# Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

OPEN ACCESS Journal of Medical Sciences

ISSN 1682-4474
DOI: 10.3923/jms.2020.24.28

# Research Article
# Reduced Birth Weight in Early-onset Preeclampsia Might Potentially Be Due to Placental Glucose Transporters Disorders

[1]Adhi Pribadi, [1]Johanes Cornelius Mose, [2]Tri Hanggono Achmad and [1]Anita Deborah Anwar

[1]Department of Obstetric and Gynecology, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia
[2]Department of Biochemistry, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia

## Abstract

**Background and Objective:** Glucose transport play an important role on fetal growth so that if this process disrupted could be stunted growth of the fetus. Preeclampsia was a pathological state so that increase risk incidence of stunted fetal growth. This study aims to investigate impaired glucose transport in preeclampsia. **Materials and Methods:** Samples were taken from 58 placental tissues after birth, divided into 2 groups by consecutive sampling. Samples sent to the Clinical Pathology laboratory then stored in a temperature of -80°C. The samples were ground and resuspended in phosphate buffer saline, subjected to an ELISA method to placental growth factor (PlGF), glucose transporter 1(GLUT1) and glucose transporter 3(GLUT3) analyzed. Chart of Lubchenko was used to further categorize infant birth weight. **Results:** Proportion of SGA samples in the early onset preeclampsia (EOP) group (44.8%) was significantly higher than late onset preeclampsia (LOP) (10.3%) group. PlGF levels for the SGA group was significantly lower than that in Non-SGA in EOP. GLUT1 and GLUT3 levels were also lower in the SGA group than in non-SGA. There were also significant differences in birth weight between the SGA with non-SGA samples. Moreover, PlGF, GLUT1 and GLUT3 showed a significant correlation with the birth weight in the EOP group, but not in LOP. **Conclusion:** The number of SGA incidents in the EOP group was higher than LOP group. Low birth weight in EOP have correlation with reduced of PLGF, GLUT1 and GLUT3.

Key words: Preeclampsia, growth factor, glucose transporter, placenta, birth weight

Citation: Adhi Pribadi, Johanes Cornelius Mose, Tri Hanggono Achmad and Anita Deborah Anwar, 2020. Reduced birth weight in early-onset preeclampsia might potentially be due to placental glucose transporters disorders. J. Med. Sci., 20: 24-28.

Corresponding Author: Adhi Pribadi, Department of Obstetric and Gynecology, Faculty of Medicine, Padjadjaran University, Bandung, Indonesia



Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

## INTRODUCTION

Gluconeogenesis did not occur in a fetus; therefore fetal glucose production depends on maternal glucose. Moreover, the transport of glucose to the placenta depends on the diffuse transport mechanism that was facilitated by glucose transporter protein (GLUT) expressed in both syncytiotrophoblast membranes[1]. Glucose transporter type 1 (GLUT1) protein was the primary transporter of glucose in the placenta and its levels increase significantly depending on the gestational age. In addition to GLUT1, the levels of which increase based on gestational age, there another relatively dominant type of GLUT, especially in early pregnancy GLUT3[2-5]. Moreover, decreased protein levels of placental growth factor (PlGF) affect to angiogenesis and disorders formation of other placental proteins, including nutrient transporter proteins that transfer glucose, protein, fat and micronutrients aided by a carrier protein have adverse effects on the fetus birth weight[6]. This study prove that was not only hypoxia in the placenta but there a decrease in placental growth factors that affect to transfer of nutrients, especially glucose[7,8]. Transport of glucose from maternal blood across the placental trophoblastic tissue barrier was critical to sustain fetal growth[9].

This research has examined role of glucose transport involvement in placenta which turns out to influence fetal output. The outcome assessed was presence of an increase in stunted growth in early onset preeclampsia (EOP) when compared to late onset preeclampsia (LOP). The role of nutrient transfer was apparently influenced by a decrease in placental growth factors in cases of preeclampsia especially in EOP. Cases of stunted growth increase in preeclampsia at initial suspicion due to increased oxidative stress.

## MATERIALS AND METHODS

This was cross-sectional study conducted by consecutive sampling and received ethical clearance from ethical committee of the medical faculty of Padjadjaran University. Placenta samples taken from pregnant women were delivered in the Obstetrics and Gynecology department of Dr. Hasan Sadikin General Hospital and 3 networking hospitals. The samples were taken from 58 placental tissues. These samples divided 2 groups, were further categorized into the EOP group (29 samples) and LOP group (29 samples). Sampling time April, 2014-March, 2015.

**Inclusion criteria:** Mothers diagnosed severe preeclampsia with a range of gestational age between 20-42 weeks. Diagnosis of severe preeclampsia if there are signs below:

- Systolic blood pressure $\geq$160 mmHg or diastolic $\geq$110 mmHg
- Proteinuria $\geq$+2 (dipstick)

Exclusion criteria consist of chronic hypertension aggravated by preeclampsia. There are disorders of glucose metabolism: Diabetes mellitus and gestational diabetes. There are kidney diseases or urinary tract infections.

**Experimental sample preparation:** Fresh placenta samples were obtained immediately postpartum. Fresh placental tissues samples were prepared via the following steps: first, the tissues samples were cut into 1 $cm^3$ cubes and washed with physiological saline. These samples were then placed into a cryotube and labeled. Next, 1 mL of red blood lytic buffer fluid was added to the cryotubes followed by shaking for about 10 min. This ensure that the erythrocytes on the tissue samples, which also possess GLUT, were lysed. This was followed by centrifugation at 2500 rpm for 5 min. The resulting pellet was resuspended in 1 mL of erythrocyte lytic buffer followed by another round of centrifugation at 2500 rpm for 3 min. The pellet obtained was then stored in a cryobox at -80°C. Finally, to extract the placental protein, the pellets were placed in a mortar and ground until smooth by the addition of liquid nitrogen. The tissues were then placed in a Eppendorf® tube followed by the addition of phosphate buffer saline and centrifugation at 2500 rpm for 5 min. The lysates containing placental PLGF, GLUT1 and GLUT3 were then analyzed by an enzyme-linked immunosorbent assay (ELISA). The kit was a sandwich enzyme immunoassay for *in vitro* quantitative of PLGF (SEA114Hu), GLUT 1 (SEB185Hu) and GLUT3 (SEB635Hu) from Cloud-Clone corp.

**Statistical analysis:** Comparative statistical comparison and correlation was conducted considering $p<0.5$ to be statistically significant. The small for gestational age (SGA) group was determine using a Lubchenko chart. An independent *t*-test analysis was used to analyze quantitative data by comparing the average difference between 2 groups with a normal distribution of data. Data normality was tested using the Shapiro Wilk test. The correlation between protein levels of the two groups was determined using the pearson and spearman tests. The association was assessed using a 95% confidence interval (CI), with the level of significance being determined at a $p<0.05$.

## RESULTS

Patient age characteristics, age classification and parity between EOP and LOP did not differ significantly. While the gestational age between the EOP and LOP groups was significantly different so gestational age in this study met the criteria of early onset and late onset preeclampsia. The number of SGA incidents in the EOP group was statistically significant higher than that in the LOP group (Table 1).

Based on the statistical analysis of tissue samples categorized under the EOP group, PlGF levels were significantly lower in the SGA group than the non-SGA groups. Birth weight (BW) was observed in SGA group (mean BW: 1152±311 g) have a weight below non-SGA group (mean BW: 1741±216 g) (Table 2).

**Correlation between birth weight and variables studied:** Body weight has a correlation with PlGF, GLUT1 and GLUT3 with different correlation strengths. PlGF levels have the strongest correlation with postpartum infant weight (Table 3).

PlGF level was parameters for early preeclampsia detection, i.e., a lower PlGF level may mean more severe hypoxia and worse preeclampsia complications. This also affects to GLUT1 and GLUT3 levels in addition to birth weight (Fig. 1). In early onset preeclampsia group, PlGF, GLUT1 and GLUT3 appears to correlate with infant weight, the higher protein content has tendency for body weight to increase

Table 1: Characteristics of research subjects

| | Preeclampsia | | |
|---|---|---|---|
| Characteristics | Early onset (n = 29) | Late onset (n = 29) | p-value |
| **Age (years)** | | | |
| Mean (SD) | 29 (6.3) | 29 (8.1) | 0.21 |
| Range | 18-41 | 16-43 | |
| **Age classification (years)** | | | |
| ≤18 | 3 | 0 | 0.177 |
| 18-35 | 21 | 25 | |
| ≥35 | 5 | 4 | |
| **Pregnancy age (weeks)** | | | |
| Mean (SD) | 32 (1.6) | 38 (1.5) | 0.001** |
| Range | 28-34 | 35-41 | |
| **Parity** | | | |
| Primiparity | 11 | 16 | 0.188 |
| Multiparity | 18 | 13 | 0.188 |
| **Preeclampsia** | | | |
| SGA | 13 (44.8) | 3 (10.3) | 0.04* |
| Non SGA | 16 (55.2) | 26 (89.7) | |

*p≤0.05 significant, **p≤0.01 highly significant

Table 2: Comparison of type of preeclampsia in the SGA and non-SGA group

| Preeclampsia | SGA | Non-SGA | p-value |
|---|---|---|---|
| Early onset | n = 13 | n = 16 | |
| PlGF (pg mL$^{-1}$) | 2084.0±1122 | 3870.0±878 | 0.001** |
| GLUT1 (pg mL$^{-1}$) | 132.0±72 | 171.0±46 | 0.09 |
| GLUT3 (pg mL$^{-1}$) | 242.0±244 | 289.0±176 | 0.56 |
| Birth weight (g) | 1152.0±311 | 1741.0±216 | 0.01** |
| Late onset | n = 3 | n = 26 | |
| PlGF (pg mL$^{-1}$) | 2905.0±1266 | 4265.0±2016 | 0.27 |
| GLUT1 (pg mL$^{-1}$) | 188.0±62 | 197.0±56 | 0.82 |
| GLUT3 (pg mL$^{-1}$) | 452.0±181 | 580.0±115 | 0.24 |
| Birth weight (g) | 1990.0±329 | 3036.0±482 | 0.01** |

SGA: Small for gestational age, Non-SGA: Non small for gestational age, *p≤0.05 significant, **p≤0.01 highly significant

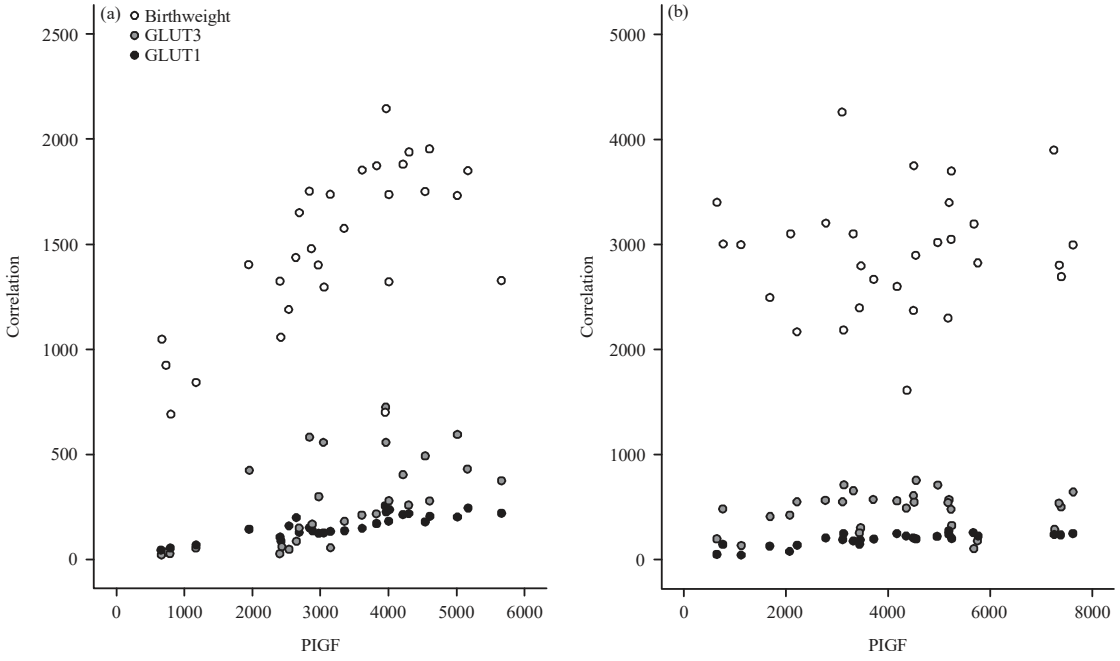


Fig. 1(a-b): Correlation PlGF to birth weight, GLUT1 and GLUT3, (a) Early onset preeclampsia and (b) Late onset preeclampsia

Table 3: Correlation between birth weight and the variables studied

| Preeclampsia | Variable correlation | R | p-value |
|---|---|---|---|
| Early onset | PlGF | 0.86 | 0.001** |
| | GLUT1 | 0.57 | 0.001** |
| | GLUT3 | 0.43 | 0.02* |
| Late onset | PlGF | 0.10 | 0.59 |
| | GLUT1 | 0.02 | 0.94 |
| | GLUT3 | -0.16 | 0.40 |

R: Correlation, *p≤0.05 significant, **p≤0.01 highly significant

(Fig. 1a). Figure 1b show a case of late onset preeclampsia, differing from the case of early onset (Fig. 1a) with a picture showing no significant correlation between body weight and placental protein content.

## DISCUSSION

Small for gestational age was higher in EOP that associated with low placental protein, especially lower glucose transporter as a supporter of metabolism and growth in the fetus. PlGF and GLUT1 protein levels in the SGA group were lower if compared to the nonSGA group and statistically showed significant differences. In the EOP group with SGA, showed that PlGF and GLUT1 levels were lower than those of NonSGA had statistically significant differences. Statistical levels of PlGF, GLUT1 and GLUT3 did not show a statistically significant difference in the LOP category between the SGA and NonSGA groups.

This show that glucose transport was important as a source of fetal energy influenced by PlGF. If PlGF was low it will affect the low of GLUT1 and will directly affect to fetal growth. The number of neonates in the SGA category at EOP was higher than LOP, that pointed to a disruption of metabolism in the placenta and reflects disruption due to more dominant placental factors, when compared to maternal factors (LOP).

Glucose was transported across the placenta through a membrane diffusion mechanism. Other nutrients pass through an active transporter that requires energy derived from the breakdown of sodium, chloride and protons. Thus, an imbalance in the availability of energy availability affects nutrient transfer[10]. During the first few days post implantation, blastocyst nutrition was derived from the interstitial fluid endometrium and surrounding maternal tissue. Therefore, maternal nutritional intake provides all the nutrients to the fetus. Moreover, food consumed by the mother could be stored in forms that could be transferred to the fetus continuously, to meet energy, tissue repair and growth needs[11]. Intrauterine fetal growth was an important risk factor for metabolic abnormalities such as cardiovascular disease, obesity and diabetes in the perinatal and adult life phases[12]. Moreover, fetal growth was predominantly influenced by the transport of nutrients from mother to the fetus and changes in nutrient transport directly affect intrauterine development disorders[13].

The placenta has a high metabolic rate with greater oxygen and glucose consumption than the fetus, which was facilitated by multiple transport and biosynthetic activities occurring simultaneously[11]. Muscular layer persistence causes the spiral artery to not widen, while the need for blood flow increases as the fetus grows. This blood flow deficit, in turn, results in chronic hypoxia that causes cellular damage. Placental pathology, in general, disrupts the remodeling process and is often characterized by a poor prognosis. However, the prognosis in LOP was generally better, because hypoxia or hypertensive exposure did not occurred as a part of the early onset, so that the risk to fetal growth was lower[14].

Under hypoxic conditions, expression levels of proteins such as PlGF, sFlt-1 and VEGF changes in the placenta and these changes can be used to detect the possibility of preeclampsia[15]. Moreover, the expression levels of these proteins decrease according to the degree of severity of hypoxia occurring in preeclampsia[1,9,16-18].

Result study showed that PlGF, GLUT1 and GLUT3 expression in the EOP group correlated with birth weight, suggesting that these placental protein factors play a role in EOP pathology. The LOP group showed no significant correlation between placental protein and birth weight. Placental tissue samples from LOP group showed the incidence of SGA was relatively lower. Another thing that causes no correlation to birth weight because not to long expose hypoxia so formation of proteins was not disturbed. The transfer of glucose to the fetus was often adversely affected by the onset and duration of hypoxia[5]. Moreover, glucose can be converted into fat, which serves as a food reserve that contribute in fetal weight gain. If it happens anomalies in glucose transfer have an effect on negatively impact the metabolism and growth of the fetus, ultimately increasing the risk of low birth weight.

The limitation of this study was not comparative examination in normal pregnancy. Examination in cases of normal pregnancy will increase information about pathogenesis of preeclampsia, especially in terms of improving pregnancy outcome in severe preeclampsia. Comparison of level protein in normal pregnancy will add information on how far down the protein formed by the placenta in the case of preeclampsia, in addition to adding information about the levels of protein PlGF, GLUT1 and GLUT3 in the placenta. This study showed the changing role

of nutrient transport in preeclampsia especially glucose due to decreased glucose transfer and influences fetal output. So the theory of hypoxia due to stunted fetal growth can be explained by the mechanism through decreased nutrient transport.

## CONCLUSION

The disorder originates from the placenta as occurred in early onset preeclampsia, it caused disruption of placental protein including placental growth factor (PlGF) and glucose transporter (GLUT1, GLUT3) so that it affected to fetal growth, therefore increasing cases low birth weight in postnatal babies.

## SIGNIFICANCE STATEMENT

This study discovers a correlation between nutrient transfer with prolonged hypoxia in the placenta in cases of early onset preeclampsia. The longer hypoxia occurs will result in disruption of the formation of placental proteins such as PlGF, GLUT1 and GLUT3. This study will help the researcher to uncover the critical areas of intrauterine growth retarded because disruption of placental protein that many researchers were not able to explore. Thus a new theory of early onset preeclampsia disrupted nutrient transporter, maybe arrived at.

## REFERENCES


1. Hay, Jr. W.W., 2006. Placental-fetal glucose exchange and fetal glucose metabolism. Trans. Am. Clin. Climatol. Assoc., 117: 321-340.
2. Lager, S. and T.L. Powell, 2012. Regulation of nutrient transport across the placenta. J. Pregnancy, Vol. 2012. 10.1155/2012/179827.
3. Simpson, I.A., D. Dwyer, D. Malide, K.H. Moley, A. Travis and S.J. Vannucci, 2008. The facilitative glucose transporter GLUT3: 20 years of distinction. Am. J. Physiol.-Endocrinol. Metab., 295: E242-E253.
4. Dubova, E.A., K.A. Pavlov, G.V. Kulikova, A.I. Shchegolev and G.T. Sukhikh, 2013. Glucose transporters expression in the placental terminal villi of preeclampsia and intrauterine growth retardation complicated pregnancies. Health, 5: 100-104.
5. Mueckler, M. and B. Thorens, 2013. The SLC2 (GLUT) family of membrane transporters. Mol. Aspects Med., 34: 121-138.
6. Zamudio, S., 2011. Hypoxia and the Placenta. In: The Placenta from Development to Disease, Kay, H.H., D.M. Nelson and Y. Wang (Eds.). Chapter 6, Wiley-Blackwell, West Sussex, UK., ISBN-13: 9781444393910, pp: 43-49.
7. Hogg, K., J.D. Blair, D.E. McFadden, P. von Dadelszen and W.P. Robinson, 2013. Early onset pre-eclampsia is associated with altered DNA methylation of cortisol-signalling and steroidogenic genes in the placenta. PLoS ONE, Vol. 8. 10.1371/journal.pone.0062969.
8. Janzen, C., M.Y.Y. Lei, J. Cho, P. Sullivan, B.C. Shin and S.U. Devaskar, 2013. Placental glucose transporter 3 (GLUT3) is up-regulated in human pregnancies complicated by late-onset intrauterine growth restriction. Placenta, 34: 1072-1078.
9. Rampersad, R., M. Cervar-Zivkovic and D.M. Nelson, 2011. Development and Anatomy of the Human Placenta. In: The Placenta from Development to Disease, Kay, H.H., D.M. Nelson and Y. Wang (Eds.). Chapter 3, Wiley-Blackwell, West Sussex, UK., ISBN-13: 9781444393910, pp: 19-26.
10. Cunningham, F.G., K.J. Leveno, S.L. Bloom, J.C. Hauth, D. Rouse and C.Y. Spong, 2010. Williams Obstetrics. 23rd Edn., McGraw-Hill, New York, USA., ISBN-13: 9780071497015, Pages: 1404.
11. Gluckman, P.D., M.A. Hanson, C. Cooper and K.L. Thornburg, 2008. Effect of in utero and early-life conditions on adult health and disease. New Engl. J. Med., 359: 61-73.
12. Brett, K.E., Z.M. Ferraro, J. Yockell-Lelievre, A. Gruslin and K.B. Adamo, 2014. Maternal-fetal nutrient transport in pregnancy pathologies: The role of the placenta. Int. J. Mol. Sci., 15: 16153-16185.
13. Gilbert, J.P., M.J. Ryan, B.B. LaMarca, M. Sedeek, S.R. Murphy and J.P. Granger, 2008. Pathophysiology of hypertension during preeclampsia: Linking placental ischemia with endothelial dysfunction. Am. J. Physiol.-Heart Circ. Physiol., 294: H541-H550.
14. Charnock-Jones, D.S., 2016. Placental hypoxia, endoplasmic reticulum stress and maternal endothelial sensitisation by sFLT1 in pre-eclampsia. J. Reprod. Immunol., 114: 81-85.
15. Costa, M.A., 2016. The endocrine function of human placenta: An overview. Reprod. Biomed. Online, 32: 14-43.
16. Abe, E., K. Matsubara, K. Oka, Y. Kusanagi and M. Ito, 2008. Cytokine regulation of intercellular adhesion molecule-1 expression on trophoblasts in preeclampsia. Gynecol. Obstet. Invest., 66: 27-33.
17. Zhong, Y., M. Tuuli and A.O. Odibo, 2010. First-trimester assessment of placenta function and the prediction of preeclampsia and intrauterine growth restriction. Prenatal Diagn., 30: 293-308.
18. Wang, A., S. Rana and S.A. Karumanchi, 2009. Preeclampsia: The role of angiogenic factors in its pathogenesis. Physiology, 24: 147-158.