# Disorders of placental glucose transporter in pregnancy with preeclampsia: Review

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*Abstract:* **Preeclampsia is a frequent complication in obstetrics cases. The real problem today is the adverse effects of preeclampsia on the mother and fetus, while the pathophysiology useful for the prevention process is still unclear. Chronic hypoxia results in stress on placental cells, thus inhibiting the formation of proteins, hormones, enzymes produced by the placenta such as Placenta Growth Factor (PlGF) and others. These formation barriers include nutrient transporter proteins or transporters. Hypoxia is generally not conducive to human body cells including the placenta. Hypoxia in cells results in reduced transfer of nutrients due to the decrease in transfers due to a decrease in the number of transporter. Similarly occurs in the process of glucose transfer facilitated by glucose transporter, although from previous studies there is a difference in the influence between acute and chronic hypoxia. While research based on clinical observations showed a decrease in glucose transporter 1 (GLUT1) in the basal membrane when exposed to long-term hypoxia. Hypoxia is generally not conducive to human body cells including the placenta. Some studies have found that PlGF levels in the serum of mothers with preeclampsia are lower than normal pregnancies. Hypoxia in cells results in reduced transfer of nutrients due to the decrease in transfers due to a decrease in the number of transporters. Disruption of nutrient transfer in preeclampsia is also thought to be influenced by the involvement of the gene of glucose transporters due to the influenced of hypoxia, thus increasing the incidence of small for gestational age (SGA).**

*Keywords:* **Preeclampsia, Hypoxia, PlGF, Glucose transporter, SGA.**

## 1. INTRODUCTION

Preeclampsia is a relatively frequent complication in obstetrics cases. The real problem today is the adverse effects of preeclampsia on the mother and fetus, while the pathophysiology useful for the prevention process is still unclear. Clinical symptoms and complications that arise are very diverse and have the same end that is the failure of various organs. Such circumstances result in preeclampsia is one of the three causes of maternal death in the world including Indonesia. The incidence of preeclampsia /eclampsia in various studies ranges from 4-10% ofpregnancy. [1,2]

In patients with preeclampsia can be a series of processes starting from the failure of the process of remodeling spiral arteries due to the failure of the invasion of trophoblasts on the walls of blood vessels. This failure of remodeling resulted in the size of the diameter of the blood vessels remained as the condition was not pregnant. The failure of the invasion ultimately resulted in spiral arteries not to be loss of muscle layers. The dilation process that does not occur results in hypoxia in placental cells because the blood flow enters the uterus is less optimal.

Chronic hypoxia results in stress on placental cells, thus inhibiting the formation of proteins, hormones, enzymes produced by the placenta such as PlGF, HCG, and others. These formation barriers include nutrient transporter proteins or transporters. This nutrient transport protein is needed to transport macronutrients and micronutrients through the placenta from the mother to the fetus. While damage to placenta cells also produces products when the cells are stressed or damaged resulting in vasospasm, resulting in increased blood vessel pressure or the onset of clinical symptoms of

preeclampsia. Symptoms of preeclampsia due to remodeling failure factors usually arise at an early gestational age due to chronic hypoxia and placental cell damage. Symptoms arise between the gestational age of 20-34 weeks, called early onset preeclampsia.

In other types of preeclampsia, symptoms arise more lately (above 34 weeks gestation), called late onset preeclampsia. Predisposition is not due to placental factors but because of the occurrence of maternal abnormalities or maternal factors, such as chronic hypertension, diabetes, dyslipidemia, etc. Placental cells in general do not suffer damage so that the proteins produced by the placenta including nutrient transporters are not disturbed. So the incidence of fetal growth is hampered lower in late onset type than when the placenta has a failure to remodel a.spiral (early onset).

Preeclampsia is a complication that has a varied clinical picture and is very dangerous during pregnancy, parturition and puerperium. [2-5] The main clinical picture are hypertension and proteinuria (not absolute), as well as impaired liver function, thrombocytopenia, and kidney abnormalities because the target organ that is mainly affected is the kidneys (glomerular endothelial). [2,3,6,7] Pathogenesis is very complex and influenced by genetics, immunology, and environmental factors. [8-15]

## 2. LITERATURE REVIEW

*Two Step Theory*

Based on the theory of 2 steps (two step theory) the journey of preeclampsia on disease is divided into 2 stages. The first stage is asymptomatic, with abnormal developmental characteristics of the placenta in the first trimester. [14,16] At this stage there is endothelial dysfunction of blood vessels in the placenta due to hypoxia due to a lack of blood supply from spiral arteries that are not remodeled. [2,3,17,18] In the end the mechanism results in placental insufficiency, and triggers the release of proteins due to damage to endothelial cells (such as interleukin, prostaglandins, etc.) into the mother's circulation. [3,16]

The release of proteins due to damage to placental endothelial cells entering the mother's blood circulation triggers the second stage of preeclamps,which is the symptomatic stage. [14,16] At this stage develop symptoms of hypertension, renal disorders, and proteinuria, as well as the occurrence of eclampsia, Syndrome of hemolysis, elevated liver enzyme, and low platelets (Syndrom HELLP) and other end organs damage. [2,3,14,19]

The process of the early stages of preeclampsia begins with a lack of trophoblast invasion resulting in the persistence of the muscularis layer in the spiral arteries (failure of remodeling). The persistence of the muscularis layer results in spiral arteries lacking to dilate so that blood flow is not able to adequately meet the needs of the placenta optimally. Early throphoblast invasion disorder results in the onset of clinical symptoms earlier (less than 34 weeks) with a worse prognosis. Such circumstances are known as early onset. Early onset is believed to be a preeclampsia on with the source of pathology of the placenta. [3,11,15,20] Another type of preeclampsion with clinical symptoms that arise later after 34 weeks is known as late onset. In this type of factors that play a role in the onset of preeclampsia are maternal factors. Maternal factors that play a role such as obesity, hyperlipidemia, diabetes, chronic hypertension, etc. The placenta at the beginning of growth is not impaired and the remodeling process runs like normal physiology. [3,11,15,20]

Hypoxia process in preeclampsia can result in changes in levels of placenta-produced proteins such as placental growth factor (PlGF), Vesicular endothelial growth factor (VEGF), placental protein 13 (PP13) and other proteins. Some studies have found that PlGF levels in the serum of mothers with preeclampsia are lower than normal pregnancies. [15,21-23] Decrease in PlGF protein affects the formation of new blood vessels or angiogenesis, and the formation of other placental proteins including proteins for the purposes of transferring maternal nutrients to the fetus (nutrient transporter). Disruption of angiogenesis and the formation of transporters, inhibits the transfer of macronutrients and micronutrients thus potentially increasing the incidence of intrauterine growth retarded. [21]

*Nutrient Transport*

Nutrient transport has a special mechanism through the process of facilitation of certain proteins. The transfer of glucose from the mother is diffusion facilitated by a type of protein but is not active and does not require energy, while for the transfer of amino acids, calcium, and potassium requires active transport that requires energy. [24-27]

Glucose is the main nutrient transferred from the mother and becomes the main source of energy for the fetus.[7,27] Other energy sources such as fat is not the main source of energy for the fetus because of the slow placental transfer process, it can not be use immediately. [28] Meanwhile the process of gluconeogenesis (the formation of glucose from the breakdown of fats) in the fetus is very minimal so that the main source of fetal energy comes from the glycolysis process, and fetal glucose is almost entirely derived from the mother through the transfer of the placenta depending on the role of glucose transporter (GLUT). [5]

Various types of GLUT play a role in various mammalian and human cells, even known to play a role in the growth of cancer cells. [29] At this time has been found many types of GLUT in various cells, such as: liver, kidneys, pancreas, brain, etc. There are 2 types of GLUT that play a dominant role for glucose transfer in the human placenta, namely: GLUT1 and GLUT3. [26,27,30-34]

Each type of GLUT in the transfer process in sinsitiotrofoblas is bidirectional. The location of GLUT protein is found in microvilli (facing the mother's side) and on the basal membrane (facing the placenta of the fetal part). GLUT protein in microvilli has 3 times more amount compared to basal membrane. The role of GLUT in microvilli membranes is thought to serve as a control function to facilitate trophoblast cells to obtain sufficient amounts of glucose. While GLUT in the basal membrane area plays a role in the regulation of the amount of glucose that will pass to the fetus. [21]

Study in mice that impaired glut3 levels at the beginning of pregnancy leads to fetal death. In the study, abortus process and fetal growth were also hampered in the next gestational age if the fetus can survive. [35,36] GLUT3 protein plays an important role in the process of first trimester glucose transfer, while GLUT1 plays a role throughout pregnancy especially in the advanced trimester ahead of aterm. [21,32]

Hypoxia is generally not conducive to human body cells including the placenta. Hypoxia in cells results in reduced transfer of nutrients due to the decrease in transfers due to a decrease in the number of transporters. [37-39] Similarly occurs in the process of glucose transfer facilitated by GLUT, although from previous studies there is a difference in the influence between acute and chronic hypoxia. The difference is that invitro (acute) cell treatment can improve gene expression through increased messenger Ribo Nucleic Acid (mRNA) slc2a (slc2a mRNA). While research based on clinical observations showed a decrease in GLUT 1 in the basal membrane when exposed to long-term hypoxia. [40,41]

Other studies have shown chronic hypoxia in pregnant women in mountainous areas with a thin oxygen layer (chronic hypoxia) showing a 40% decrease in GLUT1 in basal membrane factions, while in microvilous sinsitium (MVM) there was no difference in various altitude samples. [41] The changes are thought to result in the average weight of babies born lower on the highland when compared to babies born in the lowerlands. [41]

Glucose transport failure occurs due to a disruption in the formation of protein transporter nutrients including GLUT. [7,21] Disorders can also occur upstream, namely the process of disruption at the level of genes and protein transcription. It is known that the formation of GLUT is regulated by genes with the code solute carrier family 2 member 1 (slc2a1) for GLUT1 and solute carrier family 2 member 3 (slc2a3) for GLUT3. [32]

The regulation of gen slc2a is very important for the formation of GLUT. In the acute hypoxia period there was an increase in the expression of mRNA slc2a although the research was invitro, while in preeclampsia with chronic hypoxia conditions and resulting in the external growth of the fetus inhibited there was a decrease in the expression of genes slc2a1 and slc2a3. [32,33,42,43] Nevertheless, in one other study was invitro, showing the genes slc2a1 and slc2a3 were not affected by oxygen levels. [44]

Small of gestational age (SGA) at the time of childbirth due to preeclampsia or intrauterine growth retardation, associated with coronary heart disease, Stroke attack, Diabetes Mellitus type 2, obesity, Metabolic syndrom, and osteoporosis in adult life. Slow intrauterine growth may be associated with increased deposit formation in the form of fatty tissue during the growth process and may increase excessive weight gain during the childhood period. [45] Prevention of the incidence of SGA in each pregnancy should be done given the poor prognosis in adult life of each neonate with SGA. So if the occurrence of SGA can be prevented is a preventive measure against the occurrence of metabolic syndrome in the future.

The process of transporting glucose is memorized transport that is facilitated so that it does not require special energy for the transport process. Meanwhile, other nutrient transport including micronutrient transport such as calcium, iron, sodium,

etc., is an active transport that requires energy in the transport process. So that if there is a disturbance in glucose transport (as the main source of energy for the fetus) will affect the transport of other nutrients. Inhibition of the formation of GLUT will result in stunted fetal growth because it also affects the transport of other nutrients (lack of energy).

Currently preeclampsia are suspected to be disorders of carrier by human genes, with the discovery of several genes related to preeclampsia. Previous research has shown differences in gene expression when affected by acute and chronic hypoxia in tissues. Disruption of nutrient transfer in preeclampsia is also thought to be influenced by the involvement of the gene of glucose transporters due to the influenced of hypoxia, thus increasing the incidence of SGA.

## 3. CONCLUSION

Chronic hypoxia occurs in pregnancy complications due to pathology of the placenta that arises from the beginning of conception, with a clinical picture of early onset of preeclampsia symptoms before 34 weeks. While less time hypoxia occurs in late onset preeclampsia, the time of onset of symptoms is above 34 weeks. In both groups, the prognosis of the fetus was worse, especially in early onset due to longer exposure to hypoxia from the beginning of conception. Negative influence to glucose transfer will also cause disruption of various types of metabolism and growth of developing fetal cells due to insufficient nutrient intake.

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