifen play a role in increasing the risk of developing uterine Fibroid.

Methods: Case report.

Case: Mrs. 47 years old, Para 6, presented with chief complaints of vaginal bleeding since a year ago. The patient was diagnosed with breast carcinoma 4 years ago and has had a right mastectomy followed by 6 cycles of chemotherapy which is then continued with tamoxifen treatment for 4 years, USG examination revealed uterine myoma to which we performed bilateral salphingoophorectomy hysterectomy, with anatomic pathology results of a uterine Fibroid and chronic endometritis.

Conclusions: Selective estrogen receptor modulators (SERMs) such as tamoxifen exhibit antagonistic reactions in breast tissue which makes it appropriate to be used in the treatment of breast cancer. However, they can also be potentially agonistic on estrogen receptors in the uterus, which can cause the growth of uterine Fibroid. Nevertheless, the benefits of adjuvant tamoxifen for breast cancer outweighs its potential for developing uterine Fibroid and endometrial carcinoma, because metastatic breast cancer will always be fatal, whereas uterine myoma and endometrial cancer caused by the effects of tamoxifen can be prevented by regular evaluation and total hysterectomy.

Keywords: breast cancer, tamoxifen, uterine fibroid.

Abstrak

Tujuan: Selektif estrogen reseptor modulator (SERMs) seperti tamoksifen berperan dalam meningkatkan risiko mengembangkan mioma uteri.

Metode: Laporan Kasus.

Kasus: Ny 47 tahun Para 6, datang dengan keluhan perdarahan dari jalan lahir yang dirasakan ibu selama 1 tahun ini, pasien telah menderita kanker payudara 4 tahun yang lalu dan telah dilakukan mastektomi mammae dextra dilanjutkan kemoterapi 6 siklus kemudian dilanjutkan dengan pengobatan tamoksifen selama 4 tahun ini, dari pemeriksaan USG didapatkan adanya mioma uteri kemudian dilanjutkan dengan tindakan histerektomi salphingooforektomi bilateral, dengan hasil patologi anatomi suatu mioma uteri dan endometritis kronis.

Kesimpulan: Selektif estrogen reseptor modulator (SERMs) seperti tamoksifen merupakan reaksi antagonis reseptor estrogen pada jaringan payudara yang digunakan dalam pengobatan kanker payudara, tetapi dapat berpotensi agonis pada reseptor estrogen pada uterus sehingga dapat menyebabkan pertumbuhan mioma uteri. Tetapi penggunaan tamoksifen adjuvan untuk kanker payudara lebih bermanfaat dibandingkan dengan potensinya untuk mengembangkan mioma uteri dan karsinoma endometrium, karena kanker payudara metastatik akan selalu berakibat fatal, sedangkan mioma uteri dan kanker endometrium yang ditimbulkan oleh efek tamoksifen dapat dicegah dengan evaluasi teratur dan dilakukan tindakan total histerektomi.

Kata kunci: kanker payudara, mioma uteri, tamoksifen.

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INTRODUCTION

Uterine fibroid occurs in 20-25% of women of reproductive age.¹ According to a study conducted in the United States, the incidence of uterine Fibroid cases occurring in Caucasians is 8.9 / 1000 whereas the incidence of people of color is 30.9 / 1000. The prevalence of uterine Fibroid increases with age, peaking in women in their 40s. A study found that 77% of cases requiring hysterectomy revealed uterine Fibroids.²

Breast cancer accounts for 30% of all cancers in women and causes about 20% of all cancer deaths, second only to lung cancer. Since the beginning of its incident in the 1980s, cases of breast cancer has increased 3% per year in the western world, and it is estimated that cancer will overtake cardiovascular disease as the leading cause of death in the early twenty-first century. Tamoxifen is the endocrine treatment of choice for selected patients with all stages of breast cancer.³ Tamoxifen has been known to reduce the incidence of contralateral cancer by 40%.⁴

It is estimated that 2 out of 1000 women / year develop endometrial carcinoma while receiving tamoxifen therapy, compared with 1 in 1000 women reported by SEER in the general population. For breast cancer patients who already have a high risk for endometrial cancer, the added risk of long-term tamoxifen therapy is miniscule compared to its known benefits.⁵

The factors causing uterine Fibroid are unknown, but there are 2 theories. Stimulation theory argues that estrogen is an etiological factor, this is further supported by the following facts : Uterine Fibroid grows faster during pregnancy, this neoplasm has never ovured before menarche, uterine Fibroid usually atrophies after menopause, endometrial hyperplasia is found with uterine myoma. Cellnest Theory states that the occurrence of uterine Fibroids depends on immature muscle cells contained in the Nest cell which can then be stimulated continuously by estrogen.^{6,7}

Selective Estrogen Receptor Modulators (SERMs) such as tamoxifen are nonsteroidal hormones that act as antiestrogens in breast tissue.⁸ They were first approved by the US Food and Drug Administration for the treatment of breast cancer in 1978 and until now, tamoxifen is used among women of all ages for the treatment of all stages of breast cancer. Tamoxifen reduces the risk of subsequent contralateral breast cancer and also its recurrence and risk of mortality.

Upon further investigation, it was discovered that tamoxifen is associated with the development of endometrial cancer. Tamoxifen has a complex mechanism of action including anti-estrogenic activity in the breast and estrogenic effect on other tissues, including endometrium.⁹

Tamoxifen is a first generation breast cancer drug, developed in the 1970s, and is currently designed for the treatment of breast cancer. Tamoxifen acts as an estrogen receptor antagonist in breast tissue, but in bone and uterine tissue Tamoxifen acts as an estrogen receptor agonist, so as to maintain bone mineral density in postmenopausal women. Therefore tamoxifen is also considered for the treatment of osteoporosis.¹⁰ Tamoxifen can act as an agonist for uterine endometrial hyperplasia and polyp production, thus possibly increasing the risk of endometrial cancer.³

Tamoxifen has a complex mechanism of action including anti-estrogenic activity in the breast and estrogenic effects on other tissues, including the endometrium.⁹ Women taking tamoxifen must be informed of the risk of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcoma, and any effects caused during tamoxifen therapy such as abnormal vaginal bleeding, vaginal discharge. An encounter with any of the mentioned symptoms warrant an immediate full examination. Postmenopausal women taking tamoxifen should be monitored for symptoms of endometrial hyperplasia or cancer, premenopausal women treated with tamoxifen who are not at risk for uterine cancer do not need additional monitoring outside of routine gynecological care, unless the patient has been identified as having a high risk of endometrial cancer. Routine endometrial surveillance has not been proven effective in increasing early detection of endometrial cancer in women using tamoxifen and is not recommended. If atypical endometrial hyperplasia develops, appropriate gynecological management must be performed, and the use of tamoxifen must be reassessed.¹¹

Before conducting tamoxifen therapy, initial gynecologic screening should be done, these include transvaginal ultrasonography, sonohysterography and hysteroscopy to assess endometrial conditions. The level of endometrial cancer risk in women treated with tamoxifen depends on dose and time. Studies show that at an early stage, the degree of histology and biology of tumors that develop in individuals treated with tamoxifen 20 mg / day are no different from

those that appear in the general population. Some reports have indicated that women who are treated with tamoxifen doses higher than 40 mg / day are more likely to develop tumors that are more biologically aggressive.

Women who take tamoxifen must be informed of the potential for endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcoma, they must be educated to immediately report abnormal symptoms such as vaginal bleeding, spotting, or leukorrhea. The ability of tamoxifen to induce endometrial malignancy and other histopathological conditions seems to differ between premenopausal and postmenopausal women.

Women with endometrial lesions such as polyps diagnosed before tamoxifen treatment have a higher risk of developing atypical endometrial lesions. Therefore, these patients require annual gynecological examinations such as transvaginal ultrasound and even hysteroscopy. These examinations must be carried out even when patients present without symptoms. Hysterectomy can be considered in women with atypical endometrial hyperplasia. Tamoxifen can be used again after hysterectomy in endometrial carcinoma, this requires a consult with a doctor who has experience treating breast cancer.

CASE

A 47-year-old female, Para 6, presented with chief complaints of vaginal bleeding since a year ago,

bleeding was found in the form of spotting and the patient has been menopausal since 4 years ago. The patient was diagnosed with breast carcinoma 4 years ago and right mastectomy has been performed, followed by 6 cycles of chemotherapy which is then continued with tamoxifen treatment for 4 years. Results of a physical examination revealed a BMI of 31.25 (class 1 obesity). Our patient also suffered from hypertension since undergoing tamoxifen therapy with a dose of 20 mg twice a day and routinely consumes 10 mg of amlodipin to treat this hypertension. Gynecological examination found normal inspection of urethra and vulva, In examinations with speculum, portio was slippery, external uterine ostium was closed, fluor albus was negative, fluxus was positive. Upon bimanual examination, we found a slippery portio, closed uterine externum, uterine cavities enlarged as big as a swan's egg, closed uterine ostium, negative fluor albus and positive fluxus.

There was no mass felt in both adnexas and parametrium was limp. Laboratory examination results reveal Hb: 13.4 gr / d, Ca 125: 16.28 U / mL, CEA: 1.64 U / mL, GDS: 148 gr / dl. From ultrasound examination, we found an enlarged uterus with size 13x12x11 cm, and a hyperechoic mass 5x4x3 cm in size was seen in the myometrium with a clear boundary. In the Doppler picture was an appearance of feeding arteries which is suggestive of uterine myoma. We then proceeded with bilateral salpingoophorectomy hysterectomy then the results of PA revealed a uterine Fibroid and chronic endometritis.



Figure 1. Uterine Fibroid in a patient receiving Tamoxifen

DISCUSSION

In this patient, the uterine fibroid she suffered has caused symptoms, namely bleeding and pain. This complaint has disturbed the patient's quality of life and interferes with her daily activity due to constant menstruation and pain that does not go away with analgesics. Thus, operative management is indicated in this patient.

Considering that this patient no longer has a need for her reproductive function, is undergoing tamoxifen therapy for breast cancer for four years and that tamoxifen increases the risk of endometrial malignancy as much as 1.3 to 7.5, we have decided to perform Salphingoophorectomy hysterectomy on this patient. Another factor which made us favour this decision is that salphingooforectomi aims to increase the efficacy of tamoxifen therapy against breast cancer.

Patients are given an explanation that surgical removal of the uterus and ovaries will be performed to remove uterine myoma and to prevent endometrial cancer that can be caused by tamoxifen therapy and to also increase the efficacy of tamoxifen therapy against breast cancer.

Salphingoophorectomy hysterectomy can solve the patient's problem and reduce the side effects caused by tamoxifen therapy on the risk of endometrial cancer.

Tamoxifen is an effective treatment in reducing the recurrence rate and mortality for breast cancer patients, on the other hand, the undesirable side effects of this treatment are an increased risk of endometrial cancer and changes to the genitals. The benefits of tamoxifen treatment for breast cancer outweigh the toxicity it causes, because metastatic breast cancer is always fatal, whereas the effects of endometrial cancer and changes in gynecological components can still be evaluated periodically and treated more quickly.

CONCLUSION

Uterine fibroid can occur due to estrogen stimulation caused by the use of tamoxifen which is an estrogen receptor agonist in uterine and endometrial tissue. Nevertheless, Tamoxifen treatment is urgently needed in these patients to prevent contralateral metastases. For this patient, it was decided to perform HTSOB to remove uterine myomas and to prevent endometrial cancer and to also increase the effectiveness of tamoxifen therapy.

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