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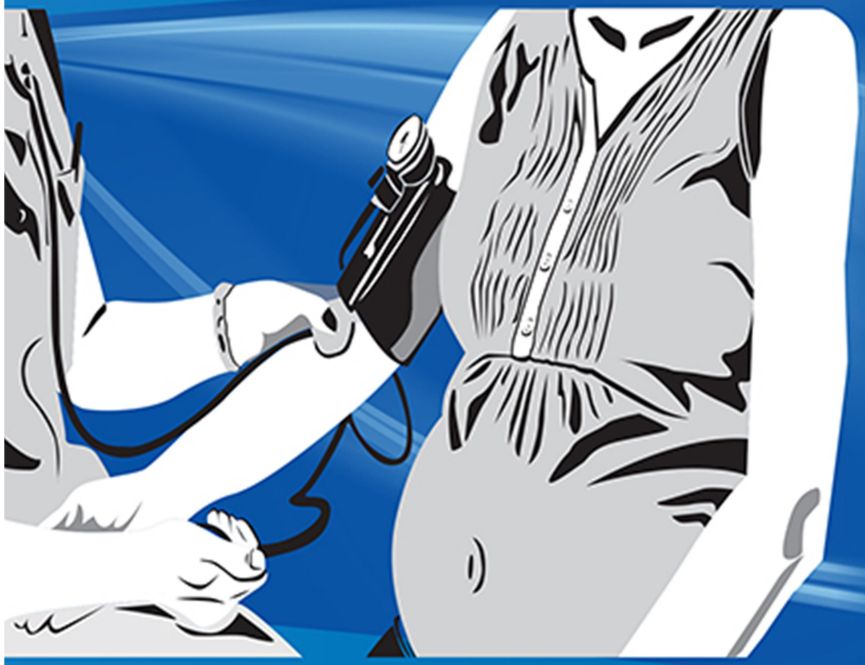
Preeclampsia



The #1 cause of maternal death

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RESEARCH ARTICLE

CASE REPORT

Editorial

Role of Biomarkers for the Screening of Preeclampsia, are we there yet?

Erry G Dachlan

Preeclampsia is a global maternal health burden due to its high maternal mortality and morbidity, especially in developing countries, which appears in Indonesia.[1] Two hundred and sixty-threemillion people occupying a large area of Indonesia gave rise the problem of the high maternal mortality rate of 305/100,000 deliveries where preeclampsia (PE) and eclampsia (E) stand out as a massive health care problem in Indonesia with some teaching hospital rates approximately ranged 22-25 %.[2] Although the precise pathophysiology of PE remains obscure,[3,4] It has beenstrongly suggested that placental dysfunction with released factors containing excessive oxidative molecules, trophoblast debris and pro-inflammatory cytokine into the maternal circulation, inducing widespread endothelial dysfunction that heralds the classic manifestations of the disease.

It has been widely accepted that serving with PE prevention much better than treatment, so early detection and risk identification from those related woman group might have been mostly considering effort into health strategic campaign. With this regard clearly biomarker assesment has posed its position to be required interestingly. The ability to predict PE would be a major advance in maternal-fetal medicine, it is known well that several proposed biomarkers comprising angiogenic markers (sFli-1,VEGF,PlGF and sEng) in maternal circulation precede the clinical onset of PE by severalweeks to months, Placental Protein-13 is a member of the galectin family, predominantly expressed by the syncytiotrophoblasts, that is involved in normal implantation and placental vascular development, Pregnancy-Associated Plasma Protein A is a peptidase produced by syncitiotrophoblast with hydrolytic activity for insulin-like growth factor- binding proteins, and Free Fetal Nucleic-Acids circulate in the maternal blood[5-8].

What would be needed largely nowadays for tropical, coastal and developing state not sophisticated and expensively aboved sort of methods but much more likely such a test of affordable, good accuracy and accountability. However, it could be not other than combined test comprising simply found history taking of risk factors (i.e. elderly primigravida less than 35 years old, genetic, obesity, twin etc.), BMI, MAP and uterine artery Doppler velocimetry (UADV). Although it was never reached the best prediction result, only a little bit lower compared to those what Espinoza et al said in their study as the prediction sensitivities of maternal plasma PlGF concentration, abnormal UADV, and the combination of these test were 61.35% and 27%, respectively. His research group conducted a prospective study of 3296 women to determine the role of UADV, maternal plasma PlGF among others, where sample collection and UADV were performed between 22 and 26 weeks. [6,7]

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Research Article

Manual Vacuum Aspiration versus Sharp Curettage for Incomplete Abortion: Which One is Better?

Aspirasi Vakum Manual dibandingkan dengan Kuret Tajam untuk Abortus Inkomplit: Mana yang Lebih Baik?

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Abstract

Objective : To acknowledge the effectiveness and safety of manual vacuum aspiration (MVA) compared with Sharp Curettage (SC) in the management of incomplete abortion below 12 weeks of gestation which compare time to perform the procedure, rates of evacuation and infection one week after the procedure, and complication during MVA and SC procedure.

Methods : A prospective study with 62 subjects with incomplete abortion came to the emergency wom of at Dr. Cipto Mangunkusumo hospital, Fatmawati hospital and Karawang hospital, divided into 31 subjects on MVA group and 31 subjects on SC group. The data was documented on the time of MVA procedure compare to SC, clinical findings on complication during the procedure, completed evacuation and infection symptoms one week after the procedure.

Results : Sixty two subjects (31 each group) with average time of procedure was 17,65 ± 4,128 minutes and SC was 22,26 ± 4,611 minutes with p = 0,00 and 95% CI; -4,513(-6,837 to -2,389 with significant statistically difference. The comparison of completed evacuation one week after procedure was 3,2% (n = 1) on MVA and 6,5% (n = 2) on SC with clinical findings, and p = 0,554, RR = 1,034 and 95% CI 0,924 – 1,158 with no statistically difference. On the other comparison, we did not find any infection symptoms one week after procedure and complication during the procedure on both procedures.

Conclusions : MVA has more effective than SC on the time of procedure in incomplete abortion with below 12 weeks of gestation. MVA has superiority from completed evacuation but no statistical difference and has equal safety to SC on clinical infection symptoms and complication during the procedure.

Keywords : incomplete abortion, manual vacuum aspiration (MVA), sharp curettage (SC).

Abstrak

Tujuan : *Mengetahui efektifitas dan keamanan dari AVM dibandingkan dengan kuret tajam pada penanganan abortus inkomplit di bawah usia kehamilan 12 minggu dengan melihat dari lama tindakan, proporsi tingkat kebersihan evakuasi sisa konsepsi 1 minggu pascatindakan, proporsi gejala–gejala infeksi 1 minggu pascatindakan dan proporsi komplikasi pada saat tindakan AVM dan kuret tajam.*

Metode : *Penelitian ini merupakan penelitian kohort prospektif (observasional) dengan jumlah sampel 62 subjek yang berkunjung dengan abortus inkomplit ke UGD RSCM, RS Fatmawati dan RSUD Karawang terbagi dalam 31 subjek pada kelompok prosedur AVM dan 31 subjek pada kelompok prosedur kuret tajam. Data dikumpulkan melalui pencatatan waktu lama prosedur AVM dibandingkan kuret tajam, pemeriksaan klinis komplikasi selama prosedur berlangsung, pemeriksaan klinis kebersihan sisa konspesi 1 minggu pascatindakan dan gejala – gejala infeksi 1 minggu pasca tindakan.*

Hasil : *Sebanyak 62 subjek (masing – masing 31 subjek), di mana didapatkan rerata dan simpang baku prosedur AVM 17,65 ± 4,128 menit dan kuret tajam 22,26 ± 4,611 menit dengan p = 0,00 dan IK 95% -4,513 (-6,837 -2,389), bermakna secara statistik. Pada perbandingan proporsi tingkat kebersihan evakuasi sisa konsepsi 1 minggu pascatindakan didapatkan pada AVM 3,2% (n = 1) dan pada kuret tajam 6,5% (n = 2) terdapat sisa konsepsi dengan penilaian klinis, p = 0,554, RR = 1,034 dan IK95% 0,924 – 1,158 tidak memiliki perbedaan bermakna secara statistik. Pada perbandingan lainnya, tidak ditemukan gejala – gejala infeksi 1 minggu pascaprosedur dan komplikasi selama prosedur berlangsung pada prosedur AVM dan kuret tajam.*

Kesimpulan : *AVM juga memiliki keunggulan dalam kebersihan sisa konsepsi namun tidak bermakna secara statitik dan memiliki keamanan yang setara dengan kuret tajam dari tingkat gejala infeksi dan komplikasi selama prosedur.*

Kata kunci : *abortus inkomplit , aspirasi vakum manual (AVM), kuret tajam*

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INTRODUCTION

Incomplete abortion is a severe problem in the field of obstetrics and gynaecology. The data from previous research told that about 12% maternal death related to abortion in Zimbabwe.[1] Among the many factors in the management of incomplete abortion, evacuation methods of the uterus hold essential role. Effectiveness and safety procedure was needed in this management. Events of morbidity and complication increased with a gestational age of abortion. The complication management of abortion are uterus perforation, laceration of the cervix, massive bleeding, incomplete evacuation and infection.[2]Manual Vacuum Aspiration (MVA) was an alternative method for incomplete abortion management. In developing co untries, MVA replaced sharp curettage as management of incomplete abortion, but lack of operator to use this device.[3,4]General anaesthesia and operating room is needed for sharp curettage procedure, otherwise, MVA procedure can be used in a delivery room without general anesthesia.[5,6]

World Health Organization (WHO) recommended Manual Vacuum Aspiration as a method evacuation uterine conception in below 12 weeks of gestation rather than sharp curettage.1Many hospital and public health care in Indonesia used MVA. Based on Juknis DAK (Dana Alokasi Khusus) national budget in 2012, MVA was one of instrument mandatory to be available in PONEK services. Many of health services use MVA, but lack of data and research was published in Indonesia related comparison between MVA and sharp curettage.[7]

OBJECTIVES

In this study, we hypothesised that the MVA has more effective and safe than the sharp curettage in the time of the procedure, proportion of incomplete evacuation, the proportion of infection and proportion of complication during the procedure. The goal of this study was To acknowledge the effectiveness and safety of MVA compare with SC in management of incomplete abortion below 12 weeks of gestation which compare time to perform procedure, rates of evacuation and infection one week after procedure, and complication during MVA and SC procedure in the ER patient obstetrics and gynecology Dr. Cipto Mangunkusumo Hospital, Fatmawati Hospital and Karawang Regional Hospital.

METHODS

This was a prospective study. Subjects were reproductive-aged women diagnosed with incomplete abortion at the Emergency Room of Cipto Mangunkusumo Hospital, Fatmawati Hospital, and karawang Hospital. The subjects were further divided into two groups: 31 subjects on MVA group and 31 subjects on sharp curettage group. The data was documented on the time of MVA procedure compare to sharp curettage, clinical findings on complication during the procedure, clinical findings on completed uterine evacuation one week after the procedure and clinical findings on infection symptoms one week after the procedure. Research has already qualified and approved by the Ethics Committee for Health Researches Faculty of Medicine Universitas of Indonesia-RSCM in September 2016.

RESULTS

A total of 62 subjects (Table 1) , consisting of 31 subjects underwent MVA and 31 subjects underwent sharp curettage. Subjects who received MVA procedure was performed in delivery room and for sharp curettage in operating theatre with sedation or general anaesthesia. We performed analysis using SpSS® Statistics Version 20. Resulting table 2x2 that were able to analyst and we analyst mean difference (Confident Interval), Relative Risk and Odds Ratio both of procedure. Statically the table was able to analysis using Chi-Square, with a p value<0,05 was significant statistically difference. In this study, we also compare the proportion of incomplete evacuation and infection one week after procedure and complication during the procedure between MVA versus sharp curettage.

Table 1. Time of Procedure Comparison MVA and Sharp Curettage

	Time of Procedure (Mean, S.D.)	***P-value***	**Mean Difference (CI 95%)**
MVA	17.65+ 4.128 minute	0.00	-4.513 (-6.837) - (-2.389)
Sharp Curettage	22.26 + 4.611 minute		Ref

We found there was a different time of procedure between MVA (17,65+ 4,128 minutes) and sharp curettage procedure (22,26 ±4,611 minute) with p = 0.00, CI 95% -4,513 {(-6,837) - (-2,389)}. There is significant difference statistically, But there is no significant difference clinically. We recorded the time of procedure from the beginning of the instrument were inserted until the procedure was finished assessed by the operator.

Based on Table.2, we analyst incomplete evacuation both of procedure (MVA vs Sharp Currettage), MVA cleaner than sharp curettage (incomplete evacuation, n =1 (MVA) vs n=2 (SC)). But there is no statistically difference among it (p = 0,554, CI 95% 0,924 – 1,158) and Relative Risk 1,034. We assessed incomplete evacuation from clinical symptom such as complaining of vaginal bleeding. From statistic data, MVA has equal with sharp curettagefrom effectiveness and safety on completed evacuation one week after the procedure.

Table 2. ProportionIncomplete Evacuation Comparison One Week after Procedure (MVA vs Sharp Curettage)

	Complete Evacuation		Incomplete Evacuation		*P-value*	RR	CI 95%
	%	n	%	n			
MVA	96.8	30	3.2	1	0.554	1.034	0,924 - 1,158
Sharp Currettage	93.5	29	6.5	2			
Total	95.2	59	4.8	3			

Table 3. Proportion Complication Comparison during Procedure (MVA vs Sharp Curettage)

	No Complication n%	Complication n%	*P-value*
MVA	100	0	α
Sharp Curettage	100	0	
Total	100	0	

Both of proportion comparison infection one week after procedure and complication during the procedure, there is no infection and complication both of procedures (MVA 0% vs Sharp curettage 0%). We assessed the proportion of infection from clinical symptoms such as fever, foully odour, uterine tenderness, and lower abdominal pain and criteria for complication during the procedure is massive bleeding, laceration of the cervix and uterine perforation. We conclude that both of the procedure is safe.There was no side effect on both procedures from this study (odds ratio = α).

DISCUSSION

In this study, we analysed both procedure MVA, and sharp curettage has the same effectiveness and safety on incomplete abortion management below 12 weeks gestational age. We performed this study in three institutions (Dr. Cipto Mangunkusumo Hospital, Fatmawati Hospital and Karawang Region Hospital) with a total of 31 samples each of the procedures. The significant result from our study and previous study because of the amount of sample.Atreya on their study shows that MVA procedure has faster than sharp curettage (7.0 (SD ±2.0) minute vs 7.7(SD±2.1) minute) with significant difference. That was proven that MVA more effective than sharp curettage.[3]Mahomed from their study showed incomplete evacuation in MVA 0% versus 0.7% on sharp curettage with p value <0.05. The difference result between this study and Mahomed study was because of the amount of sample both of study.[1] We diagnosed incomplete evacuation from clinical finding (vaginal bleeding). We gave patient diagnosed incomplete evacuation with prostaglandin E1 (misoprostol) 600µg orally in 3 days with success rate 95% .[8] It shows incomplete evacuation by MVA or sharp curettage can be administered with uterotonics (prostaglandin E1 / misoprostol). A study from Mahomed shows the proportion of infection MVA 1.6% compare to 2.5% in sharp curettage, and complication during procedure MVA was 0.7% and 4.5% in sharp curettage.[1]

CONCLUSION

From this study, MVA has the same effectiveness and safety tosharp curettage with time of procedure MVA 17.65+ 4.128 (IK 95%,-6.837 to -2,389) minute versus 22.26+ 4.611 (IK 95%,-6.837 to -2.389) was statistically differences but

has no clinical differences. From the proportion incomplete evacuation, there is differences between MVA and sharp curettage (n=1, 3.2% versus n =2, 6.5%) but there is no statistic and clinical differences both of procedure (p = 0.554, CI 95% 0.924 – 1.158). In this study, we not found any infection and complication both of procedure. From this study, we can conclude that MVA is an effective and safe procedure to performed incomplete abortion management below 12-weeks gestation age and can assess clinically by the general practitioners. We recommended MVA use in primary health care.

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Research Article

Correlation between Body Mass Index and Lipid Profile in Second Trimester with the Incidence of Hypertension in Third Trimester

Hubungan Indeks Massa Tubuh dan Profil Lipid Trimester Kedua dengan Kejadian Hipertensi pada Trimester Ketiga

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Abstract

Objective : To determine the relationship of BMI (Body Mass Index) and lipid profile (total cholesterol, triglycerides, HDL, LDL, VLDL) in the second trimester of pregnancy with the incidence of hypertension in the third trimester of pregnancy.

Methods : This was a prospective study. Subjects were the second-trimester pregnant women group which examined by BMI and lipid profile, then assessed the incidence of hypertension in the third trimester. The study was conducted in the Department of Obstetrics and Gynecology and Prof. DR.RD Kandou General Hospital, and affiliated hospital from January 2017 until May 2017. Data analysed with SPSS version 2.0

Results : Of 49 subjects, based on age, most subject with age 20-34 years with 42 subjects (85.8%). Based on the parity obtained 27 subjects (55.2%) with multigravida. By education level, most are high school with 19 subjects (38.7%). From the occupation, most are housewives with 30 subjects (61.3%). Based on BMI, most were subjects with normal BMI with 21 subjects (42.9%). Pearson test showed a significant association between BMI with total cholesterol (r = 0.500 and p = 0.000), whereas Spearman test showed significant relation between BMI with LDL cholesterol (r = 0.416 and p = 0.003) and significant relation between second-trimester LDL cholesterol with third trimester diastolic blood pressure(r = 0.303 and p = 0.034).

Conclusions : There was a significant correlation between BMI with total cholesterol & LDL in the second trimester, and there was a significant correlation between LDL in the second trimester and third-trimester diastolic blood pressure.

Keywords : BMI, HDL, hypertension, LDL, TG, VLDL, total cholesterol

Abstrak

Tujuan : *Untuk mengetahui hubungan IMT (Indeks Massa Tubuh) dan profil lipid (kolesterol total, trigliserida, HDL, LDL, VLDV) pada trimester kedua kehamilan dengan kejadian hipertensi pada trimester ketiga kehamilan.*

Metode : *Penelitian ini merupakan kohort prospektif. Subjek penelitian adalah kelompok ibu hamil trimester kedua yang diperiksa IMT dan profil lipidnya, kemudian dinilai kejadian hipertensi pada trimester ketiga. Penelitian dilakukan di Departemen Obstetri dan Ginekologi Rumah Sakit Umum Pusat (RSUP) Prof.DR.R.D Kandou, dan RS jejaring mulai Januari 2017 sampai Mei 2017. Data dianalisa dengan SPSS versi 2.0*

Hasil : *Dari 49 subjek penelitian, berdasarkan usia paling banyak usia 20 – 34 tahun dengan 42 subjek (85,8%). Berdasarkan paritas didapatkan 27 subjek (55,2%) dengan multigravida. Berdasarkan pendidikan, paling banyak adalah SMA dengan 19 subjek (38,7%). Dari jenis pekerjaan, paling banyak adalah ibu rumah tangga dengan 30 subjek (61,3%). Berdasarkan IMT, paling banyak adalah subjek dengan IMT normal dengan 21 subjek (42,9%). Uji Pearson menunjukkan hubungan bermakna antara IMT dengan kolesterol total (r = 0,500 dan p = 0,000), sedangkan Uji Spearman menunjukkan hubungan bermakna antara IMT dengan kolesterol LDL (r = 0,416 dan p = 0,003) dan hubungan bermakna antara kolesterol LDL trimester kedua dengan tekanan darah diastol trimester ketiga (r = 0,303 dan p = 0,034).*

Kesimpulan : *Terdapat hubungan bermakna antara IMT dengan kolesterol total, LDL trimester kedua dan terdapat hubungan bermakna antara LDL trimester kedua dengan tekanan darah diastol trimester ketiga.*

Kata kunci : *HDL, hipertensi, IMT, kolesterol total, LDL,VLDL, TG*

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INTRODUCTION

Maternal nutritional status is essential for the achievement of maternal and fetal. The most common method used to know the nutritional status of a person is by calculating the Body Mass Index (BMI). Body Mass Index (BMI) is body weight divided by squared height is influenced by ethnicity and genetics and can also be used for measurement of adiposity and energy balance.[1]

In early pregnancy there is an increase in fat buildup associated with increased feeding and increased fat.[2] Fat concentration in blood, lipoprotein and apolipoprotein in plasma increased significantly during pregnancy.[3] Fat accumulation occurred during midterm pregnancy.[4-8] Lipid accumulation can cause endothelial dysfunction, causing preeclampsia, lipid profiles are total cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and Very low-density lipoprotein (VLDL). It is suspected that there is an association between preeclampsia with elevated total cholesterol, triglycerides, LDL and VLDL.[9] It has been suggested that elevated plasma triglycerides and LDL during pregnancy can be used to identify women who will experience atherogenic changes in later life.[10]

Hypertension in pregnancy is a complication found in 5-10% of all pregnancies and has an increased risk of poor pregnancy outcomes.[11] The risk of poor outcome of pregnancy in hypertension in pregnancy is commonly found related to the diagnosis of preeclampsia.[11-16] Hypertension in pregnancy divided to preeclampsia or non-preeclampsia which the basis of consideration of possible disease course, appropriate management and possible outcomes.[11-13]

METHODS

This was prospective study identifying the relationship of BMI and lipid profile (total cholesterol, triglycerides, HDL, LDL, VLDL) in the second trimester of pregnancy with the incidence of hypertension in the third trimester of pregnancy. This research was conducted from January 2017 until May 2017 in RSUP Prof. dr.R.D.Kandou Manado, and affiliated hospitals in Manado. We included 49 subjects. All subjects of this study have entered the inclusion criteria and exclusion criteria and have signed a willingness form to participate in the study.

Sampling was conducted at RSUP Prof. dr.R.D.Kandou Manado and an affiliated hospital in Manado which fulfill the inclusion criteria. Samples' body weight, height, vital signs were measured, and venous blood was taken for the examination of lipid profiles in the second trimester of pregnancy and then the samples vital signs were measured and urinalysis laboratory was taken for hypertension examination in the third trimester of pregnancy which pregnant women had been explained and had signed approval statements letter to following the research that has been provided. Analysis and data processing carried out by the researcher and statistic supervisor. The data collection will be carried out by the researcher. This is done manually and computerized by using the software program Statistical Product and Service Solution (SPSS) for Windows version 22.0.

RESULTS

This research was conducted and evaluated from January until May 2017 in the Department of Obstetrics and Gynecology Faculty of Medicine Universitas Sam Ratulangi / RSUP Prof. Dr. R. Kandou Manado and affiliated hospitals in Manado. The subjects consisted of 49 samples of pregnant women.

Table 1. Characteristics of Research Subjects

Characteristics	n	%
Maternal age		
< 20	3	6,1
20 - 34	42	85.8
≥ 35	4	8.1
Parity		
Primigravida	22	44.8
Multigravida	27	55.2
Education		
Bachelor	13	26.6
D3	9	18.4
Senior High School	19	38.7
Junior High School	6	12.2
Primary School	2	4.1
Occupation		
Private Employee	2	4.1
Midwife	8	16.3
Civil Servant	9	18.3
Housewife	30	61.3
Body Mass Index		
Underweight (<18.5 kg/m2)	1	2
Normoweight (18.5 to 24.9 kg/m2)	21	42.9
Overweight (25 to 29.9 kg/m2)	17	34.7
Obese (≥ 30 kg/m2)	10	20.4

Table 2. Statistical Analysis of Second Trimester BMI and Lipid Profile with Incidence of Hypertension in Third Trimester

		Trimester III Blood Pressure			
Trimester II	**Mean (n= 49)**	**Systole**		**Diastole**	
		r	***P-value***	***r***	***P-value***
BMI (kg/m2)	25.95	0.000	0.999	0.073	0.620
Lipid Profile Serum					
Total cholesterol (mg/dl)	211.63	0.200	0.167	0.273	0.058
VLDL (mg/dl)	41.004	– 0.109	0.456	– 0.055	0.705
Triglycerides (mg/dl)	205.02	– 0.109	0.456	– 0.055	0.705
HDL (mg/dl)	60.33	0.026	0.860	0.091	0.534
LDL (mg/dl)	121.22	0.246	0.088	0.303	0.034

Table 3. Statistical Analysis of Blood Pressure

Trimester III	**Mean (n=49)**
Blood pressure	
BP-sistole (mm Hg)	130.82
BP-diastole (mm Hg)	83.88

Table 4. Statistical Analysis of Second Trimester BMI with Lipid Profile in Second Trimester

Trimester II	**Mean (n= 49)**	**Trimester II Lipid Profile Serum**								**Trimester III Blood Pressure**					
	TC	**TC**		**VLDL**		**TG**		**HDL**		**LDL**		**Systole**		**Diastole**	
		r	***P-value***	***r***	***P-value***	***r***	***P-value***	***r***	***P-value***	***r***	***P-value***	***r***	***P-value***	***r***	***P-value***
BMI (kg/m2)	25.95	0.500	0.000	0.177	0.223	0.177	0.223	0.189	0.194	0.416	0.003	0.000	0.999	0.073	0.620

DISCUSSION

In Table 1.shown the characteristic of the study were 42 subjects (85.8%) aged 20-34 years. Based on parity 27 subjects (55.2%) was found with multipara, for education obtained high school with 19 subjects (38.7%). For occupation obtained housewives with 30 subjects (61.3%), for body mass obtained normal body mass index with 21 subjects (42.9%). In Table2. Statistical analysis finds that the average value of body mass index at the second-trimester increase in the condition of pregnancy, for the average value of the lipid profile (total cholesterol, VLDL, triglycerides, HDL, LDL) increases in pregnancy. Similarly for the average results of blood pressure measurement also increased.

The correlation between Body Mass Index (BMI) with the second-trimester lipid profile using Pearson correlation test found a significant correlation between BMI with total cholesterol (r = 0.500 and p = 0.000). Increased of BMI on the second trimester is followed by an increase in total cholesterol. There is no correlation between BMI with HDL cholesterol (r = 0.189 and p = 0.194). With the Spearman correlation test, there was no significant correlation between BMI with VLDL (r = 0.177 and p = 0.223), no significant correlation between BMI with triglycerides (r = 0.177 and p = 0.223) but there is a significant correlation between BMI with LDL cholesterol (r = 0.416 and p = 0.003). Conclusion: BMI was increased in the second trimester, followed by an increase in LDL cholesterol on the second trimester.

Vahratianet al[17] studied the BMI and lipid levels (total cholesterol, triglycerides, LDL, and HDL cholesterol) were increased during gestation. Body Mass Index obtained through the interaction of gestational age was found statistically significant for total cholesterol (p= 0,01) and LDL (p <0.001). It has shown that total cholesterol and LDL were significantly lower for overweight or obese compared with normoweight in the latter half of pregnancy. Vahratian et al found that this difference may be related to metabolic dysregulation associated with maternal overweight and obesity can affect the course of pregnancy and its effects on the fetus. Increased body mass index values found in some other studies, [17-20]

For the relationship of BMI on second trimester with blood pressure measure on third trimester, we found there is no significant between BMI on the second trimester with systolic blood pressure on the third trimester (r = 0.000 and p = 0.999), and there was no significant correlation between BMI on the second trimester with diastolic blood pressure on third trimester (r = 0.073 and p = 0.620).

Savitri Ary I et al [21] suggested BMI in pregnancy determine the maternal weight levels, but not the changes in blood pressure during pregnancy and it associated with the possibility of pregnancy hypertension and preeclampsia, regardless of gestational weight gain. Based on Hogan et al [22] and Macdonald-Wallis et al [23] suggested that weight gain during pregnancy was associated with an increased risk of gestational hypertension and preeclampsia. However, this study showed different results due to IMT measurements were taken in the second trimester.

For second trimester total cholesterol with third-trimester blood pressure, total cholesterol was increased in pregnancy with value of 211.63. With Pearson correlation test there was no significant correlation between second-trimester total cholesterol and third-trimester systolic blood pressure(r = 0.200 and p = 0.167), and there was no significant correlation between second-trimester total cholesterol and third-trimester diastole blood pressure (r = 0.273 and p = 0.058).

In this study found that the mean value of VLDL increased in pregnancy condition with a value of 41.004 compared with the normal reference values (2-30 mg/dl). The Spearman correlation test found no significant correlation between second-trimester VLDL with third trimester systolic blood pressure (r = - 0.109 and p = 0.456) and no significant correlation between second-trimester VLDL and third trimester diastolic blood pressure (r = - 0.055 and p = 0.705).

In our study, the mean value of triglycerides in pregnancy was increased to 205.02 compared with the normal reference values (<150 mg/dl). There is a significant correlation between VLDL in the second trimester compared with systolic blood pressure in the third trimester using the Spearman correlation test (r = - 0.109 and p = 0.456) and there was no significant correlation between VLDL in the second trimester with blood pressure diastolic in third trimester (r = - 0.055 and p = 0.705).

In this study, the mean value of HDL in pregnancy was 60.33. Using Spearman correlation test, there is no significant correlation between HDL in the second and third trimester with systolic blood pressure (r = 0.036 and p = 0.805), and there was no significant correlation between HDL in the second and third trimester with diastolic blood pressure (r = 0.092 and p = 0.531).

The mean value of LDL in pregnancy was increased with a value of 121.22 compared with the normal reference values (<100 mg/dl). Spearman correlation showed no significant correlation between LDL cholesterol in the second trimester with systolic blood pressure on the third trimester (r = 0.246 and p = 0.088), but there is a significant correlation between LDL cholesterol on the second trimester with diastolic blood pressure third trimester (r = 0.303 and p = 0.034). These findings were similar with previous studies before, which showed an increase in total cholesterol, VLDL, triglycerides, HDL and LDL in the second trimester compared with the third trimester. Based on Pusukuru et al[24] and Jayanta De et al[25] hypertriglyceridemia are risk factors for preeclampsia, gestational diabetes and premature. Lipid profile measure is highly recommended during pregnancy to implement appropriate management strategies to prevent adverse effects of hyperlipidemia associated with pregnancy.

Takahashi et al [26], stated that total cholesterol, VLDL, triglycerides, HDL and LDL are increased from the first trimester to the second trimester. Lokhande al[27] found that association between increased of lipid profile, endothelial cells and oxidative stress are involved in the pathophysiology of hypertension in pregnancy. Increased plasma lipids cause the activation of endothelial cells. Study from Lokhande et al showed that total cholesterol levels did not affect hypertension in pregnancy (preeclampsia). However, there is a change in the lipid profile in hypertension in pregnancy (preeclampsia) that is hypertriglyceridemia.

A study from Lokhande show increase in triglycerides was statistically significant (p<0.0001) in pregnancy with hypertension when compared with women with normal pregnancies. Hypertriglyceridemia can be modulated by hyperinsulinism in pregnancy. Triglycerides, LDL and increasing free fatty acid levels in normal pregnancy which correlates with insulin resistance. In hypertension in pregnancy (preeclampsia) show excessive amounts of insulin resistance resulting in increased levels of triglycerides. In pregnancy this triglyceride endothelial dysfunction which can affect endothelial cells.

Based on Research from Kiran et al[28], which examined the lipid profile in the second trimester as a predictor of hypertension in pregnancy is getting results where pregnant women with preeclampsia had higher levels of total cholesterol, triglycerides, VLDL and LDL compared with normotensive pregnant women. This can be explained by several mechanisms: increased plasma lipid and lipoprotein (LDL) may induce endothelial dysfunction caused by oxidative stress. When oxidative stress is to a certain extent, cell damage can occur, including damage to the structure of the cell membrane of mitochondria and nucleus DNA. Dyslipidemia can also attack the trophoblasts that contribute to the occurrence of preeclampsia.

Based on Sattar N et al[29], preeclampsia can be characterised by dyslipidemia, with its predominant hypertriglyceridemia. In women with preeclampsia found increased concentrations of triglycerides in early pregnancy, and it is associated with a high concentration of free fatty acids. High levels of triglycerides associated with increased LDL. Increased levels of free fatty acids cause the accumulation of fat in the liver and kidneys that contributes to some of the complications of preeclampsia.

CONCLUSION

There is a significant correlation between BMI with total cholesterol (r = 0.500 and p = 0.000), there is a significant correlation between BMI with LDL cholesterol (r = 0.416 and p = 0.003) and there is a significant correlation between LDL cholesterol trimester II with blood pressure diastolic trimester III (r = 0.303 and p = 0.034).

SUGGESTION

It is expected that further research conducted to assess changes in lipid profile (total cholesterol, VLDL, triglycerides, HDL and LDL) in the third-trimester pregnant women. This research can be continued with a larger sample to be able to assess complication that occurs in the third trimester with the change in lipid profile.

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Research Article

The Levels of Zinc, Selenium, Iron and Copper in Preterm Pregnancy do not Differ with those of Healthy Pregnancy

Kadar Seng, Selenium, Besi dan Tembaga pada Kehamilan Prematur tidak Berbeda dengan Kehamilan Sehat

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Abstract

Objective : To compare zinc, selenium, iron and copper levels in maternal serum of healthy and preterm pregnancy.

Methods : This was a cross-sectional study with preterm and healthy pregnant woman who will carry delivery in Dr. Cipto Mangunkusumo National Hospital and Budi Kemuliaan Hospital Jakarta from January to April 2017. This study was conducted by comparing the levels of each micronutrient in both groups of subjects.

Results : From January to April 2017, there were 53 subjects divided into 30 normal pregnant women and 23 preterm pregnant women. The levels of zinc, selenium iron and copper in preterm pregnancy were 42 µg/dL, 72,39 µg/L, 74 µg/L, and 2144,52 µg/dL. Levels of zinc, selenium, iron and copper in normal pregnancy were 42 µg/dL, 67,27 µg/L, 70,5 µg/L, and 2221 µg/dL. There was no difference in micronutrients level in both groups.

Conclusions : This study concluded that there was no difference in zinc, selenium, iron and copper levels in healthy and preterm pregnancy.

Keywords : copper, iron, pregnancy, selenium, zinc.

Abstrak

Tujuan : *Membandingkan kadar seng, selenium, besi dan tembaga pada serum maternal ibu hamil normal dan preterm.*

Metode : *Penelitian dilakukan dengan uji potong-lintang dengan subjek penelitian ibu hamil baik preterm maupun aterm yang akan melaksanakan persalinan di RSUPN Dr. Cipto Mangunkusumo dan RS Budi Kemuliaan Jakarta pada Januari hingga April 2017. Penelitian dilakukan dengan membandingkan kadar masing-masing mikro nutrien pada kedua kelompok subjek.*

Hasil : *Dalam jangka waktu Januari hingga April 2017 didapatkan 53 subjek penelitian yaitu 30 ibu hamil normal dan 23 ibu dengan kehamilan preterm. Seluruh subjek dimasukkan dalam analisis data. Kadar seng, selenium, besi dan tembaga pada ibu dengan kehamilan preterm secara berurutan adalah 42 µg/dL, 72,39 µg/L, 74 µg/L, dan 2144,52 µg/dL. Sedangkan kadar seng, selenium, besi dan tembaga pada ibu hamil normal secara berurutan adalah 42 µg/dL, 67,27 µg/L, 70,5 µg/L, dan 2221 µg/dL. Tidak ada perbedaan bermakna kadar mikro nutrien pada kedua kelompok subjek.*

Kesimpulan : *Penelitian ini menyimpulkan bahwa tidak ada perbedaan kadar seng, selenium, besi dan tembaga pada ibu hamil normal dan ibu dengan kehamilan preterm.*

Kata kunci : *kehamilan, seng, selenium, besi, tembaga.*

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INTRODUCTION

Nutritional needs in pregnant women increase more than the healthy population. Nutritional needs in pregnant women consist of the macronutrients consist of protein, carbohydrates and fats and micronutrients like minerals and vitamins. Nutritional disorders, both overnutrition and undernutrition may cause amenorrhea, infertility and miscarriage and impaired fetal growth.[1]

Maternal nutrition status during pregnancy plays a vital role in determining the outcome of pregnancy. Nutrition has been known to play a role in the pathogenesis of pregnancy complications such as preterm birth, impaired fetal growth, preeclampsia, anaemia and gestational

diabetes mellitus.[2,3] Maternal malnutrition, either over-nutrition, undernutrition, or micronutrient deficiency can cause intrauterine inflammation.[4] Some micronutrients such Vitamins A, B6, B12, C, D, E, folic acid, zinc, and docosahexaenoic acid (DHA) affect immune system function and reduce oxidative damage in the placenta. Zinc, vitamin A and D act as immune system regulators and have anti-inflammatory effects.[2]

A prospective study found that dietary iron intake was associated with significantly increased risk of type 2 diabetes. Furthermore, serum ferritin levels were associated with the risk of diabetes, hypertension, metabolic syndrome, cardiovascular risk factors, and inflammation.[5] Iron deficiency affects 1.6 billion people worldwide, and pregnant women are at the highest risk. Anaemia during pregnancy is associated with labour complications, premature birth, low birth weight, decreased iron infant status, impaired maternal and infant interactions, and increased maternal and infant mortality.[6]

Zinc levels are lower in women in developing countries. This is related to 2,5 times more likely to deliver babies weighing less than 2000 g.[1] Selenium deficiency causes reproductive obstetric complications among others male and female infertility, miscarriage, preeclampsia, fetal growth restriction,[(7)] preterm labour,[7-9] and gestational diabetes.[7]

Preterm pregnancy is considered as abnormal pregnancy outcomes. Preterm labour is delivery before 37 weeks of complete gestation. Preterm labour is still a problem worldwide. The 2010 WHO report states that Indonesia is ranked fifth in the country with the highest preterm delivery of 675,700 per year.[10,11]

Preterm labour, impaired fetal growth and preeclampsia is known as "the Great Obstetric Syndrome". This all three diseases known as multifactorial diseases. In their pathophysiology known that there is implantation failure resulting in placental dysfunction. As a result, there will be Toll-like Receptor (TLR) activation followed by bonded to MyD88 forms Nuclear Factor Kappa Beta (NFκB). This activation will form pro-inflammatory cytokines such as IL, IL-1β and TNF-α. Placental dysfunction also causes oxidative stress. NFκB's aberrant and premature activities and oxidative stress cause preterm labour.[5,6,12,13]

Micronutrient levels in pregnant women are examined from maternal serum. Some studies have not come to a consistent conclusion about the relationship between micronutrient levels and preterm pregnancy. In addition, there is no similar research has been conducted in Indonesia. In this study, researchers want to know the differences in micronutrient levels in both normal pregnant women and preterm labour. The micronutrient levels assessed in this study are zinc, selenium, iron and copper.

OBJECTIVES

The objective of this study is to determine the average rate of micronutrients of zinc, selenium, iron and copper in normal labour and preterm labour. This study also wanted to know the difference between the mean level and the relationship in each group. The authors hypothesised that there were significant mean differences between the two groups.

METHODS

This was a cross-sectional study conducted for 4 months, from January until April 2017, at Emergency Room RSUPN Dr. Cipto Mangunkusumo and RS Budi Kemuliaan Jakarta. Subjects were collected using consecutive method sampling. The minimum subjects are 31 subjects in each group. The inclusion criteria for this study are mothers who will give delivery with full-term pregnancy (27-42 weeks) or had preterm labor at 28-36 weeks of gestation without premature rupture of membranes, no complications found during pregnancy, no nutritional problems and no other treatment unrelated pregnancy. The exclusion criteria in this study are multiple pregnancies, the subjects have another medical condition, and there are congenital abnormalities in the fetus.

Subjects who met the study criteria were asked their willingness to follow the study. After anamnesis and physical examination, the data are collected in research status. Right before the patient gave birth, 5 cc of blood venous was taken by an intravenous puncture for micronutrient examination. Micronutrient examination is done at Prodia Laboratory. Blood samples were

centrifuged at 3000 rpm followed by ICP-MS analysis.

Data were analyzed with SPSS version 20.0. Data with normal distribution will be reported in average and standard intersections, whereas if abnormal data distribution will be reported in the median with minimum and maximum value. Then, bivariate analysis was done unpaired T-test if the distribution of the date is normal and Mann-Whitney test if the data distribution is not normal. The relationship between the two groups was assessed from the p-value in the comparison of the two group's average.

RESULTS

There were 53 mothers from RSUPN Dr. Cipto Mangunkusumo and RS Budi Kemuliaan who met the criteria, participate in research as the subject of research. A total of 23 samples were mothers with preterm birth and 30 samples were mothers with normal pregnancies. The mean age of mothers is 27 years old with the youngest age is 16 years and the oldest age is 46 years.

Micronutrient Examination

There was no significant correlation between micronutrient levels and maternal pregnancy status in maternal serum examination. The mean values of zinc in both groups were similar and no significant difference was found between iron levels in both groups. The selenium level in preterm is 5,13 µg/L higher than the normal group. The copper levels in full-term pregnancy are 76,47 µg/L higher than preterm, but there is no statistical difference between the two groups.

Table 1. Micronutrient Levels in Full Term and Preterm Pregnancy

Variable	Group	n	Result	*P-value*
Zinc [µg/dL; median (min-max)]	Preterm Term	23 30	42 (16-64) 42 (24-59)	0,962*
Selenium [µg/L; mean ± SD]	Preterm Term	23 30	72,39 ± 18,25 67,27 ± 20,37	0,347#
Iron [µg/dL; median (min-max)]	Preterm Term	23 30	74 (22-234) 70,5 (24-292)	0,846*
Copper [µg/L; mean ± SD]	Preterm Term	23 30	2144,52 ± 658,47 2221,,00 ± 542,61	0,645#

* Mann-Whitney test
\# Unpaired T-Test

This study includes 53 subjects where 23 subjects with preterm labor and the other are full-term labor. The subjects were less than minimum number of subjects needed, 62 subjects, 31 subjects each group. The research conducted over productive age, ranged from 16 to 46 years old.

Zinc is transferred passively from mother to fetus through the placenta. During pregnancy, there is an increase in zinc binding capacity. Higher levels of zinc on the umbilical cord allow the transfer of zinc from the maternal to the fetus. This decrease of maternal zinc levels during pregnancy is considered as physiological adjustment during pregnancy due to changes in blood volume.[14] Zinc is needed during early pregnancy for organ formation and tissue development. In previous studies it was found that there was a positive correlation between gestational age and zinc levels on the umbilical cord. Meanwhile, maternal serum maternal serum levels were inversely related to gestational age.[14,15]

In this study was found that both in preterm and full-term pregnancy, the mean level of Zinc was 42 µg/dL. This level was slightly below the normal levels.[16] There was no significant difference between zinc levels in both groups. Based on a study conducted in 2000 in India, it was concluded that zinc levels in pregnant women in Indonesia are very low. The zinc levels found in maternal serum examination were 633,5 µg/L. They also concluded that zinc levels in pregnant women were higher than zinc levels in non-pregnant adult women.[17]Other study conducted in Iran stated that the level of zinc in full-term pregnancy were 654,76 µg/L.[18]

The relationship between gestational age and zinc levels in maternal blood has been widely studied. In research conducted by Khadem et al, found a significant difference between zinc levels in full-term and preterm pregnancy. Level of zinc tend to be higher in the early pregnancy.[18,19]

A study conducted in India found that zinc levels in full-term neonates were found to be significantly different than in preterm born neonates. It was found that zinc levels in maternal serum of normal pregnant women were significantly lower than in preterm pregnant women. There was a positive

relationship between maternal age and serum zinc on the umbilical cord and inversely related to zinc levels in maternal serum.[15]

This study concluded that there was no correlation between zinc level and gestational age. In contrast, a study conducted in Iran concludes that there was a statistically significant difference between zinc levels in the third trimester compared to the first and second trimesters. There was no significant difference between zinc levels in the first and second trimesters.

Some confounding factors to zinc level in maternal blood serum were not included in this study. Confounding factors may affect maternal zinc levels such as dietary nutritional intake, smoking, alcohol consumption and gastrointestinal disorders.[20]

The average selenium levels were 69,49 µg/L. The mean difference between both groups is 5,13 µg/L. The selenium levels in preterm pregnancy were higher than full-term pregnancy. However, there was no statistically significant relationship between both groups. Levels of selenium in pregnancy found in this study were 2 times higher than the level of selenium in normal pregnant women.

A study conducted in Spain showed the level of selenium in maternal blood serum ranged between 57,3 to 117,9 µg/L. The study also concluded that selenium level in maternal serum was higher than other tissue such as umbilical cord, placenta, nails and hair.[21] Other study showed that selenium level in full-term pregnancy was higher, with an average of 111 µg/L.[22] Another study conducted in Canada stated that the selenium level in pregnant women was 120 µg/L.[23] All of this study show that selenium level in maternal serum in this study was lower than the other.

Several studies support the conclusion of this study. There was no significant relationship between gestational age and maternal selenium levels. [21,22,24] A study conducted in Israel concludes that there was a significant increase of selenium levels in the umbilical cord along with increasing gestational age. This result was hypothesised due to an increased need for selenium by the placenta.

Similarly, a study by Iranpour et al. found no significant association between gestational age and plasma selenium levels but found a significant difference in mean selenium levels in the full term pregnancy with preterm in the umbilical cord. Although there was no significant difference, the levels of selenium in maternal blood full-term pregnancy were higher than in the preterm, in contrast to the results found in this study.[25] Other studies conducted in Israel suggest that selenium levels at the third trimester of pregnancy are lower than the first trimester.[22]

Iron levels in maternal serum group of preterm pregnant women in this study were 74 µg/L and 70,5 µg/L in a full-term pregnancy. The iron levels in both groups of subjects were within the normal range according to the CDC. Iron levels in full-term pregnancy the study were slightly below the lower limit of normal serum iron levels in normal women. However, there were no significant differences found. A similar conclusion also concluded by a study conducted in Jordan. The serum iron levels found in this study were also similar to the Jordanian study which is 74 µg/L.[26] Several other studies also concluded that there is no relationship between gestational age and iron content. A study conducted in India found that the iron level in full-term pregnancy were only 35,4 µg/L.[27]

From a study conducted in India, it was found that iron levels in the umbilical cord were significantly higher than maternal serum iron. Although the maternal serum iron levels were lower than normaly values, the haemoglobin and iron levels of infants were still within normal range.[28] There was a significant association between iron levels in maternal serum and iron levels in neonates. This is due to that iron is actively transported to the fetal tissue as needed. Some other things to consider in determining iron levels in pregnant women is the dietary intake of iron, Hemoglobin levels, and environmental factors such as smoking.

Copper cannot move passively diffusive from the maternal serum to the fetus. Copper from maternal serum is deposited in the placental tissue and then transferred to the fetal tissue actively according to the needs of the fetal tissue. Increased levels of copper during pregnancy occur due to increased bonding with proteins. This increase occurs physiologically because

estrogen will induce ceruloplasmin synthesis during pregnancy.14 In anaemic pregnancies, ceruloplasmin is a compensatory mechanism. Ceruloplasmin bound to copper and transported through the placental tissue to maintain copper levels in the neonate.[29]

Copper levels in this study were 2144 µg/L in the preterm group and 2221 µg/L in the full term pregnancy. There was no significant difference between copper levels in both groups. The levels of copper in this study were above the normal average according to the National Academy of Science.[30]

In a study conducted in Jordan it was found that there was a significant difference between copper levels in the first trimester and the second and third trimesters. The results of this study showed that there was an increasing level of copper levels according to gestational age.[31]Another study conducted in India it was found that there was a relationship between gestational age with copper levels in the umbilical cord, but no relationship between gestational age and copper levels in maternal blood serum.[32]

CONCLUSION

In this study, it can be concluded that iron, selenium and copper levels in preterm and healthy pregnancy are within normal range, but zinc levels in preterm and healthy pregnancies are lower than the normal range. There is no significant difference between zinc, selenium, iron and copper levels in preterm and healthy pregnancies. However, due to a small number of subjects, we suggest to do further study with larger number of samples and examine the micronutrient levels in the placental tissue and umbilical blood cord to understand the mechanism of micronutrient transfer.

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Research Article

Severe Preeclampsia – Eclampsia and their Associated Factors

Preeklamsia Berat-Eklamsia dan Faktor-Faktor Terkait

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Abstract

Objective : : To analyse factors associated with severe preeclampsia and preeclampsia at Arifin Achmad General Hospital, Pekanbaru.

Methods : This was a cross-sectional study. Data on women who were diagnosed with severe preeclampsia or eclampsia and delivered between January 2014 and December 2015 were collected. These included maternal age, educational level, gestational age, delivery method, parity and ANC provider. Data were then analysed using chi-square test with multivariate logistic regression analysis.

Results : There were 3294 deliveries happened between January to December 2015. Prevalence of severe preeclampsia during the study period was 14.54%, and that of eclampsia was 3.28%. Mothers aged >35 have more than twice the risk of developing severe preeclampsia and eclampsia (95% CI 1.1- 4.6, p = 0.0001). Gestational age has the strongest association with eclampsia (Adjusted OR 2.4, p = 0.002, 95% CI 1.3-4.2). Severe preeclamptic-eclamptic mothers were at least five times as likely as the non-preeclamptic/eclamptic to have Cesarean Section or operative vaginal delivery (p = 0.0001).

Conclusions : Prevalence of severe preeclampsia was 14.54%, and that of eclampsia was 3.28% in the period between January 2014 and December 2015. Mothers aged >35 were three times as likely as those age ≤35 to develop severe preeclampsia-eclampsia, Term pregnancy had higher risk of severe preeclampsia-eclampsia compared with preterm pregnancy; however, preterm pregnancy has 2.4 times as likely as term pregnancy to develop a worsening severe preeclampsia/eclampsia. Finally, mothers with severe preeclampsia or eclampsia have a five times greater risk of having delivered via Cesarean Section or operative vaginal delivery compared to the non-preeclamptic – non-eclamptic ones.

Keywords : eclampsia, educational level, gestational age, parity, severe preeclampsia.

Abstrak

Tujuan : *Untuk menganalisa faktor-faktor yang berhubungan dengan preeklamsia berat dan eklamsia di RSUD Arifin Achmad Pekanbaru.*

Metode : *Penelitian ini merupakan penelitian potong lintang. Data yang diambil yaitu perempuan yang didiagnosis dengan preeklamsia atau eklamsia dan melahirkan pada Januari 2014 hingga Desember 2015. Usia ibu, tingkat pendidikan, usia kehamilan, metode persalinan, paritas dan pemberi layanan ANC juga disertakan. Data kemudian dianalisis menggunakan uji chi-square dengan analisis regresi logistik multivariat.*

Hasil : *Terdapat 3.294 kelahiran pada Januari 2014 hingga Desember 2015. Prevalensi preeklamsia berat selama penelitian ini yaitu 14,54% dan eklamsia sebesar 3,28%. Usia ibu>35 tahun memiliki risiko dua kali lebih besar untuk terjadinya preeklamsia berat dan eklamsia (95% CI 1,1- 4,6, p = 0,001). Usia kehamilan memiliki hubungan yang paling kuat dengan eklamsia (Adjusted OR 2,4, p = 0,002, 95% CI 1,3-4,2). Ibu dengan preeklamsia-eklampsia lima kali lebih besar untuk dilakukan seksio sesarea atau persalinan pervaginam dengan bantuan alat dibandingkan dengan pasien tanpa preeklamsia/eklamsia. (p = 0,0001).*

Kesimpulan : *Prevalensi preeklamsia berat adalah 14,54% dan eklampsia 3,28% pada periode Januari 2014 sampai Desember 2015. Usia ibu >35 tahun memiliki tiga kali lebih besar risiko untuk terjadinya preeklamsia-eklamsia. Kehamilan cukup bulan memiliki risiko lebih tinggi untuk terjadinya preeklamsia-eklamsia dibandingkan dengan kehamilan preterm; namun, kehamilan preterm memiliki risiko 2,4 kali lebih besar untuk mengalami perburukan preeklamsia/eklampsia dibandingkan pada kehamilan cukup bulan. Ibu dengan preeklamsia atau eklamsia memiliki risiko lima kali lebih besar untuk melahirkan dengan seksio sesarea atau pervaginam dengan bantuan alat dibandingkan dengan pasien tanpa preeklamsia atau eklamsia.*

Kata kunci : *eklamsia, paritas, preeklamsia berat, tingkat pendidikan, usia kehamilan.*

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INTRODUCTION

Preeclampsia, also known as 'Toxaemia of Pregnancy', is a hypertensive; multisystem disorder of pregnancy associated with vasospasm, increased peripheral vascular resistance and decreased in organ perfusions[1]. When a seizure or coma happened in severe preeclampsia, it is termed eclampsia. Being one of the major causes of perinatal morbidity and mortality, severe preeclampsia is still a challenging health problem to be dealt with in both developing and developed countries. In Indonesia, the incidence of severe preeclampsia ranges from 3-10%, of which 39.5% led to death in 2001 and 55.56% in 2002[2,3]. A research done in several hospitals in Jakarta showed that nulliparous has 78% higher risk of severe preeclampsia compared to multiparous women[2]. It also found that less educated women were more at risk compared to the moderate and highly educated ones[2]. Another research about severe preeclampsia in low and middle-income countries showed that sociodemographic characteristics and maternal age above 30 increased the risk of severe preeclampsia and eclampsia[4]. However, a research done using a small sample in our unit showed that there were no correlations among age, parity and the incidence of preeclampsia[5]. This study intended to analyse further on factors associated with severe preeclampsia and eclampsia at Arifin Achmad General Hospital, the tertiary referral teaching hospital in Pekanbaru, Riau.

METHOD

This was a cross-sectional study using database from the Department of Obstetrics and Gynecology at Arifin Achmad General Hospital, Pekanbaru. Further data collection was taken from medical records from January 2014 to December 2015. All pregnant women who were diagnosed with severe preeclampsia and eclampsia and gave birth at our department between those periods were recruited. We excluded those whose medical records were incomplete. Definition of severe preeclampsia was taken from WHO guidelines in 2011, which was the presence of increased in blood pressure ≥160/100, heavy proteinuria or substantial maternal organ dysfunctions[6]. These organ dysfunctions could present with varied features, which include eclampsia and HELLP syndrome (hemolysis, elevated liver function and low platelet count)[6]. Eclampsia was defined as the occurrence of generalised seizures in women with preeclampsia, provided that the tonic-clonic seizures are not attributable to other causes such as epilepsy[6]. The socio-demographic characteristics collected include maternal age and educational level. The maternal age was the age of the mother at the time of delivery. Educational level was divided into 4 levels: elementary school, junior high school, senior high school and bachelor degree. The obstetric factors analysed consisted of gestational age, delivery method, parity and antenatal clinic provider. Antenatal clinic provider would be categorised into midwives/community health centre and obstetricians/hospital. Research data obtained were recorded, tabulated and analysed using SPSS. Multivariate analysis was performed with logistic regression.

RESULTS

A total of 3294 deliveries happened between the periods of January 2014 – December 2015. Out of 3294 subjects, 479 were classified as severe preeclampsia, and 108 were of eclampsia, and 2707 (82.18%) patient was non-severe preeclampsia-eclampsia. In the period between January 2014 and December 2015, the prevalence of severe preeclampsia was 14.54 %, and that of eclampsia was 3.28%.

For the purpose of study analysis, 339 of the severe preeclamptic and 64 of the eclamptic group met the inclusion and the exclusion criteria. Control was taken at random from the non-severe preeclamptic – non-eclamptic group with the ratio of 1:1. Proportion of the sample can be seen in table 2.

Table 1. Proportion of Severe Preeclampsia, Eclampsiaand non-severe preeclampsia- non eclampsia

Characteristics		Non-Severe Preeclampsia and Eclampsia		Severe Preeclampsia and Eclampsia		OR	CI	*P-value*
		n	%	n	%			
Age	< 20	22	5.5	17	4.2	ref	ref	0.0001
	20-35	309	76.7	257	63.8	1.07	0.55 - 2	
	> 35	72	17.9	129	32.0	2.3	1.1 – 4.6	
Educational level	Bachelor	39	9.43	38	9.43	ref	ref	0.53
	Senior high school	199	49.38	182	45.16	0.9	0.5 – 1.4	
	Junior high school	93	23.08	110	27.3	1.18	0.69 - 2	
	Elementary school	73	18.11	73	18.11	1	0.57 – 1.7	
Gestational age	Aterm	312	77.42	296	73.45	1.2	0.9 – 1.7	0.19
	Preterm	91	22.58	107	26.55			
Parity	Multiparous	273	67.74	279	69.23	0.93	0.69 – 1.2	0.64
	Nullipara	130	32.26	124	30.77			
Antenatal care	Obstetricians	77	19.11	57	14.14	1.4	0.98 - 2	0.058
(ANC)	Midwives	326	80.89	346	85.86			
Delivery method	spontan	194	48.14	53	13.15			0.0001
	forceps	3	0.74	28	6.95			
	vacuum	54	13.4	54	13.4			
	caesarian	170	42.18	268	66.5			

When compared with the control group, mothers ages >35 have higher risk of developing severe preeclampsia and eclampsia compared to those ages <20 (95% CI 1.1- 4.6, p = 0.0001). Multivariate analysis using logistic regression model were done to find out which variable has the strongest association with severe preeclampsia and eclampsia.

Preeclamptic-eclamptic mothers were found to be at least five times as likely as the non-preeclamptic/eclamptic to have Cesarean Section or operative vaginal delivery (p = 0.0001). The final model was shown on the table below.

Table 2. Final Regression Model of Characteristic Association

Characteristics		OR	Adjusted OR	95% CI	*P-value*
Age	<20	ref	ref		
	20-35	1.07	1.3	0.65-2.5	0.447
	>35	2.3	3	1.4-6.4	0.004
Parity	Mutipara Primipara	0.93	1.27	0.91-1.7	0.152
ANC	Obgyn midwives	1.4ref	1.46	1-2.1	0.049

Final analysis showed that characteristic with the strongest association with severe preeclampsia-eclampsia was age >35. Mothers aged >35 were three times as likely as those age ≤35 to develop severe preeclampsia-eclampsia (Adjusted OR 3, 95% CI 1.4-6.4, p = 0.004). For ANC provider, even though p was <0.05, it was not considered clinically significant since the 95% CI included 1.

Sub-analysis was done among the characteristics to see if there was any difference between severe preeclampsia and eclampsia.

Table 3. Characteristic Differences between Severe Preeclampsia and Eclampsia

Characteristics		Severe Preeclampsia		Eclampsia		OR	CI	*P-value*
		n	%	n	%			
Age	< 20	12	3.5	5	7.8	ref	ref	0.34
	20-35	217	64.0	40	62.5	0.44	0.14 – 1.32	
	> 35	110	32.4	19	29.7	0.41	0.13 – 1.3	
Educational level	Bachelor	31	9.14	7	10.94	ref	ref	0.38
	Senior high school	159	46.9	23	35,94	0.64	0.25 – 1.6	
	Junior high school	88	25.96	22	34.38	1.1	0.43 – 2.84	
	Elementary school	61	17.99	12	18,75	0.87	0.31 – 2.43	0.0029
Gestational age	Term	259	76.4	37	57.8	2.3	1.3 – 4.1	0.49
	Preterm	80	23.6	27	42.2			
Parity	Multiparous	237	69.91	42	65.23	1.2	0.69 – 2.1	0.98
	Nullipara	102	30.09	22	34.38			
Antenatal care (ANC)	Obstetricians	48	14.16	9	14.06	1.008	0.46 – 2.1	
	Midwives	291	85.84	55	85.94			

In the sub-analysis comparing severe preeclampsia and eclampsia, the two groups were similar in characteristic profile except that the term pregnancy had higher risk of severe preeclampsia-eclampsia compared with the preterm pregnancy (p = 0.0029, 95% CI 1.3-4.1). Multiple logistic regression analysis was performed to control for any potential confounding variables and to find out which variable influenced eclampsia the most.

Table 4. Characteristic Differences between Severe Preeclampsia and Eclampsia

Characteristics		Severe Preeclampsia		Eclampsia		OR	Adjusted OR	*P-value*	95% CI
		n	%	n	%				
Age	<20	12	3.5	5	7.8	ref	ref	ref	
	20-35	217	64.0	40	62.5	0.44	0.406	0.406	0.12-1.33
	<35	110	32.4	19	29.7	0.43	0.39	0.39	0.1-1.51
Gest	Term	259	76.4	37	57.8	2.4	2.4	2.4	1.3-4.2
	Preterm	80	23.6	27	42.2				
Parity	Multiparous	237	69.91	42	65.23	1.08	1.07	1.07	0.54-2.09
	Nullipara	102	30.09	22	34.38				

Table 4 showed that gestational age had the strongest association with eclampsia (Adjusted OR 2.4, p = 0.002, 95% CI 1.3-4.2). Preterm pregnancy had 2.4 times as likely as term pregnancy to develop a worsening preeclampsia/eclampsia.

DISCUSSIONS

In this cross-sectional study, it was shown that the prevalence of severe preeclampsia was 14.54% and that of eclampsia was 3.28%. The prevalence of severe preeclampsia in Arifin Achmad General Hospital was higher compared to the national number, which was only ranging between 3-10%[2,3]. This fact may be due to Arifin Achmad being the tertiary referral hospital in the province of Riau. As a referral hospital, the obstetrics and gynecology department accepts referral mostly from midwives/community health care in the area.

Our study showed that there was an increase in the risk of severe preeclampsia and eclampsia in mother aged ≥35 (OR 2.3, 95% CI 1.1- 4.6, *p* = 0.0001). The logistic regression analysis further indicated that mothers aged >35 were three times as likely as those age ≤35 to develop severe preeclampsia-eclampsia (Adjusted OR 3, 95% CI 1.4-6.4, p = 0.004). This was in line with the previous secondary analysis done by World Health Organization (WHO) in low and middle-income countries[7]There are several hypotheses trying to explain about this obstetric risk factor, one of them being theory about ageing-related

vascular damage[8,9]. However, since 'age' is a risk factor that cannot be changed or modified, but can easily be identified during antenatal check-up, risk screening and a low threshold of referral to obstetricians at early stage could help reduce the incidence of severe preeclampsia/eclampsia and its adverse outcomes.

In this study, we found that term pregnancy had higher risk of severe preeclampsia-eclampsia compared with preterm pregnancy (p = 0.0029, 95% CI 1.3-4.1). Further multiple, multi-level regression analysis concluded that preterm pregnancy has 2.4 times as likely as term pregnancy to develop a worsening preeclampsia/ eclampsia (Adjusted OR 2.4, p = 0.002, 95% CI 1.3-4.2). Diagnosis of preeclampsia before 34 weeks not only elevates the rate of preterm birth, but it also increases adverse pregnancy outcomes[10].

A multicenter study done in South Australia reported that women with pre-existing hypertension, gestational hypertension and superimposed preeclampsia have high incidence of cesarean section[11]. We found similar results on the mode of delivery among the severe preeclamptic–eclamptic mother. Comparing with the non-severe preeclamptic–non-eclamptic group, mothers who suffered from severe preeclampsia or eclampsia have five times increased in the risk of having delivered via caesarian section or operative vaginal delivery (p = 0.0001).

We found no associations among severe preeclampsia-eclampsia and mother's educational level, parity, as well as ANC providers (p>0.05). These results were in contrast to the previous study done in selected hospitals in Jakarta, which described an increased risk of preeclampsia between the nullipara and those who have low education[2].

CONCLUSIONS

Prevalence of severe preeclampsia was 14.54%, and that of eclampsia was 3.28% in the period between January 2014 and December 2015. Mothers aged >35 were three times as likely as those age ≤35 to develop severe preeclampsia-eclampsia. Term pregnancy had a higher risk of severe preeclampsia-eclampsia compared with preterm pregnancy; however, preterm pregnancy has 2.4 times as likely as term pregnancy to develop a worsening severe preeclampsia/ eclampsia. Finally, mothers with severe preeclampsia or eclampsia have a five times greater risk of having delivered via Cesarean Section or operative vaginal delivery compared to the non-preeclamptic – non-eclamptic ones.

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Research Article

Maternal Mortality Rate at East Ogan Komering Ulu (East OKU) Regional Public Hospital Over a Four Year Period: Trends, Its Associated Factors and Neonatal Outcome

Angka Kematian Ibu di RSUD Ogan Komering Ulu Timur (OKU Timur) dalam Periode Empat Tahun : Pola, Faktor yang Berkaitan dan Luaran Neonatus

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Abstract

Objective : To determine the MMR trends, its associated factors, and neonatal outcome at East Ogan Komering Ulu Regional Public Hospital from 2013 until 2016.

Methods : This descriptive study was performed from January 2013 until December 2016 in maternity ward and Intensive Care Unit (ICU) of East Ogan Komering Ulu Regional Public Hospital, South Sumatera. Data were collected from medical records. There were 17 maternal deaths, but one was excluded due to lack of data.

Results : We recorded 2,191 pregnancies and 17 maternal deaths. Over four years, the lowest MMR occurred in 2013 (229/100,000) and achieved its peak in 2014 (1,306/100,000). Then, MMR followed a downward trend dropping from 1,087/100,000 in 2015 until 588/100,000 in 2016. Most of the deceased were childbearing age women (50.0%), multigravida (62.5%), but nulliparous (50.0%), and aterm (87.5%). The major aetiology of maternal deaths were hypertensive disorders (37.5%), followed by hypertensive disorders combined with haemorrhage and hypertensive disorders combined with infection in the same proportion. MMR was higher in inborn cases (87.5%), born via C-section (87.5%), and treated for less than 48 hours (93.75%). Alive neonatal were born in most cases (62.5%).

Conclusions : MMR trends in our hospital were fluctuating with a downward trend, but still much higher than the MDGs target in 2015 (102/100,000). Hypertensive disorder plays a significant role in maternal deaths. In addition, most of the neonates were born alive. We hope that this study can be feedback for the hospital to do maternal and perinatal audit.

Keywords : factors, maternal mortality rate, neonatal outcome, regional public hospital, trends

Abstrak

Tujuan : *Untuk menentukan pola, faktor yang berkaitan, dan luaran neonatus di RSUD Ogan Komering Ulu Timur dari 2013 hingga 2016.*

Metode : *Studi deskriptif dilakukan dari Januari 2013 hingga Desember 2016 di bangsal kebidanan dan unit perawatan intensif RSUD Ogan Komering Ulu Timur, Sumatera Selatan. Data dikumpulkan dari rekam medik. Terdapat 17 kematian ibu, tetapi 1 data dieksklusi karena data yang kurang lengkap.*

Hasil : *Terdapat 2.191 kehamilan, dan 17 kematian ibu. Selama 4 tahun, AKI terendah terjadi pada 2013 (229/100.000) dan mencapai puncaknya pada 2014 (1.306/100.000). Kemudian, AKI mengalami penurunan dari 1.087/100.000 pada 2015 hingga 588/100.000 pada 2016. Mayoritas sampel berusia reproduktif (50,0%), multigravida (62,5%) dan nulipara (50,0%), serta aterm (87,5%). Mayoritas kematian ibu disebabkan oleh hipertensi dalam kehamilan (HDK) (37,5%), diikuti oleh HDK + perdarahan dan HDK + infeksi dalam jumlah yang sama. AKI lebih tinggi pada ibu yang melahirkan di RS (87,5%), melahirkan melalui seksio sesarea (87,5%), dan dirawat selama kurang dari 48 jam (93,75%). Mayoritas neonatus dilahirkan hidup (62,5%).*

Kesimpulan : *Pola AKI di RSUD berfluktuasi dengan pola menurun, tetapi masih jauh lebih tinggi dari target MDGs pada tahun 2015 (102/100,000). Hipertensi dalam kehamilan berperan signifikan terhadap kematian ibu. Mayoritas neonatus dilahirkan hidup. Studi ini diharapkan dapat menjadi masukan bagi rumah sakit untuk melakukan audit maternal dan perinatal.*

Kata kunci : *angka kematian ibu, faktor, luaran neonatus, pola, rumah sakit umum daerah*

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INTRODUCTION

One of the Millenium Developmental Goals (MDGs) 2015 was improving maternal health with two specific targets and six indicators. Firstly, reducing Maternal Mortality Rate (MMR) by ¾ between 1990 and 2015. Secondly, achieving universal access to reproductive health. MMR was one of the indicators for predicting maternal health status. It was determined from the number of maternal deaths (during pregnancy, childbirth, or within 42 days of termination of pregnancy) during a given period per 100,000 live births during the same period. [1-4]

Maternal deaths were defined by WHO as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by pregnancy and its management, but not from accidental or incidental causes. Direct cause of MMR accounted for about 75-80 percent, consisting of hemorrhage (25.0%), infection/sepsis (15.0%), eclampsia (12.0%), unsafe abortion (13.0%), obstructed and/or prolonged labor (8.0%), and other (8.0%).[1,3,5-9]

Overall, South-East Asia had moderate mortality with moderate access, but Indonesia was one of the countries with high MMR in South-East Asia.[6] Therefore, the government took several strategic implementations for reducing MMR faster by taking clinical intervention and improving health access.[3,4] In 1987, safe motherhood initiative (ensuring all women got the appropriate treatment so that they could be safe and healthy during pregnancy and childbirth) was launched by WHO and other groups.[4,5] Then, in 1996, the government launched "Gerakan Sayang Ibu" programme which involved all governmental sectors. In 2000, the Ministry of Health launched Making Pregnancy Safer strategy.[4]

According to data from the Indonesian Demographic and Health Survey (SKDI) in 2012, MMR increased from 228 to 359 deaths per 100,000 live births. It was still far from MDGs 2015 target (102 deaths per 100,000 live births). Because of that, comprehensive-strategic interventions involving the government and society must be done in order to achieve that target. One of them was Expanding Maternal and Neonatal Survival (EMAS) programme which was launched by the Ministry of Health for decreasing MMR and NMR by 25%.[4]

In order to determine the magnitude of and trends in MMR, its associated factors, and neonatal outcome, we are motivated to conduct a study about MMR at East OKU Regional Public Hospital from 2013 until 2016.

METHODS

This descriptive study was performed from January 2013 until December 2016 in the maternity ward and Intensive Care Unit (ICU) of East OKU Regional Public Hospital, South Sumatera. Data were collected from medical records. All maternal deaths caused by pregnancy and its management were included in this study. Over four years period, there were 17 maternal deaths, but one was excluded when we analysed the maternal and neonatal variables due to lack of data. The total live birth during the corresponding year was also recorded. We described several maternal variables, such as age, gravida, parity, gestational age, diagnosis, delivery location, delivery method, and length of stay. In addition, only one neonatal variable was described, namely neonatal outcome. Then, all data were studied and analysed using Stata/MP 13.0.

RESULTS

The total number maternal deaths in 2013, 2014, 2015 and 2016 were 1, 7, 4, 5 corresponding to the total number of live births of 436, 536, 368, and 851 respectively. Over four years period, the lowest MMR occurred in 2013 (229/100,000) and reached its peak in 2014 (1,306/100,000). Then, MMR followed a downward trend dropping from 1,087/100,000 in 2015 until 588/100,000 in 2016. Hence, the mean of MMR during those years were 802.5/100,000 live births. *(See figure 1)*

In table 1, there were eight maternal variables described. The highest risk of MMR was among childbearing age women: 20-35 years old (50.0%) with the mean age of 29.9 years old. Moreover, most of them were multigravida (62.5%), but nulliparous (50.0%), and aterm: 37-42 weeks (87.5%). The major direct aetiology of maternal deaths were hypertensive disorders (37.5%), followed by hypertensive disorders combined

with haemorrhage and hypertensive disorder + infection in the same proportion (12.5%). The other five classifications, such as hypertensive disorder + obstructed labour, haemorrhage, hypertensive disorder + haemorrhage + infection, obstructed labour, obstructed labour + haemorrhage also had the same proportion (6.25%). The indirect aetiology found in our cases was acute myocardial infarct (6.25%).

Maternal deaths were higher in those who bore via C-section (87.5%) and inborn cases (87.5%). As much as 15 maternal deaths (93.75%) occurred within 48 hours of admission. From table 2, we could see that most neonates were born alive (62.5%).

Table 1. Maternal Variables of Maternal Mortality Rate

	2013	2014	2015	2016	Total (%)
Age					
< 20	0	1	1	0	2 (12.5)
20-35	0	5	1	2	8 (50.0)
> 35	1	1	1	3	6 (37.5)
Gravida					
Primigravida	0	3	2	1	6 (37.5)
Multigravida	1	4	1	4	10 (62.5)
Parity					
Nulliparous	0	4	3	1	8 (50.0)
Primiparous	0	1	0	3	4 (25.0)
Multiparous	1	2	0	1	4 (25.0)
Grandemultiparous	0	0	0	0	0 (0.0)
Gestational Age					
< 37 weeks	0	0	1	1	2 (12.5)
37– 42 weeks	1	7	2	4	14 (87.5)
> 42 weeks	0	0	0	0	0 (0.0)
Diagnosis					
HD	0	2	2	2	6 (37.5)
HD + H	0	2	0	0	2 (12.5)
HD + I	0	1	1	0	2 (12.5)
HD + OL	1	0	0	0	1 (6.25)
H	0	0	0	1	1 (6.25)
HD + H + I	0	1	0	0	1 (6.25)
OL	0	0	0	1	1 (6.25)
OL + H	0	1	0	0	1 (6.25)
Others (Acute Myocardial Infarct)	0	0	0	1	1 (6.25)
Delivery Location					
Unborn	0	0	0	1	1 (6.25)
Inborn	1	7	3	3	14 (87.5)
Outborn	0	0	0	1	1 (6.25)
Delivery Method					
Unborn	0	0	0	1	1 (6.25)
Spontaneous	0	0	0	1	1 (6.25)
C-Section	1	7	3	3	14 (87.5)
Length of Stay					
< 48 hours	1	6	3	5	15 (93.75)
>48 hours	0	1	0	0	1 (6.25)

Note:
HD : Hypertensive Disorders I : Infection
H : Hemorrhage OL : Obstructed Labor

Table 2. Neonatal Variables of Maternal Mortality Rate

	2013	2014	2015	2016	Total (%)
Neonatal Outcome					
Alive	1	5	2	2	10 (62.5)
Died	0	2	1	3	6 (37.5)

DISCUSSION

ur study showed that the mean of MMR in our hospital from 2013 until 2016 was about eight times higher than the MDGs target. This fluctuating MMR trends indicated a dynamic process probably associated with certain precipitating factors.[7]There were three delays which might correlate with high MMR. Firstly, delays in recognising an emergent situation and/ or seeking care to health practitioners. Secondly, delays in reaching appropriate care due to lack of access to transport or resources to pay for transport. Thirdly, delays in receiving appropriate care, including adequate quality of care, after arrival at a health facility.[5]

Childbearing age women were the greatest risk for maternal mortality in our hospital. In the age group < 20 years and > 35 years, there were 2 (12.5%) and 6 (37.5%) cases respectively. This was different from a previous study by Ujah IAO, et al (2005) which stated that the highest risk of maternal mortality was among early teenagers and older women.[7]The difference was probably because of the difference in sociodemographic characteristic. Moreover, we only analysed 4 years period, compared with 17 years period done by Ujah IAO, et al.[7]

We found that nulliparous was the most common group with high MMR, followed by primiparous and multiparous in the same proportion. Based on gravida criteria, most of the deceased were multigravida (62.5%). This study revealed that most women had abortion history, but no women died because of abortion. In contrast, historical trends in England and Wales from 1872-1876 and 1976-1981 showed that a small percentage (4.0-8.0%) of women died from abortion.[10]

During 2013-2016, our study revealed that direct cause plays a significant role in most cases of maternal death. This is similar to a previous study by Chakraborty S. and Kassebaum NJ.[1,8,11] The major direct causes of MMR in our

hospital were hypertensive disorder followed by hypertensive disorder + hemorrhage and hypertensive disorder + infection.

The largest proportion of maternal mortality in our study was those bore in health care facilities where the aetiology could be treated more comprehensively. This group delivered their babies by caesarean section due to their underlying medical conditions. This correlated with the previous study by Bauserman, M, et al who presumed that women were delivered by caesarean section due to the condition that put them in higher risks of death.[11,12]

Fifteen maternal deaths (93.75%) occurred within 48 hours of admission. This implied that most women came to seek medical care when their condition had already became serious.[7] Maternal death increased the risk of perinatal and neonatal death. However, in our study, we found that most of the neonates were born alive (62.5%). This difference was because we did not follow up the neonates prospectively.

The limitation of our study was that we did not record other factors which might contribute to MMR. For instance, education level, economic status, maternal nutritional status, antenatal care (ANC), timing of referral, access to health care, etc. Incomplete and manual medical record also limited us to conduct a thorough analysis regarding MMR. Through this study, we hoped that annual maternal and perinatal audits could be done.

CONCLUSION

MMR trends in our hospital were fluctuating with a downward trend and reaching its peak in 2014. It was still much higher than the MDGs target in 2015 (102/100,000). Because of that, Expanding Maternal and Neonatal Survival (EMAS) programme which was launched by the Ministry of Health must be reviewed and well-implemented in all over Indonesia, especially East OKU.

Direct cause plays a significant role in maternal deaths. Hypertensive disorder had the biggest proportion in our study. In addition, most of the neonates were born alive. Further analysis and complete medical records are needed in order to investigate the risk factors. We hope that this study can be feedback for the hospital to do maternal and perinatal audit

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Research Article

Elevated Serum Ferritin and Interleukin-6 Level are Risk Factors for Preterm Labour

Kadar Feritin dan Interleukin-6 Serum yang Tinggi Merupakan Faktor Risiko Terjadinya Persalinan Preterm

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Abstract

Objective : To investigate the association of serum ferritin and Interleukin-6 (IL-6) elevation as the risk factors for preterm labor.

Methods : This study was a case-control study conducted at the Obstetrics and Gynecology Outpatient and Emergency Department at Sanglah General Hospital Denpasar, Bali in November 2014 until June 2015. The sample selection was done by consecutive sampling with total sample as many as 20 case samples (women with preterm labor) and 20 control samples (women with normal preterm pregnancy).

Results : Based on the analysis, there was no significant difference of patient demografic such as age, gestational age, and parity among the two groups. Chi-square analysis showed that the increased serum ferritin level had 5 fold increased risk of developing preterm labor (OR = 4.89, 95% CI = 1.20-19.94; p = 0.022), and increased serum IL-6 level had 9 fold increased risk of developing preterm labor (OR = 9.33, 95% CI = 2.18-39.96; p = 0.001) compared to normal preterm pregnancy.

Conclusions : It can be concluded that level of IL-6 and serum ferritin was the risk factor for preterm labor.

Keywords : Interleukin-6, preterm labor, serum ferritin

Abstrak

Tujuan : *Untuk membuktikan hubungan kadar feritin dan Interleukin-6 (IL-6) serum yang tinggi sebagai faktor risiko terjadinya persalinan preterm.*

Metode : *Penelitian ini bersifat observasional dengan studi case-control yang dilakukan di Poliklinik dan IGD Kebidanan dan Penyakit Kandungan RSUP Sanglah Denpasar, yang dilakukan mulai bulan November 2014 hingga Juni 2015. Pemilihan sampel dilakukan dengan cara berurutan dengan sampel penelitian sebanyak 20 sampel kasus (ibu dengan persalinan preterm) dan 20 sampel kontrol (ibu hamil preterm normal).*

Hasil : *Tidak didapatkan perbedaan bermakna dari demografik pasien yaitu usia, usia kehamilan, dan paritas pada kedua kelompok. Analisa chi-square menunjukkan peningkatan kadar feritin serum memiliki peningkatan risiko 5 kali terjadinya persalinan preterm (OR = 4,90, IK 95% = 1,20-19,94; p = 0,022), dan peningkatan kadar IL-6 serum memiliki peningkatan risiko 9 kali terjadinya persalinan preterm (OR = 9,33, IK 95% = 2,18-39,96; p = 0,001) dibandingkan dengan kelompok ibu hamil preterm normal.*

Kesimpulan : *Kadar feritin dan IL-6 serum adalah faktor risiko terjadinya persalinan preterm.*

Kata kunci : *feritin serum, interleukin-6, persalinan preterm.*

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INTRODUCTION

Preterm labor causes complication towards the neonates due to the immaturity of the preterm babies, such as respiratory distress syndrome, anemia and retinopathy of prematurity, and systemic infection.[1] This correlates with the high number of Neonatal Mortality Rate in Indonesia which was 19 out of 1000 live births based on *Survei Demografi dan Kesehatan Indonesia* (SDKI).[2] The mortality and morbidity of preterm babies are relatively high despite the intensive care for neonates have been improved throughout the world. Early detection towards preterm labor is one of prevention that can be conducted, by detecting risk factor, evaluating cervical length, fetal fibronectin and also measuring biological and genetical marker.[3]

Various etiology of preterm labor have been identified, which one of them is the infection by the entrance of microorganism towards maternal body that initiates the inflammation cascade and increase the inflammation cytokines. This cascade will increase the level of prostaglandin and metalloproteinase that triggers the preterm labor.[4,5]Infection or inflammation will increase Interleukin-1 (IL-1) as the primary mediator, that initiates the other interleukin such as Interleukin-6 (IL-6), and also increase the translation of ferritin.[6] By evaluating the serum ferritin and IL-6 level as the inflammatory biomarker,the result from this study was designed to improve the early detection method towards preterm labor, that can prevent and decrease the preterm labor and also neonatal mortality rate.

METHODS

A case-control study was performed. The inclusion criteria for the case samples was pregnant women with preterm labor, while the control samples were pregnant women in preterm gestational age without sign of labor. Both group was evaluated for the serum ferritin and and IL-6 by obtaining venous blood. The exclusion criteria for both group were pregnancy with known congenital anomaly, cervical incompetence, maternal medical disorder, and history of previous threatened preterm labor in current pregnancy. This study was conducted in November 2014 until Juni 2015.

Samples were obtained in the Outpatient Department of Obstetrics and Gynecology and Emergency Department in Sanglah General Hospital Denpasar, Bali. The serum ferritin evaluation was using ELISA in the Immunology Laboratory, while the IL-6 examination was using the Interleukin-6 Kit in the Pathology Anatomy Laboratory. The cut-off point for serum ferritin value to be considered high was if elevated more than 22.5ng/ml, while the IL-6 value was if elevated more than 6.14ng/ml.

Data was collected and analyzed using SPSS for Windows version 17.0. Descriptive analysis of the demographic data was involving maternal age, gestational age, and parity. Normality of data was evaluated with Shapiro-Wilk, the homogeneity of data was using Levene's and the comparative was using T-independent test with correlation test was using Chi-square test.

RESULTS

There were 20 samples of preterm labor cases with 20 samples of normal preterm pregnancy without sign of labor, with demographic characteristics were presented in the Table 1 below :

Table 1. Demographic Characteristics of the Subjects

Characteristics	Preterm Labor (Case) (n=20)		Preterm Pregnancy (Control) (n=20)		*P-value*
	Mean	SD	Mean	SD	
Maternal age (yrs)	24.15	5.82	23.60	3.75	0.724
Gestational age (wks)	32.05	1.40	31.05	1.91	0.066
Parity	1.95	0.95	1.95	0.76	1.000

Table2. Correlation between Serum Ferritin Level and Preterm Labor

		Group		OR	95% CI	*P-value*
		Case	Control			
Ferritin	High	16	9	4.89	1.20-19.94	0.022
	Low	4	11			

Table3. Correlation between Serum IL-6 value and Preterm Labor

		Group		OR	95% CI	*P-value*
		Case	Control			
IL-6	High	16	6	9.33	2.18-39.96	0.001
	Low	4	14			

There was no significant difference for all characteristics between two groups, with p > 0.05 for each variable. Table 2 shows there was correlation between serum ferritin level with preterm labor, with 5 fold increased risk of developing preterm labor (OR = 4.89, 95% CI = 1.20-19.94; p=0.022) compared to samples with low serum ferritin level. Table 3 also show similar result for correlation between serum IL-6 level with preterm labor, with 9 fold increased risk of developing preterm labor (OR = 9.33, 95% CI = 2.18-39.96; p=0.001).

DISCUSSION

Serum ferritin level is hypothesized to be as one of the risk factors in preterm labor through the preceeding mechanism of inflammation or infection. The initial proinflammatory cytokines is IL-1, which its increasing value will also increase the translation rate of serum ferritin that is mediated by IL-1β, which also promote the number of free ferrous released from ferritin or mitochondria. This was the basis of hypothesis why ferritin also can act as inflammatory biomarker or acute phase reactant.[7]

Moreover, IL-1 also increass IL-6 level if the inflammation or infection occurs.[6,8] Interleukin-6 is the cytokines that envolve in the process of inflammation and infection, regulating the metabolic process, and also regeneration.[9]Local response in the inflammation area will initiate the systemic inflammatory response that is induced by neuroendocrine changes such as pain, and also the release of systemic mediator such as arginine, vasopressine, corticotropine, and insulin-like growth factor.[9]

The other research was reporting that IL-1 and TNF were high in the amniotic fluid of pregnant women with preterm premature rupture of membrane. This cytokines were produced by decidua that was exposed with endotoxin, and both of them will trigger the decidua and amnion to produce prostaglandin that finally will initiates preterm labor. The increasing level of IL-6 will also initiates the production of Metalloproteinase-9 (MMP-9), that will weaken the chorioamniotic layer which is prone to be ruptured due to degradation of collagen.[5]

Due to the role of IL-6 as the early biomarker in the inflammation cascade, the level of IL-6 is found to be increased after 3-4 hours exposure of endotoxin. As the result, in some research, the evaluation of IL-6 also used as the early detection for bacterial infection in neonates.[10]

CONCLUSION

The elevated level of serum ferritin and IL-6 were found to be the risk factor for preterm labor. As a consequechle, the evaluation of serum ferritin and IL-6 can be used for the early prediction of preterm labor. Thus the rate of preterm labor can be decreased, and the neonatal mortality rate can also be reduced.

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Research Article

Urinary Tract Infection as a Risk Factor for Preterm Delivery : A Tertiary Hospital-Based Study

Infeksi Saluran Kemih (ISK) sebagai Faktor Risiko Persalinan Preterm : Penelitian Berbasis Rumah Sakit Tersier

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Abstract

Objective : To investigate the correlation between the incidence of urinary tract infection (UTI) and preterm delivery.

Methods : We conducted a cohort retrospective research using patients medical records. We analysed the incidence of UTIandpreterm delivery from January to December 2015, in Dr. Sardjito Hospital, Yogyakarta.

Results : The sample of this study covers medical records of 45 patients with preterm delivery.From total sampel, only 25 patients (55.6%) underwent urinalysis. Of these 25 patients, 15 (60%) had UTIs and all of them had preterm delivery. The result showed that 13 (86.7%) of 15 patients with bacteriuriawere asymptomatic. Bacteriuria that was found in 15 subjects was not statistically significant when compared to preterm delivery indicatedwith relative ratio of 1,083 (p = 0.581 > 0.05). Multivariate logistic regression analysis showed that preterm delivery were not directly related to UTI (p = 0.704), gestational age (p = 0.274), symptom of UTI (0.699), history of UTI (p=0.999), and history of coitus (p = 0.872).

Conclusions : The study revealed that preterm delivery was not related to UTI. Other causes should be considered. Routine urinalysis test is recommended for pregnant women to prevent preterm delivery.

Keywords : bacteriuria, preterm delivery, UTIs.

Abstrak

Tujuan : *Mengetahui hubungan antara infeksi saluran kemih dengan kejadian persalinan preterm.*

Metode : *Penelitian ini merupakan penelitian kohort retrosprektif, menggunakan data rekam medis pasien. Analisis dilakukan terkait adanya infeksi saluran kemih pada pasien yang mengalami persalinan preterm, mulai bulan Januari sampai dengan Desember 2015, di RSUP Dr. Sardjito Yogyakarta.*

Hasil : *Sampel penelitian diambil dari data rekam medis 45 pasien dengan persalinan preterm. Dari seluruh sampel, hanya 25 pasien (55,6%) yang memiliki data pemeriksaan urinalisis. Dari 25 pasien ini, 15 (60%) dengan infeksi saluran kemih (ISK) serta persalinan prematur. Hasil urinalisis menunjukkan 13 (86,7%) dari 15 pasien adalah dengan bakteri uria asimtomatik. Bakteriuria yang ditemukan pada 15 subyek tidak bermakna secara statistik bila dibandingkan dengan terjadinya persalinan preterm, rasio relatif 1,083 (p = 0,581> 0,05). Analisis regresi logistic multivariate menunjukkan bahwa persalinan premature tidak terkait langsung dengan ISK (p-value = 0,704), usia gestasi (p-value = 0,274), gejala ISK (0,699), riwayat ISK (p = 0,999), dan riwayat koitus (p-value = 0,872).*

Kesimpulan : *Penelitian menunjukkan bahwa persalinan premature tidak terbukti secara statistik memiliki hubungan dengan kejadian ISK. Perlu dipertimbangkan penyebab lain. Pemeriksaan urin alisis rutin untuk perempuan hamil dapat dipertimbangkan sebagai upaya pencegahan persalinan preterm.*

Kata kunci : *bakteri uria, ISK, persalinan preterm*

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INTRODUCTION

Preterm delivery is the leading cause of perinatal morbidity and mortality in developing countries[1] Recurrent urogenital infections in pregnant women can cause preterm delivery. Yet, the correlation between asymptomatic bacteriuria and preterm delivery is still controversial.[1] Preterm delivery is defined as delivery before 37 weeks gestation. This term will be further divided into two, early and late preterm[2] Early preterm is defined as gestational age below 33 weeks, while gestational age of 34 until 36 weeks is called late preterm. Preterm delivery is the major cause of neonatal mortality. About 1 in 10 births in the US are preterm delivery, and 40% of preterm deliveries are caused by various kinds of infections[3] UTI is one of the infections that often occur in pregnant women[4].

UTI is a term that indicates the presence of microorganisms in urine[5]. Significant bacteriuria implies pure growth of microorganisms of more than 10^5 colony forming units (CFU / ml) in the urine culture. Significant bacteriuria might occur without causing any clinical symptoms of UTI. This condition is called asymptomatic (covert) bacteriuria. Conversely, significant bacteriuria with clinical presentation of UTI is called significant symptomatic bacteriuria[5]

A pregnant woman has a 2-10% risk of UTIs, where 20-40% cases are asymptomatic bacteriuria, 1-4% are cases of acute cystitis, even 0.5-2% is pyelonephritis. Cases of acute pyelonephritis are commonly found in the second trimester, with complications such as preterm delivery, low birth weight, preeclampsia, hypertension, kidney failure and fetal death[6] Many microorganisms cause symptomatic and asymptomatic infections which then cause preterm delivery, preterm rupture of membranes, or both. The most likely mechanism is the stimulation of bacteria by prostaglandins synthesis. This can happen through the phospholipase A2 and C pathway or as a result of bacterial endotoxins entering amniotic fluid that stimulate decidual cells, which in turn produce cytokines and prostaglandins that trigger preterm delivery. The indirect pathway that does not go through substances such as interleukin 1, tumour necrosis factor and platelet-activating factor, can be found in the infected amniotic fluid [7].

Meanwhile, according to Cuningham et al. 2014, it happened due to the ascending colonies of microorganisms in cervix, decidua, membrane, even up into the amnion. Lipopolysaccharide or toxins produced by the bacteria induces immune cells in the reproductive tract, production of cytokines by immune or cervix cells, decidua, and the membrane itself. It affects the myometrium and cervical effacement. Some microorganisms such as Gardnerellavaginalis, Fusobacterium, Mycoplasma hominis, and Ureaplasmaurealyticum were detected more frequently than other bacteria in the amniotic fluid of pregnant women with preterm delivery. This discovery proves that pathogenic bacteria can trigger preterm delivery[2].

UTI during pregnancy is a type of complicated UTIs. If left untreated, the presence of symptomatic bacteriuria potentially causes pyelonephritis, premature infants, anaemia, or pregnancy-induced hypertension. UTI that happened in the third trimester have risks such as mental retardation, slow infant growth, cerebral palsy, and fetal death[5]. In 2012, ACOG recommended screening for bacteriuria in the first antenatal visit. In the advanced state, the principle of management of UTIs in adult patients includes fluid intake, adequate antibiotics, and if necessary, symptomatic treatment for urine alkalinization[5]. This study investigates the correlation between the incidences of UTI and preterm delivery.

METHODS

This study was an observational study with retrospective study design. This design was used to find the correlation between the incidence of UTIs and preterm delivery. The study population was all pregnant patients who had symptomatic and asymptomatic UTI at the time of preterm pregnancy, which then had preterm delivery at Dr. Sardjito Hospital, from January to December 2015. The study was done by collecting data from the medical records of these patients. Researchers recorded all the data needed to support the research. Inclusion criteria in this study were patients with preterm delivery who suffer from symptomatic and asymptomatic UTI. Exclusion criteria were patients with premature rupture of membranes and or receive induction of labour. The dependent variable was patients with preterm delivery, and the independent variable was patients with UTIs. External variables

were history of UTIs, sexual history, and history of leukorrhea.

All the data was tabulated, continued by statistical analyses (statistical significance defined as $p < 0.05$). Data analysis was done using univariate, bivariate and multivariate analyses. In bivariate analysis, we assessed using Chi-square and in the last step was multivariate analysisusing logistic regression analysis. This research had received an approval letter from the ethics committee to conduct basic/clinical research at Dr. Sardjito Hospital / Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta.

RESULT

The study involved 45 of 47 medical records of patients who experienced preterm delivery in Dr. Sardjito Hospital from January to December 2015.

Table 1. Descriptive Statistics of Subject

Variable	n	Min	Max	Mean	SD
Age	45	16	43	26.289	6.851
Gestational Age	45	25	36	30.644	3.046
Birth Weight	45	525	2860	1539.98	589.49

The mean age of the patients was 26.29 ± 6.85 years; mean gestational age 30.64 ± 3.04 weeks; and mean birth weight 1539.98 ± 589.49 grams. Thirty-seven births were early preterm, and the remaining 8 were late preterm.

Tabel 2. Demographic Characteristic of Subject

Variable	Category	n	Percentage (%)
UTI	Bacteriuria	15	33.30
	Nonbacteriuria	30	66.70
Preterm Delivery	Early	37	82.20
	Late	8	17.80
High-Risk Pregnancy	Yes	12	26.70
	No	33	73.30
Symptom of UTI	Yes	5	11.10
	No	40	88.90
History of UTI	Yes	2	4.40
	No	43	95.60
History of coitus	Yes	6	13.30
	No	39	86.70

Out of 45 patients, only 25 patients (55.6%) underwent urinalysis (21 patients of early preterm delivery with gestational age less than 33 weeks, and 4 patients of late preterm delivery at gestational age 34 to 36 weeks). Of these 25 patients, 15 (60%) had UTIs and all of them had preterm delivery.Based on gestational age, there were 12 (26.7%) subjects were classified in high-risk pregnancy, and 33 (73.3%) were not. From 45 women who experienced preterm delivery, 40 subjects did not have any symptom while 5 subjects had symptoms. 95.6% subjects did not have any history of UTI.

Tabel 3. Chi-square Test

Variable		Preterm Delivery		RR	CI		*P-value*
		Early	Late		Low	Upper	
UTI	Yes	13 (28.9)	2 (4.4)	1.083	0.829	1.415	0.581
	No	24 (53.3)	6 (13.3)				
High-Risk Pregnancy	Yes	3 (6.7)	2 (4.4)	1.417	0.684	2.932	0.168
	No	34 (75.6)	6 (13.3)				
Symptom of UTI	Yes	4 (8.9)	1 (2.2)	0.970	0.612	1.537	0.890
	No	33 (73.3)	7 (15.6)				
History of UTI	Yes	2 (4.4)	0 (0)	0.814	0.706	0.939	0.501
	No	35 (77.8)	8 (17.8)				
History of Coitus	Yes	5 (11.1)	1 (2.2)	0.985	0.669	1.450	0.939
	No	32 (71.1)	7 (15.6)				

Bacteriuria found in 13 (28.9%) early preterm delivery and 2 (4.4%) late preterm delivery was not statistically significant when compared to preterm delivery with relative ratio of 1.083 (p-value = 0.581 > 0.05). The women who had high-risk pregnancy was not statistically significant when compared with those with preterm delivery with numbers relative ratio 1.417 (p-value = 0.168> 0.05). The number of the relative ratio indicated that those aged older than 35 years of age has the possibility to have early preterm delivery 1.4 times compared to late preterm delivery. 4 (8.9%) cases that were symptomatic founded at early preterm delivery, 1 (2.2%) cases founded at late preterm delivery with relative ratioof 0.970 (p-value = 0.890>0.05).

The relative ratio of 0.970 indicated that the probability of symptomatic UTI that provokes early preterm delivery and late preterm delivery was practically comparable. All subjects with a history of UTI were 2 (4.4%) cases, founded at early preterm birth had numbers relative ratio 0.814 (p-value = 0.501> 0.05). The number showed that the possibility between those with history of UTI in early and late preterm birth was equal. The correlation between preterm delivery with a history of coitus found 5 (11.1%) cases at early preterm delivery, and 1 (2.2%) case at late preterm delivery showed relative ratioof 0.985 (p-value = 0.939> 0.05). The relative ratio indicated that the odd from a history of coitus at early and late preterm delivery was compatible.

Table 4. Binary Logistic Regression Analysis

Variable	B	Sig.	OR	CI	
				Low	Upper
UTI	0.346	0.704	1.414	0.237	8.443
High-Risk Pregnancy	1.176	0.274	3.242	0.394	26.674
Symptom of UTI	-0.540	0.699	0.699	0.038	9.008
History of UTI	-20.069	0.999	0	0	-
History of Coitus	0.200	0.872	1.222	0.106	14.079

From multivariate logistic regression analysis, preterm delivery was not directly related to UTI (p = 0.704), gestational age (p-value = 0.274), symptomatic UTI (0.699), history of UTI (p-value=0.999) and history of coitus (p-value = 0.872). One study showed that patients with asymptomatic bacteriuria had a higher average of preterm delivery compared to patients with bacteriuria. About 40 to 80 per cent of pregnancy complications due to acute pyelonephritis can be prevented by treating asymptomatic bacteriuria[3].

DISCUSSION

Bacteriuria is one of the clinical problems which is quite serious in pregnancy. If left unhandled, can there are many such complications ascendent infection (pyelonephritis), the occurrence of premature rupture of membrane, preterm delivery, until infection in the neonate [9]. Prevalence of UTI diagnosis from the result of urinalysis reach 55.17% at this study. Another study obtained a diagnosis of UTI in reaching pregnancy 2.5%-8.7%. Maternal age is not is a risk factor significant in this study, where results it cannot be a role model due to lack of sample size [10].In a previous study, reported that the incident bacteriuria was associated with preterm delivery [11].In this study, the association between age pregnancy with bacteriuria not significant meaning. Parity has a relationship with the occurrence of bacteriuria on pregnancy. Multiple patient more risk 4.78 times to get findings of bacteriuria were compared with primigravida patients[10].From the results of this study, parity is not related directly with bacteriuria.

The findings of this retrospective study revealed that the average age of the patients with preterm deliverywas 26.29 ± 6.85 years which means none of the samples was in high-risk pregnancy according to their age.These findings are almost comparable with the earlier study done by Patel[1]. The result showed that 13 (86.7%) of 15 patients with bacteriuria were asymptomatic. In one study present that women with asymptomatic bacteriuria have higher preterm delivery incidence compared with women with symptomatic bacteriuria. Around 40-80% of pregnancy complications due to acute pyelonephritis can be prevented by giving therapy in asymptomatic bacteriuria.[3].

From multivariate logistic regression analysis, preterm delivery was not directly related to UTI (p-value = 0.704) which is different from the

findings of a study conducted by Patel[1]. Other factors such as age, symptoms of UTI, history of UTI, and history of coitus also showed no significant effect on preterm delivery. Moreover, the history of UTI had a number of odds ratio of0which indicated that it was not identified contributing any influence on preterm delivery.

The difference of the results in these two studies was likely due to the existence of other risk factors that have a more dominant influence to cause preterm delivery in each patient and required further investigation. These other risk factors include the history of previous preterm birth as the most common cause, history of vaginal discharge, examination of vaginal swab to diagnose bacterial vaginosis, current infection in the system and other organs such as periodontal disease, lifestyle, and possible genetic involvement.

The results showed unsatisfactory results because no significant variable effect on preterm delivery was found. The number of medical records data (45 observations) within one year (2015) is not sufficiently related to cases of preterm labour. Research should be developed further by extending the time of data collection in order to find more scientific results. Furthermore, consideringthat this study only comprised premature delivery (early and late delivery), the involvement of normal deliverycanclearly present the comparison between both normal and preterm delivery.

CONCLUSION

This study revealed that preterm delivery was not related to UTI. It should be considered some other causes. However, the discovery of asymptomatic bacteriuria in patients with preterm delivery indicated that this might be one of the risk factors for preterm delivery. A urinalysis should be performed routinely in every pregnancy for reducing the risk factor.

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Research Article

Factors Associated with Reproductive Age Couples' Selection of Sterilization in the Era of the National Health Insurance Program

Faktor – Faktor yang Berhubungan dengan Pemilihan Kontrasepsi Mantap pada Pasangan Usia Subur pada Era Program Jaminan Kesehatan Nasional

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Abstract

Objective : To assess factors associated with the selection of contraceptive sterilization in reproductive age couples in Dr. Mohammad Hoesin Palembang hospital in the era of National Health Insurance program.

Methods : This cross sectional study was conducted between January - December 2017. The study sample was reproductive age couples (RAC) who were married and came to P2 UGD, maternity room and midwifery ward of Dr. Mohammad Hoesin Palembang hospital and metour inclusion criteria. All study participants were given a questionnaire to assess factors that influence the selection of contraceptive methods in women. Data were analyzed using SPSS software version 17.

Results : We found a significant relationship between number of children (PR = 3.988; p-value = 0.016), knowledge level (PR = 3.893; p-value = 0.024) and husband support (PR = 5.233; p-value = 0.009) with sterilization contraceptive selection. In addition, there were no significant correlation between age (PR = 2.311, p-value = 0.210), education level (PR = 1.893, p-value = 0.331), woman attitude (PR = 1.567, p-value = 0.758), availability of contraception ((PR = 1.969, p-value = 0.342), officer attitude (PR = 1.088, p-value = 0.000) and information given by officer (PR = 1.378; p-value = 0.719) 1,310; p-value = 0.802) with selection of sterilization. With logistic regression test, we found that husband support was the most important factor to selection of sterilization contraception (PR = 4.266, p-value = 0.040) followed by knowledge (PR = 3.620, p-value = 0.041).

Conclusions : Sterilization selection in reproductive age couples at Dr. Mohammad Hoesin Palembang Hospitalis influenced by female knowledge and husband support.

Keywords : reproductive age couple, sterilization, tubal ligation, vasectomy

Abstrak

Tujuan : *Mengetahui faktor-faktor yang mempengaruhi pemilihan metode kontrasepsi mantap pada Pasangan Usia Subur di RSUP Dr. Mohammad Hoesin Palembang pada era Program Jaminan Kesehatan Nasional.*

Metode : *Penelitian potong lintang ini dilakukan antara Januari - Desember 2017. Sampel penelitian adalah pasangan usia subur (PUS) yang sudah menikah yang dating ke P2 UGD, kamar bersalin, dan bangsal kebidanan RSUP Dr. Mohammad Hoesin Palembang dan memenuhi kriteria inklusi. Semua peserta penelitian diberikan kuisioner untuk melihat faktor-faktor yang mempengaruhi pemilihan metode kontrasepsi pada perempuan. Data dianalisis dengan menggunakan SPSS versi 17.*

Hasil : *Pada penelitian ini didapatkan hasil terdapat hubungan yang bermakna antara jumlah anak (PR = 3,988; p = 0,016), tingkat pengetahuan (PR = 3,893; p = 0,024) dan dukungan suami (PR = 5,233; p-value = 0,009) dengan pemilihan kontrasepsi mantap. Selain itu, didapatkan hasil terdapat hubungan yang tidak bermakna antara usia (PR = 2,311; p-value = 0,210), tingkat pendidikan (PR = 1,893; p-value = 0,331), sikap ibu (PR = 1,567; p-value = 0,758), ketersediaan alat kontrasepsi (PR = 1,378; p-value = 0,719), ketersediaan SDM (PR= 1,769; p-value = 0,552) , alur rujukan (PR = 1,976; p-value = 0,342), sikap petugas (PR = 1,088; p-value = 1,000) dan informasi petugas (PR = 1,310; p-value = 0,802) dengan pemilihan kontrasepsi mantap. Dengan uji Regresi Logistik didapatkan hasil dukungan suami merupakan faktor yang paling berperan terhadap pemilihan kontrasepsi mantap (PR = 4,266, p-value = 0,040) diikuti oleh pengetahuan (PR = 3,620, p-value = 0,041).*

Kesimpulan : *Dukungan suami dan pengetahuan ibu merupakan faktor yang mempengaruhi pemilihan kontrasepsi mantap pada pasangan usia subur di Rumah Sakit Dr. Mohammad Hoesin Palembang.*

Kata kunci : *Kontrasepsi mantap, MOP,MOW, pasangan usia subur*

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INTRODUCTION

Population problem currently faced by Indonesia is high population growth rate. The expected population growth rate was 1.1% in 2014, but in fact rate of population growth rose by 0.4% from 1.45% (population census of 2000) to 1.49% (population census of 2010). High population growth rate will affect level of life and welfare of the population.

Projected number of reproductive age couples throughout Indonesia in 2012 reached 48.2 million. Only 61.9% of them use contraception. 57.9% using modern contraception and 4.0% using traditional contraception. Distribution of modern contraceptive methods in Indonesia is intrauterine device (IUD) 3.9%, tubal ligation 3.2%, vasectomy 0.2%, subdermal implant 3.3%, condom 1.8%, injection 31.9%, and pills 13.6%. Percentage of traditional contraceptivemethod in Indonesia is abstinence 1.3%, intercourse 2.3%, and other methods 0.4%.[1]Factors associated with low coverage of national family planning program are lack of contraceptives supply, lack of human resources and poorcontraceptive counseling quality, besides that government policy in each region is not equal.[2,3]

Many factors influence the selection of contraceptive methods. Lawrence Green analyzes human behavior from health level. These behaviors are defined or formed from three factors: predisposing factors embodied in characteristics, knowledge, attitudes, beliefs, values, etc; enabling factors, embodied in social environment, availability or unavailability of facilities or health facilities; and reinforcing factors embodied in support of the nearest person, supportive attitudes and behavior of health workers in providing health education.

Based on those facts, we are interested in examining factors associated with the selection of contraceptive sterilization in reproductive age couples in Dr. Mohammad Hoesin Palembang Hospital in the era of the National Health Insurance Program.

METHODS

This cross sectional study was conducted between January - December 2017. Study sample was reproductive age couples (RAC) in the age of 15 – 49 years old that were married and came to P2 UGD, maternity room and midwifery ward of Dr. Mohammad Hoesin Palembang hospital and met our inclusion criteria. Data was collected using a questionnaire. Research questionnaire contained questions about maternal characteristics (age, belief, number of children, education level), level of knowledge, woman's attitude toward contraceptive methods, availability of contraceptives, availability of human resources, referral flow, and information of family planning given by officers. Data were analyzed using SPSS software version 17.

RESULTS

During the study period, we included 106 women of reproductive age who met our inclusion and exclusion criteria. General characteristics of study subjects are shown in table 1.

Table 1. General Characteristics of Study Subjects

Characteristics	Groups			*P-value*
	Sterilization	**Non Sterilization**	**Total**	
Age (years), mean ± SD	31.44 ± 6.61	29.89 ± 7.15	30.15 ± 7.06	0.396[a]
Age, n (%)				0.210[b]
≤ 35	11 (61.1)	69 (78.4)	80 (75.5)	
> 35	7 (38.9)	19 (21.6)	26 (24.5)	
Residency, n (%)				0.082[b]
Downtown	6 (33.3)	52 (59.1)	58 (54.7)	
Suburban	12 (66.7)	36 (40.9)	48 (45.3)	

Education level, n(%)				0.353[c]
Uneducated	0 (0)	1 (1.1)	1 (0.9)	
Elementary school	5 (27.8)	22 (25.1)	27 (25.5)	
Junior high school	5 (27.8)	12 (13.6)	17 (16.0)	
Senior high school	5 (27.8)	41 (46.6)	46 (43.4)	
University	3 (16.6)	12 (13,6)	15 (14.2)	
Employment, n(%)				0.158[c]
Housewives	13 (72.1)	75 (85.2)	88 (83.0)	
Doctor	1 (5.6)	0 (0)	1 (0.9)	
Teacher	1 (5.6)	1 (1.1)	2 (1.9)	
Private employee	2 (11.1)	7 (8.0)	9 (8.6)	
Civil servant	0 (0)	3 (3.4)	3 (2.8)	
Farmer	1 (5.6)	1(1.1)	2 (1.9)	
Business	0 (0)	1 (1.1)	1 (0.9)	
Number of children, n (%)				
> 2	10 (55.6)	21 (23.9)	31 (29.2)	0.016[b]
≤ 2	8 (44.4)	67 (76.1)	75 (70.8)	
Total	18	88	106	

[a]*Independent T Test,* p= 0.05, [b]*Chi Square test,* p-value = 0.05, [c]*Pearson Chi-Square,* p-value = 0.05

In chi square analysis we found a significant relationship between the number of children with the utilization of sterilization (p-value = 0.016). Couples with more than two children were 3,988 times more likely to choose sterilization. We did not find any relationship between age and education level with the utilization of sterilization (p> 0.05) (Table 2).

There was a significant correlation between knowledge level and selection of sterilization (Table 2). Respondents with good knowledge level were 3.89 times more likely to choose sterilization compared to respondents with poor knowledge level (PR = 3.893; p-value = 0.024). There was also a significant relationship between husband supports with sterilization choice. Woman with supportive husbands 5.2 times more likely to choose sterilization (PR = 5.233; p-value = 0.009). There was no significant correlation between woman's attitude (p-value = 0.758), availability of contraception supply (p-value = 0.719), availability of human resources (p-value = 0.552), referral flow (0.342), officer's attitude (p-value = 1.000), and information given by officer = 0.802) with selection of sterilization.

Table 2. Relationship between Knowledge, Attitude, Availability of Contraception and Human Resources, Referral Flow, officer's Attitude, and Information Given by Officer with Selection of Sterilization

Characteristics	Group		Total	PR* (CI 95%)	*P-value*
	Sterilization	Non Sterilization			
Age					0.210
>35	7	19	26	2.311	
≤35	11	69	80	(0.789-6.772)	
Number of children					0.016
>2	10	21	31	3.988	
≤2	8	67	75	(1.394-11.408)	
Education level					0.331
High	10	35	45	1,893	
Low	8	53	61	(0.680-5.265)	
Knowledge					0.024
Good	8	15	23	3.893	
Poor	10	73	83	(1.318-11.500)	
Attitude					
Good	15	67	82	1.567	0.758
Poor	3	21	24	(0.413-5.943)	

Contraceptive supply					
Equipped	9	37	46	1.378	0.719
Unequipped	9	51	60	(0.499-3.808)	
SDM supply					
Available	15	65	80	1.769	0.552
Unavailable	3	23	26	(0.469-6.674	
Referral flow					
Easy	13	50	63	1.976	0.342
Complicated	5	38	43	(0.648-6.022)	
Officers attitude					
Good	11	52	63	1.088	1.000
Not good	7	36	43	(0.385-3.073)	
Officer Information					
Good	11	48	59	1.310	0.802
Poor	7	40	47	(0.465-3.692	
Husband support					
Yes	15	48	58	5.233	0.009
No	3	40	48	(1.444-19.357)	

*Fisher exact test, 95% CI

From the logistic regression test we found that woman's knowledge and husband support significantly influence sterilization choice. Respondents with good knowledge 3.62 times more likely to choose sterilization (PR = 3.620; p-value = 0.041) while woman with supportive husbands 4.266 times more likely to choose sterilization (PR = 4.266; p-value = 0.040). However, the number of children and age were not significantly associated with sterilization choice (p> 0.05).

Table 3. Factors Associated with Sterilization Choice

Variables	Unadjusted*		Adjusted**	
	PR	*P-value*	PR	*P-value*
Husband support	5.233	0.009	4.266	0.040
Knowledge	3.893	0.024	3.620	0.041
Number of children	3.988	0.016	3.156	0.059
Age	2.311	0.210	2.318	0.203

DISCUSSION

Female sterilization is a permanent female contraceptive method. Sterilization in women is done by binding or cutting or attaching a ring to both fallopian tubes that can be achieved by laparoscopy or minilaparotomy. Tubectomy or sterilization is a permanent and preferred way of contraception if women no longer wish for pregnancy.[4,5]

From 106 respondents in this study, only 34.9% used contraception. Sterilization is only selected by 17% of respondents. 65.1% of respondents refused to use contraception because they still wanted to have children, husband did not allow using contraception and pain/discomfort.

In this study subdermal implants were used by 16.7% of respondents, IUD by 44.4%, sterilization by 33.3% and vasectomy by 5.6% of respondents. Results of this study were in accordance with data of contraceptive use in Dr. Moh. Hoesin Palembang Hospital in 2013. It was reported that implants were used by 71 acceptors (7.1%), IUD by 687 acceptors (68.7%) and tubal sterilization by 241 acceptors (24.1%). While in 2014 implants were used by 25 acceptors (2.5%), IUD by 627 acceptors (62.7%) and tubal sterilization by 270 acceptors (27%).

There are three main factors that influence behavior. First is the predisposing factor that becomes the basis of behavior. Predisposing factors include knowledge, attitudes, beliefs, traditions, perceptions, and socio-demographic statuses such as age, education, number of families, tribes and incomes.[6]In this study there were no differences in age, age, residency, education and employment between groups.

We found a significant correlation between knowledge level and selection of sterilization. Respondents with good knowledge level were 3.89 times more likely to choose sterilization compared to respondents with poor knowledge level (PR = 3.893; p-value = 0.024). This resultis in accordance results of Ismail and Sisca's study in

Karangampel Kidul Village Indramayu. They found that respondents with good knowledge were 2.474 times more likely to choose sterilization. From our experience and study reports, we can conclude that behavior based on good knowledge will give a better resultsdue to high awareness, interest, and the existence of consideration and positive attitude.[7,8]

In this study we assessed availability of contraception and human resources, referall flow and information provided by officer as enabling factors. Based on statistical analysis, we did not found any significant relationship between availability of contraception (PR = 1.378; p-value = 0.719), and human resources (PR = 1,769; p-value = 0.552), referral flow (PR = 1.976, p-value = 0.342), and information provided by officer (PR = 1.310; p-value = 0.802) with sterilization selection.

Reinforcing factor is a factor that determines whether health measures receive support from close related person including health worker.6 In this study we did not find any significant relationship between information provided by the officers (PR = 1,310; p = 0.802) with sterilization selection. However, there was a significant relationship between husband support (PR = 5.233, p-value = 0.009) with sterilization selection.

Based on logistic regression tests, we found that the most contributing factor in contraceptive participation is the husband's support.Woman with supportive husbands was 4,266 times more likely to choose sterilization. Thus results were supported by Herlinawati et al (2012) that showed that there was a significant correlation between family support with sterilization participation in Pirngadi Hospital Medan (OR = 12.016; p-value = 0.001).[9]

Husband's participation is a manifestation of the husband's responsibility in women's reproductive health. Husband will participate if he receives full information. It is known that limited information on family planning and reproductive health has resulted in lower men/husbands' participation.[10,11]

Inability to communicate in the decision-making process puts a woman in a relatively low bargaining position, so that their needs and wants are difficult to achieve. Women's decisions tend to be dominated by her husband's interests, even if it is related to the survival of women themselves such as reproductive health problems.

In this study the husband's support is the main determinant of sterilization. 83.3% of women who chose sterilization received husband support; itwas 2 times higherthan women who did not choose sterilization (48.9%).

CONCLUSION

Sterilization selection in reproductive age couples at Dr. Mohammad Hoesin Palembang Hospital is influenced by female knowledge and husband support.

SUGGESTION

Acceptors husband needs to receive counseling about the benefits of female sterilization, and further research on the factors that affect the husband's support against sterilization is needed to reveal its effect on women sterilization selection.

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Research Article

The Association between Endometriosis Appearance during Laparoscopic Surgery and Pain Characteristic in Pelvic Endometriosis

Hubungan Tampilan Susukan Endometriosis pada saat Pembedahan Laparoskopik dengan Karakteristik Nyeri pada Endometriosis Pelvik

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Abstract

Objective : To evaluate the correlation between the American Society of Reproductive Medicine (ASRM) score in endometriosis and severity pelvic pain in a group of women with endometriosis.

Methods: A total of 131 patients with pelvic pain who: conduct laparoscopy for diagnosis and therapy of endometriosis, have pain symptoms>3 months, and absence of pelvic anomalies. Dysmenorrhea, deep dyspareunia, dyschezia, dysuria, and chronic pelvic pain were evaluated using a 10-point visual analogue scale. The data was collected by assessing the medical record, and retrospective analysis was performed. Disease stage according to the American Society of Reproductive Medicine, the presence of adhesion, lesion type (Deep Infiltrating Endometriosis (DIE) or without DIE), and severity of pain symptoms were analysed by Spearman analysis. Different VAS between DIE vs non DIE group was analysed by Mann-Whitney analysis.

Results : Stage IV endometriosis accounts for 79.4%. Based on the macroscopic appearance, ovarian endometriosis accounts for 92.4%, peritoneal endometriosis 82.4%, DIE was 40.5%, and adenomyosis was 19.1%. There was significant correlation between total ASRM, ovarian endometriosis, peritoneal lesion, Douglas pouch obliteration, adnexal adhesion score and VAS dysmenorrhea (r=0.303; 0.187; 0.203; 0.278; 0.266, p<0.05). There was significant VAS difference of DIE vs non DIE group; the difference was on dyspareunia (5.18±2.4 and 4.58±1.0, p<0.001] and dyschezia [5.28±2.2 and 4.86±0.7,p<0.001]

Conclusions : There was a positive correlation between ovarian endometriosis score and severity of dysmenorrhea. There was also a difference in the degree of endometriosis-associated pain between DIE and non DIE group.

Keywords : endometriosis, deep infiltrating endometriosis, dysmenorrhea, dyspareunia, dyschezia

Abstrak

Tujuan : *Untuk mencari hubungan antara skor endometriosis ASRM dan karakteristik nyeri pelvik pada pasien endometriosis*

Metode : *Sebanyak 131 pasien dengan nyeri pelvik yang menjalani laparoskopi untuk diagnosis dan terapi endometriosis, memiliki nyeri > 3 bulan, dan tidak mengalami kelainan organ pelvis. Dilakukan evaluasi terhadap dismenorea, dispareunia dalam, diskezia, disuria, dan nyeri pelvic kronik dengan menggunakan nilai 1-10 dari skala analog visual. Penelitian ini dilakukan di Rumah Sakit Umum Pusat Rujukan Nasional Dr. Cipto Mangunkusumo, Jakarta. Stadium endometriosis berdasarkan American Society of Reproductive Medicine, kejadian adhesi, jenis lesi (ada Endometriosis Susukan Dalam/ESD atau tanpa ESD), dan derajat keparahan nyeri dianalisis dengan analisis Spearman. Perbedaan skala nyeri antara ESD dan non ESD dianalisis dengan metode Mann-Whitney.*

Hasil : *Sebanyak 79,4% pasien tergolong ke dalam endometriosis stadium IV. Berdasarkan tampilan makroskopik, endometriosis ovarium terdapat pada 92,4%, endometriosis peritoneal 82,4%, ESD 40,5%, dan adenomiosis pada 19,1%. Terdapat korelasi positif bermakna antara skor ASRM total, sub-skorkista endometriosis, endometriosis superfisial, obliterasi kavum douglas, dan adhesi adheksa dengan VAS dismenorea (r=0,303; 0,187; 0,203; 0,278; 0,266, p<0,05). Pada kelompok ESD dan tanpa ESD, didapatkan perbedaan VAS dismenorea, dispareunia dalam, diskezia, dan nyeri pelvic kronik yang bermakna (6,13±1.7 dan 5,95±1,7, p = 0,560 ; 5,18±2.4 dan 4,58±1,0, p < 0,001; 5,28±2,2 dan 4,86±0,7 , p < 0,001; 2,20±2,8 dan 0,60±1,8, p <0,001)*

Kesimpulan : *Terdapat korelasi positif bermakna antara skor ASRM dengan VAS dismenorea. Terdapat perbedaan VAS dismenorea, dyspareunia dalam, diskezia, dan nyeri pelvic kronik pada kelompok ESD dan tanpa ESD*

Kata kunci : *endometriosis, endometriosis susukan dalam, dismenorea, dispareunia dalam, diskezia*

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INTRODUCTION

Controversies on the relationship between endometriosis stage, adhesion, lesion type, and severity of pelvic pain remain for years, even though clinical experience has connected those with the severity of pelvic pain. Endometriosis is characterised by the presence of endometrial tissue outside the uterine cavity that may cause pain and/or infertility.[1] Endometriosis is strongly associated with a decrease in the quality of life of women due to various problems it causes, such as endometriosis pain consisting of dysmenorrhea, dyspareunia, and chronic pelvic pain. Symptoms of the most common pain in endometriosis are dysmenorrhea, chronic pelvic pain, and deep dyspareunia.[2,3]In Dr. Cipto Mangunkusumo General Hospital, chronic pelvic pain account for 82.5% cases, dysmenorrhea 81%, and infertility 33.7%.[4]

The relationship between endometriosis and pelvic pain has been widely known, but the explanation of why this may occur is still not clear. Severe pain could be found in patients with mild endometriosis, but on the contrary, insignificant pain was found in patients with severe endometriosis. Therefore, based on the explanation above, the research was conducted to find the correlation between the appearance of endometriosis and the characteristics of pelvic pain. Endometriosis appearance includes American Society of Reproductive Medicine (ASRM) scores, adhesion events, Douglas pouch obliteration, and the presence of Deep Infiltrating Endometriosis (DIE). Especially for DIE, in addition to dysmenorrhea, will also be assessed for susceptibility to deep dyspareunia, chronic pelvic pain, dyschezia, and dysuria. This study is expected to clarify factors related to pain characteristics in endometriosis patients so that effective endometriosis pain management can be applied and deterioration in the quality of life of patients is preventable.

METHODS

This research used retrospective design with correlative analysis between two numeric variables. This research was done in Dr. CiptoMangunkusumoGeneral Hospital, Jakarta. Data entry was done by collecting data from the medical record from the subjects experienced laparoscopy procedure due to endometriosis from the year 2012 – 2016. Inclusion criteria were: women on reproductive age (18-40 years old) who did laparoscopy surgery from 2012 to 2016, and diagnosed as endometriosis from based on history taking, physical and supporting examination. Exclusion criteria were: had disease located on the uterus, adnexa, or another organ that could cause pelvic pain, for example, pelvic inflammatory disease, genital malformation, malignancy and the second exclusion criteria was being diagnosed as neurosis or psychiatric disorder.

This research used secondary data from the medical record completed by Gynecology residences who were in charge of Gynecology Clinic. On history taking, the patients were asked to classify the severity of pelvic pain using 1 to 10 Visual Analogue Scale (VAS) which described the most left side as the less pain and the most right side as the worst pain felt by the patients. Next step was data collection from laparoscopy operation report and video which showed intraoperative endometrial lesion characteristic. The researcher then took closer at each video and fulfilled the ASRM questionnaire to calculate the ASRM score with the detailed description of each lesion.

ASRM Questionnaire

American Society for Reproductive Medicine (ASRM) has introduced a classification system based on laparoscopic findings. The scoring depends on size, depth, location, and adhesion of the lesion with its surrounding structures.

Statistical Analysis

Statistical analysis was performed by using SPSS 23® software for MacBook® operating system. The analysis was done by bivariate analysis Spearman correlation test and Mann-Whitney test.

RESULTS

Subjects were those who had dysmenorrhea and underwent laparoscopy procedure in Dr. Cipto Mangunkusumo General Hospital in year 2012 – 2016. Total subject enrolled was 164, from which, 131 fulfilled inclusion criteria and were analysed.

In this research, the average age was 33.5 years old, 13 years old was the highest frequency of menarche, and average BMI was 22.8. 64.1% was included in infertility case (Table 1).

Table 1. Subjects' Characteristics

Variable	n	Proportion (%)	Mean (SD) Median	Min	Max
Age (years)	131		33.55(7,98)		
Parity			0.68	0	5
Menarche (years)			13	9	17
BMI (kg/m2)			22.8	14.3	36
Endometriosis associated pain					
Dysmenorrhea	131	100			
Deep dyspareunia	22	16.8			
Dyschezia	13	9.9			
Dysuria	1	0.8			
Chronic pelvic pain	31	23.7			
Severity of pain (VAS)					
Dysmenorrhea			6	2	9
Deep dyspareunia			5	3	7
Dyschezia			5	4	6
Dysuria			4		
Chronic pelvic pain			5	2	8
Macroscopic appearance					
Ovarian endometriosis cyst	121	92.4			
Peritoneal endometriosis	108	82.4			
Deep Infiltrating Endometriosis (DIE)	53	40.5			
Adenomyosis	25	19.1			
Endometriosis stage based on ASRM score	2	1.5			
Stage I (minimal)	3	2.3			
Stage II (mild)	26	16.8			
Stage III (moderate)	104	79.4			
Stage IV (severe)					
ASRM score description					
Total ASRM score			86.4(44.2)		
Ovarian endometriosis subscore			31.2(11.6)		
Peritoneal lesion subscore			6.2(5.3)		
Douglas pouch obliteration subscore			20.5(19.2)		
Adnexal adhesion subscore			28.5(20.7)		

All of the subjects included had dysmenorrhea, followed by chronic pelvic pain as the second most common endometriosis-associated pain (23.7%). Based on macroscopic appearance, 92.4% consisted of ovarian endometriosis cyst, 82.4% were peritoneal endometriosis, 40.5% were DIE, and 19.1% were adenomyosis. Majority cases (79.4%) were stage IV or severe endometriosis case. ASRM score was counted as total score and subscore. The subscore was divided into ovarian endometriosis, peritoneal lesion, Douglas pouch obliteration, and adnexal adhesion subscore.

Table 2 showed the correlation between ASRM score and severity of pelvic pain. There was a positive correlation between dysmenorrhea and any variable in ASRM score, the higher the score was, there were more severe pelvic pain with different degree of correlation. There was also a correlation between VAS dyspareunia and Douglas pouch obliteration, and chronic pelvic pain with peritoneal lesion.

Table 2. Correlation between ASRM score and severity of pelvic pain in VAS

Correlation[1]	r	*P-Value*
Total ASRM score and VAS of dysmenorrhea	0.303	<0.001
Ovarian endometriosis subscore and VAS of dysmenorrhea	0.187	0.032
Peritoneal lesion subscore and VAS of dysmenorrhea	0.203	0.02
Douglas pouch obliteration subscore and VAS of dysmenorrhea	0.278	0.001
Adnexal adhesion subscore and VAS of dysmenorrhea	0.266	0.002
Douglas pouch obliteration subscore and VAS of dyspareunia	0.195	0.026
Peritoneal lesion subscore and VAS of chronic pelvic pain	0.180	0.04

[1]*Spearman correlation test*

In table 3, there was a statistically significant VAS difference on deep dyspareunia, dyschezia, and chronic pelvic pain between DIE and non-DIE group. VAS comparison of dysmenorrhea, deep dyspareunia, dyschezia, and chronic pelvic pain were 5.18±2.4 and 4.58±1.0, p < 0.001; 5.28±2.2 and 4.86±0.7, p < 0.001; 2.20±2.8 and0.60±1.8, p <0.001.

Table 3. VAS difference between DIE and non-DIE group[2]

Variable	n	VAS dysmenorrhea		VAS deep dyspareunia		VAS dyschezia		VAS chronic pelvic pain	
		Value	P-value	Value	P-value	Value	P-value	Value	P-value
DIE	53	6.13±1.7	0.560	5.18±2.4	<0.001	5.28±2.2	<0.001	2.20±2.8	<0.001
Non DIE	78	5.95±1.7		4.58±1.0		4.86±0.7		0.60±1.8	

[2] *Mann-Whitney test*

DISCUSSION

In this study, the age of patients with dysmenorrhea with suspicion of endometriosis was age 30-39 years, i.e. 52%. A similar prevalence was found in a study conducted by Ferrero et al. who stated that age group 30-39 was the highest percentage of dysmenorrhea obtained with suspicion toward endometriosis, which was 52.9%.[5] In this study, the mean age of patients was 33.55 ± 7.98 years. A similar average was found in the Parazzini et al. study, which was 33.69 years.[6]

In addition to dysmenorrhea, infertility became a common complaint in endometriosis patients. In this study, 64.1% of patients came with a major complaint of infertility, the prevalence gained in this study is smaller than the prevalence obtained from Ferrero et al research that is 64.7%.5 This may be due to the Indonesia insurance referral system that makes endometriosis patients with infertility can be handled at a referral centre other than Dr Cipto Mangunkusumo General Hospital.

There was a positive correlation between the Douglas pouch obliteration subscore and VAS dysmenorrhea, dyspareunia, dyschezia and chronic pelvic pain with correlation coefficient (r) and p respectively, i.e., r = 0.31 and p <0.05; r = 0.366 and p <0.05; r = 0.328 and p <0.05; and r = 0.293 and p <0.05. Ideally, the classification of the macroscopic type of endometriosis should be endometrioma alone, peritoneal endometriosis only, and endometrioma together with peritoneal endometriosis. However, in this study it is difficult to find patients who have only one type of lesion, as more than 70% belong to the classification of stage IV ASRM that has a macroscopic variety of lesions, in one patient may be found endometrioma, peritoneal lesions, and DIE simultaneously. In addition, endometriosis lesions are more easily detected by ultrasound examination than peritoneal lesions or DIE, thus leading to laparoscopic action performed in patients with ovarian endometriosis lesions rather than patients with peritoneal lesions or ESD. Both of these can be biased in the study.

In the study of Kaya et al., it was explained that there is a possibility of pelvic adhesion more im-

portant than cyst diameter as the cause of pain. This is indicated by the large size of endometrioma unrelated to the extent of adhesion.[7]In a study conducted by Chopin et al. involving 239 patients stated that the degree of dysmenorrhea was not associated with endometriosis cysts, but more associated with DIE in the rectum.[8] Vercellini et al. also showed that dysmenorrhea is less common in endometrial cysts than in lesions at other sites.[9] Porpora et al. mention that there is an association between dysmenorrhea and endometriosis by univariate analysis, but this association is not available after adjustment for confounding factors, and further analysis indicates that the degree of pain was associated with adhesions in the ovarian fossa rather than the size of the cyst itself.[10]In addition, in the study conducted by Parazzini et al., there was no clear association between stage, location and morphological characteristics between pelvic endometriosis and pain.[11]

In the DIE and non-DIE groups, there were significant differences in deep dyspareunia, dyschezia, and chronic pelvic pain. Based on several studies, the mechanisms responsible for the severity of endometriosis-associated pain include the interaction between ectopic endometriosis implants, nociceptors, and nerve fibres. The most likely explanation of the relationship between symptom and location of pain was found in histological studies. DIE implants can infiltrate the surrounding tissues and cause subperitoneal nerve compression or infiltration.[12] In retro cervical DIE, this area is often exposed at the time of penetration, that can cause deep dyspareunia. In addition, endometriosis lesions have neurotropic properties associated with increased expression of nerve growth factor compared with peritoneal and ovarian implants.[13] Therefore, in laparoscopy, it is essential to conduct systematic explorations to see the presence of DIE and peritoneal endometriosis because both types of endometriosis can cause pain in the patient.

This study shows that with laparoscopy we can show that severe pain could occur in patients with low ASRM score and vice versa. For example, in bilateral endometriomas with a diameter of more than 3 cm, the ASRM score will be 40, but may not lead to a dominant pain complaint because pathophysiology of pain is associated with neurotrophic pain-causing fibres less commonly present in endometrioma. Severe pelvic pain is associated with DIE; however, the degree of depth of endometriosis does not affect the ASRM stage. This makes the ASRM scoring system does not always correlate with the severity of pain. Most endometriosis patients experience dysmenorrhea and dyspareunia, but some do not experience pain at all. This can be due to pain in endometriosis not only due to the presence or absence of nerve fibres but also determined by the type of nerve fibres or molecules present in endometriosis lesions. Several molecules can sensitise the nerve fibres so that the pain does not arise.[14]

The clinical implication of this finding is that if in anamnesis there is one of the deep dyspareunia, dyschezia or chronic pelvic pain, it must be followed up by a careful physical examination and then followed by laparoscopy by looking for lesions that are likely to cause pain such as adhesions in the fossa ovarian, DIE, and peritoneal lesions. If in anamnesis there is one of the deep dyspareunia, dyschezia, or chronic pelvic pain but in physical examination there is no DIE nodule, this may be due to the anatomical location of the lesion is difficult to reach with the fingers such as the nodule on the bladder or in the sigmoid which is located far from the anal canal, if it happens like this transvaginal ultrasound could be done.

CONCLUSION

Based on macroscopic appearance, 92.4% consisted of ovarian endometriosis cyst, 82.4% were peritoneal endometriosis, 40.5% were DIE, and 19.1% were adenomyosis. Majority cases (79.4%) were stage IV or severe endometriosis case. There was correlation between dysmenorrhea and any kind of variable in ASRM score, the higher the score was, there were more severe pelvic pain with different degree of correlation ($r = 0.31$ and $p < 0.05$; $r = 0.366$ and $p < 0.05$; $r = 0.328$ and $p < 0.05$; $r = 0.293$ and $p < 0.05$). There was also correlation between VAS dyspareunia and Douglas pouch obliteration, and chronic pelvic pain with peritoneal lesion ($r = 0.195$ and $p < 0.026$; $r = 0.180$ and $p < 0.04$). There was statistically significant VAS difference on deep dyspareunia, dyschezia, and chronic pelvic pain between DIE and non-DIE group (5.18 ± 2.4 and 4.58 ± 1.0, $p < 0.001$; 5.28 ± 2.2 and 4.86 ± 0.7, $p < 0.001$; 2.20 ± 2.8 and 0.60 ± 1.8, $p < 0.001$).

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Research Article

Estradiol Level and Psychosocial Stress in Perimenopausal Women

Kadar Estradiol dan Stres Psikososial pada Perempuan Perimenopause

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Abstract

Objective : To determine the relationship between estradiol levels and psychosocial stress in perimenopausal women.

Methods : Sixty perimenopausal included in a cross-sectional study from July to December 2016. Blood samples obtained from the women to measure the estradiol and the cortisol levels. Stress level measured with visual. Data presented as the mean and standard deviation (mean±SD) with p-value <.05 was considered statistically significant.

Results : There was no significant difference between the estradiol levels and the stress level (p=0.27) during perimenopause period. The estradiol levels were higher compared with the cortisol levels. The non-parametric correlations analysis show that the estradiol levels were not correlated with the cortisol levels (p=0.352). However, the cortisol levels were correlated with the stress levels (p<0.05).

Conclusions : Estradiol does not cause psychosocial stress during perimenopause period in our study population.

Keywords : estradiol, perimenopause, psychosocial stress.

Abstrak

Tujuan : *Untuk mengetahui hubungan antara kadar estradiol terhadap stres psikososial pada perempuan perimenopause.*

Metode : *Enam puluh perempuan perimenopause dilibatkan penelitian potong lintang dari Juli sampai Desember 2016. Sampel darah diperoleh dari perempuan untuk mengukur kadar estradiol dan kortisol. Tingkat stres diukur dengan visual analog scale (VAS). Data yang disajikan sebagai rerata dan standar deviasi (mean±SD) dengan tingkat kemaknaan 0,05.*

Hasil : *Tidak ada perbedaan yang signifikan antara kadar estradiol dan tingkat stres (p=0,27) selama periode perimenopause. Kadar estradiol lebih tinggi dibandingkan dengan kadar kortisol. Analisis korelasi non parametrik menunjukkan kadar estradiol tidak berkorelasi dengan kadar kortisol (p= 0,352). Namun, kadar kortisol berkorelasi dengan tingkat stres (p<0,05) perempuan perimenopause.*

Kesimpulan : *Estradiol tidak menyebabkan stres psikososial selama periode perimenopause pada populasi penelitian kami.*

Kata kunci : *estradiol, perimenopause, stres psikososial*

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INTRODUCTION

Perimenopause is a crucial transitional stage in a woman's life.[1] Perimenopausal stage usually begins at the end of age 40. Irregular of menstruation is an objective indicator to diagnose this period. The mean age of perimenopausal occurs at the age of 47.5 years and 51 years for menopause.[2] In perimenopausal period, there is an increase in FSH (follicle stimulating hormone), decreased inhibin levels, a slight increase in estradiol levels and change in luteinizing hormone (LH). In the last year before menopause, there is a decrease in estradiol levels below 40 pg /ml. Perimenopause period is the period which the FSH levels begin to increase until postmenopausal levels above 20 IU, and LH levels remain within normal levels even though menstruation still occurs. Seventy per cent of perimenopausal and postmenopausal women experience symptoms associated with estrogen deficiency, i.e., vasomotor, psychosocial symptoms such as depression, anxiety, sensitivity, sleep disorders and decreased libido.[3]

Perimenopause associated with increased mood changes for depressive symptoms and increases the early onset of depression.[4] There is research that states that during perimenopause

an increased risk of depression, including in women who have a history of depression. Alteration in estrogen levels results in depression. Perimenopausal estrogen levels affect mood and cognitive changes through alteration in acetylcholine and serotonin levels in the central nervous system. Estrogen is a steroid hormone that has a mechanism to increase the expression of genes in nucleus cells. There are two crucial estrogen receptors: alpha receptors that affect cognitive function, and beta receptors (β receptor) that affect the serotonergic system.

Estrogen regulates neuroendocrine, autonomy, and response to stress. Therefore, estrogen proved to regulate related functions of inflammatory processes, pain, anxiety, depression, and cognitive function.[5] Mood and cognition are affected by estrogen on the central nervous system. Estrogens increase serotonin levels by decreasing monoamine oxidase that metabolised the serotonin.[2]

Perimenopausal period is a long period so that it is important to comprehend the role of estradiol in psychosocial stress symptoms because mood changes and psychosocial stress can reduce the quality of life of women during this period. This study aims to determine the relationship between estradiol levels and psychosocial stress in perimenopausal women.

METHODS

A cross-sectional study was conducted in RS. Dr. Wahidin Sudirohusodo and affiliated hospitals at the Department of Obstetrics and Gynecology at Universitas Hasanuddin from July to December 2016. The study involved perimenopausal women with the criteria: aged 40-50 years, irregular menstruation and FSH levels>20 IU. Blood samples obtained from the women to measure the estradiol and the cortisol levels. Stress level measured with visual. The study protocol was approved by analogue scales (VAS). The study protocol was approved by the Health Research Ethics Committee of Medicine Faculty Hasanuddin University Makassar. Data presented as the mean and standard deviation (mean±SD) with p-value <.05 was considered statistically significant.

RESULTS

The perimenopausal women in the current study were 28(46.7%) aged 45-49 years old, 36(60%) multiparous, 40(67%) normal BMI and all of them were smokers. The characteristics of the perimenopausal women listed in Table 1.

Table 1. Subject Characteristics

Characteristics (N=60)	n	%
Age (years)		
40-44	21	25
45-49	28	46.7
>50	11	18.3
Parity		
Nulliparous	7	11.7
Primiparous	6	10
2-3	36	60
>3	11	18.3
Body Mass Index (kg/m^2)		
<18.5	8	13.3
18.5-25	40	66.7
>25	12	20
Smoking status		
Yes	60	100
No	0	0
Education (years)		
<9	10	16,66
>9	50	83,33

There was no significant difference between the estradiol levels and the stress level (p=0.27). The estradiol levels were higher compared with the cortisol levels (Table 2). Further analysis using the non-parametric correlations show that the estradiol levels were not correlated with the cortisol levels (p=0.352) (Table 3). However, the cortisol levels were correlated with the stress levels (p<0.05) (Table 4).

Table 2. Psychosocial Stress and Oestradiollevels

Psychosocial stress	n	Estradiol levels (mean±SDpg/ml)	*P-value*
Stress	30	76.1±97.6	0.27
Not stress	30	95.2±112.8	

Table 3. Correlation between Estradiol Levels and Cortisol Levels in the Perimenopausal Women

Variables	n	Mean±SD (pg/ml)	Median (pg/ml)	*P-value*
Estradiollevels	60	85.63±105.01	44.31	0.352
Cortisollevels	60	5.11±4.58	4.27	

Table 4. The Cortisol Levels and the Stress Level in the Perimenopausal Women

	n	Mean±SD	Median	*P-value*
Cortisollevels (pg/ml)	60	5.11±4.58	4.27	0.04
Stress level	60	18.32±5.58	19.5	

DISCUSSION

Stress occurs when an individual is under pressure beyond the adaptability. Stress is often caused by the surrounding environment which involves the ability of the individual to respond to any event that exceeds the capacity of the individual.[6]Estradiol levels affect the mood changes in perimenopausal women[7], and low levels of estradiol are one of the factors on depression in perimenopausal women. Transdermal estradiol administration may decrease depressive symptoms in perimenopausal women.[7]Heisler and colleague suggested that serotonin may affect the hypothalamic-pituitary-adrenal (HPA) axis through the 5HT2CR3 receptor as the receptor of corticotropin-releasing hormone (CRH) neurons in the brain.[8] In addition, the current study also shows no significant differences between estradiol levels and cortisol levels in perimenopausal women. Our result is consistent with a study by Avis that found no direct effect of estradiol with the depression in perimenopausal women. Perimenopausal women who experience depression is not caused by the direct effect of low levels of estradiol but due to vasomotor symptoms that interfere with the quality of life of women.[9]

The current study also shows that higher stress levels were correlated with cortisol levels in the study group. Otherwise produced by adrenals, cortisol is also produced by adipose cells by converting the inactivated 11β-Hydroxysteroid dehydrogenase type 1 (HSD11β1), and estrogens can up-regulate the expression of mRNA HSD11β1 in female adipose tissue.[10]The stress levels in the current study was comparing with the cortisol serum levels as hormonal stress, in addition, to interview using questionnaire. Combining this measurement, the results show that the level of stress measured with questionnaires significantly corresponds to the levels of cortisol.

Factors that affect psychological stress include smoking, body mass index, previous history of depression and hot flushes. In the current study, all the women not smoking and the previous history of depression was excluded. Smoking status can affect the onset of menopause. Study show women who smoke will experience early menopause.[11]

The limitations of the current study were blood sampling for the examination of the hormone estradiol performed only once. Hormone levels have a wide range of variability during the perimenopausal period so that the results might not be represented the true levels of estradiol in our study group. This limitation affects the current study findings that different from the previous studies.

CONCLUSION

In conclusion, the psychosocial stress during perimenopause was not affected by the estradiol levels.

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Research Article

The Role of Maternal Progesterone and Estradiol Levels in Predicting the Success of Induction of Labour : A Preliminary Study

Hubungan Kadar Progesteron dan Estradiol Ibu terhadap Keberhasilan Induksi Persalinan : Suatu Studi Pendahuluan

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Abstract

Objective : to evaluate whether maternal progesterone and estradiol levels could be used to predict the success of induction of labour (IOL).

Methods : This cross-sectional study was conducted at the Women's Health Clinic as well as the delivery suite of Dr. Cipto Mangunkusumo Hospital during the period of May 2016 to April 2017. Blood samples of term pregnant women who were indicated for IOL were obtained before birth.

Results : A total of 44 subjects were recruited in this study. Of these, 24 subjects had successful IOL while the other 20 subjects had IOL failure. There was no significant difference in progesterone among both groups (66,7% vs 75%, p=0,55). The estradiol levels in subjects who successfully performed induction had an average of 16,916.28 ± 2,574.75 pg/mL which did not differ significantly from the failed of induction group with estradiol levels of 14,832.24 ± 2374.47 pg/mL (p = 0,65).

Conclusions : We found no significant association between both maternal progesterone and estradiol levels and the success rate of IOL. Further studies with larger sample sizes are required to confirm whether progesterone and estradiol play pivotal roles in the success of IOL.

Keywords : estradiol, induction of labour, progesterone.

Abstrak

Tujuan : *mengevaluasi kadar progesteron dan estradiol ibu sebagai prediktor kesuksesan induksi persalinan.*

Metode : *Penelitian ini menggunakan desain potong lintang yang berlangsung pada bulan Mei 2016 hingga April 2017 di Poliklinik dan IGD Kebidanan Rumah Sakit Umum Pusat Rujukan Nasional Cipto Mangunkusumo. Pasien hamil aterm yang dilakukan induksi persalinan dan memenuhi kriteria penelitian akan diambil sampel darah sebelum persalinan.*

Hasil : *Dari 44 subjek yang mengikuti penelitian, 24 subjek berhasil dilakukan induksi persalinan dan 20 subjek gagal. Tidak terdapat perbedaan bermakna pada kadar progesteron Antara kedua grup (66,7% vs 75%, p=0,55). Kadar estradiol pada pasien yang berhasil dilakukan induksi memiliki rata-rata 16.916,28 + 2.574,75pg/mL yang tidak berbeda jauh dengan kadar estradiol pasien yang gagal induksi yaitu 14.832,24 + 2374,47pg/mL (p = 0,65).*

Kesimpulan : *Tidak terdapat perbedaan bermakna antara kadar progesteron dan estradiol maternal terhadap keberhasilan induksi persalinan. Penelitian lebih lanjut dengan jumlah sampel yang lebih besar dibutuhkan untuk mengkonfirmasi hubungan ini dengan lebih baik.*

Kata kunci : *estradiol, induksi persalinan, progesteron*

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INTRODUCTION

Induction of labour (IOL) is one of the most common procedures in modern obstetrics, performed in approximately 20% of all deliveries[1-3]. Despite being frequently performed, IOL does not always result in vaginal delivery, particularly when the cervix is not ready for induction[4,5]. Therefore, it is important to determine the most appropriate method to predict successful IOL and vaginal delivery.

Previously, the traditional method to assess whether induced labour will result in successful vaginal delivery is the Bishop's score. However, Bishop's score is subjective, and it is not accurate for predicting the outcome of labour induction[6-9], especially when the external ostium is closed[6,10]. In addition, the procedure of calculating Bishop's score is painful. By considering these limitations, the necessity of finding alternative measures to predict the success of IOL is obvious.

Progesterone and estradiol are considered essential hormones in the process of parturition. At term, human parturition requires an orchestrated set of hormonal and morphological changes within uterine tissues[11], some of which include up-regulation of myometrial progesterone A, estrogen α, prostaglandin, and oxytocin receptors. A decreased progesterone/estradiol ratio has been associated with successful labour[12].

To our knowledge, no studies regarding the role of progesterone and estradiol levels in predicting IOL successfulness have been conducted. We aimed to investigate whether maternal progesterone and estradiol could be used to predict the success of IOL.

METHODS

A cross-sectional study design was used. This study was conducted at Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, during the period between May 2016 and April 2017. Subjects were term pregnant women who were indicated to undergo IOL. Exclusion criteria were twin pregnancy and breech presentation. Maternal progesterone and estradiol levels were assessed immediately before birth in all subjects.

Blood sampling

Blood (5 mL) samples were collected by venipuncture of the brachial vein immediately before birth in all cases. Collected blood samples would be sent directly to a laboratory to assay serum analysis of progesterone and estradiol.

Statistical analysis

All statistical analysis was performed using SPSS 23 for Mac. Normally distributed continuous variables were compared using the Student's unpaired t-tests, while nonnormal distributed variables were compared using the Mann-Whitney*U* test. For categorical variables, the Chi-Square or Fisher's exact test was carried out as appropriate. *P*values less than 0.05 were considered statistically significant.

RESULTS

A total of 44 subjects were recruited in this study. Twenty-four subjects successfully induced labour, while 20 had induction failure. Maternal age, parity, and gestational age were similar among groups (Table 1). Statistical analysis revealed that cervical length and initial pelvic score differed among both groups (p = 0,02 and p < 0,01, respectively). We did not find significant difference between maternal progesterone and estradiol levels among both groups (p = 0,55 and p = 0,65, respectively) Types of induction, progesterone levels, estradiol levels, estimated fetal weight, amniotic fluid index, and the presence of anaemia, rupture of membranes, and severe preeclampsia were not significantly associated with the success of IOL.

Table 1. Baseline Maternal and Fetal Characteristics of the Subjects

Characteristics	Induced labour (n = 24)*	Induced labour (n = 24)*	*P-value*	OR (CI 95%)
Age (years)	31.08 +1.18	28.35 +1.13	0.11[D]	
Parity				
Nulliparous	12 (50%)	14 (70%)	0.18[B]	0.429 (0.12-1.49)
Multiparous	12 (50%)	6 (30%)		
Gestational age (weeks)	38 (37-41)	37 (37-41)	0.54[C]	
Methods of IOL				
Misoprostol	22 (91.7%)	19 (95%)	1.000[A]	0.58 (0.49-6.99)
Other (Foley catheter and oxytocin)	2 (8.3%)	1 (5%)		
Progesterone levels				0.67 (0.18-2.50)
>60 ng/mL	16 (66.7%)	15 (75%)	0.55[A]	
≤60 ng/mL	8 (33.3%)	5 (25%)		2084.03 (- 5097.28-
Estradiol levels	16.916.28 + 2.574.75	14.832,24 + 2.374,47	0.65[D]	9265.35)
Estimated fetal weight (grams)	2890.17 + 98.76	2813.15 +109.98	0.61[D]	
Amniotic fluid index	8.81 (7-32)	10 (5-19)	0.64[C]	
Cervical length (centimeters)	2.82 (1.8-3.56)	3.09 (1.8-3.49)	0.02[C]	
Initial pelvic score	2.5 (0-7)	1 (0-4)	<0,01[C]	
Anemia	5 (20.8%)	6 (30%)	0.484[B]	0.61 (0,16-2.42)
Rupture of membranes	17 (70.8%)	10 (50%)	0.16[B]	0.41 (0,12-1.43)
Severe preeclampsia	21 (87.5%)	16 (80%)	0.65[A]	1.75 (0.34-8.95)

*Categorical data are presented in frequency (percentage), while numerical data are presented in mean ± SD
[A]Using Fisher's exact test, [B]Using Chi-Square test, [C]Using Mann Whitney *U* test, [D]Using student's unpaired t-test

DISCUSSION

Several factors that affect the successfulness of IOL include maternal progesterone and estradiol levels, maternal age, gestational age, parity, body mass index, initial cervical dilatation, initial pelvic score, methods of IOL, amniotic fluid index, the presence of anemia, the presence of severe preeclampsia, doses of misoprostol, oxytocin, birthweight, and rupture of membranes[12-14]. In our study, we did not find significant association between maternal age, parity, gestational age, methods of IOL, estimated fetal weight, initial pelvic score, amniotic fluid index, anaemia, rupture of membranes, and severe preeclampsia, and the success of IOL. However, cervical length and initial pelvic score were significantly associated with IOL successfulness ($p = 0,02$ and $p < 0,01$, respectively).

In the present study, we did not find a significant association between progesterone level and the successfulness of IOL. This is in line with a previous study by Konopka et al[12]which reported that patients with high progesterone levels also achieved successful dinoprostone-induced labour. In viviparous species, progesterone withdrawal is a main trigger for parturition. In the majority of animals, parturition is preceded by a decrease in circulating progesterone levels mediated by hormonal interactions that inhibit progesterone production by either placenta or corpus luteum[15]. However, in human, parturition occurs without a decrease in systemic progesterone levels. Labour would still occur even if the myometrial cells are exposed to high levels of progesterone[16-18]. One possible explanation is that progesterone withdrawal in human parturition is partly mediated by changes in the relative levels of the nuclear progesterone isoforms, progesterone receptor-A (PR-A) and progesterone receptor-B (PR-B), in myometrial cells. When PR-A expression is elevated, it inhibits the anti-inflammatory actions of PR-B and stimulates-inflammatory gene expression in response to progesterone, which may result in labour[19].

Previous studies in women have found that one of the keys to initiation of parturition is local steroid hormone metabolism[20]. Estrogen, particularly estradiol, promotes labour by stimulating biochemical and physical changes in myometrial cells that affect uterine contractility and excitability. Numerous studies have suggested that estradiol increases the expression of genes in myometrium cells that promote synchronised contractions. In this study, although maternal estradiol level in the induced labour group was higher, it was not significantly associated with the success of IOL. This is in contrast to a previous study by Konopka et al[12] which found that higher estradiol level was linearly associated with the success of dinoprostone-induced labour. In pregnancy, the myometrium is exposed to high levels of estrogen in the forms of estradiol, estrone, and estriol for the majority of pregnancy. Prior to labour onset, systemic estrogen levels remain roughly the same[21]. Despite the high levels of circulating progesterone and estrogen levels during pregnancy, the levels of estradiol could decrease. This might occur due to changes in 17β-hydroxysteroid dehydrogenase (17βHSD) type 2.Cervical epithelium possessed high oxidative 17βHSD activity by efficiently converting estradiol to estrone. Increased 17βHSD type 2 expression in the cervical epithelia maintains elevated progesterone levels with a decrease in estradiol, similar to the steroid hormonal environment of the mouse cervix during the softening phase of remodelling. However, during parturition, 17βHSD type 2 was down-regulated, thereby leading to increased estradiol levels[21].

To this date, studies concerning the levels of estradiol prior to labour onset are scarce. We speculate the insignificant association between estradiol levels and the success of IOL is due to complex biomolecular interactions underlying the metabolism of estrogen and its receptors, particularly estrogen receptor □(ER□) and estrogen receptor β (ERβ). Progesterone may inhibit ERα and ERβ expression, which may prevent labour[22,23].

CONCLUSION

We find that both maternal progesterone and estradiol levels are not significantly associated with the success rate of IOL. Further studies with larger sample sizes are required to confirm whether progesterone and estradiol play pivotal roles in the success of IOL.

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Research Article

The Role of Genital Hiatus (Gh), Perineal Body (Pb), Summation (Gh+Pb) of POP-Q Examination in Maximum Levator Hiatal Area of Women with Symptomatic Pelvic Organ Prolapse

Peran Hiatus Genitalis, Badan Perineum dan Penjumlahannya dari Pemeriksaan Pop-Q pada Luas Area Hiatus Levator Maksimal pada Perempuan dengan Prolaps Organ Panggul Simtomatik

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Abstract

Objective : To provide data on the correlation of levator hiatus area measurements in symptomatic POP using 3D / 4D Ultrasound with clinical examination of Gh, Pb and summation (Gh+Pb).

Methods : Secondary data analysis of 160 POP patients examined from January 2012 to April 2017 at the Urogynecology Clinic of Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Patient characteristics, maximum 3D / 4D Ultrasound measurement of Levator Hiatus Area, and clinical measurement results using pelvic organ prolapse quantification system (POP-Q) were recorded.

Results : There was a positive correlation between clinical examination and measurement of hiatal area area using ultrasound with r = 0.43 for Gh length, and the medium correlation on the sum of Gh and Pb with r = 0,51. No correlation for Pb length with r = 0.23. The optimal cut to differentiate degrees 2 by 3 is 7.5 cm / 29.7 cm2 and degree 3 by 4 is 8.3 cm / 32.1 cm^2

Conclusions : Clinical examination by summing the lengths of Gh and Pb may be consider reflects the examination of the hiatal area by using transperineal ultrasound to see the strain on levator ani called "ballooning" in an area with limited resources.

Keywords : genital hiatus, levator hiatus area, pelvic organ prolapse, perineal body.

Abstrak

Tujuan : *Untuk memberikan data mengenai korelasi pengukuran area hiatus levator pada POP simtomatik mengunakan Ultrasonografi 3D/4D dengan pemeriksaan klinis yaitu panjang Gh, panjang Pb dan penjumlahannya.*

Metode : *Analisa data sekunder sebanyak 160 pasien POP yang diperiksa dari Januari 2012 hingga April 2017 di poliklinik Urogynecology Rumah Sakit Dr. Cipto Mangunkusumo (RSCM), Jakarta, Indonesia. Diambil data karakteristik pasien, pengukuran Ultrasonografi 3D/4D maksimal Area Hiatal Levator, dan hasil pengukuran secara klinis dengan menggunakan pelvic organ prolapse quantification system (POP-Q)*

Hasil : *Terdapat korelasi positif antara pemeriksaan klinis dengan pengukuran luas area hiatal menggunakan USG dengan r = 0,43 untuk panjang Gh, dan korelasi pada penjumlahan Gh dan Pb dengan r=0,51 termasuk kategori sedang, sedangkan untuk panjang Pb dengan r = 0,23 tidak didapatkan adanya korelasi. Didapatkan titik potong optimal untuk membedakan derajat 2 dengan derajat 3 adalah 7,5 cm / 29,7 cm2 dan derajat 3 dan derajat 4 adalah 8,3 cm / 32,1 cm^2*

Kesimpulan : *Pemeriksaan klinis dengan menjumlahkan panjang Gh dan panjang Pb dapat dipertimbangkan untuk mencerminkan pemeriksaan area hiatal dengan mengunakan USG 3 / 4 dimensi transperineal pada daerah dengan sarana terbatas untuk melihat regangan pada levator ani atau yang disebut sebagai "ballooning*

Kata kunci : *badan perineum, genital hiatus, hiatal levator ani, prolaps organ panggul.*

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INTRODUCTION

Pelvic organ prolapse (POP) is an abnormal descent of pelvic organs such as the uterus, bladder, urethra, and rectum from the normal position into the vagina or out of the vagina due to decreased function of the pelvic organ supporting system.[1,2] This support function results from interactions between the pelvic bone, muscles, ligaments, fascia and nerves.[2] POP is part of pelvic floor dysfunction, strongly associated with other pelvic floor disorder symptoms such as urinary incontinence, constipation, decreased sexual quality.[3,4] The incidence of pelvic organ prolapse in a study was 30.8% at age above 50 years. An American study found that 79-year-old women had an 11.1% risk for at least one POP surgery or urinary incontinence, with a possible 29.2% reoperation.[5,6] Based on studies in the United States, the operating costs for POP and urinary incontinence reached more than 1 billion dollars.[7] An increase in financing is also expected to occur, as it is estimated that over the next 30 years the number of women seeking treatment will double, as a result of age and lifestyle changes.[8]

The levator hiatus area is an area formed by the levator ani muscle that is strongly associated with prolapsed occurrence and is a potentially high-potential site or portal for the occurrence of POP and rectal prolapse.[9] It is also a central opening of the levator plate, which is known to be strongly associated with signs and symptoms of POP and risk for recurrence. There are several explanations that cause excess strain of levator hiatus or so-called ballooning due to congenital or acquired abnormalities. The existence of microtrauma for example over distention, due to hormonal effects on labor and because of the process of childbirth. Subsequent over distence leads to secondary avulsion of the puborectal muscle, where the muscle escapes from its insertion in the symphony bone. Prolapse of the anterior portion of the vagina or cystocele is the most common type of prolapse, and is the most persistent place and the highest incidence of recurrence.[10]

Vaginal delivery is a major risk factor for POP. A study found a mean peak pressure on the baby's head and pelvic floor when straining at 238.2 ± 82.4 mm Hg. Such pressure is potentially resulting in temporary or permanent strain or injury to maternal tissue. Avulsion levator ani occurs in 15-30% of women who deliver vaginally Avulsion is a risk factor for 'ballooning' (an abnormal hiatal area at Valsalva maneuver > 25 cm2) and is a risk factor for POP, especially in the anterior and middle compartments.[9,11]

In addition to avulsion, microtrauma or traumatic over distention leads to changes in levator hiatus biometry and boils down to POP.11 Damage to pelvic floor muscle structure during vaginal delivery eliminates the ability to keep the urogenital always closed, so that eventually the ligaments fail to retain the pelvic organs due to persistent intra-abdominal pressure.[12]

In 2005 Dietz HP et al found a significant association between pelvic organ mobility with levator hiatus area at rest and Valsalva maneuvers.[13] Their further study has suggested that measurement of levator ani distensibility is the most basic approach for determining the biomechanical properties of the muscle, and labor increases the distensibility of the levator ani hiatus, although without significant levator ani trauma. They also found that the levator hiatus area has a very strong statistical relationship with clinical symptoms of POP. Therefore, the distensibility of hiatus may be an independent etiologic factor of POP.[9] Rodrigues Jr AA et al found that the Levator Ani Subtended Volume (LASV) demonstrated a strong association with the increase in POP levels defined by POP-Q.[14] Punarbawa shows a correlation between the maximum of hiatal levator area and the degree of uterine prolapse, the optimal cut off point with the highest sensitivity and specificity was 28.5 cm2.[15]Santoso showed the optimal cut off point of the levator ani muscle area in distinguishing cystocele grade I-II and III-IV was 29 cm^2.The optimal cut of point of the levator ani muscle area in distinguishing rectoceles grade I-II and III-IV was 30 cm^2.[16] In addition to the ultrasound examination of the above-mentioned hiatal area, there is also a study by Khunda A et al linking the levator hiatal area with clinical examination of the sums of Gh and Pb where a 7 cm cutoff point is defined as an excessive strain of levator hiatus.[17] Gerges B et al states that the measurements of length of Gh and Pb can clinically determine the degree of excess stretching of levator hiatus without the need for ultrasound.[18] All of these clinical examinations were conducted in

Caucasian races and have not been studied in the Malay race.

The use of 3 and 4-dimensional ultrasound is ideal for assessing the morphology as well as the dimensions of the pelvic floor. The emergence of ultrasound 3 and 4 dimension provides an advantage in imaging, which can imaging the three areas of the body. This allows both qualitative and quantitative assessment of the pelvic floor support structure, the integrity of the levator ani muscle, the avulsion and in addition to the internal and external sphincters at the same time. Data at the time of examination can be saved and transfer for analysis and interpretation in the future.[19]

The use of Utrasound 3 and 4 dimensions to measure the hiatal levator ani preoperative area is the goal to determine the operating technique to be performed to reduce the genitals of hiatus, whether the use of mesh or the reduction of the genitals hiatus with zakarin levatorplasty.[20,21] Procurement of ultrasound 3 and 4 dimensions of course requires considerable funds and required special skills to assess the pelvic floor.[22] Not all hospitals in Indonesia have this facility. Pelvic floor examination with POP-Q is currently a common clinical examination to assess the degree of POP. The measurement sum of the length of the genital hiatus (Gh) and the perineal body (Pb) taken from clinical POP-Q examination can be to determine the degree of hiatal or ballooning strain that equivalent with ultrasound examination.[18]However, there is a research that shows the suitability of Gh length with the degree of weight of POP while Pb does not show a meaningful suitability.[23,24] Therefore, research needs to be conducted so that methods and techniques of clinical measurement of length of Gh, length of Pb and addition can be studied in relation to the area of hiatal levator and can be used for clinical benefit and used by many people in the future.

METHOD

This was a cross-sectional study, where the data source was from secondary data of medical record in POP patient in Urogynecology and reconstruction subdivision department of Obstetrics and Gynecology Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Data was taken from January 2012 to April 2017. Inclusion criteria were patients who underwent POP-Q examination, underwent transperineal 3D / 4D ultrasound and summation length of Gh and Pb. The POP diagnosis used in this study was a combined diagnosis which used the heaviest degree of the three compartments. Exclusion criteria were patients who could not doing valsava maneuver, pelvic organ malignancy, intra-abdominal tumor and had a history of pelvic surgery. Medical records of patients who have met the inclusion criteria will be taken secondary data of patients covering general patient data, clinical examination data in the form of POP-Q examination that has been done by trainees urogynecology with supervision from consultant urogynecology, and examination data of translabial 3D / 4D ultrasound done by one competent urogynecology consultant using GE Voluson E8 Expert BT09 (GE Medical Systems, Zipf, Austria) with 4.0-9.0 MHz convex volume probe RIC5-9-D (acquisition angle 1200).

All medical records of study subjects who have data of length Gh and Pb, and hiatal area data, although the other characteristic data are not included in the data analysis process. Numerical data is assessed by Kolmogorov Smirnov's assay for normality and with Coefficient of Variance (COV) calculations for its homogeneity. If the Kolmogorov Smirnov test produces p> 0,05 or COV <25% then the statistical calculation was done with parametric approach and presented as mean. Mean and Standard Deviation, whereas if it did not meet the requirement it is done with nonparametric approach and presented in median mean and ranges. Assessment of the relationship between two numerical variables was done by statistical correlation method based on Spearman test because the distribution was not homogeneous. Relationship with the value of correlation coefficient (R) above 0.3 followed by the determination of the regression formula. R values between 0.3 to 0.5 were included as weak relations categories, between 0.5 to 0.7 as moderate, and above 0.7 include strong relationships.[25]

The determination of the numerical variable intersection value to estimate the degree of POP was done by the Receiver Operating Curve (ROC) method to calculate the amount of Area Under Curve (AUC) as well as the sensitivity,

specificity, positive predictions, and negative predictions. The limit of statistical significance was used alpha value of 0.05. This research was proposed to the ethics commission at the Faculty of Medicine, Universitas of Indonesia, so that in the implementation meet the ethical clearance to conduct a research. All patient identities and research results are kept confidential.

RESULT

In this study, there were 237 initial samples, 77 samples were not performed pelvic floor ultrasound, and among 77 samples there were also prolapse patients already done operation as many as 8 samples. After screening and adjusted for acceptance criteria, 160 samples participated in this study. The results are presented descriptively and analytically.

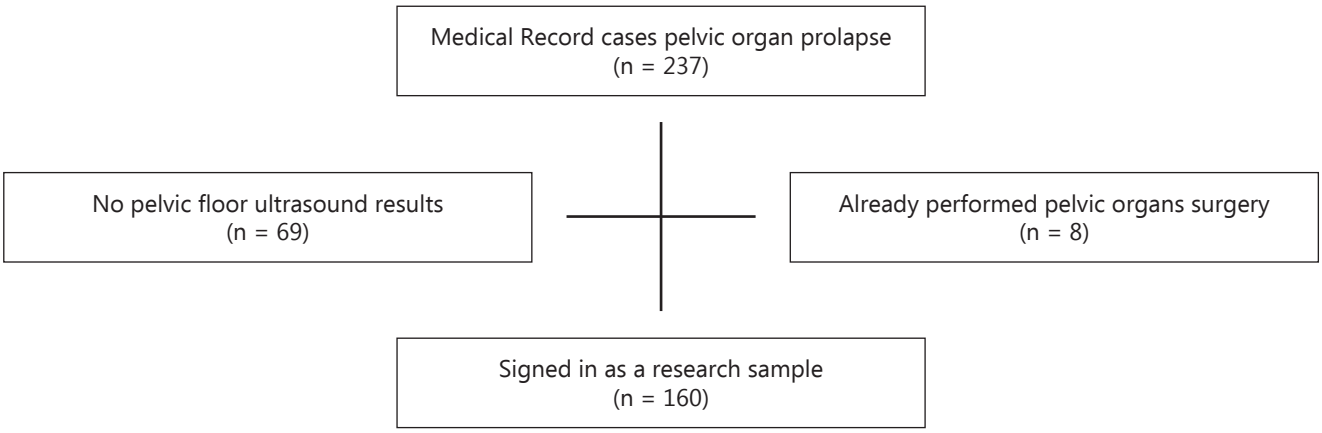


Diagram 1 : The process of collecting research data

Table 1. Distribution of Subjects According to the Characteristic.

Subject Characteristics	Frequency	%
Age group(n=160)		
< 50 year	32	20.0
50 – 59 year	56	35.0
60 – 69 year	48	30.0
70 + year	24	15.0
Mean and SD	X = 57.97	SD = 11.5
Body Mass index (BMI) (n=112)		
Normo (18 – 23)	39	34.8
Over (23 – 27)	46	41.1
Obese (> 27)	27	24.1
Mean and SD	X = 25.10	SD = 3.73
Parity (n=145)		
Nulipara	3	2.1
Primipara	7	4.8
Sekundipara	33	22,8
Multipara (3 – 5)	83	57.2
Grande multipara (> 5)	19	13.1
Median and Range	Med = 3	0 – 13
Delivery method (n=141)		
Spontaneus	131	92.9
Assisted delivery	8	5.7
C section	2	1.4
Mean and SD	X = 3531	SD = 504

Subject Characteristics	Frequency	%
Menopause status (n=121)		
Not yet menopause	29	24,0
1 – 5 year	22	18,2
6 – 10 year	25	20,7
11 + year	45	37,2
Median and range	Med = 9	0 – 25

From table 1, it was observed that not all characteristic variables of the subjects were recorded in the medical record under study. Only the age variable of the subject was fully recorded. Most subjects aged between 50 to 69 years covered 65.6% with a mean age of 57,97 years and standard deviation was 11,5 year. Nutritional status was only present in 112 subgroups with the overweight group until obese reached 65.2% with an average body mass index of 25.1 +/- 3.73. Data on parity rate reached 145 subjects with multi parity reaching 70.3% and median averages of 3 deliveries with a maximum of 13 births.

A total of 141 subjects had a record of the last delivery method and 92.9% were spontaneous labor with an average birth weight of 3351 +/- 504 grams. The history of menopause was recorded in 121 medical records with a majority of more than 5 years, which reached 57.9% with a median of 9 years and the longest reaching 25 years.

Table 2 shows that the degree of uterine prolapse majority in the central compartment at third degrees with 32.5% and at first degree as a asymptomatic reaches 15%. Based on the cystocele in the anterior compartment, it was also the third degree with 55.0% and there were normal subjects of 0.6% and the first degree was 1.9%. Rectocel in the posterior compartment gives normal conditions in 3,1% subjects and first degree at 7,5% while the majority was at second degrees with 67,5%.

After the merging of the highest degree of the three compartments, the majority was in the third degree with the number 53.1%. POP Abnormalities of urinary incontinence were recorded in 3.8% of subjects, while the majority did not experience avulsion which reached 90.6%.

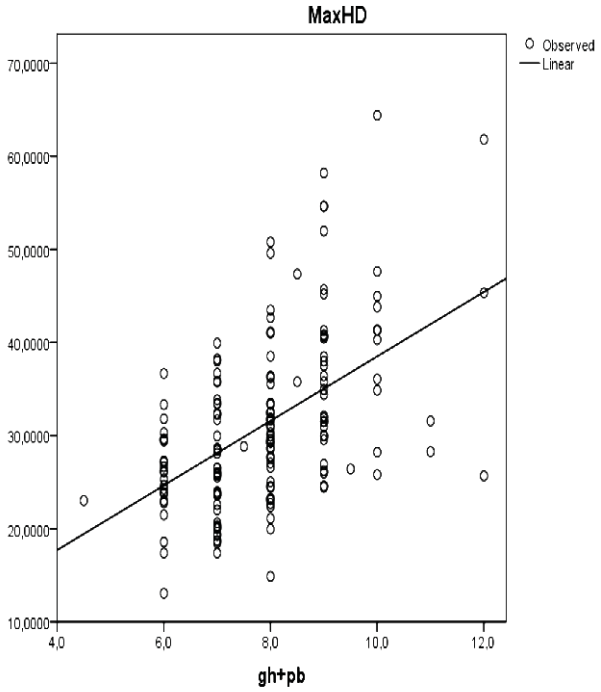
Table2. Distribution of Subjects According to Pelvic Organ Prolapse Conditions

Prolapse condition	Frequency	%
Uterine prolapse		
0 Degree	0	0.0
1st Degree	24	15.0
2nd Degree	45	28.1
3rd Degree	52	32.5
4th Degree	39	24.4
Cystocele		
0 Degree	1	0.6
1st Degree	3	1.9
2nd Degree	41	25.6
3rd Degree	88	55.0
4th Degree	27	16.9
Rectocele		
0 Degree	5	3.1
1st Degree	12	7.5
2nd Degree	108	67.5
3rd Degree	24	15.0
4th Degree	11	6.9

Prolapse condition	Frequency	%
Degrees by merge		
0 Degree	0	0.0
1st Degree	0	0.0
2nd Degree	32	20.0
3rd Degree	85	53.1
4th Degree	43	26.9
Incontinent		
no	154	96.2
yes	6	3.
Avulsion m. levator ani		
Negative	145	90.6
Unilateral	8	5.0
Bilateral	7	4.4

Correlation between Clinical Examination and Hiatal Area

Correlation between uterine prolapse component and hiatal area measured using Spearman methods because the distribution of hiatal area were not homogen. R value of spearman for correlation between Gh size and hiatal area can be categories as weak correlation with R=0.43. Regression formula may be used to predict hiatal area based on Gh value according to Gh number, however with the weak R value, there were high error deviation number. And there were no correlation between Pb value with hiatal area with R=0.23, so we cannot make the regression formula from this relationship.



R = 0,51 p = 0,000
Hiatal = 3,87 + 3,47 x (GH+PB)

Figure 1. Correlation between addition of Gh and Pb with hiatal area (n=160)

Figure 1 showed moderate correlation between combination of Gh+Pb with hiatal area that may reach R=0.51. Regression formula may be used to predict total hiatal area based on the combination of Gh+Pb may be used considering the accuracy of the formula that should also be considered.

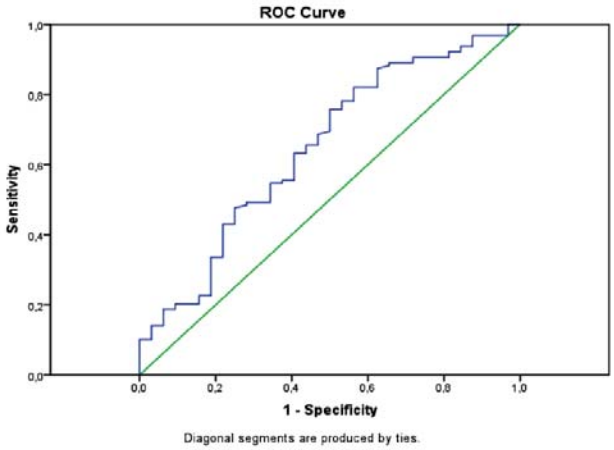


Figure 2. ROC curve from total addition of Gh and PB between 2nddegree and 3rd&4th degree

Area under the curve of this condition was 69.8% with confidence interval of 95% between 59.4% - 80.1%. The cut off point was observed to differentiate between 2nd degree and 3rd & 4th degree was 7.25 cm with sensitivity 64.8%, specificity 68.8%, positive predictive value 89.2% and negative predictive value 32.8%.

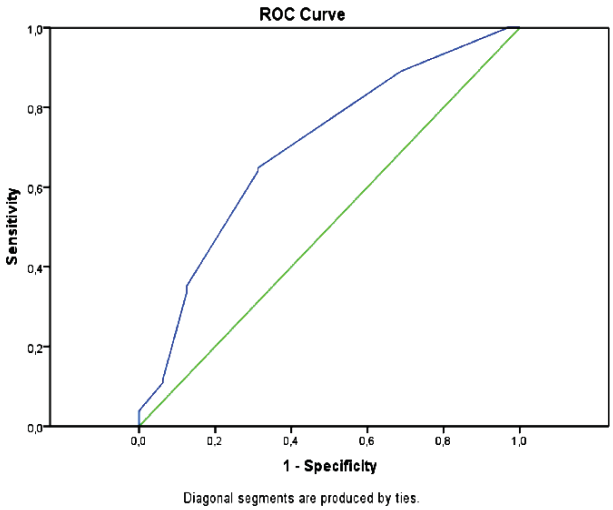


Figure 3. ROC curve with total hiatal area between 2nd degree and 3rd&4th degree

For hiatal area cut off point based on prolapse severity between 2nd degree and 3rd& 4th degree, the area under the curve was 64.7% with confidence interval 95% between 53.7% until 75.6%. It was found that the cut off point to differentiate 2nd degree and 3rd or 4th degree were 28.15 cm^2 with sensitivity 63.3%, specificity 59.4%, positive predictive value 86.2% and negative predictive value 28.8%.

Table 3. Cut off Point between Gh+Pb and Hiatal Area between Combined Prolapse

Prolapse severity	n	Mean	SD	95% CI		Cut of point
				Lower	Upper	
2nd degree	32					
GH+PB		7.14	1.23	6.75	7.53	
Hiatal		27.59	7.53	24.98	30.20	7.5
3rd degree	85					29.7
GH+PB		7.71	1.06	7.52	7.9	
Hiatal		31.21	9.49	29.19	33.23	8.3
4th degree	43					32.1
GH+PB		8.74	1.49	8.35	9.1	
Hiatal		33.65	8.73	31.04	36.26	

Table 3 demonstrated that the cut off point between 2ndand 3rd degree of prolapse and 3rd and 4thdegree of prolapse accordingly based on data distribution and overriding data calculated with 95% confidence interval. For Gh+Pb combined value we can find cut off point of 2nd and 3rd degree were 7.5 cm. For 3rd and 4th degree were 8.3 cm. For hiatal area, cut off point between2nd and 3rd degree were 29.7cm^2. Between 3rd and 4th degree were 32.1 cm^2

DISCUSSION

POP prevalence were higher in older population until it reach the fifth decade of female life, the prevalence relatively stable from the fifth decade onwards. Wu et al mentioned that 45 years old female may not showed any POP signs / symptoms until she reached 50 or 60 years old.[26] Tegersted et al, in 2005 did research in Sweden and found that the prevalence of symptomatic POP increased until the age of 60. In women aged 30-39, 40-49, and 50-59 found that the prevalence of POP were 4.1, 6.2, 11.8%. After that, the prevalence of POP remains constant. Between women age 60-69 and 70-79 years, the prevalence of POP were 12,2% and 11%. Using women aged 30-39 years old as a reference, Odd Ratio POP increased three folds after the age of 50 years old and remain the same in older generations.[27] The mean age in this research were 57.97 years old (range 26-80 years old)

Vaginal delivery caused pudenda nerve damage, levator ani muscle damage, and damage of the fascia surrounding the pelvic organ. Traumatic structural damage on the supporting facia and muscle during delivery was the main contributors of urinary incontinence and POP.[28] Dietz et al showed that spontaneous delivery increased the risk of POP more than three times the baseline level (OR 3.19; 95%, CI 1.07-9.49),

Assisted delivery increased the risk of POP more than 5 times of the baseline (OR 5.52; 95% CI 1.79-17.3) compared to C-Section[29] Parity may have significant correlation with dimension of hiatal area during Valsalva maneuver and this effect may have influence on the first delivery.[30] In this research, the mean number of parity are 3 dominated with vaginal delivery 92.9%, assisted delivery 5.75% and C-section 1.4%.

Santoso BI showed that dysfunction of the pelvic floor caused by biggest baby's weight, Receiver Operating Characteristic (ROC) curve found optimal cut off point of infant weight more than 3325 grams that may cause levator ani muscle trauma.[31] Different with Boyles, found vaginal delivery with baby weight more than 8 pounds (> 3600 grams) that may have significant relationship with urinary incontinence post partum.[32] In this research, found that baby's body weight during vaginal delivery was 3,531, 31gr (range between 2500- 5200 grams)

Obesity was one of the risk factor of emerging signs and symptoms of prolapse, even though it's relationship with objective measurement's not apparent. In SWEPOP research (Swedish Pregnancy, Obesity and Pelvic Floor), symptomatic prolapse organ may increase 3% with each increase of BMI (Body Mass Index) with OR 1.03; 95% CI 1.01-1.05.[33] There are some evidence that obesity is a strong risk factor for incidence and progressivity of urinary incontinence and incontinence alvi.[34] Chen et al stated that obese women was 4 times more likely to get urinary incontinence and 2 times more likely to get incontinence alvi compared to non-obese women.[35] From this research, BMI was 2.51 (range 18-39.1) was considered as overweight.

Many researchers made conclusion that menopause was one of the risk factor for POP. A research on 5489 women found that 454 of those with POP signs/symptoms showed an increasing prevalence of POP based on their age, the prevalence will not increase further after 60 years old.[36] Tegerdst et al found that the prevalence and risk factors of POP increased significantly after 60 years old and the prevalence was stable at those older than 60 years old.[26] Mothes et al in their research showed that in those that already had had menopause for more than 10 years that menopause is an independent risk factors for prolapse ($p<0.001$).[27] In this research, we found that the average length of menopause are 8.67 years and those that already had menopause >10 years in 45 samples (32.7%).

In combined diagnosis of POP we found that 2nd degree was found in 32 samples (20%), 3rd degree was found in 85 samples (53.1%), 4th degree was found in 43 samples (26.9%), there were no sample with non-prolapse and 1st degree, according to criteria, symptomatic prolapse were those that higher than 2nd degree.[28,29]

Avulsion (macrotrauma) and overdistention traumatic (microtrauma) were the most common etiology of POP.[11] Majida et al (2012) done research to compare the morphology and function of pelvic floor in 157 POP women with and without the defect of pubovisceral muscle. They found that he prevalence of major pelvic floor muscle defect's around 34%, similar with other research that showed prevalence between 21-37%. This finding was different with previous opinion by Shek (2009) that stated 15-30% of female that experienced vaginal delivery had levator ani trauma (avulsion).[11]In this research, we found that the incidence of avulsion in levator ani muscle's around 9.4%.

Urinary incontinence that's mainly stress incontinence have strong relationship with vaginal delivery.[30] In female Swedish population aged 20 years old during their first labor, found that vaginal delivery had significant relationship with degree of urinary incontinence severity (OR 1.68, 95% CI 1.40-2.03) and urinary incontinence problem (OR 1.85, 95% CI 1.42-2.39).[30] In cohort research in women between 5 years until 10 years after first labor. History of one or more vaginal delivery has significant relationship with odds of stress incontinence (OR 2.9, 95%, CI 1.5-5.5) but not with overactive bladder (OR 1.7, 95% CI 0.8-3.5). The effect of vaginal delivery in urinary incontinence mainly happened in postpartum periods. Different compared to the population in this research that's dominated with vaginal delivery in 92.9% with incidence of urinary incontinence was 3.8%. This supported Dietz that compared pelvic organ mobility in Caucasians with Asian we found that there's a difference in mobility in anterior compartment and posterior compartment that is smaller, and the central compartment remains the same.[31]

The correlation between Gh length and hiatal area showed the correlation coefficient was 0.43. This show weak but positive relationship between these 2 variables. Lowder et al in 2016 did a research that showed Gh length is a strong predictor of prolapse of apical structure with Gh length > 3.75 cm (ROC >0.8).[32] Khunda et al also showed positive correlation between Gh length and hiatal area with correlation coefficient of 0.52.[17]

Correlation between Pb length and hiatal area had correlation coefficient 0,24, this showed no relationship between these 2 variables. This results is the same with previous findings by Dunivan et al in 2015 that showed Pb length does not have any relationship with prolapse degree but Gh length have relationship with prolapse degree until it reached 3rd degree.[33]

Correlation between the total of Gh and Pb length with hiatal area had correlation coefficient of 0.51 showed that there are positive correlation with moderate relationship.[25] This research results was similar to those written by Khunda et al in the year of 2012 in which the total of Gh and Pb may have strong relationship with hiatal area (r=0.722). [17]We found formula to get the total hiatal area from clinical examination of summing Gh and Pb length was 3.87 + 3.47 x (Gh+ Pb), this formula may be used in area without 3D / 4D USG. The sensitivity results of this examination was 64.8% and indicates that the total of Gh and Pb length greater than 7.25 cm^2could show POP 3rd and 4th degree in 64.8% of cases. Specificity results showed that 68.8%, means that total of Gh and Pb <7.25 cm^2 may reveal 2nd degree of POP in 68.8% of case. The result of positive predictive value of 89.2% is higher compared than negative predictive value (32.8%). This result showed that clinical examination result of Gh and Pb total >=7.25cm^2 may predict 3rd and 4th degree POP with high accuracy, clinical examination results of Gh and Pb less than 7.25 cm^2 may have low predicting power of 2nd degree of POP, in other words the prevalence of grade 2 POP based on clinical examination may be in reality are undiagnosed 3rd and 4th degree of POP. This may be caused by multifactorial cause of POP, and hiatal levator area (reflexion from pelvic floor muscles)'s not only the main causing factors of POP. Anatomy of pelvic floor supporting muscle's divided into passive and active structure. Passive structure encompassed pelvic bones and supporting tissue such as ligament and endopelvic fascia, active supporting tissue encompasses pelvic floor muscle and the nerves that facilitates tonic contraction and contraction both voluntary and involuntary. Intermittent contraction. Active and passive component of pelvic floor function works as an integrated system that works with each other.[34] Other factors that may have important repercussions were the damage of supporting tissue (both the collagen and elastin). POP's closely related with a decrease in total collagen and the decrease of collagen solvability, an increase in intermediate intermolecular cross-links and advanced glycation cross links in prolapse tissue. Changes in collagen in prolapse tissue are four times more prevalent, this was clearly shown by matrix metalloproteinase and increased of collagenolytic activity that may in turn cause prolapse of tissue lose collagens. Fibroblast may decrease the collagen production in prolapse tissue; and an increase in the activity of MMP-1, 2 and 9 and a decrease of TIMP-1 activity may cause an increase in collagen turnover. Thus may cause the production of immature new collagen. Most of the researchers found that an increase type III collagen and a decrease of type 1 collagen, thus it may cause a decrease in type I/ type III collagen.[35]

Dietz conducted measurement of hiatal area during Valsalva on 544 women and classified the results to this following findings: mild 25-29.9 cm^2, moderate 30-34.9 cm^2, marked in 35-39.99 cm^2, and severe ≥ 40cm29 In a study conducted at Cipto Mangunkusumo Hospital, Jakarta, Indonesia, Punarbawa found that relationship between maximal area of levator hiatal area with degree of uterine prolapse, the optimal cut off point that have the highest sensivity and specificity was 28.5 cm^2.[15] Santoso showed that optimal cut off point to differentiate it with 1st-2nd degree and 3rd-4th degree of cystocele was 29 cm^2. Optimal cut off point of hiatal levator ani muscle that differentiate it with 1st-2nd degree and 3rd-4th degree of rectocele was 30 cm^2.[16] It is clearly shown that hiatal area that may differentiate 2nd degree and 3rd-4th degree was smaller in this research.

Research by Gerges et al showed that abnormal hiatal distention which is often called

as "ballooning" were divided into mild, moderate, marked and severe according to total Gh+Pb divided with mean hiatal area which lies between 7.0-7.99cm/ 27.3cm^2, 8.00-8.9 cm/ 27.3cm^2, 9.0-9.99cm/ 35.1cm^2 and>10cm/ 41.9 cm^2. This result was different from our findings which showed marked results in 7.5cm/ 29.7cm^2 and severe 8.3/ 32.1cm^2. We can see in this research that severe degree has more smaller result compare with western research, in accordance with Cheung et al that compared pelvic floor biometry and hip mobility in nullipara Caucasian and Asian women in Hongkong. It was found that Asian has significantly more dense puborectalis muscle, smaller genital hiatus and less mobile pelvic organ compared to Caucasian.[30] Many research also showed that in different ethnicity, the total hiatal area's also different, and less pelvic organ mobility if compared to Caucasian. Many research also showed that In different ethnicity, total hiatal area may be different from each other.[36,37]

The limitations of this study were primarily cross sectional using secondary data, where sample selection cannot be randomized nor blinding because prolapse degree can be estimated when the patient performed a Valsalva maneuver during pelvic floor transperineal ultrasound examination

CONCLUSION

Clinical examination by summing Gh and Pb length have moderate correlation level (R=0.51) with hiatal area examination using 3D or 4D USG examination that can be used in many health care facilities with limited facility.

RECOMMENDATION

More research needed to find hiatal area with low severity as a cut off point in asymptomatic and symptomatic patient, to complete data of pelvic organ prolapse in South-East Asian Race especially Indonesian race.

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Research Article

Postpartum Urinary Retention after Vaginal Delivery

Retensi Urin pada Pasien Pascasalin Pervaginam

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Abstract

Objective : To determine the incidence of postpartum urinary retention (PUR) after vaginal delivery and to specify any obstetric risk factors of PUR.

Methods : Case-control study. Six hours after vaginal delivery, urethral catheterisation was implemented for estimation of post-void residual bladder and diagnosis PUR. Patient data, including age, gestational age, body mass index, parity, mode of delivery, labour duration, perineal laceration or episiotomy, and fetal birth weight, were compared between women with and those without PUR to determine which obstetric factors that develop PUR.

Results : Of the 365 participants recruited, 38 (10,67%) had PUR: 33 (9,27%) with covert PUR and 5 (1,4%) with overt PUR. Women with perineal laceration or episiotomy (p<0,05), instrument-assisted delivery (p<0,05), first stage duration of labor more than 12 hours (p<0,05), second stage duration of labor more than one hour in multipara (p=0,041), and fetal birth weight more than 3800 grams (p<0,05) more prone to develop PUR.

Conclusions : The incidence of PUR were associated with several obstetric risk factors: perineal laceration or episiotomy, instrument-assisted delivery, first stage duration of labour more than twelve hours, second stage duration of labour more than one hour in multipara, and fetal birth weight more than 3800 grams.

Keywords : postpartum urinary retention, risk factor, vaginal delivery.

Abstrak

Tujuan : *Mengetahui angka kejadian retensi urin di kota Manado dan mengetahui faktor risiko obstetri yang berperan dalam terjadinya retensi urin pascasalin pervaginam.*

Metode : *Penelitian kasus kontrol. Dilakukan pemeriksaan residu urine 6 jam pascasalin pervaginam untuk mengetahui kejadian retensi urine. Data pasien yang diambil berupa usia, usia gestasi, indeks massa tubuh, paritas, jenis persalinan, durasi kala I, durasi kala II, laserasi perineum / episiotomi, dan berat badan lahir bayi kemudian dibandingkan antara yang menderita retensi urin dan tanpa retensi urin pascasalin untuk mengetahui faktor risiko obstetri yang berperan.*

Hasil : *Dari 365 sampel penelitian, 38 (10,67%) menderita retensi urin: 33 (9,27%) retensi urin asimptomatis dan 5 (1,4%) retensi urin simptomatis. Pasien dengan laserasi perineum / episiotomi (p<0,05), persalinan dengan bantuan instrumen (p<0,05), durasi persalinan kala I ≥ 12 jam (p<0,05), persalinan kala II ≥ 1 jam pada multipara (p=0,041), dan berat badan lahir bayi ≥ 3800 gram (p<0,05) memiliki risiko lebih tingi menderita retensi urin pascasalin pervaginam.*

Kesimpulan : *Kejadian retensi urin pascasalin pervaginam berhubungan dengan beberapa faktor risiko obstetri yaitu laserasi perineum / episiotomi, persalinan dengan bantuan instrumen, durasi persalinan kala I ≥ 12 jam, persalinan kala II ≥ 1 jam pada multipara, dan berat badan lahir bayi ≥ 3800 gram.*

Kata kunci : *faktor risiko, persalinan pervaginam, retensi urin*

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INTRODUCTION

Postpartum urine retention (PUR) is a common puerperal condition and is defined as the inability to (completely) urinate after childbirth.[1]The recent study (adopting Yip et al)[2] classified PUR as overt (symptomatic) and covert (asymptomatic). PUR overt defined as the inability to urinate spontaneously within six hours after delivery and require catheterisation. PUR covert defined as a post-void residual volume (PVRV) volume of 150 ml after spontaneous micturition.[3,4]The estimated incidence of PUR varies widely from 1,7% to 17,9% because of different definitions and diagnostic criteria.[5,6]

The precise pathophysiology of PUR is still unknown. However, it is likely to be multifactorial, including physiological, neurological, and mechanical processes in the postpartum period. It

is almost impossible to predict which patients will develop PUR; all patients on the postpartum ward should be considered to be at high risk; however, studies have identified several independent risk factors. These risk factors include prolonged first and/or second stage of labour, birth weight >3800 grams, and primiparity.[7,8] Mulder et.al[1] studies show that instrument-assisted delivery, regional anaesthesia, episiotomy, and nulliparity are statistically significantly associated with a higher incidence of overt PUR.

PUR can cause complications such as persistent bladder distension, uremia, and sepsis which may lead to death.[9] Persistent urinary retention may also cause irreversible detrusor muscle damage as well as recurrent urinary tract infections.[10,11]

METHODS

This study was conducted by a case-control study. The study population consisted of women who delivered between November 2017 to February 2018 that meet the inclusion and exclusion criteria. The inclusion criteria are normal or instrument-assisted vaginal delivery. Six hours after vaginal delivery, all of the participants that have agreed to follow the research and signed informed consent will be asked about postpartum voiding complaints and the measurement of residual urine with catheterisation.

PUR was defined as a post void residual volume more than 150 ml without any complaints and was classified as asymptomatic PUR (covert). Women with voiding complaints such as urinary difficulties, urinary dissatisfaction, pain and tension in the bladder are classified as symptomatic PUR (overt).

All samples were taken and recorded data including age, gestational age, parity, body mass index, mode of delivery, perineal laceration or episiotomy, duration of labour, and birth weight. The data obtained were then tested statistically and compared between those women who had PUR and those who did not.

Statistical analysis was performed using SPSS version 22.0. Normally distributed data were tested by Kolmogorov-Smirnov and presented as mean ± standard deviation. Quantitative variables are presented with the number (percentage). Statistical comparison performs by chi-square test ($\chi 2$), Fischer exact test, and Mann-Whitney U. The p-value <0,05 was considered statistically significant.

RESULTS

Table 1. Incidence of Postpartum Urinary Retention

Postpartum urinary retention	Frequency	Cumulative %
Absent	318 (89.33)	89.33
Present : Covert	33 (9.27)	10.67
Overt	5 (1.4)	
Total	356 (100)	100

There were 356 samples meeting the inclusion criteria, 38 samples (10.67%) had PUR and 318 samples without PUR (table 1). Of 38 women with PUR: 33 cases (9.27%) had asymptomatic PUR (covert), and 5 cases (1.4%) had symptomatic PUR (overt).

The demographics of cases and controls are shown in Table 2. The mean age was 26.58 ± 5.93 years in women with urine retention, and 25.70 ± 6.09 in those without urinary retention; the difference was not significant (p=0.996).

The mean gestational age in women with PUR was 38.71 ± 1.16 years, and 38.26 ± 1.73 years in women without PUR (p = 0.095). Mean body mass index (BMI) in women with PUR 27.49 ± 3.54 compared with body mass index of women without PUR 25.37 ± 3.46; statistically significant (p<0.05) (table 2).

Table 2. Demographic of Cases and Controls

Characteristic	Cases (n=38)	Controls (n=318)	*P-value*
Age (years)	26.58 ± 5.93	25.70 ± 6.09	0.996
Gestation (weeks)	38.71 ± 1.16	38.26 ± 1.73	0.095
BMI (kg/m^2)	27.49 ± 3.54	25.37 ± 3.46	<0.05

Table 3. Risk Factors Affecting PUR

Risk Factors	PUR (n=38)	No PUR (n=318)	*P-value*
Parity			
Primiparous	16 (42.10)	132 (41.51)	0,944
Multiparous	22 (57.89)	186 (58.49)	
Mode of delivery			
Instrument-assisted	9 (23.68)	9 (2.83)	<0.05
Spontaneous	29 (76.31)	309 (97.17)	
Perineal laceration			
Yes	38 (100)	202 (63.52)	<0.05
No	0 (0)	116 (36.48)	
First stage of labor			
≥ 12 hours	16 (42.11)	21 (6.60)	<0.05
< 12 hours	22 (57.89)	297 (93.40)	
Second stage of labour			
Primiparous			
≥ 2 hours	1 (6.25)	1 (0.76)	0.205
< 2 hours	15 (93.75)	131 (99.24)	
Multiparous			
≥ 1 hour	3 (13.63)	5 (2,69)	0.041
< 1 hour	19 (86.37)	181 (97.31)	
Birth weight			
≥ 3800 grams	21 (55.26)	12 (3.77)	<0.05
< 3800 grams	17 (44.74)	306 (96.22)	

The association between obstetric risk factors with incidence of PUR was presented in Table 3. Sixteen cases (42.10%) of primiparous women who had PUR compared with 132 cases (41.51%) of primiparous women without PUR; parity was not associated with PUR (p=0.944). Instrument-assisted delivery (p<0.05), perineal laceration (p<0.05), prolonged 1st stage of labor (p<0.05), prolonged 2nd stage of labor at multipara (p=0.041), and birth weight >3800 grams (p<0.05) there was a significant relationship with incidence of PUR.

DISCUSSION

The purpose of this study was to determine the incidence of postpartum urinary retention (PUR) after vaginal delivery in Manado and to specify any obstetric risk factors that contribute to PUR. In this study, the incidence of PUR was 10.67% (38/356), consisting of 9.27% covert PUR and 1.4% overt PUR. In the literature, the incidence of PUR varies, this was most likely due to inaccurate and varying definitions and the difference in the diagnostic criteria and treatment modalities.[12-14]

In the literature, many different obstetric risk factors have been considered for the pathogenesis of PUR such as parity, prolonged labour duration, perineal laceration, instrument-assisted delivery, macrosomic baby, labour induction, fundal pressure, epidural analgesia; however, the exact etiology of PUR had not been clearly identified.[8]

The incidence of PUR had been found to be higher in primiparous than in multiparous. In primipara, the risk of postpartum urinary retention increases as the group was at risk of prolonged labour duration, instrument-assisted delivery, or perineal laceration.[15] In a recent study and present study, parity was not a risk factor for postpartum urinary retention.[8]

This study found a significant relationship between instrument-assisted delivery and incidence of urinary retention. In labor with instrument-assisted delivery may cause urinary neurological disorders due to trauma to the nerves around the pelvis, in addition to labor with instrument-assisted occurs mechanical outlet obstruction resulting in perineal edema or direct trauma to the bladder.[15,16]

We also found out that the incidence of PUR was higher in women with perineal laceration or episiotomy. Pain from repair of episiotomy and perineal laceration may cause urethral spasm reflex, then cause urinary retention.[6] In cases with perineal laceration or episiotomy, prevention of PUR by reducing perineal repair pain with adequate analgesia.[17]

Prolonged duration of labor and large baby birth weight was also a risk factor for PUR. In labor with a large baby or macrosomia was associated with prolonged labor. Prolonged labor was a risk factor of trauma to the pelvic floor muscle due to continuous stretching, otherwise it can cause damage to the pudendal nerve resulting in neurological damage to the micturition.[8,16] In the case of prolonged labor, prevention of urinary retention by catheterization.[17]

The conclusions of statistical test results in this study showed that the risk factors that significantly influence the occurrence of postpartum urinary retention were instrument-assisted delivery (p<0.05), perineal laceration or episiotomy ($\chi 2=20.56$; p<0.05), first stage duration of labor ($\chi 2=66.33$, p<0.05), second stage duration of labor (p<0.05) and birth weight > 3800 grams (p<0.05),

whereas parity had no significant relationship to the incidence of urinary retention. This result was in accordance with previous studies from Mulder et al.[1] and a recent study by Kekre et al.[18] who investigated the risk factors for postpartum urinary retention after vaginal delivery. PUR was a condition associated with labor, but this relationship was not fully investigated. An early undiagnosed and untreated postpartum urinary retention event may lead to persistent urinary retention, irreversible detrusor muscle damage, urinary tract infection, and permanent urinary difficulties.[12] In addition, the risk of uremia and sepsis, even spontaneous bladder rupture may occur. By identifying obstetric risk factors, urinary retention can be prevented in those at risk and can be given appropriate therapy.[9] Many studies suggest that risk factors for urinary retention are primigravida, prolonged duration of labor, instrument-assisted delivery, perineal laceration, and baby birth weight.[15,18-20] Nevertheless these risk factors affect each other and not stand alone so that when tested with strict control, then certain risk factors are more significant than others.[21] After vaginal delivery, there are changes in mucosal congestion, submucosal hemorrhage, especially in the trigonum region. If there was an acute overdistended-bladder then the bladder will experience hypoxic, followed by increased blood flow to the serosa of the bladder. Then there was compensation in the form of bladder hypertrophy. If it continues, there will be a decompensated stage in the form of decreased bladder function. Awareness of risk factors may allow the obstetrician to prevent this complication. [8,16,22,23]

CONCLUSION

The incidence of postpartum urinary retention after vaginal delivery in Manado was 10.67%, consisting of 9.27% covert PUR and 1.4% overt PUR. The statistical analysis showed risk factors that significantly affected the incidence of urinary retention after vaginal delivery were instrument-assisted delivery, perineal laceration or episiotomy, duration first stage duration of labour, second stage duration of labour, and birth weight> 3800 grams.

SUGGESTION

Examination of post-void residual volume 6 hours postpartum should be performed in patients with risk factors such as instrument-assisted delivery, prolonged labour, perineal laceration or episiotomy, baby birth weight>3800 grams. In patients with risk factors for the emergence of postpartum urinary retention can be done prevention such as adequate analgesics, antibiotics, or catheterisation.

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Research Article

Malignancy Risk Factors of Hydatidiform Mole

Faktor-Faktor Risiko Keganasan pada Molahidatidosa

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Abstract

Objective : to determine risk factors in hydatidiform mole patients who will develop into Gestational Trophoblast Neoplasm (GTN) in Dr. Mohammad Hoesin Hospital Palembang

Methods : An observational analytical study with case-control design was conducted in the Department of Obstetrics and Gynecology in Dr. Mohammad Hoesin Hospital Palembang / Faculty of Medicine Sriwijaya Universitas Palembang from January 2017 to August 2017. The frequency and distribution of data are described in tables. Bivariate analysis was done to determine the correlation between the independent variable and dependent variable using Chi-Square/Fisher Exact test and multivariate analysis was used to know which independent variable has the most significant influence to the occurrence of Gestational Trophoblast Neoplasm (GTN) post-evacuation of hydatidiform mole. Data analysis was done using SPSS version 21.0.

Results : 45 patients fulfilled inclusion criteria with a control group and case group ratio 1 : 2 (15 cases and 30 controls). Statistical analysis showed a significant correlation between patient age, preevacuation β HCG level, parity, and histopathologic appearance with the occurrence of Gestational Trophoblast Neoplasm (GTN) after the evacuation of hydatidiform mole (p <0,05). From multivariate analysis, it was found that pre-evacuation β HCG levels ≥ 134,182.5 mIU/ml were a risk factor of Gestational Trophoblast Neoplasm (OR = 77.008, p-value = 0.004).

Conclusions : Preevacuation β HCG levels ≥ 134,182.5 mIU / ml isa risk factor for the occurrence of Gestational Trophoblast Neoplasm (GTN).

Keywords : age, blood type, hydatidiform mole, histopathology feature, GTN, preevacuation β HCG level, parity, uterine size.

Abstrak

Tujuan : *Untuk mengetahui faktor-faktor risiko pada pasien–pasien molahidatidosa yang akan berkembang menjadi Tumor Trofoblas Gestasional (TTG) di Rumah Sakit Dr. Mohammad Hoesin Palembang*

Metode : *Penelitian analitik observasional dengan studi case control ini dilakukan di Departemen Obstetrik dan Ginekologi RSUP Dr. Mohammad Hoesin Palembang/ Fakultas Kedokteran Universitas Sriwijaya Palembang sejak bulan Januari 2017 sampai Agustus 2017. Frekuensi dan distribusi data dijelaskan dalam bentuk tabel, analisis bivariat untuk mengetahui ada tidaknya hubungan secara statistik antara variabel bebas dengan variabel terikat menggunakan ujiChi Square/ Fisher Exact dan analisis multivariate untuk mengetahui variabel independen mana yang paling besar pengaruhnya terhadap kejadian Tumor Trofoblas Gestasional (TTG) pascaevakuasi molahidatidosa. Analisis data menggunakan SPSS versi 21.0.*

Hasil : *Didapatkan sampel sebanyak 45 pasien yang memenuhi kriteria inklusi. Dengan perbandingan kasus banding kontrol yaitu 1:2; sehingga didapatkan 15 pasien sebagai kasus dan 30 pasien sebagai kontrol. Dengan analisis statistika didapatkan hasil terdapat hubungan yang signifikan antara usia pasien, kadar β HCG praevakuasi, paritas dangan gambaran histopatologi dengan kejadian Tumor Trofoblas Gestasional (TTG) pascaevakuasi molahidatidosa (p< 0,05). Denganan alisis multivariate didapatkan kadar β HCG praevakuasi dengan nilai ≥ 134.182,5 mIU/ml merupakan faktor risiko Tumor Trofoblas Gestasional (OR = 77,008, p value = 0,004).*

Kesimpulan : *Kadar β HCG praevakuasi dengan nilai ≥ 134.182,5 mIU/ml merupakan faktor risiko kejadian Tumor Trofoblas Gestasional (TTG).*

Kata kunci : *gambaran histopatologi, golongan darah, kadar β HCG praevakuasi, molahidatidosa, paritas, TTG, ukuran uterus, usia.*

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INTRODUCTION

Hydatidiform mole is the most common form of gestational trophoblastic disease (GTD). Hydatidiform mole is an abnormal pregnancy in which some or all chorionicvillus degenerate into grape-like vesicles.[1] Hydatidiform moles may be malignant or benign. The frequency of hydatidiform mole is generally higher in Asian women (1 in every 120 pregnancies) than in Western women (1 in every 2,000 pregnancies).[2] In Indonesia, hydatidiform moles are considered an important disease with high incidence (data at in hospitals in Indonesia, 1 per 40), multiple risk factors, uniform distribution and most of the data is still hospital-based.[3]

Several theories have been proposed to explain the pathogenesis of hydatidiform mole. According to a theory by Hertig and Mansell, the cause of hydatidiform mole is an inadequacy of fetal blood circulation. Trophoblast cells receive nutrition from the mother through the intervillous chamber then send the liquid to the villi. Due to the dysfunctional villous blood circulation, fluid accumulates in villous mesenchymal tissue and forms small cysts. This continues and will eventually result in hydatidiform mole.[4,5]

Patient with normal pregnancy who has previous history of hydatidiform mole is considered healthy, and hence, follow-up supervision is no longer necessary. If malignancy occurs, it is not caused by the former hydatidiform mole, but as a result of the last labour. A theory states a number of trophoblast cells in hydatidiform mole sometimes appear quiet (dormant cells) for some time and the existence of pregnancy (the influence of estrogen) reactivates these cells. In this case, the choriocarcinoma arises not from the last pregnancy, but the previous mole.[4,5]

Malignancy following evacuation of hydatidiform mole occurs in 15-20%. Post-mole malignancy develops very rapidly with a high mortality number of 31-51 %.[6,7] The risk of malignancy after the evacuation of the mole is not clearly known. Several demographic, clinical and laboratory variables have been studied as malignant risk factors such as age, parity, uterine size, lutein cyst, histopathological features and also pre-evacuation β-human chorionic gonadotropin (β-HCG) level.[8-10]

This study aimed to determine risk factors of the occurrence of Gestational Trophoblast Neoplasm (GTN) following hydatidiform mole evacuation, so it can be used to predict whether hydatidiform mole will develop into GTN (Gestational Trophoblastic Neoplasm) or return to normal.

METHOD

This observational analytic study with case-control (retrospective) design was conducted in the Department of Obstetrics and Gynecology in Dr. Mohammad Hoesin hospital Palembang/ Faculty of Medicine Universitas Sriwijaya Palembang from January to August 2017. Data was collected by gathering medical record data of hydatidiform mole patients who came and were treated in the Department of Obstetrics and Gynecology in Dr. Mohammad Hoesin hospital Palembang from January 1st 2014 to December 31st 2016. Samples were selected using purposive sampling by choosing patient who met the research criteria. The sample was then divided into 2 groups, with 1:2 proportion between the case group and the control group. The control group was the hydatidiform mole group that had regressed, and the case group was the hydatidiform mole group that developed into GTN. Independent variables were age, pre-evacuated HCG levels, blood type, parity, uterine size, histopathologic features.

Univariate analysis was performed on sample demographic characteristics. Bivariate analyses using chi-square or Fisher exact test were performed to assess the association between age, pre-evacuation HCG levels, blood type, parity, uterine size, histopathologic features and malignancy occurrences in hydatidiform mole. Logistic regression analysis was performed to determine which independent variables had the greatest effect on the occurrence of GTN after hydatidiform mole evacuation.

RESULT

There were 45 hydatidiform mole patients who met the inclusion criteria. Of the 45 patients with hydatidiform mole, 15 patients developed Gestational Trophoblast Neoplasm, and 30 patients regressed.Of 45 patients,30 regressed patients(66,7%) have mean age 27,37 ± 7,63 (age range 17-45 years old) and 15 patients

who developed into GTN(33.3%) have mean age 35.13 ± 10.01 (age range 17-50 years old). Based on statistical analysis, there was a significant difference in age between regressed patients and GTN patients (p = 0.006).

The mean of pre-evacuation β HCG level in the regressed group was 69617,6 ± 38449,7 mIU/ml and the mean of pre-evacuation β HCG level in the GTN group was 515286,4 ± 346728,0 mIU/ml. From statistical analysis, it was found that there was a significant difference in pre-evacuation HCG levels between the two groups (p = 0,000). No significant difference was observed in both groups for other demographic and clinical characteristics (p> 0.05) as shown in Table 1.

Table 1. Characteristics of Subjects

Characteristics	Hydatidiform Mole		*P-value*
	GTN	Non-GTN	
Age (years), mean ± SD	35.13 ± 10.01	27.37 ± 7.63	0.006*
Education, (n,%)			
Elementary	0 (0)	2 (6,7)	
Junior High School	3 (20)	3 (10)	0.496**
Senior High School	10 (66,7)	23 (76.7)	
College	2 (13.3)	2 (6.7)	
Occupation, (n,%)			
Housewife	11 (73.3)	25 (83.3)	
Farmer	0 (0)	3 (10)	0.106**
University student	0 (0)	1 (3.3)	
Employee	2 (13.3)	1 (3.3)	
Civil servant	2 (13.3)	0 (0)	
Pre-evacuation β HCG Levels, mean ± SD	515286.4 ± 346728.0	69617.6 ± 38449.7	0.000***
Blood Group			
A	6 (40)	10 (33.3)	0.470**
B	7 (46.7)	11 (36.7)	
O	2 (13.3)	9 (30)	
AB	0 (0)	0 (0)	
Uterine size			
Bigger	15(100)	29 (96.7)	1.000****
Smaller/appropiate	0 (0)	1 (3.3)	

*Independent T Test, p = 0,05 , **Pearson Chi Square, p = 0,05, ***Mann Whitney test, p = 0,05
*****Fisher Exact test, p=0,05

ROC curve analysis was performed to obtain the cut-off point with the best sensitivity and specificity values for age, parity and preevacuation β HCG level. Based on the ROC curve, the cut-off point was 29.5 years for age, the best parity at 1.5 and the best preevacuation β HCG level at 134.182,5 mIU / ml. Analysis results from ROC curve for age, parity and β HCG is used to analyse the relationship between the independent variables and the occurrence of Gestational Trophoblast Neoplasm (GTN) in hydatidiform mole patients.

In GTN patients the majority (73.3%) of patients was ≥ 29.5 years old whereas in non-GTN patients the majority (66.7%)was<29.5 years old. For parity variables, in GTN patients the majority of patients had a parity of ≥ 1.5 (66.6%) whereas the majority non-GTN patients (73.3%) had parity <1.5. Meanwhile, for the predominant β HCG levels, the majority of patients (93.3%) of the GTN had pre-evacuation β HCG ≥ 134.182.5 mIU / ml, whereas the majority non-GTN patients (93.3%) of had pre-treatment β HCG levels <134.182.5 mIU / ml. Table 2 shows that there is a significant association between age, parity, pre-evacuation βHCG levels and histopathology features and gestational trophoblast neoplasm occurrence in hydatidiform mole patients (p <0.05).

Table2. Association between Age, Parity, pre-evacuation β HCG Level, Histopathology Feature and Gestational Trophoblast Neoplasm Occurrence in Hydatidiform Mole Patients

Characteristics	Hydatidiform Mole		Total	OR* (CI 95%)	*P-value*
	GTN	Non-GTN			
Age (years old)					
≥ 29.5	11	10	21	5.500	0.025
< 29.5	4	20	24	(1.393-21.715)	
Parity					
≥ 1.5	10	8	18	5.500	0.024
< 1.5	5	22	27	(1.434-21.096)	
Pre-evacuation β HCG level					
≥ 134.182,5mIU/ml	14	2	16	196.000	0.000
< 134.182,5mIU/ml	1	28	29	(16.337-2351.532)	
Histopathology Feature					
Moderate-severe proliferation	14	6	20	56.000	0.000
Mild Proliferation	1	24	25	(6.099-514.189)	

* Fisher Exact test, p-value = 0.05

Based on the logistic regression test in table 3, it was found that pre-evacuation β HCG level significantly influenced the occurrence of GTN. Risk of progressing to GTN in patients with pre-evacuation β HCG level ≥134.182,5mIU / ml was 77 times greater than in patients with pre-evacuation β HCG levels <134.182,5 mIU/ml (OR = 77.008, P value = 0.004). While age, parity and histopathology feature were significantly associated with β HCG level (OR > 1, p-value <0.05).

Table3. Risk Factors of Gestational Trophoblast Neoplasm

Variable	Unadjusted*		Adjusted**	
	OR	*P- value*	OR	*P- value*
β HCG level	196.000	0.000	77.008	0.004
Histopathology feature	56.000	0.000	7.423	0.227
Parity	5.500	0.024	5.025	0.295
Age	5.500	0.025	0.813	0.890

**Regression logistic test,p-value=0.05

DISCUSSION

Gestational trophoblast disease (GTD) is defined as a neoplastic process, derived from fetal chorion during pregnancy.[11,12] This includes a spectrum of diseases such as molar pregnancy, persistent invasive mole, gestational choriocarcinoma and placental-site trophoblast tumor.[13,14]

Gestational Trophoblast Neoplasm (GTN) is a disease condition where there is clinical evidence of invasive mole or choriocarcinoma. The incidence of gestational trophoblast neoplasm in Indonesia varies between 11.47 - 29.3%.[3] In this study, we obtained 45 patients of hydatidiform moles; 15 (33.3%) of which developed into GTN. The number is relatively higher when compared to the incidence of post-mole GTN in Indonesia in previous studies, which range from 11.47 to 29.3% .[3] This may be due to Dr. Mohammad Hoesin Hospital Palembang status as a tertiary health care facility and a regional referral hospital. Hence, many subspecialists cases that cannot be handled at a local hospital can be found in Dr. Mohammad Hoesin Hospital.

Mean age of GTN patients in this study was 35.13 ± 10.01 (age range 17-50), with statistical analysis showed significant difference between mean age of the non-GNT patient and mean age of patients where mean age in GTN patients was higher. The results of this study are similar to the study by Azis et al who found an increasing incidence of invasive mole and choriocarcinoma in patients over 35-40 years old.[15,16]

Bivariate analysis showed that hydatidiform mole patients age ≥ 29.5 years old were 5.5 times more at risk of progressing to GTN than patients age<29.5 years old. This result is not much different from Soeharyono's research in which patients age ≥ 35 years were 6.6 times more at risk of trophoblastic disease. However, a study conducted by Curry did not show a significant relationship between age andpost-mole malignancy.[13-15]

Majority of patients in this study, both in groups of GTN and non-GTN, have blood type B, followed by blood type A and blood type O. However, no AB blood type was found in both groups. With statistical analysis, there was no difference of blood type groups between the two groups. A research by Soeharyono (1996) showed that most malignancy cases occurred in blood type O patients, then blood type B, blood type A, and blood type AB. This difference is probably due to the smaller number of samples in this study compared to Soeharyono's study (321 samples), so the possibility of finding blood type O is higher. [13,16]In the study by Aziz et al, patients with blood type O and B were found to be more likely to develop malignancy than patients with other blood types.[13] While in the research conducted by Martaadisubrata in 2005, it was found that 33.3% of blood type A patients developed into choriocarcinoma.[1] The results of Bagshawe's study found that blood type A had a higher risk for choriocarcinoma when the blood type of the husband was O.[17]

The association between parity (gravidity) and post-mole malignancy is still unclear. Some studies have found that the risk of malignancy was higher in higher parity, while other authors did not find a relationship between parity and the risk of post-mole malignancy. [13,16] In this study, we found that hydatidiform mole patients with parity ≥ 1.5 were 5.5 times more at risk of progressing to GTN than patients with parity<1.5. Statistical analysis showed a significant association.

Curry found that patients with larger uterine size and an enlarged ovary have higher risk of post-mole malignancy. However, in this study, no difference in uterine size was found between the two groups. All GTN patients had larger uterine size than gestational age, and only one non-GTN patient had a uterine size in accordance with gestational age.[15,16,18]

The serum concentration of β HCG is recognised as an important prognostic indicator of gestational trophoblastic disease. According to FIGO, postevacuation treatment of hydatidiform mole involves examining β-HCG every week during the first month until undetectable. The β-HCG level in most cases will return to normal within eight weeks, and the others will return to normal within 14-16 weeks after evacuation. Meanwhile, according to Berkowitz and Goldstein, β-HCG levels in hydatidiform mole patients usually will return to normal within 9-11 weeks after evacuation. However, if, during the follow-up, there is an elevated β-HCG level or plateau then the diagnosis of GTN can be established.[13,19,20]

In this study, the mean pre-evacuation β HCG level was 515286,4 ± 346728,0 mIu/ml. Then the preevacuation β HCG level was divided into ≥134.182,5mIU/ml and <134.182,5 mIU/ml based on analysis results with ROC curve. With bivariate analysis, we found that hydatidiform mole patients with preevacuation β HCG level ≥134.182.5 mIU/ml were significantly more at risk (196 times more at risk)of progressing to GTN than patients with pre-evacuation β HCG level <134.182,5 mIU/ml. This result is similar to the study by Goldstein and Berkowitz which concluded that high pre-evacuation β HCGtiter above 100,000 SI / l was a high-risk factor for malignancy. [14,15,17]

In this study, we found that hydatidiform mole patients with moderate-to-severe proliferation from histopathology feature were significantly more at risk (56 times higher) of progressing to GTN than patients with mild proliferation. This result is consistent with the study by Hertig and Sheldon, which found an association between the severity of trophoblastic hyperplasia in hydatidiform mole and the onset of malignancy. The more severe the hyperplasia and anaplasia found in histopathologic examinations, the more likely it is to become malignant. Based on the severity of hyperplasia and trophoblast cell anaplasia, a histologic hydatidiform mole classification was formulated in 1956 and was simplified by Hertig and Mansel.[17]

Based on multivariate analysis, the risk factor for the occurrence of gestational trophoblast neoplasm was preevacuation β HCG level ≥ 134.182,5 mIU/ml while other variables were not risked factors because no statistically significant correlation was found. The results were slightly different from the studies by Lurain JR and Loh KY et al. They reported that the risk factors for post hydatidiform mole malignancy were histopathologic features with severe proliferation, uterine size, lutein cysts> 6 cm and pre-evacuation β-HCG levels> 100,000 mIU / mL.[8- 10]

CONCLUSIONS

Pre-evacuation β HCG levels ≥ 134,182.5 mIU/ml is a risk factor for the occurrence of GTN.

SUGGESTION

Follow-up studies with prospective cohort designs and large sample, which incorporate other risk factors should be conducted to provide more valid and targeted results and conclusions.

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Case Report

Making Diagnosis of Gestational Trophoblastic Neoplasia: What, When, How to Treat and What to do Next?

Membuat Diagnosis Gestational Trophoblastik Neoplasia: Apa, Kapan, Bagaimana Cara Mengobati dan Apa yang Harus Dilakukan Selanjutnya?

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Abstract

Objective : Delay on diagnosing GTN may increase the GTN score from low risk become high risk, as follow.

Methods : case report

Results : Mrs I, 29 yo, P1A7 came with vaginal bleeding. Four months before admission, she had surgery of ectopic pregnancy, and the left salphynx and ovary had already taken out. No histopathology examination was performed. After the surgery, she had vaginal bleeding and underwent curettage, but the tissue was not sent for histopathology exam. US exam one week after procedure shows mass protruding in the uterine, with BhCG 225.000 IU/ml. The patient was planned to undergo chemotherapy. While waiting for chemotherapy, patient complaints of acute abdomen due to hemoperitoneum due to perforation of trophoblastic mass. Emergency laparotomy was performed.

Conclusions : Inadequate treatment due to inadequate staging is the most common reason for unsuccessful GTN treatment, and increase patient morbidity. Histopathology result also plays an important role to decide the mode of treatment should be given since PSTT and ETT treatment of choice is not using chemotherapy.

Keywords : ectopic pregnancy, gestational trophoblastic neoplasia, molar gestation, vaginal bleeding pathology.

Abstrak

Tujuan : *Penundaan dalam mendiagnosis GTN dapat meningkatkan skor GTN dari risiko rendah menjadi risiko tinggi, sebagai berikut.*

Metode : *laporan kasus*

Hasil : *Ny. I, 29 tahun, P1A7 datang dengan pendarahan vagina. 4 bulan sebelum masuk, dia menjalani operasi kehamilan ektopik, dan salphynx dan ovarium kiri sudah diambil. Tidak ada pemeriksaan histopatologi yang dilakukan. Setelah operasi, dia mengalami pendarahan vagina dan menjalani kuret, tetapi jaringan itu tidak dikirim untuk pemeriksaan histopatologi. Ujian AS 1 minggu setelah prosedur menunjukkan massa menonjol di uterus, dengan BhCG 225.000 IU / ml. Rencanakan kemoterapi. Sambil menunggu kemoterapi, keluhan pasien perut akut karena hemoperitoneum karena perforasi massa trofoblas. Laparotomi darurat dilakukan.*

Kesimpulan : *pengobatan yang tidak memadai karena pementasan yang tidak memadai adalah alasan yang paling umum dari pengobatan GTN tidak berhasil, dan meningkatkan morbiditas pasien. Hasil histopatologi juga memainkan peran penting untuk menentukan cara pengobatan yang harus diberikan, karena pilihan pengobatan PSTT dan ETT tidak menggunakan kemoterapi.*

Kata kunci : *kehamilan ektopik, kehamilan mola, neoplasia trofoblastik gestasional, patologi perdarahan pervaginam.*

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INTRODUCTION

A delay on diagnosing Gestational Trophoblastic Neoplasia (GTN) may cause an increase of morbidity to the patient. The important things that OBGYN usually forgot are that GTN may develop not only from previous molar gestation (50-60%), but also from abortions or ectopic pregnancy (25-30%) and term or preterm deliveries (10-25%).[1,2]This can cause a delay on diagnosing that may increase the GTN score from low risk become high risk, such as this case, as follow.

CASE

Mrs I, 29 yo, P1A7 came with vaginal bleeding. Four months before admission, she had surgery of ectopic pregnancy, and the left salphynx and

ovary had already taken out. No histopathology examination was performed. After the surgery, she had vaginal bleeding and underwent curettage, but the tissue was not sent for histopathology exam. She had US exam one week later, there is tissue remnant and invaded to the uterine wall, given primolut for 15 days, then checked for b-hCG, and the result was 225.000 IU/ml. The patient was then referred to our hospital. Ultrasonographic findings found a solid mass on the posterior part, irregular, no clear border, size 60x10 mm malignant trophoblastic mass. Mass on left anterior corpus invaded the left adnexa, left ovary sized 100x110 mm. Liver, spleen, and both kidneys were normal. Conclusion: malignant trophoblastic disease with invasion to left adnexa.

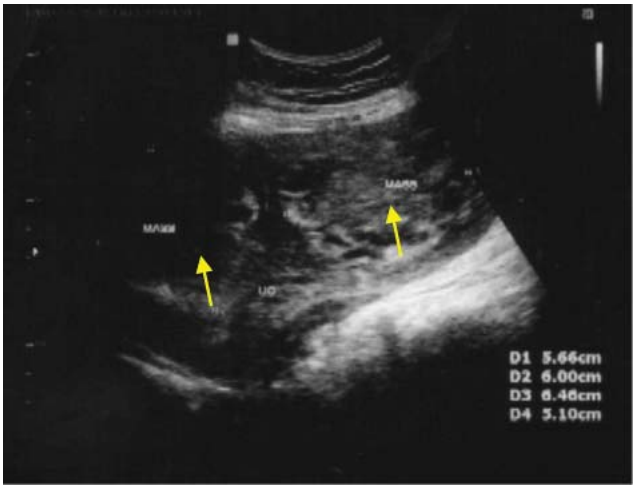

Figure 1. Malignant mass invaded to myometrium

While waiting for chemotherapy, patient complaints of acute abdomen due to hemoperitoneum due to perforation of trophoblastic mass. Emergency laparotomy was performed, found hemoperitoneum and perforation on the upper left side of the uterus, total hysterectomy was performed.

Figure 2. The specimen demonstrated perforation on the upper left side of the uterus

Based on the fact that there were several cases of GTN found too late, we try to explain about GTN "What, When, How to Treat and What to do Next ?" What kind of GTN could be managed by general obgyn and when to refer the patient to Oncology-gynecologist. In this article, only treatment with single-agent chemotherapy will be discussed deeply.

What is Gestational Trophoblastic Neoplasia (GTN)?

Gestational trophoblastic neoplasia (GTN) is the term used to describe malignant lesions that originate in the chorionic villi and the extravillous trophoblast. GTN includes four different proliferation, invasion and dissemination, such as invasive mole (IM), choriocarcinoma (CCA), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT). The overall cure rate with chemotherapy is around 90%, but for PSTT and ETT are relatively resistant for chemotherapy.[2] Therefore, the first-line treatment in these cases is surgery, particularly in no metastatic cases[3].PSTT and ETT, however, develop after term deliveries or non-molar abortions in 95% of the cases[4].

When we have to think about GTN?

Most of GTN develops from postmolar gestation (50-60%) while GTN could also develop from previous abortion, ectopic pregnancy and term or preterm deliveries.[1-3]Following a molar pregnancy, the risk of a further hydatidiform mole increases around 1%.[5,6] After two molar gestations, the risk of a third mole is 15%–20% and is not decreased by changing partners.[7] Most of PSTT and ETT (95%) usually develop after term delivery or non-molar abortion[2]. That is why the pathology result of the tissue that had been evacuated previously plays a vital role in diagnosing GTN.

The components needed to diagnose postmolar GTN, based on FIGO 2002 include at least 1 of the following; hCG plateau for 4 consecutive values over 3 weeks; hCG rise of ≥10% for 3 values over 2 weeks; hCG persistence 6 months after molar evacuation; histopathologic diagnosis of choriocarcinoma; or presence of metastatic disease. While PSTT and ETT are classified separately.[1-3] hCG value measured after mole evacuation use as a reference value. A rise,

plateau or persistence value of hCG, the presence of metastatic disease, or picture of invasive mass out of uterine cavity (such as myometrium) after molar evacuation could be used to diagnose GTN. On the other side histopathology results was used to classify GTN by its characteristics, for example: invasive mole have a risk of perforation, choriocarcinoma have a high risk of metastases, ETT or PSTT usually resistance to chemotherapy.

When GTN is suspected or established, a metastatic workup and an evaluation for risk factor should be performed. Along with complete history and physical examination, complete blood count, including coagulation studies, renal and liver function test and quantitative hCG level should be performed. Radiologic studies, such as pelvic ultrasound, chest x-ray, CT scan or brain MRI also recommended, if there was a sign of neurologic deficits, to detect any site of metastases. [2,5]

GTN metastases occur by hematogenous spread to the lungs (80%), vagina (30%), brain (10%) and liver (10%). Biopsies are not recommended because of the high risk of bleeding.[2,5]

What to do after diagnosing GTN? [2,5]

Treatment of GTN is based on risk groups classification by stage and scoring system using FIGO or modified WHO prognostic scoring and the pathology findings. Only GTN that originated from previous molar pregnancy or low-risk GTN with single chemotherapy agent could be managed by general OBGYN; others should be managed by oncology-gynaecologist.

Prior to treatment, OBGYN should classify the disease to choose the right treatment plan. There were several classifications of GTN, such as Hammond, FIGO and WHO modified FIGO classification. Chemotherapy given did not correlate with the staging (FIGO), but depend on the Hammond classification or WHO modified FIGO classification.

Hammond classifies malignant GTN divided into good prognostic GTN and poor prognostic GTN; metastatic GTN is diagnosed when we found nodules on other organs, except vagina and lungs.

Table 1. Metastatic GTN Classification Based on Hammond (1981)

	Good Prognosis	Poor Prognosis
Urinary hCG	$<10^5$ IU/lt	$>10^5$ IU/lt
Serum hCG	$<4x10^4$ mIU/ml	$>4x10^4$ mIU/ml
Symptom	< 4 months	> 4 months
present	No	Yes
Liver or brain metastases Prior chemotherapy	No	Yes
Following term pregnancy	No	Yes

Table 2. GTN Staging by FIGO

Stage	Description
I	Disease confined to the uterus
II	Disease extend outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)
III	Disease extends to lungs with or without genital tract involvement
IV	Disease involves other metastatic sites

The FIGO stage is followed by the Modified WHO score and separated by a colon. Based on Hammond nonmetastatic classification (FIGO: stage I) and low-risk metastatic (FIGO: stages II and III or score<7 due to WHO modified FIGO classification) GTN can be treated with single-agent chemotherapy resulting in a survival rate approaching 100%.[2,5]

High-risk GTN (FIGO: stages II-IV, score≥7 due to WHO modified FIGO classification) requires initial multiagent chemotherapy with orwithout adjuvant radiation and surgery to achieve a survival rate of 80-90%.[2,5]

The overall cure rate was 90% with chemotherapy. However, for PSTT and ETT, Hysterectomy with lymph node dissection is the treatment of choice with survival rate is approximately 100% for nonmetastatic disease and 50-60% for metastatic disease.[2,5]

Table 3. Modified WHO Prognostic Scoring System as Adapted by FIGO

Risk factor	Score			
	0	**1**	**2**	**4**
Age, yo	≤39	>39	-	-
Antecedent pregnancy	mole	abortion	term	
Pregnancy even to treatment interval, mo	<4	4-6	7-12	>12
Pretreatment hCG, mIU/ml	$< 10^3$	10^3-10^4	10^4-10^5	$> 10^5$
Largest tumour mass including uterus, cm	<3	3-4	≥5	-
Site of metastases	-	Spleen, kidney	GI tract	Brain, liver
No. of metastases	-	1-4	5-8	>8
Previous failed chemotherapy	-	-	Single-drug	≥ 2 drug

How to treat low-risk GTN?

There were several different outpatient chemotherapy protocols have been used. Benefits seem to be greater when hCG concentration is below 1500 IU/L at the time of evacuation[2], and the adverse side effect rate was much greater with combination therapy (62%) than with single-agent methotrexate (29%) or actinomycin D (19%).[5]

The three most common regimens used are: weekly low-dose intramuscular (IM) MTX 0.4 mg/kg (maximum 25mg/day) for 5 day, repeat every 14 days; pulsed doses of ActD 1.25mg/m^2repeat every two weeks; and several other dosing regimens of MTX 1mg/kg IM (d 1,3,5,7) with or without folinic acid (FA) rescue 0.1 mg/kg IM (d 2,4,6,8) repeat every 15-18 days. The survival rate using this kind of regiments was more than 90%.[2,5]

Mortality rates associated with IM reached 15%. In the presence of metastases, CCA had a mortality rate of 100%, and about 60% when the hysterectomy was performed to treat apparent nonmetastatic disease.[2]

What to do next?

Definitive follow up requires serial quantitative hCG measurements every 1-2 weeks until achieving the normal level, and it is consolidation dose by continuing the follow up with three consecutive tests that show normal level (depend on the normal laboratory value) after treatment. After that, hCG levels should be determined every 1-month intervals for 12 months. The relapse risk was about 3% in the first year after completing the therapy.[3,7-8]

Follow up

Contraception (preferably using oral contraceptives) should be maintained during treatment and for one year after completion of chemotherapy.[1-3,9] Because there is 1-2% risk of second gestational trophoblastic disease in subsequent pregnancies, pelvic ultrasound is recommended in the first trimester to confirm a normal gestation. The products of conception or placentas should be examined by histopathology and serum quantitative hCG level should be determined six weeks after any pregnancy.[3]

Most woman resumes normal ovarian function after chemotherapy and exhibits no increase in infertility. No evidence for reactivation of the disease because of subsequent pregnancy.[3,10.] Primary remission was achieved in 48-67% of patients with the first single-agent chemotherapy regimen. From 1-14% of patients needed multiagent chemotherapy after failed sequential single-agent chemotherapy with or without surgery to achieve remission, but eventually, all patients were cured.[3]

The most common reasons for unsuccessful GTN treatment are use of single-agent chemotherapy for patients with high-risk disease; inappropriate use of weekly IM methotrexate chemotherapy for treatment of patients with metastatic disease, FIGO scores ≥ 7, and/or nonpostmolar choriocarcinoma.[3]

CONCLUSION

Inadequate treatment due to inadequate staging is the most common reason for unsuccessful GTN treatment, and increase patient morbidity. It is important to know how to perform GTN staging using the WHO modified staging score, adapted by FIGO and how to perform adequate treatment for this disease. Histopathology also plays an essential role to decide the mode of treatment that should be given since PSTT, and ETT treatment of choice is not using chemotherapy.

Since there is a risk of repeated gestational trophoblastic disease, it is important to use contraception during treatment and one year after completion of chemotherapy. It is also recommended to examine the conception product or placenta by histopathology and serum quantitative hCG level should be determined six weeks after any pregnancy.

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