

Editorial

Disruption of Nutrient Transport, Especially Glucose, in Preeclampsia Triggers Stunted Fetal Growth

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Preeclampsia is a relatively common complication in obstetrics. The real problem currently faced is the adverse effects of preeclampsia on the mother and fetus, while the pathophysiology useful for prevention remains unclear. The clinical symptoms and complications that arise are highly variable and ultimately lead to multi-organ failure. This condition results in preeclampsia being one of the three causes of maternal death worldwide, including in Indonesia. The incidence of preeclampsia/eclampsia in various literature and studies ranges from 4 to 10% of pregnancies.¹

Preeclampsia is a complication with a varied clinical presentation and is very dangerous during pregnancy, childbirth, and the postpartum period.¹⁻⁴ The main clinical features are hypertension and proteinuria because the primary target organ affected is the kidney (glomerular endotheliosis). Its pathogenesis is very complex and influenced by genetic, immunological, and environmental factors.⁵

Based on the two-step theory, the course of preeclampsia is divided into two stages. The first stage is asymptomatic, characterized by abnormal placental development in the first trimester.⁶ In this stage, endothelial dysfunction in the placenta occurs due to hypoxia caused by insufficient blood supply from the spiral arteries, which have not undergone remodeling.⁷ Ultimately, this mechanism leads to placental insufficiency and triggers the release of proteins resulting from endothelial cell damage (such as interleukins, prostaglandins, etc.) into the maternal circulation.

The release of proteins resulting from placental endothelial cell damage into the maternal circulation triggers the second stage of preeclampsia, the symptomatic stage. This stage leads to the development of symptoms of hypertension, renal impairment, and proteinuria, as well as the potential for eclampsia, hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, and other end-organ damage.⁸

The initial stage of preeclampsia begins with insufficient trophoblast invasion, resulting in persistence of the muscularis layer in the spiral arteries (failed remodeling). This persistence of the muscularis layer results in under-dilation of the spiral arteries and their inability to optimally meet placental needs. This condition results in chronic placental hypoxia. This disruption of trophoblast invasion early on results in earlier clinical symptoms (less than 34 weeks) and a poorer prognosis. This condition is known as early onset. Early onset is believed to be preeclampsia with a placental origin.⁹

Another type of preeclampsia with later clinical symptoms (34 weeks) is known as late onset. In this type, maternal factors contribute to the development of preeclampsia. These maternal factors include obesity, hyperlipidemia, diabetes, chronic hypertension, and others. The placenta is unaffected during early development, and the remodeling process follows normal physiology. Undisturbed placental growth results in relatively undisturbed fetal growth and has a better prognosis than early onset.

The hypoxic process in preeclampsia can result in changes in the levels of placental proteins,

such as placental growth factor (PlGF), vesicular endothelial growth factor (VEGF), placental protein 13 (PP13), and other proteins. Several studies have found that PlGF levels in the serum of mothers with preeclampsia are lower than in normal pregnancies.¹⁰ Decreased PlGF protein levels affect the formation of new blood vessels, or angiogenesis, and the formation of other placental proteins, including proteins involved in the transfer of nutrients from the mother to the fetus (nutrient transporters). Disruption of angiogenesis and transporter formation inhibits the transfer of macronutrients and micronutrients, potentially increasing the incidence of fetal growth restriction.¹⁰

Nutrient transport has a specific mechanism through the facilitation of certain proteins. Glucose transfer from the mother is by diffusion, facilitated by a type of protein but not actively, while the transfer of amino acids, calcium, and potassium requires active transport, which requires energy.¹¹

Glucose is the primary nutrient transferred from the mother and serves as the primary source of energy for the fetus.¹² Other energy sources, such as fat, are not a primary source of energy for the fetus due to the slow placental transfer process, making it unavailable for immediate use. Meanwhile, gluconeogenesis (the formation of glucose from the breakdown of fat) in the fetus is minimal, so the fetus's primary energy source comes from glycolysis. Fetal glucose is almost entirely derived from the mother through placental transfer, which relies on the role of glucose transporters (GLUTs). Various types of GLUTs play a role in various mammalian and human cells and have even been known to play a role in cancer cell growth. Two types of GLUTs play a dominant role in glucose transfer in the human placenta: GLUT1 and GLUT3.¹³

Each type of GLUT in the syncytiotrophoblast transfer process is bidirectional. GLUT proteins are located in the microvilli (facing the maternal side) and in the basement membrane (facing the fetal side of the placenta). GLUT proteins are present in microvilli threefold more than in the basement membrane. GLUT in the microvilli membrane is thought to play a controlling role, facilitating the trophoblast cells' access to sufficient glucose. GLUT in the basement membrane, on the other hand, plays a role in regulating the amount of glucose passing to the fetus.

Studies in mice have found that impaired GLUT3 levels in early pregnancy can lead to fetal death. These studies also found abortions and fetal growth retardation in later gestations, if the fetus survives.¹⁴ GLUT3 proteins play a crucial role in the glucose transfer process in the first trimester, while GLUT1 plays a role throughout pregnancy, especially in the later trimesters, leading up to term.

Hypoxia is generally an unfavorable condition for human cells, including the placenta. Cellular hypoxia results in reduced nutrient transfer due to a decrease in the number of transporters.¹⁵ This also applies to the glucose transfer process facilitated by GLUT, although previous research has shown differences in the effects of acute and chronic hypoxia. This difference is that in vitro (acute) cell treatment can increase gene expression through increased SLC2A mRNA. Meanwhile, research based on clinical observations shows a decrease in GLUT 1 in the basement membrane when exposed to long-term hypoxia.¹⁶

Another study showed that chronic hypoxia in pregnant women in mountainous areas with a thin oxygen barrier (chronic hypoxia) showed a 40% decrease in GLUT 1 in the basement membrane, while the microvillous syncytium (MVM) showed no differences across different altitude samples. These changes are thought to contribute to the lower average birth weight of babies born at high altitudes compared to babies born at lower altitudes.¹⁶

Glucose transport failure occurs due to disruptions in the formation of nutrient transporter

proteins, including GLUTs. Disruptions can also occur upstream, with disruptions at the gene and protein transcription levels. GLUT formation is known to be regulated by the genes encoding solute carrier family 2 member 1 (slc2a1) for GLUT1 and solute carrier family 2 member 3 (slc2a3) for GLUT3.

Placental glucose transporter 1 is significantly down-regulated, particularly on the apical membrane of the syncytiotrophoblast. This reduction in expression and function compromises glucose transport to the fetus, contributing to fetal growth restriction. While placental GLUT1 decreases, platelet GLUT3 may be overexpressed, indicating complex, tissue-specific, and sometimes contradictory regulation of glucose transporters in this condition.

Key Findings on Glucose Transporters in Preeclampsia:

- **GLUT1 Reduction:** Studies consistently show a decrease in GLUT1 protein expression in the placental apical plasma membrane, while mRNA levels may not change significantly. This down-regulation likely results from placental malperfusion and oxidative stress.
- **Reduced Transport Function:** The reduced GLUT1 expression directly correlates with lower glucose transport activity, limiting the energy supply to the fetus and leading to potential Intrauterine Growth Restriction (IUGR).
- **GLUT3 and Others:** Although GLUT1 is the main transporter affected, some studies suggest that platelets in preeclamptic patients overexpress GLUT3 to manage the inflammatory state. Other studies have looked at the expression of GLUT1-3 in placental terminal villi, with GLUT1 showing more marked changes than others.
- **Impact on Fetal Development:** The impaired placental transport of glucose due to altered GLUT1 contributes to the altered fetal programming and growth restrictions commonly seen in preeclampsia pregnancies.

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