

Placental Glucose Transporter Opportunities to Improve Prognosis Preeclampsia Fetal Outcome in the Future

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Abstract: *Preeclampsia is a complication that relatively common in obstetric. For these circumstances, preeclampsia become one of the three leading causes of maternal mortality. It also increasing mortality and morbidity of the neonatal, especially growth restriction and prematurity. Glucose is the main nutrient for growth and plays an important role to provide energy needs of the fetus. Glucose is an essential nutrient that transferred from mother to the fetus. Process of trophoblast invasion to spiral arteries are not perfect, resulting high vascular resistance and reduced blood flow to the placenta. Results of end pathological process, the placenta undergo to hypoxia condition. Inadequate of blood flow due to vasoconstriction leads to reduced glucose transporter protein. Glucose may affect the transfer of proteins and fats and micronutrients due to the transfer process is active and requires glucose as an energy source. Preeclampsia causes hypoxia in the placental cells and lead to decreased production of glucose transporters in particular and other nutrient transporters generally and potentially caused growth restricted. If the pregnancy continues reaching to full term, the neonatal outcome can be low birth weight, and in long term possibility of suffering metabolic syndrome including hypertension and diabetes in adulthood.*

Keywords: Preeclampsia, Glucose transporter, growth restricted

1. Introduction

Preeclampsia is a complication that relatively common in obstetric cases. The real problems is the adverse effects of preeclampsia to the mother and fetus. Clinical symptoms and complications are very diverse and finally cause organ failure. For these circumstances, preeclampsia become one of the three leading causes of maternal mortality in the world. It also increased mortality and morbidity of the neonate, especially problem of growth restriction and prematurity. The incidence of preeclampsia / eclampsia in various literature and research ranging from 4-10 % of pregnancies.[1-3]

2. Glucose and the Fetal Growth

Glucose is the main nutrient for the growth and energy of the fetus. It is reasonable if during pregnancy there is a mechanism to minimize the use of glucose by the mother, so the mother's supply can be administered to the fetus. Three main storage of glucose in the mother include: liver, muscle, and fat tissue, with the contribution of hormone insulin, plays an important role in the metabolism of nutrients absorbed from the intestine. Maternal storage of glucose as glycogen primarily in the liver and muscle, and storing the excess as fat. Maternal fat storage peaked in the second trimester, and then decreased with the increasing needs of the fetus in late pregnancy.[2]

Placenta plays an important role in provide energy to meet all the needs of the fetus, especially glucose. Glucose is an essential nutrient that is transferred from the mother and a source of energy to the fetus.[2,4] Another energy, such as fat, is not the main energy source for the fetus because slowly transfer process and so can not be directly used.[5]

3. Protein Carrier (Transporters) of Glucose

Process of the Glucose transfer is divided into two mechanisms according to its transporter protein. First, depend on natrium ion (Na⁺ dependent transporter), which included Sodium Glucose Transporter family (SGLT) produced by gene SLC5A (Solute Carrier Family 5). There were 6 type of SGLT protein. Other group is not depend on natrium ion known as glucose transporter family (GLUT) produced by SLC2A gene clusters. Two families of glucose transporter has now been studied mainly in the adult human body and its role in the metabolism of the various organs. [4,6]

Various types of GLUT role in various mammalian cells and human, have even been known to present in cancer cells. At this time have discovered 14 types of GLUT in a variety of cells, such as liver, kidney, pancreas, brain, etc.[4,6] Family GLUT in humans that has been known, divided into three main groups or classes. Class I includes GLUT1-4 and 14, class 2 includes GLUT 5,7,9,11, and class 3 includes GLUT 6,8,10,12, HMIT (H⁺ + myoinositol symporter) .[4,6] GLUT type of dominant placenta are GLUT1 and GLUT 3.[6]

Each type of GLUT on the transfer process in the syncytiotrophoblast is a 2-way or bidirectional. Mikrovilli area on GLUT protein (maternal membrane) has a 3-fold number compared to the basal membrane area (fetal membranes). GLUT role in mikrovilli allegedly serves as a control function to facilitate trophoblast cells get a sufficient amount of glucose from the mother. While in the area of the basement membrane acts as a regulator number of glucose that will pass to the fetus [7,8,9]

A disease that has been known and associated with GLUT on extrauterine period is GLUT1 deficiency syndrome (G1DS). Symptoms of this syndrome associated with nerve, because in general there's a lack of glucose transport in nerve cells.

4. Pathological state: Hypoxia-Preeclampsia

Reduced transfer of nutrients to the placenta can be caused by three process. First, maternal nutritional status, inadequate blood flow, nutrient transport failure or combination⁸ Maternal nutritional status can occur due to poor nutritional intake or suffering from chronic diseases such as cancer and infections. Second, inadequate blood flow occurs in cases of hypertension and thrombosis of blood disorders such as antiphospholipid syndrome, immunological disorders and diseases Lupus.[2] And third, failure transport of nutrients, allegedly on this case, there was disruption of the formation or function of this protein carrier.[10-14]

At preeclampsia, the process of trophoblast invasion of spiral arteries are not perfect, resulting in high resistance and reduced blood flow to the placenta. At the end of the pathological process results in the placenta undergo hypoxia.[3,9] Hypoxic conditions resulted in reduced transfer of nutrients due to the decrease in the transfer sensitiotrofoblas.[14]

Preeclampsia supposed to influence the growth of the fetus, especially if the onset is early in pregnancy (less than 34 weeks) with a poorer prognosis, known as early onset. However, in late onset of Preeclampsia (>34 weeks), sometimes fetal growth was not impaired and prognosis was good.[15] This is due to a longer exposure to hypoxia in early onset.

Inadequate of blood flow due to vasoconstriction leads to reduced glucose transporter protein which is dominant in the placenta (GLUT1 and GLUT3).[16] The disruption process of transfer not only for glucose but overall nutrition possible due to the reduced surface area for nutrient transfer processes. Glucose may affect the transfer of proteins and fats and micronutrients due to the transfer process is active and requires glucose as an energy source. While the transfer of glucose does not require energy merely by facilitated diffusion.

5. Low Birth Weight and Disease in the Future

Low birth weight due to preeclampsia, associated with coronary heart disease, stroke attack, diabetes mellitus type 2, obesity, metabolic syndrome, and osteoporosis in adult life.[8] There is a direct relationship between birth weight with the disease in adulthood. Tissue structure and organ development may be impaired and affecting individual lives in the long-term, besides even pathological condition could transfer to the next generations.[2,17-19]

The relationship between weight loss or a small body size at birth and the occurrence of long-term illness is an interpretation and reflection consequences of intrauterine life fetal adaptive response in the long term. Restricted growth is

not a cause of the disorder in the long term, but rather fetus coordinated adaptive intrauterine response to very limited resources can change the structure of tissue and organ development that might affect for long life.[20]

The relationship between fetal growth period and mature period as a representation of the effects of gene transmission from mother to fetus. Nevertheless influence of maternal environment more important than the genes inherited trait purely on derivatives. The relationship between prenatal nutrition with metabolic disease in the next period likened to form the letter "U", which increases the risk in the event of a shortage or excessive nutrients, while relatively low frequency on the normal condition.[2,21]

6. Basic Physiology, Cellular and Molecular of Development Plasticity

In animals experimental appears that imbalanced nutrition can be induced by lacking maternal diet, a strict protein diet or exposure to glucocorticoids (without a change in diet). In mice, there's a change in development of multiple organ when given a low protein diet during preimplantation period. If pregnancy continues reaching full term, neonatal outcome are low birth weight, hypertension in adulthood and excessive weight gain during the postnatal (infant obese). This outcome may be a direct effect on the environment with poor resources than normal condition when the ovum fertilized. Preconception period is a period that sensitive to changes, and some nutritional deficiencies affect the subsequent development, such a deficiency of folic acid, vitamin B12, and metionin.[16]

Maternal nutritional imbalance can result deviation development of the kidney, especially deviation ratio between body mass with the number of nephrons. Disadvantages of this nephron number at risk for changes in renal function and trigger hypertension in the next period and the potential failure of kidney function that can potentially cause death at the young age.[17] Beside interference the number of nephrons, other anomaly organs impaired is heart muscle. Mouse suffering hypoxia have less number of heart muscle cells but have a larger size than the parent exposed normal environment, and have a tendency easily occurs myocardial ischemia.[8,19]

7. Opportunity in the Future

Several studies have demonstrated the role of glucose and its transporter essential to fetal growth. Condition preeclampsia causes hypoxia in the placental cells and lead to decreases production of glucose transporters in particular and other nutrient transporters generally, and also potentially lead to low birth weight. The incidence of low birth weight in turn, decreases quality of life in later adult life due to increased metabolic syndrome diseases. These mechanisms showed that improve fetal outcomes in order to achieve normal body weight improve the quality of future life a individual.

Decreased Transporter production in preeclampsia whether it can be replaced with supplementation?, In pathophysiology,

the answer is possible. The shape of supplementation and the form of transporter that can reach in deep to the cell membrane of the placenta should invent. So that can improve the fetal outcomes in preeclampsia.

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