Comparison between Early-onset and Late-onset Preeclampsia by Echocardiographic Examination of Cardiac Output, Total Vascular Peripheral Resistance, and Doppler Velocimetry Examination of Uterine Artery Resistance Index

Muhammad Ilham Aldika Akbar, Erry Gumilar Dachlan
Departement Obstetry & Gynecology, Faculty of Medicine, Airlangga University, Dr. Soetomo Hospital

ABSTRACT

Preeclampsia is still a leading cause (15-20%) of maternal death in developing country. Clinical manifestation of Preeclampsia can have a wide spectrum, from mild disease until severe disease that caused maternal death. From advanced observation, it is found that clinical manifestation of the disease is worst when preeclampsia manifest earlier. It raise the view that onset of the disease is one of the main factor of this difference. Recent view subclassifice Preeclampsia based on onset of clinical manifestation, Early-onset preeclampsia (<34 weeks) and Late-onset preeclampsia (>34 weeks). The objective of this study was to evaluate and compare uterine artery resistance index, cardiac output, and total peripheral vascular resistance value between early-onset and late-onset preeclampsia. This was a cross-sectional observational analytic study was performed at Departement Obstetry and Gynecology Soetomo Hospital, between Desember 2010-June 2011. We analyzed 17 severe preeclampsia pregnant women and 20 normal pregnant women matched by gestational age and inclusion and exclusion criteria. The Preeclampsia group was divided become two groups, early onset preeclampsia (< 34 weeks) and late onset preeclampsia (> 34 weeks) based on gestational age during onset of the disease. We examine using doppler velocimetry ultrasound and echocardiography in 1-2 days after the patient admitted to hospital. Primary outcome included uterine artery resistance index, cardiac output, and total peripheral vascular resistance value. In conclusion, early onset preeclampsia has higher cardiac output and uterine artery resistance index, and lower total vascular peripheral resistance than late-onset preeclampsia. (MOG 2011;19:63-68)

Keywords: Early-onset preeclampsia, late-onset preeclampsia, doppler velocimetry, uterine artery resistance index, echocardiography, cardiac output, total peripheral resistance.

对应: Muhammad Ilham Aldika Akbar, Departement Obstetry & Gynecology, Faculty of Medicine, Airlangga University, Dr. Soetomo Hospital, Surabaya, dokter_aldi@yahoo.com

INTRODUCTION

Preeclampsia is still a leading cause (15-20%) of maternal death in developing country because of prematurity and fetal growth restriction. In Soetomo Hospital, there are 12 from 20 maternal death because of preeclampsia during 2007, with total delivery around 2393. Maternal death because of Preeclampsia in East Java around 117 (28.2%) from 414 death in 2007, and about 64 (22.9%) from 279 maternal death in 2008. Pathogenesis preeclampsia has changed significantly this day because a lot of new finding about this disease. One of the important finding is the diversity of the clinical manifestation of this disease.
manifestation of Preeclampsia can have a wide spectrum, from mild disease until severe disease that caused maternal death. On one side preeclampsia caused intracranial bleeding, lung edema, HELLP syndrome, fetal and maternal death, but on the other hand preeclampsia only caused increase blood pressure and proteinuria without significant impact on maternal/fetal health.

From advanced observation, it is found that clinical manifestation of the disease is worst when preeclampsia manifest earlier. On preeclampsia which manifest less than 34 weeks tends to have worst fetal and maternal outcome, fetal growth restriction, placental lesion, and uteroplacental perfusion impairment which seen from abnormality of doppler velocimetry examination of uterine artery. All this result was not found in preeclampsia manifest more than 34 weeks.

It raise the view that onset of the disease is one of the main factor of this difference. Recent view subclassific Preeclampsia based on onset of clinical manifestation, Early-onset preeclampsia (<34 weeks) and Late-onset preeclampsia (>34 weeks).

Sibai explain that early-onset preeclampsia maybe caused by plasental factor, and late-onset preeclampsia caused by maternal factor. This hypothesis was supported by variety of experiment that found an association between early-onset preeclampsia with placental lesion, PIGF, sFLT-1, and STBM, but not with late-onset preeclampsia.

One of the main pathophysiological difference that is assumed causing difference outcome between both group is hemodynamic model difference. Hemodynamic model of Preeclampsia until now is still controversial because many research found a variety result. From hyperdynamic model (increased cardiac output and decreased total peripheral resistance) by Easterling, hyperdynamic model on latent phase turn to be hypodynamic model during onset of the disease, and hypodynamic model turn to be hyperdynamic because therapeutic effect.

Sibai composed a theory that woman whom destined to be an late-onset preeclampsia or gestational hypertension, will has an exaggerated increased of cardiac output (hyperdynamic model). On the other hand, woman whom destined to bearly-onset pre-eclampsia, gestational hypertension with certain complication, or fetal growth restriction had abnormal-ity placental function that released some factor that caused general vasoconstriction and decreased cardiac output (hypodynamic model).

This was proved by Valensise et al. that early-onset preeclampsia group has significantly higher total vascular resistance and lower cardiac output compared with late-onset preeclampsia (on 24 gestational weeks), and early-onset preeclampsia group also had significantly increased notch finding during uterine artery doppler velocimetry examination compared with late-onset group.

Start from controversy around subclassification preeclampsia, hemodynamic difference, etiology, and fetal outcome difference between both group, we decided to held this research. Our research want to see hemodynamic model and uteroplacental perfusion of preeclampsia during onset of the disease. Valensise research has proved that hemodynamic model before and after onset of the disease is different between both group. So we want to know how the hemodynamic model of preeclampsia between both group during gonset of the disease.

**MATERIALS AND METHODS**

This study is an observational analytic cross sectional that was done in Soetomo Hospital start from 2010 Desember until 2011 June. In this study, we divide into 4 group: early-onset preeclampsia, late-onset preeclampsia, early normal gestational, and late-normal gestational group. Early-onset preeclampsia was defined as severe preeclampsia which onset of the disease less than 34 weeks. Late-onset preeclampsia was defined as severe preeclampsia which onset of the disease more than 34 weeks, without known preeclampsia sign/symptoms on antenatal care before 34 weeks.

The control group was divided into two groups based on gestational age, early-onset (<34 weeks) and late-onset (>34 weeks). We excluded preeclampsia group which has: uncertain gestational age, smoking, multifetal gestation, woman with cardiac disease, chronic medical disease, history chronic hypertension, woman who consumed anti hypertension drugs and β-mimetic asthma drugs, woman which onset of the disease is not clear.

Sampel was taken from all severe preeclamptic patient which came to the delivery room Soetomo Hospital, which meet inclusion and exclution criteria. Severe preeclampsia was uphold by ACOG criteria (Blood pressure >160/100 on 2 examination with 6 hours interval apart, and proteinuria dipstick (+) 3/5 g/24 hour). The preeclamptic group was then divided based on gestational age during onset delivery.
On 2 x 24 hours both group was done an echocardiographic and USG doppler velocimetry examination. The examination was done in single blind (the examiner did not know the diagnosis of the patient that he examined). From echocardiographic examination we got the cardiac output and total peripheral vascular resistance value. From USG Doppler velocimetry we got uterine artery resistance index.

Cardiac output is the volume of the blood that was pumped by the heart during one minute. Cardiac output value was achieved by multiply the stroke volume and heart rate from echocardiographic examination. Total Vascular Resistance is a velocity resistance that should be passed to pump blood to systemic circulation. Total Vascular Resistance value was achieved from the formula: TVR=(MBP/CO) x 80, which MBP is mean blood pressure. Uterine artery resistance index was performed by USG doppler velocimetry to know how the uteroplacental perfusion on preeclamptic patient. We examined right uterine artery for all the patient.

We also examine normal gestational woman as a control and was divided into two group based on gestational age (</ 34 weeks). Normal control group was achieved from the obstetric clinic Soetomo Hospital on a normal gestational woman who has a routine antenatal visit in our clinic.

The data than collected and analyzed using statistical methods and compared between four groups. We examined the difference cardiac output, total vascular resistance, and uterine artery resistance index between all group using paired T test. To simplify the statistical calculations of the data, we used SPSS software tools.

**RESULT AND DISCUSSION**

Our study got 37 woman as a research subject, which divided into two group: 17 severe preeclamptic patient and 20 normal gestational woman. Based on gestational age, severe preeclamptic group was divided into early-onset/</34 weeks (10 woman) and late-onset/>34 weeks (7 woman). Control group was divided into two group: early-onset (14 woman) and late-onset (6 woman). We analyzed characteristic subject of the study by age, parity, and body mass index.

From USG doppler velocimetry, we compared uterine artery resistance index between early-onset and normal early control, late-onset and normal late control, and both preeclamptic group directly. From USG doppler velocimetry, we found no statistically significant difference between early-onset preeclampsia & control, late-onset preeclampsia & control, and early-onset and late-onset preeclampsia. Echocardiography examination was performed to evaluate cardiac output and total peripheral vascular resistance on preeclamptic and normal group.

### Table 1. Characteristic Subject by Age, Parity, and Body Mass Index

<table>
<thead>
<tr>
<th>Age</th>
<th>Primipara</th>
<th>Multipara</th>
<th>BMI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 y.o</td>
<td>0</td>
<td>5 (50%)</td>
<td>25.75+5.22 kg/m²</td>
<td>0.515</td>
</tr>
<tr>
<td>20-35 y.o</td>
<td>5 (50%)</td>
<td>6 (86%)</td>
<td>30.38+4.68 kg/m²</td>
<td></td>
</tr>
<tr>
<td>&gt;35 y.o</td>
<td>1 (14%)</td>
<td>1 (14%)</td>
<td>30.38+4.68 kg/m²</td>
<td></td>
</tr>
</tbody>
</table>

### Cardiac Output

Echocardiographic examination of cardiac output show no statistically significant difference between early-onset preeclampsia & control, late-onset preeclampsia & control, and also early-onset and late-onset preeclampsia. But from the value itself, early-onset preeclampsia tend to has a higher value compared to late-onset preeclampsia. The preeclamptic group also tend to had a higher cardiac output value compared to normal group.

Echocardiographic examination of total peripheral vascular resistance show no statistically significant difference between early-onset preeclampsia & control, late-onset preeclampsia & control, and also early-onset and late-onset preeclampsia. But from the value itself, early-onset preeclampsia tend to has a lower value.
compared to late-onset preeclampsia. The preeclamptic group also tend to have a higher total peripheral vascular resistance value compared to normal group. From two severe preeclampsia group we compared some characteristic that was a main risk factor of preeclampsia: age, parity, and body mass index. From statistical analysis we found average value of age on early-onset preeclampsia group was 34.78 years old, and late-onset preeclampsia group was 28.75 years old. This finding appropriated with Valensise study. \(^{18}\) that average age of early-onset was older than late-onset preeclampsia.

**Table 3. Cardiac output value of Early-onset, Late-onset preeclampsia, and control**

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Output (liter/minutes)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset</td>
<td>6.06±1.17</td>
<td>p = 0.079</td>
</tr>
<tr>
<td>Early-control</td>
<td>4.67±1.74</td>
<td></td>
</tr>
<tr>
<td>Late-onset</td>
<td>5.17±1.43</td>
<td>p = 0.467</td>
</tr>
<tr>
<td>Late-control</td>
<td>4.47±1.65</td>
<td></td>
</tr>
<tr>
<td>Early-onset</td>
<td>6.06±1.17</td>
<td>p = 0.446</td>
</tr>
<tr>
<td>Late-onset</td>
<td>5.17±1.43</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4. Total Peripheral Vascular Resistance value of Early-onset, Late-onset preeclampsia, and control**

<table>
<thead>
<tr>
<th></th>
<th>Total Peripheral Vascular Resistance (dynes.s/cm(^{2}))</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset</td>
<td>1.76±0.434</td>
<td>p = 0.481</td>
</tr>
<tr>
<td>Early-control</td>
<td>1.58±0.498</td>
<td></td>
</tr>
<tr>
<td>Late-onset</td>
<td>2.29±0.796</td>
<td>p = 0.527</td>
</tr>
<tr>
<td>Late-control</td>
<td>1.82±0.947</td>
<td></td>
</tr>
<tr>
<td>Early-onset</td>
<td>1.76±0.434</td>
<td>p = 0.342</td>
</tr>
<tr>
<td>Late-onset</td>
<td>2.29±0.796</td>
<td></td>
</tr>
</tbody>
</table>

Preeclampsia was once known as disease of a first pregnancy, because increased risk of preeclampsia on first pregnancy/nulipara (Decker G, Sibai B, 2001). Our study show that the number of multipara woman was more than primipara in early-onset preeclampsia group (60%) and late-onset preeclampsia group (57%). But this did not means that preeclampsia primy-paternity theory not right. Because many factor was not calculated in this study, like: husband factor, age, and interval between pregnancy. Obesity is definitive risk factor for preeclampsia, the risk is increased with increasing body mass index (Sibai BM, \(^{6}\) Valensise study show that late-onset preeclampsia has a higher body mass index compared to early-onset preeclamp-sia. \(^{18}\) In our study, we found late-onset preeclampsia tend to have a higher body mass index compared to early-onset preeclampsia, although no statistically significant.

Preeclampsia and fetal growth restriction was marked by abnormal placental function, that caused inadequate uteroplacental perfusion. From his study, Valensise proved that early-onset preeclampsia group has a higher incidence bilateral notching on uterine artery examination during 24 weeks, compared with late-onset preeclampsia and control. Abnormality on doppler examination maybe associated with uteroplacental perfusion impairment or placental lesion that associated with early-onset, but not late-onset preeclampsia. \(^{18}\)

Our study show no significant difference between preeclamptic group and control. On late-onset preeclampsia this result is appropriated with our hypothesis that late-onset was not associated with placental abnormality so the uterine artery doppler examination should be normal. But our finding in early-onset preeclampsia did not fit our hypothesis. What should be noted form this result is, although the value of resistance index uterine artery from early-onset did not differ from control, but the absolute value (0.68 ± 0.079) is higher than normal and can be a predictor of preeclampsia. Coleman et al showed that resistance index value of uterine artery > 0.58 has a sensitivity 91% to predict preeclampsia (Odendall H, 2005).

A lot of study showed that onset of preeclampsia is one of main factor predictor of outcome in preeclamptic patient. The disease that manifest earlier has a worst outcome. \(^{4}\) One of factor that was suspected makes this difference is hemodynamic model difference, just like Mei et al showed in her study. Valensise et al proved that early and late-onset preeclampsia come from different hemodynamic models, early-onset preeclampsia had a high total vascular peripheral resistance and low cardiac output and vice versa. \(^{18}\)

From our study we found that on preeclamptic group (either early-onset and late-onset) had a higher value on cardiac output and total vascular peripheral resistance, compared with control. This finding was different from Valensise finding that showed hemodynamic difference on both group, and also different from our hypothesis. \(^{18}\) Our finding with high cardiac output and total vascular peripheral resistance is similiar with Easterling and Mei finding from their study. \(^{9}\)

Mei et al explain that this cardiac output increased possibly precede total vascular peripheral increased in preeclampsia. Endothelial injury is the trigger of pre-
An elevated cardiac output could result in compensatory vasodilatation to maintain blood pressure at a higher level. The excessively dilated terminal arterioles would then expose the delicate endothelium of capillary beds to high systemic pressures and flow, which could exacerbate the endothelial damage already present in latent phase pre-eclampsia. It looks like hemodynamic changes exacerbate endothelial damage, exhaust the vasodilatory rescue functions of the endothelium and trigger a threshold level of dysfunction resulting in the clinically damaging, fixed vaso-constricted state of severe pre-eclampsia.

Our study shows that hemodynamic model of preeclampsia has a complex variety and can not be strictly divided into two kind of model. The diversity of hemodynamic model of preeclampsia is similar with Mei S study that found 7 hemodynamic model on preeclampsia. Our study did not actually showed that the theory of different onset preeclampsia with different hemodynamic model and outcome is totally wrong, but its showed that hemodynamic model on preeclampsia had a complex variety, and further advanced study should be held to establish the true nature of early-onset and late-onset preeclampsia, with their hemodynamic and outcomes different.

CONCLUSION

Early onset preeclampsia has higher cardiac output and uterine artery resistance index, and lower total vascular peripheral resistance than late-onset preeclampsia.

REFERENCES

Identify Uncomplicated Gestational Hypertension. BJOG. 2006;113:1044-1052.