

# Intra-uterine Growth Retardation and Development of Hypertension

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## ABSTRAK

*Bayi berat lahir rendah (BBLR) didefinisikan sebagai bayi yang lahir dengan berat <2500 gram. Penyebab BBLR di negara maju umumnya adalah prematuritas, sedangkan di negara berkembang sebagian besar oleh karena gangguan pertumbuhan intra-uterin. Konsep perkembangan penyakit pada usia dewasa khususnya hipertensi dan penyakit ginjal dihubungkan dengan lingkungan intrauterin, gangguan pertumbuhan intrauterin, kelahiran prematur dan nutrisi janin. Hipotesis "The Fetal Origin" menyatakan bahwa penyakit metabolik secara langsung berhubungan dengan status nutrisi yang buruk pada fase awal kehidupan. Terdapat hubungan terbalik antara BBLR dengan risiko kejadian hipertensi di masa mendatang. Patomekanisme hubungan antara BBLR dan hipertensi bersifat multifaktorial yaitu hambatan nefrogenesis, faktor gen, hiperaktifitas saraf simpatik, disfungsi endotel, defisiensi elastin, resistensi insulin dan aktivasi sistem renin angiotensin.*

**Kata kunci:** gangguan pertumbuhan intra-uterin, hipertensi.

## ABSTRACT

*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. 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).<sup>1</sup> 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.<sup>2</sup>

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, hydroamnios, gemelli and low maternal body size may lead to LBW.<sup>3</sup>

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.<sup>4</sup> A study by Barker et al.<sup>5</sup> 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.<sup>6</sup>

## 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.<sup>7</sup>

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.<sup>8</sup> Baker et al.<sup>9</sup> 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 induce 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.<sup>3</sup>

## 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.<sup>10</sup> 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.<sup>11</sup> Keller et al.<sup>12</sup> 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, nephromegali, 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.<sup>12</sup> 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 organ such as the brain by sacrificing the nutrition for less vital organ, in this case, including the kidney.<sup>12</sup> b). 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. 11 $\beta$ -hydrosteroiddehydrogenase (11 $\beta$ -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 reduced level of 11 $\beta$ -HSD2 enzyme in experimental animals with low-protein diet that may explain the increased glucocorticoid level in fetus.<sup>13</sup> Fetal hypoxia can also reduce 11 $\beta$ -HSD2 level and the activity of cytotrophoblasts. 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 those experimental animals, in which the autopsy study has found reduced nephron number as many as 40% compared to control.<sup>14</sup> 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 reduced expression of rennin 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 glomerulus 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.<sup>15</sup>

### Genetic Factors

In the neonates of rats whose mothers have received low protein intake during pregnancy, there is an increased expressions of several genes including genes that code sodium transports such as bumetanide-sensitive Na-K-2 Cl co-transporter (BSC1) and thiazide-sensitive Na-Cl co-transporter (TSC). Increased expressions of glucocorticoid receptors such as  $\alpha$ 1 and  $\beta$ 1 sub-unit 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.<sup>11</sup>

### 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.<sup>1</sup>

### 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

vascular reactivity and inflammatory activity, in which those processes have been known to have roles in the development of hypertension and atherosclerosis. Endothelial dysfunction in LBW is caused by reduced expression and activity of endothelial nitric oxide synthase (eNOS), reduced substrate availability for NO production and increased oxidative stress.<sup>11</sup>

### **The Role of Elastin**

One of factors, which are assumed to have role on the correlation between LBW and hypertension include the amount and proportion and elastin of blood vessels. Elastin is a polymer protein with high molecular weight located in the aorta with a function to regulate the elasticity of blood vessels, both vasoconstriction and vasodilatation. Elastin turnover has a half-life time of approximately 40 years. With increasing age, the amount of elastin is getting less and therefore, it causes vascular rigidity. A study has demonstrated that the amount of vascular elastin is lower in LBW than those who are non-LBW.<sup>14</sup>

### **Insulin Resistance**

Barker and Hales<sup>16</sup> have made a hypothesis, which is called the thrifty phenotype. The hypothesis suggests that fetal under-nutrition causes metabolic and/or physiological adaptation, which is aimed to assure nutritional supply to vital organs, such as brain by sacrificing the less vital organs such as pancreas. Adaptation that occurs during the critical periods may be permanent, such as reduced pancreatic  $\beta$ -cells and insulin skeletal receptors, which later can develop insulin resistance. It has been known that insulin resistance has a role in pathomechanism of hypertension through some effects such as stimulation of sympathetic nerves and sodium retention.

### **STUDIES ON HYPERTENSION IN LBW**

The incidence of hypertension due to LBW is associated with birth weight of the born infants. A study of 8,760 males and females in Finland shows that 1,404 of them have hypertension treatment during their adulthood. The incidence of hypertension is 20.2% in those who have birth weight of up to 3 kg; 16.7% in those who

have birth weight up to 3.5 kg, 13.6% in those with birth weight up to 4 kg and 12.3% in those with birth weight over 4 kg. Age affects the incidence of hypertension in LBW. American Nurses Study shows that in LBW, the incidence of hypertension is 3% in young age and it is increased to 8.5% in older age.<sup>1</sup>

A meta-analysis of 80 studies shows that there is lower systolic blood pressure of approximately 2 mmHg for each increase of 1 kg birth weight. Another study has found that every increase of 1 kg birth body weight is associated with a decrease of 2-3 mmHg blood pressure in children and teenagers; and a decrease of 2-4 mmHg in adults.<sup>3</sup>

The Enigma Study by Miles et al.<sup>18</sup> involves 882 participants in England to evaluate the correlation between birth weight, blood pressure, arterial stiffness and pulse reflection. The study has found that in male with LBW, there are high brachial SBP ( $p=0.04$ ) and central pulse rate ( $p=0.03$ ). Mu et al.<sup>19</sup> conducted a meta-analysis study of 27 studies to evaluate the correlation between birth weight and the development of hypertension. They have found that LBW (<2500 gram) is associated with increased risk of hypertension compared to those with birth weight of >2500 gram (OR 1.2; 95% CI, 1.13, 1.30). When LBW (<2500 gram) is compared to birth weight of >2500 gram, there is an increase of mean SBP as many as 2.28 mmHg (95% CI 1.24; 3.33). The result indicates that there is an inverse linear correlation between birth weight and the risk of hypertension and the correlation is particularly obvious on SBP increase.

However, there is a study with different result, the study by Chiolo et al.<sup>20</sup>, that performed an analysis on three cohort studies involving 1004 subjects aged 5.5–9.1 years, 1886 subjects aged 9.1–12.5 years and 1575 children aged 12.5–15.5 years in Seychelles, Africa. The study concludes that changes in body weight regardless of the age since childbirth have an important role on blood pressure in childhood and teenagers, in which blood pressure gives greater response on the current changes of body weight compared to changes of body weight before birth.

## 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, endothel dysfunction, elastin deficiencies, insulin resistance and activation of renin-angiotension system.

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