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Original Article

Relationship between small for gestational age and aortic intima-media thickness in newborns

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Abstract

Background Small for gestational age (SGA) has been associated with adult cardiovascular disease. Small for gestational age newborns may undergo early aortic wall intima-media thickening (aIMT) in utero.

Objective To determine the relationship between SGA as a risk factor for increased aIMT, as a sign of atherosclerosis onset.

Methods We conducted a case-control study in the Neonatal Ward and Rooming-in Nursery at Dr. Mohammad Hoesin Hospital, Palembang, between April to June 2012. Subjects were allocated to either the case group (aIMT ≥ 0.9 mm) or to the control group (aIMT <0.9 mm). Newborns were classified as SGA if their birthweight (BW) was <10th percentile, and appropriate for gestational age (AGA) if their BW was between 10th - 90th percentile, according to the Lubchenco curve. Abdominal aortic intima-media thickness was measured by echocardiography examination.

Results The case and control groups consisted of 30 newborns each. The proportion of SGA newborns was higher in the case group than the control group. The likelihood of infants in the case group being SGA was significantly higher compared to the control group, with odds ratio of 10.8 (95%CI 3,26 to 35,72). The mean aIMT was significantly higher in SGA than in AGA infants, 0.9 (SD 0.16) mm vs. 0.8 (SD 0.13) mm, respectively, with a mean difference of 0,13 (95% CI 0,050 to 0,209 mm; P=0,02).

Conclusion Increased aIMT is more likely found in SGA newborns. **[Paediatr Indones. 2014;54:57-61.]**

Keywords*: Small for gestational age, aortic intima-media thickness, newborns ine, sulfadoxine-pyrimethamine.*

Small for gestational age (SGA) has been associated with adult cardiovascular disease.[1-5] The mechanisms by which slowed intrauterine growth confers vascular risk have not been clearly established.[1,6-15] The fetal origins hypothesis proposes that these diseases originate through metabolic or endocrine adaptations when the fetus is undernourished and result in permanent changes in the structure and function of the body, including vasculature changes.[1,4,6,13-28] Early aortic wall intima-media thickening (aIMT) occuring in utero may play an important role in premature stiffening of the aortic vessels and may predispose these individuals to adult cardiovascular disease.[1,6,17,29,30]

The first atherosclerotic lesions begin to develop in the abdominal aorta.[3,31] Ultrasound-based measurement of aIMT is considered to be a feasible, accurate, and sensitive marker of atherosclerotic risk.[3,32-34] In previous studies, albeit not consistently, SGA was associated with increased aIMT,[1,3,5,9,29] but none of these studies used a case-control as design,[3,5,9,29] in which one can evaluate the risk factors' (SGA or AGA) degree of influence in contributing to increased aIMT. Therefore,

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we performed this study to evaluate the nature of SGA as a risk factor for increased aIMT.

Methods

For this case-control study, we recruited subjects from the Neonatal Ward and Rooming-in Nursery at Dr. Mohammad Hoesin Hospital, Palembang between April and June 2012. Written informed consent was obtained from parents before enrollment and the study protocol was approved by the Ethics Committe of Sriwijaya University. Mother's demographic data were obtained using questionnaires. Subjects were consecutively allocated to either the case group for aIMT ≥0.9 mm or the control group for aIMT <0.9 mm. The ratio of subjects in the case to control groups was 1:1.

Inclusion criteria for the case and control groups were full term newborns and single pregnancy. Exclusion criteria were complicated pregnancy by maternal history of cardiovascular disease or endocrine disorders, such as diabetes, or hypercholesterolemia, and maternal history of using alcohol, nicotine, or medications, such as ritoridin or corticosteroids.

Newborns were classified as SGA if their birthweight (BW) was $<10^{th}$ percentile, and AGA if their BW was between 10^{th} - 90^{th} percentiles, according to the Lubchenco curve.[2,11,12,24] Maternal body mass indexes (BMI) were grouped as <18.5 kg/m^2 and ≥18.5 kg/m^2. Maternal hemoglobin level was grouped as <10 g/dL and ≥10 mg/dL. Gestational age was determined by Ballard Score or last menstrual period.

We measured aIMT in all SGA and AGA subjects by high resolution echocardiography (Phillips IE-33) using a L11-3 linear array transducer, before subjects reached the age of 28 days. A pediatric cardiologist performed all ultrasound studies in all subjects using the same equipment, while unaware of the infants' clinical course and classification groups. All subjects were examined in a supine position. We examined aIMT at the midpoint between the renal arteries and the aortic bifurcation. The IMT was measured on the far wall of the vessel, between the blood-intima and media-adventitia interfaces in the B-mode technique. The image was frozen in diastole. Based on manual cursor placement, the investigator drew a line on the upper border of the intima and a second line on the lower border of the media. Using this method, IMT was calculated digitally by computer. Three consecutive frozen images were recorded and then reported as an average measurement.

Data were presented as proportion, percentage, mean (standard deviation) and median (range). Differences between groups were tested using the Chi-square and Fischer's exact test for categorical variables and the unpaired–t and Mann-Whitney U tests for continuous variables. The association between gestational age and aIMT was assessed with odds ratio. P values <0.05 were considered to be statistically significant. Statistical analyses were performed using SPSS 15 software package.

Results

Sixty newborns were recruited in this study. Case and control groups consisted of 30 newborns each. Baseline and clinical characteristics of the study population are shown in **Table 1.** Except for the body

Table 1. Baseline and clinical characteristics of subjects

Characteristics	Case group aIMT ≥9 mm (n=30)	Control group aIMT<9 mm (n=30)
Newborn		
Gender, male/female	12/18	12/18
Median age (range), days	2 (1 to 20)	1 (1 to 7)
Median gestational age (range), weeks	39 (37 to 42)	39 (37 to 42)
Mean birth weight (SD), g	2,508.3 (468.14)	3,016.7 (566.34)
Mean birth length (SD), cm	45.6 (2.92)	47.4 (2.40)
Mean aIMT (SD), mm	1.0 (0.1)	0.7 (0.05)
Maternal		
Mean age (SD), years	28.9 (6.32)	30.1 (7.63)
Median BMI (range), kg/m^2	20.3 (16.8 to 31.2)	20.3 (14.6 to 36.3)
Meang hemoglobin (SD), gr/dL	10.7 (1.73)	10.7 (1.58)

aIMT: aortic intima-media thickness; BMI: body mass index.

weight and height measurements, the characteristics of both groups were similar.

The mean aIMT in the case and control groups were 1.0 (SD 0.1) mm and 0.7 (SD 0.05) mm, respectively, significantly higher in the case group than in the control group (P<0.001) with a mean difference of 0.26 (95% CI 0.205 to 0.313) mm.

Increased aIMT was significantly found higher among SGA babies compared to AGA group, as shown in **Table 2.**

The mean aIMT was significantly higher in SGA babies than in AGA babies, 0.9 (SD 0.16) mm vs. 0.8 (SD 0.13) mm, respectively, (P=0.02), with a mean difference of 0.13 (95% CI 0.050 to 0.209) mm.

Table 2. Proportion of SGA/AGA in each study group

Group	Group		OR (95% CI)
	Case aIMT ≥0.9mm	Control aIMT <0.9mm	
	n	n	
SGA	23	7	10.8 (3.26 to 35.72)
AGA	7	23	
Total	30	30	

aIMT: aortic intima-media thickness; SGA: small for gestational age; AGA: appropriate for gestational age.

Discussion

At the beginning of this study we faced difficulties in setting the upper limit value to categorize newborns into case or control groups, as there is no standard for normal thickness of aIMT in newborns. We used the results of Skilton *et al*., which confirmed the value of 0.9 mm as the upper limit of the normal range for aIMT in newborns.[3] This set value could have been higher or lower in our patient population due to differences in genetics, environment, and nutrition, during pregnancy.

We enrolled full term newborns in this study. There was no relationship between gestational age and aIMT. Previous studies compared aIMT of SGA and AGA newborns, regardless of their gestational age as one of the inclusion criteria.[3,5,7,9,17] We thought it might be necessary to use full term pregnancy as one of the inclusion criteria, since prematurity is often accompanied by comorbidities which might influence aIMT.[30] Ikari *et al*. also reported that intima formation starts from gestational age of 30 weeks.[31]

Maternal BMI and hemoglobin level were also evaluated as variables in this study. In addition, maternal nutritional status may also influence fetal intake. According to Hay *et al*., mothers with small body proportion likely have smaller placentas due to smaller uteri, leading to insufficient uterine-placenta circulation and subsequent SGA newborns.[2,11] We found no differences in these variables between the case and control groups.

Aortic intima-media thickening has been hypothesized to occur through the inflammation process during pregnancy in SGA fetuses.[22,35-45] The possibility of having postnatal inflammation which might influence aIMT was eliminated in our study, since none of newborns in our population suffered from this condition.

The mean aIMT in SGA newborns was significantly higher than that of AGA newborns, similar to reports from Skilton *et al.*[3], Zanardo *et al.*[5], and Koklu *et al.*,[29] whilst Pesonen *et al.*[9] reported no difference found. Moreover, the mean aIMT in our study was significantly higher than the population in previous studies,[3,5,9,29] indicating that there may have been differences in antenatal factors which influenced outcomes in infancy. It is presumed that in developing countries malnourishment during pregnancy is the culprit for SGA, while in developed countries, maternal diseases during pregnancy are the leading cause.[8,13,14,18,19,23,24,28] These factors, including the role of genetics, need to be explored in future studies.

In this study, increased aIMT was more likely found in SGA compared to AGA newborns. Our results support the theory of Barker *et al*. and Hales *et al*. which proposed SGA to be a risk factor for early aortic intima-media thickening.[1,4,6]

We found seven SGA newborns with aIMT <0.9 mm. Their mean birth weight was 2,257 g. It is possible that aIMT differences reflected

different causes of SGA, such as intruterine growth retardation or constitutional SGA. Those who are born constitutionally SGA have similar organ growth and development as normal infants, so they do not have aortic intima-media thickening.[11,12] We also found seven AGA newborns with aIMT ≥ 0.9 mm. Their mean birth weight was 3,200 g. We could not find any potential risk factors in these seven babies to explain this phenomenon, nor did the literature reveal a possible cause of this finding.

Furthermore, this study shows early aortic wall-intima-media thickening, as a sign of atherosclerosis onset was profoundly found in SGA newborns. As such, screening in SGA newborns may be performed to make early diagnoses part of preventive efforts.

To our knowledge, this is the first study using a case-control design to assess for a possible association between SGA as a risk factor for aIMT. Most previous studies used a cross-sectional design to compare aIMT between SGA and AGA subjects.[3,5,7,9,20]

A limitation of this study was that the data on maternal body weight and history of maternal illnesses were collected by questionnaire. Also, maternal hemoglobin level was examined after delivery. We did not know the hemoglobin level at pregnancy, as low maternal hemoglobin may have a role in SGA newborns.

In conclusion, our findings indicate that SGA is a significant risk factor for increased aortic intima-media thickness in newborns. Follow up studies are needed to evaluate if the thickness will decrease, persist or even increase through the infants' lifetime.

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