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Intra-uterine Growth Retardation and Development of Hypertension

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ABSTRAK


Kata kunci: gangguan pertumbuhan intra-uterin, hipertensi.

ABSTRACT

Low birth weight (LBW) is defined as a birth weight of a live born infant of <2,500 grams. In developed countries, LBW is commonly caused by preterm birth; while in developing countries, it is mostly due to intrauterine growth retardation. The concept of developmental origins of adult diseases, particularly on late-onset diseases such as hypertension and kidney disease, implies that there is a correlation between intrauterine milieu, intrauterine growth retardation, premature birth and infant feeding. The fetal origin hypothesis suggests that metabolic diseases are directly related to poor nutritional status in early life.

There is an inverse association between LBW and later risk of hypertension. The pathomechanism that links LBW and hypertension is multifactorial including delayed nephrogenesis, genetic factors, sympathetic hyperactivity, endothel dysfunction, elastin deficiencies, insulin resistance and activation of renin-angiotension system.

Keywords: intra-uterine growth retardation, hypertension.
INTRODUCTION

Low birth weight (LBW) is defined as a birth weight of a liveborn infant of <2,500 gram. In developed countries, LBW is commonly caused by preterm birth; while in developing countries, it is mostly due to intrauterine growth retardation. When it is associated with gestational age, LBW can be categorized into LBW that is appropriate for gestational age (AGA) and LBW that is small for gestational age (SGA). It has been estimated that 8-26% of all child birth worldwide is LBW, in which higher prevalence is found in developing countries compared to the developed countries.

Fetal size is affected by maternal nutritional intake and available uterine space on fetal development. Impaired fetal nutritional intake due to undernutrition during pregnancy, uterine vascular abnormalities (preeclampsia and cardiovascular risk factors including hypertension and smoking) as well as primiparity, hydramnios, gemelli and low maternal body size may lead to LBW. The concept of developmental origins of adult diseases, particularly on late-onset diseases such as hypertension and kidney disease, implies that there is a correlation between intrauterine milieu, intrauterine growth retardation, prematurity birth and infant feeding. A study by Barker et al. indicates that intrauterine factors have roles on adult-onset cardiovascular and metabolic diseases. Various studies have also demonstrated the tendency of increased blood pressure in adult life in infants with small size at birth, small head circumference, small placenta size and disproportional birth weight to placenta size.

FETAL PROGRAMMING

During intrauterine period, body tissues experience rapid cell divisions, which is called the critical periods. Poor nutritional supply will reduce the capacity for cell division. Low birth weight is an important indicator for nutritional status and fetal growth. The ‘fetal origin hypothesis’ suggests that metabolic diseases are directly related to poor nutritional status in early life. Nutritional deprivation during pregnancy usually will cause low birth weight. Baker et al. have demonstrated that impaired fetal growth is associated with increased mortality due to cardiovascular disease in later life.

Suboptimal intrauterine condition will cause fetal growth retardation and reduce phenotype changes in consistent with the condition. Such adaptive process is aimed to increase the capacity of intrauterine life and postnatal condition. For example, blood supply and nutritional delivery to the brain remain optimal by sacrificing the blood flow and nutritional supply to organs considered less vital. However, the adaptive response may result in later consequences such as hypertension, kidney disease, insulin resistance and type-2 diabetes mellitus, particularly in supporting postnatal conditions such as obesity, high salt intake and stress.

PATHOMECHANISM LINK BETWEEN LBW AND HYPERTENSION

Blood pressure is affected by intravascular volume and peripheral resistance. An increase in one of those two factors will cause hypertension. The pathomechanism of hypertension development in subjects with LBW has not been fully understood, but the available evidences have demonstrated that it may result from interactions of various factors:

Nephrogenesis Inhibition

Experimental animal and human studies have demonstrated that kidney has a role on the correlation between maternal undernutrition and intrauterine programming of hypertension. Brenner et al. suggest that a reduced nephron number is associated with hypertension. Kidney structure, in this case, the nephron number, is the predictor of hypertension and chronic kidney disease incidences. In Afro-American population, in which has high prevalence of hypertension and progressive kidney disease, autopsy studies have found smaller kidney size and less number of nephron. Keller et al. has also demonstrated that patients with hypertension have smaller number of nephron than the control group that have normal blood pressure.

Reduced nephron number will cause glomerular hyperfunction. In this case, nephromegaly, intraglomerular hypertension and glomerular hyperfiltration occur. In long term, the
process will lead to glomerulosclerosis, damage of nephrons and increased blood pressure. Rapid weight gain after birth can cause exacerbation of glomerular damage as the immense body mass will increase excretion load. Other factors assumed as the cause of nephrogenesis impairment in intrauterine under-nutrition are: a) Life history theory. It is assumed that impaired nephrogenesis is caused by a mechanism, which is known as the life history theory. The theory suggests that in under-nutrition condition, energy allocation will be prioritized for vital organs such as the brain by sacrificing the nutrition for less vital organ, in this case, including the kidney. The effect of maternal glucocorticoid on fetus. Glucocorticoid has an important role on fetal growth due to its effect on the expressions of various proteins at cellular and molecular levels. During pregnancy, there is a lower glucocorticoid level in fetus than the maternal level. 11β-hydroxysteroiddehydrogenase (11β-HSD2) is an enzyme that converts active cortisol into inactive form. The enzyme expression is increased in the placenta and it inhibits maternal glucocorticoid entering fetal blood circulation. It has been demonstrated that there is a reduced level of 11β-HSD2 enzyme in experimental animals with low-protein diet that may explain the increased glucocorticoid level in fetus. Fetal hypoxia can also reduce 11β-HSD2 level and the activity of catabolosephoblasts. There are evidences that glucocorticoid causes organogenesis inhibition in fetus. A study with lambs that had received only dexamethasone for 2 days (day 26 and day 28 of 150 days of pregnancy) shows that it can cause increased blood pressure starting from the 4th month afterbirth until the later life of these experimental animals, in which the autopsy study has found reduced nephron number as many as 40% compared to control. c. The role of angiotensin II. Angiotensin II (Ang-II) has been known to have an important role on organogenesis including the kidney. During the under-nutrition condition, the intrauterine renin-angiotensin (RA) system is suppressed. A study shows that there is a reduced expression of renin gene with protein restriction during pregnancy. Cellular mechanism of organ development shows that growth depends on the balance between cell proliferation and apoptosis. In experimental animal, intrauterine growth restriction (IUGR) is associated with increased apoptosis of kidney.

The neonates of rats that were born from mothers with low protein intake during pregnancy have less glomeruli than those whose mothers had normal protein intake. Morphological and molecular analysis has found that there is an increased metanephric apoptosis in IUGR group. Apoptosis has a role in normal nephrogenesis.

Genetic Factors

In the neonates of rats whose mothers have received low protein intake during pregnancy, there is an increased expression of several genes including genes that code sodium transporters such as bumetanide-sensitive Na-K-2 Cl co-transporter (BSC1) and thiazide-sensitive Na-Cl co-transporter (TSC). Increased expression of glucocorticoid receptors such as a1 and b1 subunit Na-K-ATPase have been found in pregnant mothers with protein restriction. These genes will increase sodium and water reabsorption, which have roles in the pathogenesis of hypertension.

Hyperactivity of Sympathetic Nerves

It has been known that increased sympathetic activity has a role in pathomechanism of hypertension. In LBW, increased heart rate and reduced heart rate variability during sleep has been found compared to infants with normal birth weight, which indicate impairment of autonomic nerve activity. In adult life, infants with LBW also show increased resting pulse rate. This condition has been demonstrated by an experimental animal study using rats model of placenta insufficiency. Kidney denervation in rat neonates prevents the development of hypertension. Increased sympathetic activity may affect the pressure natriuresis and vasoconstriction, which result in increased blood pressure.

Endothelial Dysfunction

Endothelial dysfunction has an important role in the pathomechanism of cardiovascular diseases including hypertension. In LBW, endothelial dysfunction occurs, which in various studies is demonstrated by the presence of impaired flow-mediated dilatation. Endothelial dysfunction causes disturbed vascular remodeling, increased
CONCLUSION

Low birth weight is a risk factor for cardiovascular and metabolic disorder in adulthood. Epidemiological studies indicate that there is a correlation between LBW and hypertension in adulthood. The pathomechanism that links LBW and hypertension is multifactorial including delayed nephrogenesis, genetic factors, sympathetic hyperactivity, endothelial dysfunction, calcium deficiencies, insulin resistance and activation of renin-angiotension system.

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