SRIWIJAYA JOURNAL OF MEDICINE

# Placental Factors Affecting Birth Weight of Late Onset Severe Preeclampsia

Martadiansyah A[1*], Pangemanan WT[1], Bernolian N[1], Maulani H[2], Theodorus[3]

[1]Department of Obstetrics and Gynecology of Medical Faculty of Sriwijaya University / Dr. M. Hoesin Hospital, Palembang, Indonesia
[2]Department of Pathology Anatomy of Medical Faculty of Sriwijaya University / Dr. M. Hoesin Hospital, Palembang, Indonesia
[3]Department of Public Health Faculty of Medical Faculty of Sriwijaya University / Dr. M. Hoesin Hospital, Palembang, Indonesia
E-mail: drabarhammartadiansyah@gmail.com

## Abstract

Preeclampsia (PE) is one of the leading causes of maternal and perinatal mortality and morbidity. Placental insufficiency is considered as the main pathogenesis in the early onset PE. Objective of the study is to determine the correlation of placenta and birth weight in late onset preeclampsia. A case-control study of prevalence was conducted in Moh. Hoesin Hospital Palembang from August 2015 to August 2016. Samples were women who giving birth in Moh. Hoesin Hospital Palembang. They were divided into two groups, severe preeclampsia as case group and normotension as control. Data were analyzed by $X^2$, Exact Fisher's and logistic regression test using SPSS 16.0. There were 180 subjects (90 cases and 90 controls). There was a positive correlation between placental macroscopic and late onset preeclampsia (p=0.009; OR=6.9), in contrast there was only one different placental microvascularisation of 16, between late onset preeclampsia and normotension, the mural or occlusive fibrin thrombi chorion (p=0.005; OR=9.9). Birth weight in late onset preeclampsia tended to be small but still in normal range and it was not statistictly significant (p=0.112; OR=10.4). There was a positive correlation between placental macroscopic and SGA baby on late onset preeclampsia (p=0.026; OR=16.6), but it wasnot proven microscopically. Placenta remains contributed to the pathogenesis of the late onset preeclampsia, but not as dominant as the early one.

***Keywords**: birth weight, late onset severe preeclampsia, placental factor*

## 1. Introduction

Preeclampsia (PE) is one of the leading causes of maternal and perinatal mortality and morbidity. The incidence was 7-10% of all pregnancies, with maternal mortality rate 529.000 (99% in the developing countries).[1,2] The incidence varied in Indonesia, between 3-10%. In Moh. Hoesin Hospital, the incidence was 17% (medical record data 2010-2015). PE is divided into early and late onset. Placental insufficiency is considered as the main pathogenesis in the early onset, meanwhile maternal factors in late onset. Early onset characterized by poorpregnancy outcome, but late onset characterized by normal outcome.[1,3-5]

Variation of placental and neonatal outcome in severe PE was the interest of this study. The correlation assessment of placental weight and microvascularisation to the birth weight gave us important information aboutthe placental role in severe PE pathogenesis.[6,7] Recent studies in Moh. Hoesin Hospital by Rahman and Malasi suggested that there was a significant correlation between placental outcome and the pathogenesis of early onset severe PE and its neonatal outcome.[8,9] But these particular studies has not been well observed in late onset severe PE.

The aim of this study was to determine the correlation between placental outcome and birth weight in late onset severe PE.

## 2. Methods

This study was conducted in Obstetric and Gynecology Department and Pathology Anatomy Department of Faculty of Medicine University of Sriwijaya / Moh. Hoesin Hospital Palembang, from August 2015 to Agustus 2016. The protocol of this study was approved by Bioethics Humaniora Unit of Medical Faculty of Sriwijaya University.

Consecutive sampling was performed, and samples were divided into two groups, severe PE as case group and normotension as control group. The inclusion criterias were full term pregnancy, single life fetus, agreed to participate the study and signed the informed consent. The exclusion criterias were obesity, diabetic mellitus, intrapartum infection, premature rupture of membrane and anemia. Due to the double proportion case control formula, we had minimal samples were 47 for each group.

### 2.1 Sampling Procedure

- Study samples who met the inclusion criterias were given the questioner.
- Blood pressure, body weight and height, and laboratory examination was performed.
- Birth weight and placental examination.
- After birth, the umbilical cord was cut on 5 cm of its insertion and birth weight was measured after the resuscitation (if needed).
- A cleaned fresh placental weight was measured (including amniotic membrane and umbilical cord). The placental weight was noted in gram, and classified as small if ≤460 gram and normal if >460 gram.[8,9]
- Four outer and one central cotyledons and 3 cm of the umbilical cord were placed in a bag contained buffer formalin 10%, processed and analyzed for its vascular damage by at least two pathologists using the electric lamp binocular microscope with 10, 40, 100 magnification. Itwas assigned due to Salafia Score.[10,11]

Data was analyzed using $X^2$, Exact Fisher's and logistic regression test. All those analysis were performed using SPSS version 16.

## 3. Results

Table 1 showed that mostly case group have placental weight <460 gram. Samples with placental weight <460 gram tended to have PE(OR 6.9; p=0.009;CI: 1.7-27.8).

**Table 1. Relationship between placental weight and late onset preeclampsia ($n_1$= $n_2$ controls = 90)**

| Placental Weight | Cases | | Controls | | p | OR (95%CI) |
|---|---|---|---|---|---|---|
| | $n_1$ | % | $n_2$ | % | | |
| < 460 g | 39 | 81.2 | 9 | 18.8 | 0.009 | 6.882 |
| ≥ 460 g | 51 | 38.6 | 81 | 61.4 | | (1.707-27.752) |

Exact Fisher's test, p = 0.05

Table 2 showed the microscopic finding. Placenta with mural or occlusive fibrin thrombi chorion (MO) and placenta with terminal villous fibrosis (TVF) tended to have PE (OR 5.7; p=0.007; 95%CI1.7-8.9 and OR 7.0; p=0.024; CI1.4-35.5).

We performed logistic regression test (Table 3) to the placental factors that probably reveal important role in PE pathogenesis (p<0.25). The sewere MO, mural hyperplasia (MH), fibrinoid necrosis and atherosis (FNA), villous infarcts (VI), TVF, and cytotrophoblast proliferation (SP). Using the Backward LR method, we found that MO was the only placental factor that statistically significant (OR=9.9; p=0.005).

Severe PE tended to have SGA baby (Table 4; OR=10.4; p=0.112), butnot statistically significant. Severe PE with low placental weight tended to have SGA baby (Table 5; OR 16.6; p=0.026).

**Table 2. Relationship between placental microvascularisation and late onset preeclampsia ($n_1$= $n_2$= 90)**

| Placental Microvascularisation | | Cases | | Controls | | p | OR (95%CI) |
|---|---|---|---|---|---|---|---|
| | | $n_1$ | % | $n_2$ | % | | |
| **Placental Vaso-Occlusive Lession** | | | | | | | |
| Mural or occlusive fibrin thrombi chorion | Score 1 | 75 | 64,1 | 42 | 35,9 | 0.007 | 5.714 (1,724-8,944) |
| | Score 0 | 15 | 23,8 | 48 | 76,2 | | |
| Avascular terminal villous | Score 1 | 27 | 64,3 | 15 | 35,7 | 0.360 | 2.143 (0,622-7,387) |
| | Score 0 | 63 | 45,7 | 75 | 54,3 | | |
| Hemorrhagic endovasculitis | Score 1 | 78 | 52,0 | 72 | 48,0 | 0.729 | 1,625 (0,408-6,469) |
| | Score 0 | 12 | 40,0 | 18 | 60,0 | | |
| Villous stromal hemorrhage | Score 1 | 81 | 48,2 | 87 | 51,8 | 0.612 | 0.310 (0,030-3,168) |
| | Score 0 | 9 | 75,0 | 3 | 25,0 | | |
| Mural hyperplasia | Score 1 | 81 | 47,4 | 90 | 52,6 | 0.237 | 0,129 (0,026-3,008) |
| | Score 0 | 9 | 100 | 0 | 0,0 | | |
| Mural disorganization | Score 1 | 72 | 46,2 | 84 | 53,8 | 0.254 | 0.286 (0,053-1,549) |
| | Score 0 | 18 | 75,0 | 6 | 25,0 | | |
| Abnormally thin walled arteries | Score 1 | 81 | 49,1 | 84 | 50,9 | 1.000 | 0.643 (0,100-4,153) |
| | Score 0 | 9 | 60,0 | 6 | 40,0 | | |
| **Uteroplacental Endothelial Dysfunction** | | | | | | | |
| Fibrinoid necrosis and atherosis | Score 1 | 72 | 45,3 | 87 | 54,7 | 0.103 | 0.138 (0,016-1,226) |
| | Score 0 | 18 | 85,7 | 3 | 14,3 | | |
| Abruption | Score 1 | 66 | 46,8 | 75 | 53,2 | 0.531 | 0.550 (0,157-1,931) |
| | Score 0 | 24 | 61,5 | 15 | 38,5 | | |
| Villous infarcts | Score 1 | 87 | 53,7 | 75 | 46,3 | 0,195 | 5,800 (0,635-3,012) |
| | Score 0 | 3 | 16,7 | 15 | 83,3 | | |
| Terminal villous fibrosis | Score 1 | 84 | 58,3 | 60 | 41,7 | 0.024 | 7,000 (1,381-35,478) |
| | Score 0 | 6 | 16,7 | 30 | 83,3 | | |
| Increased syncytiotrophoblast knot | Score 1 | 75 | 48,1 | 81 | 51,9 | 0.706 | 0.556 (0,120-2,569) |
| | Score 0 | 15 | 62,5 | 9 | 37,5 | | |
| Villous hypovascularity | Score 1 | 12 | 66,7 | 6 | 33,3 | 0.671 | 2.154 (0,363-12,764) |
| | Score 0 | 78 | 48,1 | 84 | 51,9 | | |
| Cytotrophoblast proloferation | Score 1 | 57 | 42,2 | 78 | 57,8 | 0.074 | 0.266 (0,073-0,964) |
| | Score 0 | 33 | 73,7 | 12 | 26,7 | | |
| **Coagulation Disorders** | | | | | | | |
| Uteroplasental vascular thrombosis | Score 1 | 81 | 50,9 | 78 | 49,1 | 1,000 | 1.385 (0,282-6,796) |
| | Score 0 | 9 | 42,9 | 12 | 57,1 | | |

$X^2$ and Exact Fisher'stest, p = 0.05

In the other hand, table 6 showed the placental risk factors for SGA baby in late onset severe PE. These were hemorrhagic endovasculitis (HE), villous stromal hemorrhage (VSH), abnormally thin walled arteries (ATW), abruption (A), TVF, villous hypovascularity (VH) and increased of syncytiothrophoblast knot (ISK). Having been performed Exact Fisher's test, all of those risk factors were not statistically significant.

## 4. Discussion

Preeclampsia is a specific pregnancy syndrome characterized by the increased of

blood pressure and proteinuria on gestational age >20 weeks and disappeared ≤12 weeks after delivery. The risk factors are parity, maternal age, placentomegaly, genetic, history of preeclampsia in previous pregnancy, maternal disease and environment, while the protecting factors are smoking and oral sex.[1-5,13-15]

**Table 3. Multivariate analysis of placental microvascularisation and late onset preeclampsia relationship**

| Plasental Microvascularisation | Unadjusted | | | Adjusted | | |
|---|---|---|---|---|---|---|
| | B | OR (95%CI) | p | B | OR (95%CI) | p |
| Mural or occlusive fibrin thrombi chorion | 1,739 | 5,714 (1,724-8,944) | 0,007 | 2,302 | 9,996 (1.989-50.238) | 0,005 |
| Mural hyperplasia | -36,785 | 0,129 (0,026-3,008) | 0,237 | -22,156 | 0,000 | 0,999 |
| Fibrinoid necrosis and atherosis | -2,174 | 0,138 (0,016-1,226) | 0,103 | -2,454 | 0,086 (0.005-1,421) | 0,086 |
| Villous infarcts | 19,824 | 5,800 (0,635-3,012) | 0,195 | | | |
| Terminal villous fibrosis | -0,539 | 7,000 (1,381-35,478) | 0,024 | -2,139 | 0,118 (0.015-0,956) | 0,045 |
| Cytotrophoblast proliferation | -2,290 | 0,266 (0,073-0,964) | 0,074 | | | |
| **Constant** | **22,408** | | | **26,659** | **3,782E11** | **0,999** |

Logistic regression test, p = 0.05

**Table 4.** Relationship between Late Onset Severe PE and Birth Weight (n1 = n2 = 90)

| Severe PE | SGA | | AGA | | p | OR |
|---|---|---|---|---|---|---|
| | n | % | n | % | | |
| Yes | 12 | 13.3 | 78 | 86,7 | 0,112 | 10,358 |
| No | 0 | 0,0 | 90 | 100,0 | | |

Exact Fisher's test, p = 0.05

**Table 5.** Relationship between Placental Weight and SGA Fetus (n = 90)

| Placental Weight in PE | SGA | | AGA | |
|---|---|---|---|---|
| | n | % | n | % |
| <460 g | 12 | 30,8 | 27 | 69, |
| ≥460 g | 0 | 0,0 | 51 | 100 |

Exact Fisher's test, p = 0.05

Redman, et al (2009) divided PE into early and late onset. Stage one or early onset (≤34 weeks) was caused by the false remodeling in spirals artery by the trophoblast, and characterized by placental insufficiency and poor pregnancy outcome. In contrast, the late onset or stage two (>34 weeks), the role of placenta was not significant and mostly caused by maternal factors, and these was 80% of all PE cases. Although the incidence of early onset PE was 20%, it revealed important role in causing higher maternal and perinatal mortality and morbidity. [1-5,12,16-20]

Hertig (1962) said that when the nidation process, blastula cell differentiated intoembrio and trophoblast cell (cytotrophoblast inside and sincytiotrophoblast outside). Cytotrophoblast invaded the spirals artery and replaced its myoendothel. Spirals artery that was thick, narrow and high resistance will dilate 4-6 times in diameter, less elastic, lower resistance, higher blood flow (10.000 times) and loose its neovascular control. This condition will cause the adequate oxygen and

nutrition supply for the babies. Mature placenta is round, 15-20 cm in diameter, approximately 500 gram or 1/6 ofbirth weight, 10-25 mm in thickness and consist of 10-30 lobules called cotyledons. It consist of uteroplacental and fetoplacental circulation separated by the plasental barrier.[1,8,9,19-24]

The placental pathoanatomy does not occur only in PE. The placenta condition in PE was determined by its onset. Infarct, thrombus, and perivillous fibrin also found in normal pregnancy, but these increased in early onset PE. Contrastly in late onset PE, those tended to similiar with normal one. Dahlstrom, et al (2008) in Oslo University said that small sized placenta correlated to PE. This correlation was more significant in preterm PE compared to full term one. The result was similar to Palaskar's study in Parel Mumbai. Palaskar et al, said that 56% of placenta in normotension pregnancy had 451-550 grams, meanwhile 77% PE had placental weight <450 grams. Furthermore, the mean of normal placental weight was 475 gram dan 372 grams in PE.[1,8,25,26] The result of this study was alike to those previous studies. Samples whose placental weight <460 gram were 6.9 times tended to have PE compared to placental weight ≥460 grams (p=0.009).

**Table 6. The relationship between placental microvascularitation and SGA fetus in severe PE (n = 90)**

| Placental Microvascularisation | | SGA | | AGA | | p | OR (95% CI) |
|---|---|---|---|---|---|---|---|
| | | n | % | n | % | | |
| **Placental Vaso-Occlusive Lession** | | | | | | | |
| Mural or occlusive fibrin thrombi chorion | Score 1 | 9 | 12,0 | 66 | 88,0 | 0.538 | 0,545 |
| | Score 0 | 3 | 20,0 | 12 | 80,0 | | (0,045-6,654) |
| Avascular terminal villous | Score 1 | 3 | 11,1 | 24 | 88,9 | 1,000 | 0,750 |
| | Score 0 | 9 | 14,3 | 54 | 85,7 | | (0,067-8,363) |
| Hemorrhagic endovasculitis | Score 1 | 12 | 15,4 | 66 | 84,6 | 1,000 | 1,800 |
| | Score 0 | 0 | 0,0 | 12 | 100 | | (0,408-6,469) |
| Villous stromal hemorrhage | Score 1 | 12 | 14,8 | 69 | 85,2 | 1,000 | 1,340 |
| | Score 0 | 0 | 0,0 | 9 | 100 | | (0,030-3,168) |
| Mural hyperplasia | Score 1 | 9 | 11,1 | 72 | 88,9 | 0.360 | 0,250 |
| | Score 0 | 3 | 33,3 | 6 | 66,7 | | (0,017-3,660) |
| Mural disorganization | Score 1 | 9 | 12,5 | 63 | 87,5 | 1,000 | 0.714 |
| | Score 0 | 3 | 16,7 | 15 | 83,3 | | (0,061-8,397) |
| Abnormally thin walled arteries | Score 1 | 12 | 14,8 | 69 | 85,2 | 1.000 | 1,340 |
| | Score 0 | 0 | 0,0 | 9 | 100 | | (0,030-3,168) |
| **Uteroplacental Endothelial Dysfunction** | | | | | | | |
| Fibrinoid necrosis and atherosis | Score 1 | 9 | 12,5 | 63 | 87,5 | 1,000 | 0.714 |
| | Score 0 | 3 | 16,7 | 15 | 83,3 | | (0,061-8,397) |
| Abruption | Score 1 | 9 | 13,6 | 57 | 86,4 | 1,000 | 1,105 |
| | Score 0 | 3 | 12,5 | 21 | 87,5 | | (0,098-2,472) |
| Villous infarcts | Score 1 | 12 | 13,8 | 75 | 86,2 | 1,000 | 0,5294 |
| | Score 0 | 0 | 0,0 | 3 | 100 | | (0,015-3,012) |
| Terminal villous fibrosis | Score 1 | 9 | 15,0 | 51 | 85,0 | 1,000 | 1,588 |
| | Score 0 | 3 | 10,0 | 27 | 90,0 | | (0,144-7,561) |
| Increased syncytiotrophoblastknot | Score 1 | 12 | 16,0 | 63 | 84,0 | 1,000 | 2,302 |
| | Score 0 | 0 | 0,0 | 15 | 100 | | (0,120-5,569) |
| Villous hypovascularity | Score 1 | 3 | 25,0 | 9 | 75,0 | 0.454 | 2,556 |
| | Score 0 | 9 | 11,5 | 69 | 88,5 | | (0,197-3,161) |
| Cytotrophoblast proloferation | Score 1 | 6 | 10,5 | 51 | 89,5 | 0,611 | 0,529 |
| | Score 0 | 6 | 18,2 | 27 | 81,8 | | (0,064-4,410) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Coagulation Disorders** | | | | | | | |
| Uteroplasental vascular thrombosis | Score 1<br>Score 0 | 9<br>3 | 11,1<br>33,3 | 72<br>6 | 88,9<br>66,7 | 0,360 | 0,250<br>(0,017-,660) |

Exact Fisher's test, p = 0.05

The placental histopathological appearance might be thrombus in blood vessels, infarct, abruption and cytotrophoblast cell proliferation. Salafia made the placental vascular damage score, and these were histologicallydivided into:

- Uteroplasental vaso-occlusive lesions
  - Mural or occlusive fibrin thrombus chorion: blockage in chorion orthe villous vessel by the mural/fibrin thrombus.
  - Avascular terminal villous: eosinophylicvillous strome caused by the capillary deficiency innutrient transfer.
  - Haemorrhagic endovasculitis*:* stromal erythrocyte that fragmented into extravascular.
  - Villous stromal haemorrhage*:* erythrocyte in extravascular strome.
  - Mural hyperplastic*:* obliteration of villous vessel and thickening of blood vessel.
  - Mural disorganization: vascular smooth muscle was broken more than 50%.
  - Abnormally thin walled arteries: stem villous vascular wall had the similar structure in arteries and veins.
- Uteroplacental vascular pathology
  - Fibrinoid necrosis and atherosis: blood vessel wall degeneration, eosinophylic appearance with or without mural foamy cells.
  - Abruption: there was sign of abruption (villous hematome).
  - Villous infarcts: there was sign of villous infarct.
  - Terminal villous fibrosis: there was sign of terminal villous fibrosis.
  - Increased syncytiotrophoblast knotting
  - Villous hypovascularity
  - Cytotrophoblast proliferation
- Uteroplacental vascular thrombosis
  - Complete luminal occlusion
  - Excessive perivillous fibrin on the villous trofoblas surface: 10% of villous covered with fibrin.[6,7,10,11]

Those microvascularisation rarely appeared as single pathological appearance, because PE itself is multifactorial. We usually discovered two or more of those appearance in a placenta.

This was the third study of PE placental microvascularisation in Moh. Hoesin Hospital. Rahman (2003) discovered seven differences between PE and normotension, while Malasi (2005) discovered 16 differences. In contrast, this study only admitted two placental microvascularisation differences, these were MO and TVF. Furthermore, performing logistic regression test we discovered MO was the only placental factor of late onset severe PE, while TVF became the protective factor. This probably caused by the small ratio comparison between the sample and control. The result of this study tended to be different to others because it focused on placental role in late onset PE pathogenesis, so that this study only allowed the term pregnancy as study sample. Huppertz B (2008) found normal fetal growth, spirals artery and placental appearances in late onset PE, or only small differences compared to normotension, and there was notany difference in uterine spirals artery flow between them.[18]

Pregnancy outcome in PE was determined by the onset of preeclampsia too. Huppertz (2008) in his journal entitled Placental origins of preeclampsia: challenging

the current hypothesis, said that the pregnancy outcome in early onset PE tended to be smaller, premature or even and as intra uterine fetal death. Meanwhile the neonatal outcome in late onset PE tended to be normal and there was not any difference compared to the normotension.[18] The same result was also found by Egbor in Ghana with the samples sized 11.784.[20] Romundstad et al (2009) said that the small placenta correlated to SGA baby in both PE and normotension. In the research held in Norway included 317.688 samples, found that small placenta was found in 36% SGA baby of PE and 14% in SGA baby of normotension (RR 2.6; 95%CI 2.3:2.8). SGA baby risk increased in lower placental weight.[8,25]

Although this study suggested positive correlation between placental weight and SGA baby in late onset severe PE, but on microscopic examination, we did not find any microvascularisation different that was statistically significant. The interpretation of this result was that placenta had a role in pathogenesis of late onset severe PE, but not as a dominant one.

## 5. Conclusion and Comments

Placental weight correlated to late onset severe PE (p=0.009; OR=6.9). Placental microvascularisation factors in late onset PE were MO (p=0.007; OR=5.7) and TVF (p=0.024; OR=5.7). Performing logystic regression test, MO was the only statistically significant factor (p=0.005; OR=9.9). Birth weight in late onset PE tended to be smaller than normotension (p=0.112; OR=10.4), but it was not statistically significant. There was correlation between placental weight and SGA baby in late onset PE (p=0.026; OR=16.6). Placental microvascularisation did not correlate to SGA baby in late onset PE. Further study such as cohort study is needed, including bigger sample size and longer duration. Sample characteristics, genetic factors and gestational age analysis are required in order to discover a better result. Limitation of the study: Small ratio comparison of case and control and short duration of this study causedthe sample invaried. There were not any grouping and analysist on sample posture and gestational age.

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